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Health Economics & Outcomes Research

# Il valore delle associazioni precostituite, nuovi approcci terapeutici


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# Argomenti in discussione

- Soluzioni operative per la sostenibilità della spesa farmaceutica
  - Utilizzo farmaci a brevetto scaduto (equivalenti)
    - Compartecipazione alla spesa (co-payment) e aderenza alla terapia
  - Appropriatezza ed aderenza terapeutica
- Strategie per migliorare l'aderenza terapeutica
  - Il ruolo delle *single pill combination*
- Discussione e conclusioni

# Possibili soluzioni operative per la sostenibilità della spesa farmaceutica

- **Spendere MENO**
  - trasferire la spesa pubblica dal SSN ad altri attori
    - al paziente → inasprimento ticket
    - al produttore → taglio prezzi
    - al distributore → taglio margini
    - al medico → controllo prescrizioni

- **Spendere MEGLIO**
  - strumenti che aumentano **l'efficienza del sistema**, ossia più salute a parità di risorse spese
    1. Maggiore selettività nell'ammettere alla rimborsabilità i prodotti in base a criteri di efficacia e di economicità
       - **Valutazione economica dei farmaci (HTA)**
    2. Utilizzo farmaci *a* ***brevetto scaduto***
    3. Miglioramento ***dell'appropriatezza e aderenza terapeutica***
    4. Attivazione di Percorsi Diagnostico-Terapeutici Assistenziali **(PDTA)**

# I farmaci equivalenti come strumento di contenimento della spesa

Tra i meccanismi di contenimento della spesa farmaceutica merita attenzione gli **strumenti** che si propongono non tanto di bloccare i consumi, imporre sconti o tagliare i prezzi, ma quelli **che mirano ad aumentare l'efficienza del sistema economico** attraverso il ripristino della concorrenzialità e stimolando la "***price competition***" dei produttori

# Principi attivi che hanno perso la copertura brevettuale durante il 2013 e 2014 e la relativa riduzione di prezzo determinata dai medicinali equivalenti

| Principio attivo | Decorrenza riduzione di prezzo | Riduzione prezzo |
|---|---|---|
| ***Principi attivi o nuove confezioni che hanno perso la copertura brevettuale prima del 1/12/2012*** | | |
| Acido zoledronico | 20/05/2013 | 66% |
| Acido ibandronico | 12/02/2013 | 40% |
| Acido acetilsalicilico | 16/09/2013 | 35% |
| Montelukast | 15/01/2013 | 60% |
| Acitretina | 15/04/2013 | 27% |
| ***Principi attivi che hanno perso la copertura brevettuale tra il 1/12/2012 e il 1/12/2013*** | | |
| Irbesartan e idroclorotiazide | 16/10/2013 | 72% |
| Rizatriptan | 16/09/2013 | 60% |
| Ziprasidone | 15/05/2013 | 45% |
| Raloxifene | 16/09/2013 | 48% |
| Lamivudina/zidovudina | 24/04/2013 | 55% |
| Nevirapina | 24/06/2013 | 57% |
| ***Principi attivi o nuove confezioni che hanno perso la copertura brevettuale prima del 1/12/2013*** | | |
| Efavirenz | 02/12/2013 | 35% |
| Atosiban | 04/09/2014 | 30% |
| Omega 3 | 16/06/2014 | 37% |
| Metoclopramide | 15/07/2014 | 33% |
| Limeciclina | 17/02/2014 | 45% |
| Capecitabina | 04/12/2013 | 60% |
| ***Principi attivi che hanno perso la copertura brevettuale tra il 1/12/2013 e il 1/12/2014*** | | |
| Memantina | 15/11/2013 | 47,5% |
| Escitalopram | 16/06/2014 | 65% |
| Moxifloxacina | 15/07/2014 | 55% |
| Telmisartan/idroclorotiazide | 27/06/2013 | 60% |
| Telmisartan | 10/12/2013 | 70% |

AIFA, Agenzia Italiana del Farmaco, Roma, 2015. Osservatorio Nazionale sull'impiego dei Medicinali. L'uso dei farmaci in Italia. Rapporto Nazionale 2014.

