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sulla Ricerca Sanitaria**

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Direzione scientifica  
MINISTERO DELLA SALUTE

**NH** National Health  
Research Conference **RC**

# **UNA PROPOSTA DELLA CONSULTA PER MIGLIORARE L'ADERENZA ALLA TERAPIA E GLI ESITI NELLA PREVENZIONE CARDIOVASCOLARE**

**A.L. Catapano, G. Corrao**



## Aderenza alle terapie croniche nella pratica clinica corrente



**Dimensione ed impatto** (dati ed evidenze disponibili)



**Interventi possibili** (dati ed evidenze insufficienti)



**La proposta** (dati ed evidenze di cui dovremmo/potremmo disporre)

## I TRIALS CLINICI CONTROLLATI

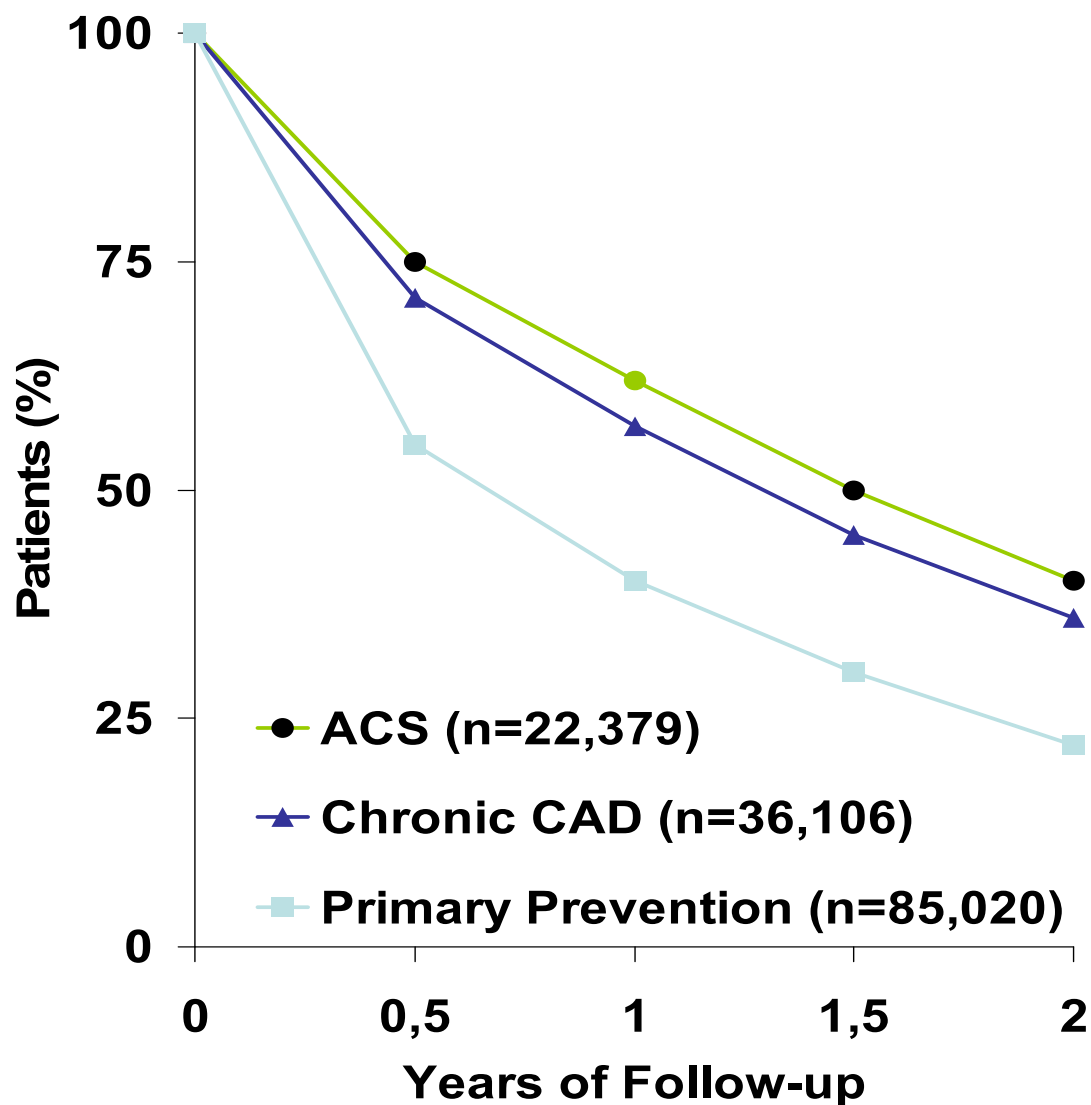
### I TRIAL CLINICI CONTROLLATI FORNISCONO DATI DI ELEVATA QUALITÀ MA:

- Escludono sottogruppi di pazienti
- Escludono trattamenti concomitanti che interferiscono con la procedura/farmaco allo studio
- Escludono pazienti ritenuti non adeguati alla partecipazione
- Sono caratterizzati da una terapia con adesione e persistenza molto elevate

## NEL MONDO REALE

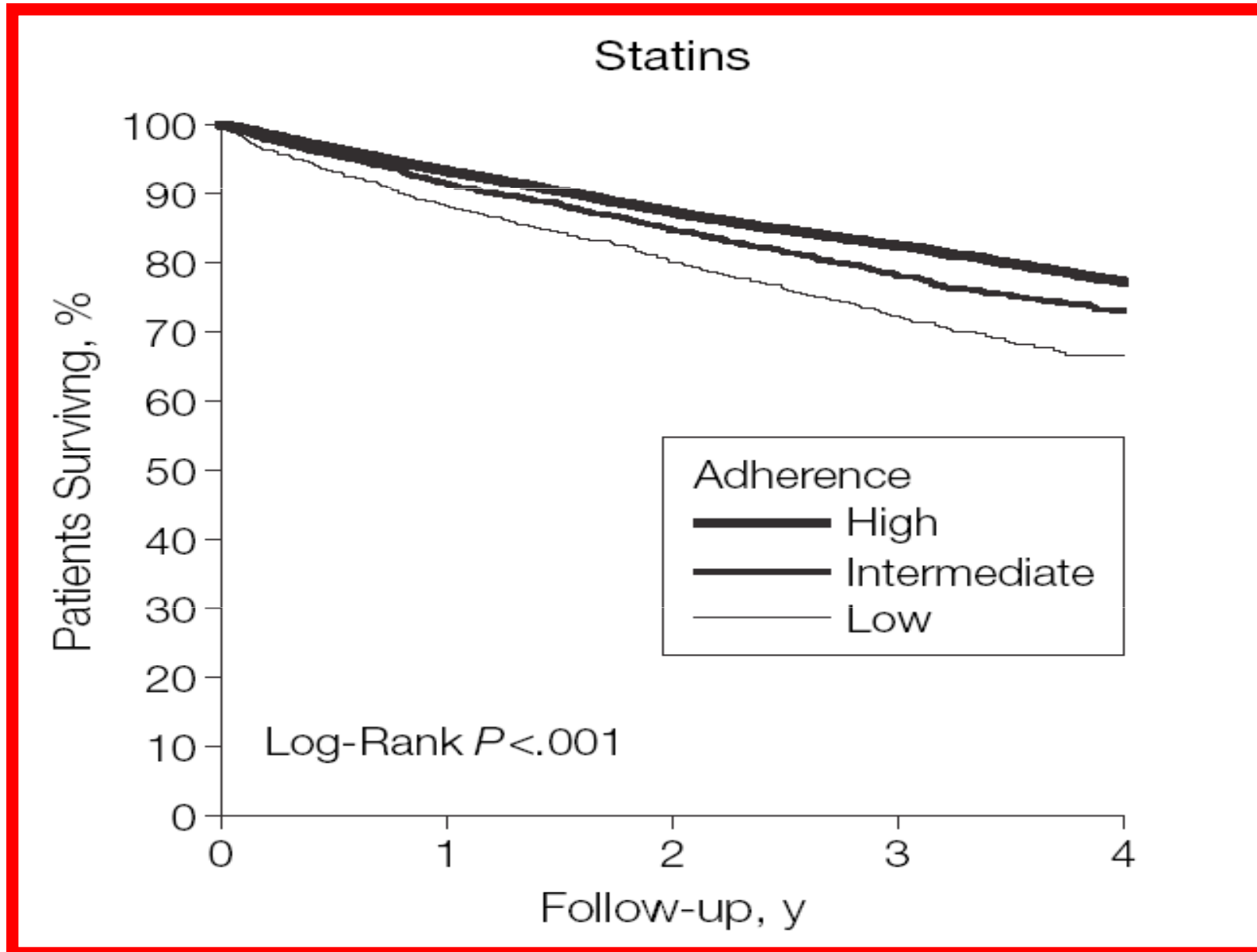
- I PAZIENTI SONO MENO SELEZIONATI
- SPESSO SI CO-SOMMINISTRANO FARMACI INTERFERENTI
- ADESIONE E PERSISTENZA ALLA TERAPIA NON SONO OTTIMALI