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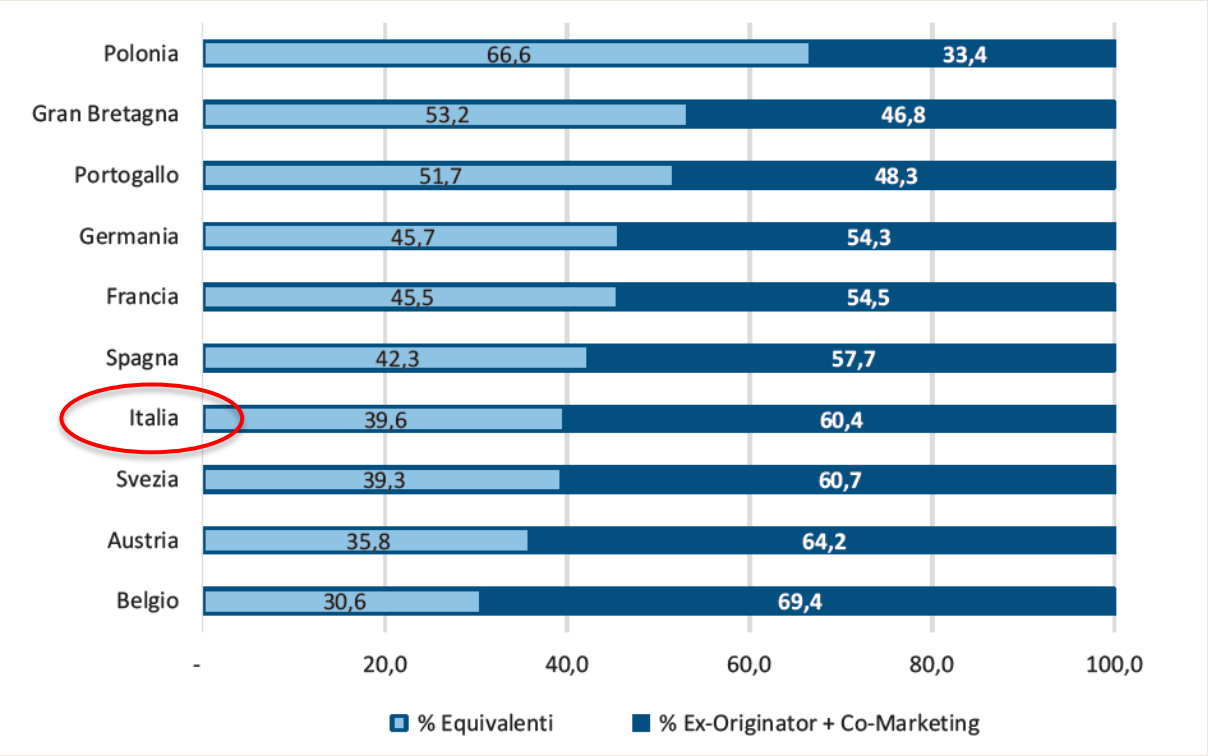
# Confronto internazionale della distribuzione percentuale della spesa farmaceutica territoriale 2019 per i farmaci a brevetto scaduto




AIFA, Agenzia Italiana del Farmaco, Roma, 2020

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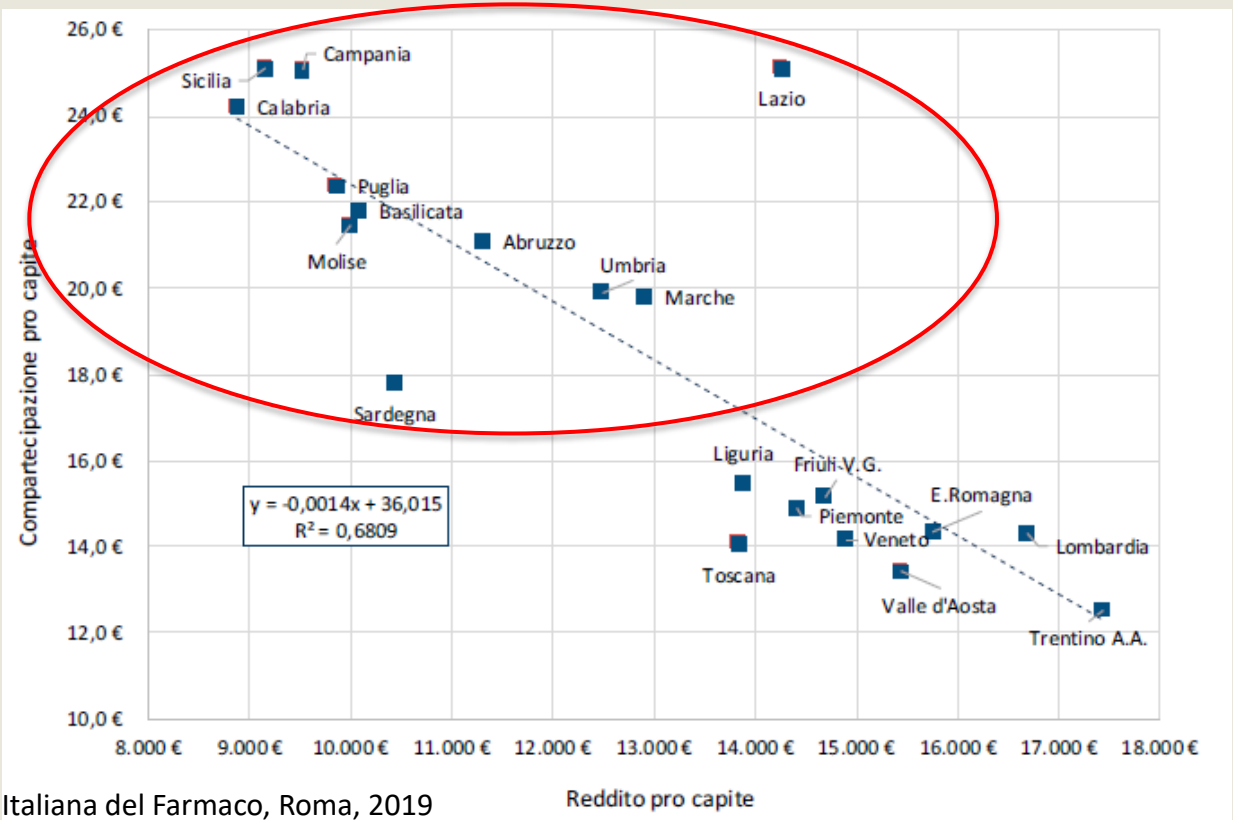
# Compartecipazione dei cittadini alla spesa

- A livello nazionale, la compartecipazione alla spesa sostenuta dai cittadini italiani ammonta a **1,58 miliardi di euro, pari al 15,7% della spesa farmaceutica convenzionata**.
- La compartecipazione del cittadino per il **70,0% è** data dalla differenza di prezzo tra il medicinale a brevetto scaduto prescritto ed il prezzo di riferimento definito dalle liste di trasparenza AIFA.
  - con un valore di spesa pari a 1.126 milioni di euro, ossia 1,1 miliardi
    - in crescita del +7,2% rispetto all'anno precedente,
  - mentre il ticket per confezione ha pesato solo per il 30,0%, con un valore di spesa di 482 milioni di euro

- Fonte: AIFA, Agenzia Italiana del Farmaco, Roma, 2019

# Analisi di correlazione tra la spesa per compartecipazione (*ticket*) e reddito procapite




Fonte: AIFA, Agenzia Italiana del Farmaco, Roma, 2019

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JAMA®

Online article and related content current as of November 17, 2009.

# Pharmacy Benefits and the Use of Drugs by the Chronically Ill

Dana P. Goldman; Geoffrey F. Joyce; Jose J. Escarce; et al.

*JAMA*. 2004;291(19):2344-2350 (doi:10.1001/jama.291.19.2344)

http://jama.ama-assn.org/cgi/content/full/291/19/2344

**Context** Many health plans have instituted more cost sharing to discourage use of more expensive pharmaceuticals and to reduce drug spending.

**Objective** To determine how changes in cost sharing affect use of the most commonly used drug classes among the privately insured and the chronically ill.

**Design, Setting, and Participants** Retrospective US study conducted from 1997 to 2000, examining linked pharmacy claims data with health plan benefit designs from 30 employers and 52 health plans. Participants were 528969 privately insured beneficiaries aged 18 to 64 years and enrolled from 1 to 4 years (960791 person-years).

**Main Outcome Measure** Relative change in drug days supplied (per member, per year) when co-payments doubled in a prototypical drug benefit plan.

**Results** Doubling co-payments was associated with reductions in use of 8 therapeutic classes. The largest decreases occurred for nonsteroidal anti-inflammatory drugs (NSAIDs) (45%) and antihistamines (44%). Reductions in overall days supplied of antihyperlipidemics (34%), antiulcerants (33%), antiasthmatics (32%), antihypertensives (26%), antidepressants (26%), and antidiabetics (25%) were also observed. Among patients diagnosed as having a chronic illness and receiving ongoing care, use was less responsive to co-payment changes. Use of antidepressants by depressed patients declined by 8%; use of antihypertensives by hypertensive patients decreased by 10%. Larger reductions were observed for arthritis patients taking NSAIDs (27%) and allergy patients taking antihistamines (31%). Patients with diabetes reduced their use of antidiabetes drugs by 23%.