**SI PAGA UN PREZZO PER QUESTE  
DIFFERENZE?**



### Independent Predictors of Statin Therapy Discontinuation

- Older age ( $\geq 75$  years)
- Lower socio-economic status
- Depression or dementia
- $\geq 10$  prescribed medications
- No acute events in previous



## Proportion of Days Covered With Statins and All-Cause Mortality, Maccabi Healthcare Services, Israel, 1998-2006

PDC, %	HR (95% CI)					
	Primary Prevention			Secondary Prevention		
	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 3 <sup>c</sup>	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 3 <sup>c</sup>
<10	1 [Reference] <sup>d</sup>	1 [Reference] <sup>d</sup>	1 [Reference] <sup>d</sup>	1 [Reference] <sup>d</sup>	1 [Reference] <sup>d</sup>	1 [Reference] <sup>d</sup>
10-19	1.16 (1.04-1.28)	1.34 (1.21-1.49)	1.35 (1.22-1.50)	1.27 (1.17-1.37)	1.27 (1.17-1.38)	1.28 (1.18-1.39)
20-29	0.97 (0.86-1.09)	1.06 (0.94-1.20)	1.07 (0.95-1.21)	0.95 (0.87-1.04)	0.98 (0.89-1.07)	0.98 (0.90-1.08)
30-39	0.77 (0.67-0.87)	0.87 (0.77-1.00)	0.88 (0.77-1.00)	0.79 (0.72-0.87)	0.81 (0.74-0.89)	0.81 (0.74-0.89)
40-49	0.75 (0.66-0.86)	0.86 (0.75-0.98)	0.86 (0.75-0.98)	0.68 (0.62-0.75)	0.73 (0.66-0.80)	0.73 (0.66-0.80)
50-59	0.70 (0.62-0.81)	0.76 (0.67-0.87)	0.77 (0.67-0.88)	0.64 (0.58-0.70)	0.69 (0.63-0.76)	0.69 (0.63-0.76)
60-69	0.55 (0.48-0.64)	0.63 (0.54-0.72)	0.63 (0.55-0.73)	0.63 (0.58-0.69)	0.67 (0.61-0.73)	0.67 (0.62-0.74)
70-79	0.53 (0.47-0.61)	0.59 (0.52-0.68)	0.59 (0.51-0.68)	0.56 (0.51-0.61)	0.60 (0.55-0.66)	0.61 (0.56-0.67)
80-89	0.56 (0.49-0.64)	0.60 (0.53-0.69)	0.61 (0.53-0.69)	0.51 (0.47-0.55)	0.54 (0.50-0.59)	0.54 (0.50-0.59)
≥90	0.53 (0.47-0.58)	0.54 (0.49-0.60)	0.55 (0.49-0.61)	0.46 (0.43-0.49)	0.49 (0.46-0.52)	0.49 (0.46-0.53)

Abbreviations: CI, confidence interval; HR, hazard ratio; PDC, proportion of days covered.

<sup>a</sup>Adjusted for age and sex.

<sup>b</sup>Also adjusted for marital status, nationality, socioeconomic status, years of living in Israel, residence area, chronic condition, visits to primary care physician during the year before the index date, number of hospitalizations during the year before the index date, cancer, diabetes mellitus, and use of antihypertensives and diuretics during the year before the index date.

<sup>c</sup>Also adjusted for mean level of low-density lipoprotein cholesterol during the year before the index date.

<sup>d</sup>P for trend <.01.

Shalev V, et al. Arch Intern Med 2009; 169:260-268

# Hints to help adherence to lifestyle changes

- Develop a good alliance with the patient.
- Make sure that the patient understands how lifestyles affect cardiovascular disease and use this to gain commitment to the change in behaviour.
- Explore potential barriers to the change.
- Design with the patient a lifestyle change plan that is realistic and encouraging.
- Reinforce the patient's efforts to change.
- Involve other experts wherever needed and possible.
- Arrange a schedule of follow-up visits.

# Tips to help compliance with multiple drug therapies

- Simplify the dosing regimen if possible by reducing daily doses and concomitant medications.
- Choose cheaper alternatives.
- Provide clear written and oral instructions.
- Undertake a dialogue with the patient regarding adherence.
- Tailor the regimen to the patient's lifestyle and needs.
- Involve the patient as partner in the treatment.
- Use behavioural strategies (reminder systems, cues, self-monitoring, feedback, reinforcement)

## Aderenza



### Dimensione ed impatto



### Interventi possibili



### La proposta



	Nuovi trattati / anno	Proporzione giorni coperti dalla terapia
<b>Anti-ipertensivi</b> <sup>1</sup>	~ 200,000	<b>50 %</b>
<b>Ipolipemizzanti</b> <sup>2</sup>	~ 100,000	<b>40 %</b>
<b>Ipoglicemizzanti orali</b> <sup>3</sup>	~ 40,000	<b>60 %</b>

1 Corrao G, Mancia G, et al. 1. Discontinuation of and changes in drug therapy for hypertension among newly treated patients: a population-based study in Italy. *J Hypertens* 2008;**26**:819-24

2 Corrao G, Catapano A, Mancia G, et al. 1. Adherence to statin therapy and risk of nonfatal ischemic heart disease in daily clinical practice. *Clin Ther* 2010;**32**:300-10

3 Corrao G, Romio S, Zambon A, et al. 1. Multiple outcomes associated with use of metformin and sulphonylurea in type 2 diabetes: a population-based cohort study in Italy. *Eur J Clin Pharmacol* 2010;**67**:289-99

Antihypertensives

## Aderenza al trattamento e riduzione di esiti cardiovascolari maggiori



### Aderenza

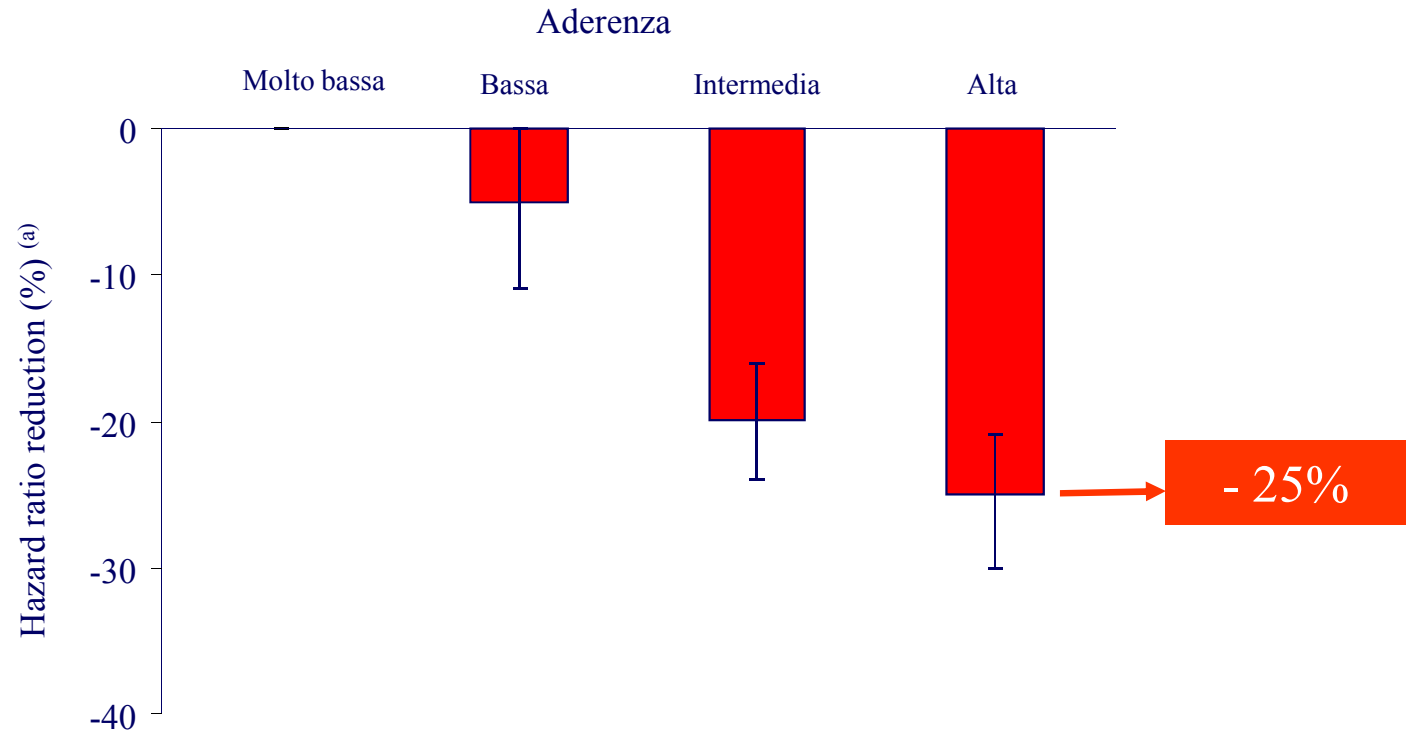
#### Dimensione ed impatto



#### Interventi possibili



#### La proposta



Corrao G, Mancia G, et al. Better compliance to antihypertensive medications reduces cardiovascular risk *J Hypertens* 2011;**29**:610-8

Antihypertensives



Se l'aderenza media passasse dal 52%  
all'80%...

Aderenza

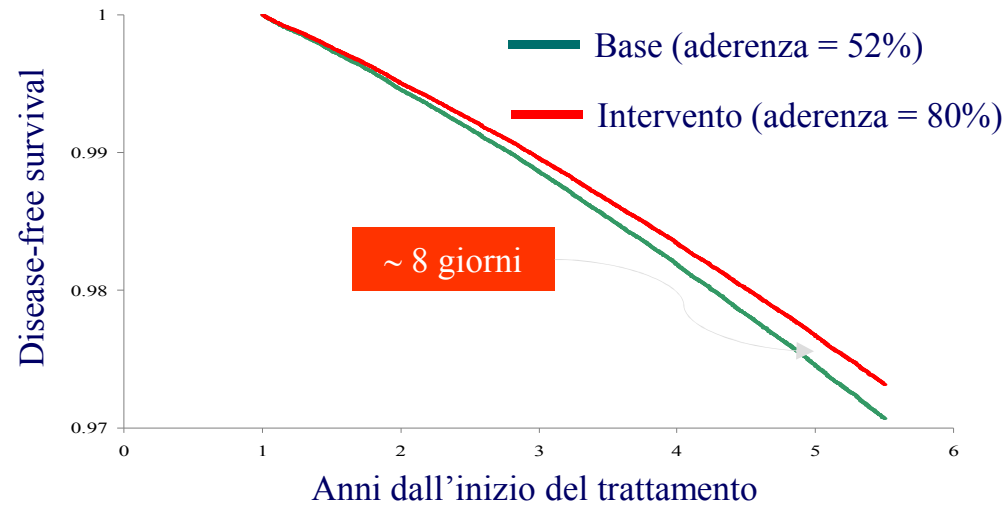
Dimensione ed impatto



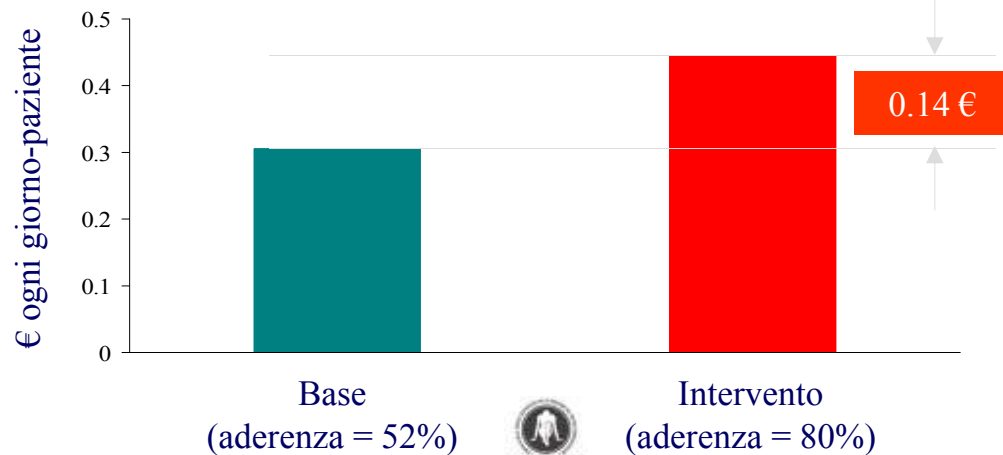
Interventi possibili



La proposta



... ogni paziente  
guadagnerebbe in  
media circa 8 giorni  
liberi da malattia



... si genererebbe  
una spesa giornaliera  
addizionale di 0.14 €  
per ogni paziente (51  
€ / anno)

## Dati ed evidenze disponibili

### Aderenza



#### Dimensione ed impatto



#### Interventi possibili



#### La proposta



### Farmacoutilizzazione



La gestione farmacologica dei pazienti portatori di condizioni croniche è insoddisfacente nella pratica clinica corrente a causa della scarsa compliance alla terapia

### Impatto clinico



La scarsa aderenza spiega una quota rilevante degli eventi cardiovascolari che si verificano nella popolazione

### Bilancio tra impatto clinico ed economico



Gli interventi indirizzati a migliorare l'aderenza sembrano efficaci ed economicamente sostenibili

## Aderenza



Dimensione ed impatto



Interventi possibili



La proposta



*J Med Econ.* 2011;14(5):594-608. Epub 2011 Jul 7.

### Pharmacoeconomic aspects of poor adherence: can better adherence reduce healthcare costs?

*Golay A.*

**BACKGROUND:** Poor adherence to medical treatment is one of the main reasons why patients do not achieve the full benefits of their therapy. It also has a substantial financial weight in terms of money wasted for unused medication and increased healthcare costs including hospitalization due to clinical complications.

**OBJECTIVE:** To provide an overview and examples of the financial and economic consequences of poor adherence to treatment, techniques and devices for monitoring adherence and interventions for improvement of treatment adherence.

**RESULTS:** New electronic devices with monitoring features may help to objectively monitor patients' adherence to a treatment regimen that can help a healthcare professional determine how to intervene to improve adherence and subsequent clinical outcome. Interventions that aim to enhance adherence may confer cost-effectiveness benefits in some indications and settings. The nature of the intervention(s) used depends on a range of factors, including patient preference, therapy area and cost of the intervention. However, there is a pressing need for rigorous trials, as current studies often have major flaws in the economic methodology, especially in terms of incremental analysis and sensitivity analysis.

**LIMITATIONS:** This review has focused on a limited number of therapeutic areas as coverage of a more extensive range of diseases may be beyond the scope of such a summary. Nevertheless, the examples are representative of the challenges encountered in many other diseases.

**CONCLUSIONS:** The clinical and economic consequences of non-adherence and interventions to improve compliance reflect the nature and severity of non-adherence, as well as the pathophysiology and severity of the disease. Interventions that aim to enhance adherence may confer cost-effectiveness benefits in some indications and settings, and good adherence can help payers and providers contain costs by extracting maximum value from their investment in therapies.

## The Modeled Lifetime Cost-Effectiveness of Published Adherence-Improving Interventions for Antihypertensive and Lipid-Lowering Medications

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<sup>1</sup>US Health Economics and Outcomes Research, IMS Health, Falls Church, VA, USA; <sup>2</sup>Pfizer Inc, New York, NY, USA

### ABSTRACT

**Objective:** We sought to compare the cost-effectiveness of different interventions that have been shown to improve adherence with antihypertensive and lipid-lowering therapy, by combining a burden of nonadherence model framework with a cost-effectiveness model.

**Methods:** MEDLINE, EMBASE, and Cochrane databases were searched for adherence interventions other than self-monitoring. The cost-effectiveness of each intervention was assessed as incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained versus no adherence intervention versus a 2007 US\$, and compared with the ICER of the most cost-effective nonadherence intervention. The model was applied to a previous study of adherence in hypertensive patients. Incremental health-care costs per QALY gained were compared with incremental health-care costs per QALY gained for the most cost-effective nonadherence intervention.

**Results:** After screening, 23 eligible adherence-improving interventions were identified from 18 studies. Relative Improvement ranged from 1.13 to 3.60. After eliminating more costly/less effective interventions, two remained. Self-monitoring, reminders, and educational materials incurred total health-care costs of \$17,520, and compared with no adherence

**Conclusions:** Of published interventions shown to improve adherence, reminders and educational materials, and a pharmacist/nurse management program, appear to be cost-effective and should be considered before other interventions. Understanding relative cost-effectiveness of adherence interventions may guide design and implementation of efficient adherence-improving programs

### Aderenza

Dimensione ed impatto



Interventi possibili



La proposta



## Dati ed evidenze insufficienti

### Aderenza

L'impatto clinico ed economico degli interventi di miglioramento dell'aderenza alle terapie dipende da:



Dimensione ed impatto



Interventi possibili



La proposta



### Assistenza sanitaria

copertura assicurativa (pubblica o privata),  
organizzazione delle cure primarie, assistenza  
domiciliare, ruolo delle farmacie, ecc...



### Popolazione

caratteristiche sociali, culturali ed economiche

**C**osts &  
**e**ffectiveness of  
**m**ultifaceted intervention for  
**en**hancing adherence to **t**herapies

## Aderenza



Dimensione ed impatto



Interventi possibili



La proposta



## 1. Obiettivo primario

Valutare l'efficacia e il profilo costo-efficacia di  
un intervento multifattoriale teso a migliorare  
l'aderenza alle terapie croniche  
dell'ipertensione, dell'iperlipidemia e del  
diabete di tipo 2

**C**osts &  
**e**ffectiveness of  
**m**ultifaceted intervention for  
**en**hancing adherence to **t**herapies

## Aderenza



Dimensione ed impatto



Interventi possibili



La proposta



## 2. Disegno sperimentale

2.1. Identificazione delle Regioni collaborative

2.2. Misura della *compliance* e dell'appropriatezza prima dell'intervento (DB amministrativi e clinici)

2.3. Assegnazione causale delle ASL a uno dei due bracci sperimentali (*cluster randomization*)

2.4. Somministrazione dell'intervento

2.5. Misura della *compliance* a periodiche scadenze dalla randomizzazione (*brief-term soft outcome*)

2.6. Misura dell'impatto clinico ed economico (*long-term hard outcome*)



**C**osts &  
**e**ffectiveness of  
**m**ultifaceted intervention for  
**en**hancing adherence to **t**herapies

## Aderenza



Dimensione ed impatto



Interventi possibili



La proposta



## 3. Risultati attesi

Ci si attende di acquisire dati ed evidenze che mettano il decisore nelle condizioni di valutare l'opportunità di allocare le scarse risorse disponibili per implementare interventi tesi a migliorare l'aderenza alle terapie

Ipotizzando:

che 5 Regioni partecipino al progetto ognuna delle quali contribuisce con 2 aziende sanitarie locali

che le 10 aziende partecipanti vengano assegnate casualmente a uno dei due interventi (nessuno o intervento sperimentale)

accettando un errore di primo tipo a due code di 0.05

richiedendo che lo studio sia in grado di evidenziare un aumento dell'aderenza del 10% (ad esempio dal 50% al 60%) con una potenza del 90%

è sufficiente

che ogni azienda estragga casualmente ~ 250 pzt (presi in carico per prima volta per uno dei trattamenti farmacologici in studio) da sottoporre a monitoraggio

Hemming K, Girling AJ, Sitch AJ, et al. Sample size calculations for cluster randomised controlled trials with a fixed number of clusters. BMC Medical Research Methodology 2011, 11:102



### 3.1. Medico di medicina generale

- 3.1.1. Realizzazione di corsi intensivi (comunicazione con pzt)
- 3.1.2. Organizzazione di incontri periodici (raccomandazioni basate su evidenze e linee guida)
- 3.1.3. Adozione di check list (nella presa in carico e nel monitoraggio del pzt)
- 3.1.4. Inserimento di *warning* automatici (nel software di gestione del pzt)
- 3.1.5. Adozione di meccanismi premiali (non necessariamente economici al raggiungimento degli obiettivi)

### 3.2. Paziente

- 3.2.1. Materiale educativo
- 3.2.2. Dispositivi per autocontrollo domiciliare
- 3.3.3. Passaporto / diario autogestito