**Conclusions** The use of medications such as antihistamines and NSAIDs, which are taken intermittently to treat symptoms, was sensitive to co-payment changes. Other medications—antihypertensive, antiasthmatic, antidepressant, antihyperlipidemic, antiulcerant, and antidiabetic agents—also demonstrated significant price responsiveness. The reduction in use of medications for individuals in ongoing care was more modest. Still, significant increases in co-payments raise concern about adverse health consequences because of the large price effects, especially among diabetic patients.



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The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

# The Effect of Incentive-Based Formularies on Prescription-Drug Utilization and Spending

Haiden A. Huskamp, Ph.D., Patricia A. Deverka, M.D., Arnold M. Epstein, M.D., Robert S. Epstein, M.D., Kimberly A. McGuigan, Ph.D., and Richard G. Frank, Ph.D.

**BACKGROUND**

Many employers and health plans have adopted incentive-based formularies in an attempt to control prescription-drug costs.

**METHODS**

We used claims data to compare the utilization of and spending on drugs in two employer-sponsored health plans that implemented changes in formulary administration with those in comparison groups of enrollees covered by the same insurers. One plan simultaneously switched from a one-tier to a three-tier formulary and increased all enrollee copayments for medications. The second switched from a two-tier to a three-tier formulary, changing only the copayments for tier-3 drugs. We examined the utilization of angiotensin-converting–enzyme (ACE) inhibitors, proton-pump inhibitors, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins).

**RESULTS**

Enrollees covered by the employer that implemented more dramatic changes experienced slower growth than the comparison group in the probability of the use of a drug and a major shift in spending from the plan to the enrollee. Among the enrollees who were initially taking tier-3 statins, more enrollees in the intervention group than in the comparison group switched to tier-1 or tier-2 medications (49 percent vs. 17 percent, $P<0.001$) or stopped taking statins entirely (21 percent vs. 11 percent, $P=0.04$). Patterns were similar for ACE inhibitors and proton-pump inhibitors. The enrollees covered by the employer that implemented more moderate changes were more likely than the comparison enrollees to switch to tier-1 or tier-2 medications but not to stop taking a given class of medications altogether.

**CONCLUSIONS**

Different changes in formulary administration may have dramatically different effects on utilization and spending and may in some instances lead enrollees to discontinue therapy. The associated changes in copayments can substantially alter out-of-pocket spending by enrollees, the continuation of the use of medications, and possibly the quality of care.

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# Drug Copayment and Adherence in Chronic Heart Failure: Effect on Cost and Outcomes

J. Alexander Cole, D.Sc., M.P.H., Heather Norman, M.A., Lisa B. Weatherby, M.S., and Alexander M. Walker, M.D., Dr.P.H.

**Study Objective.** To measure the association among prescription copayment, drug adherence, and subsequent health outcomes among patients with chronic heart failure (CHF).

**Design.** Retrospective cohort study.

**Data Source.** Database of a large, national health insurance plan.

**Patients.** Patients with CHF receiving commercial and Medicare supplemental benefits.

**Conclusion.** Among patients with CHF, higher drug copayments were associated with poorer adherence. The change was relatively small and did not affect predicted total health care costs, but it was sufficient to increase the predicted risk of hospitalization for CHF.

Table 2. Predicted Medication Possession Ratios and Predicted Costs and Risks of Hospitalization for Chronic Heart Failure According to Group and Copayment

| Group, Copayment ($) | Predicted Medication Possession Ratio, 2002 (%) | Predicted Medical Cost, 2003 ($) | Predicted Frequency of Hospitalization, 2003 (%) |
|---|---|---|---|
| ACE inhibitor | | | |
| 5 | 94.5 | 7583 | 13.0 |
| 10 | 93.2 | 7554 | 13.3 |
| 15 | 91.9 | 7524 | 13.7 |
| 20 | 90.7 | 7495 | 14.0 |
| 25 | 89.4 | 7466 | 14.4 |
| 30 | 88.1 | 7437 | 14.7 |
| β-Blocker | | | |
| 5 | 94.3 | 8903 | 10.0 |
| 10 | 93.5 | 8779 | 10.4 |
| 15 | 92.6 | 8657 | 10.8 |
| 20 | 91.7 | 8536 | 11.2 |
| 25 | 90.8 | 8417 | 11.7 |
| 30 | 89.9 | 8300 | 12.1 |

ACE = angiotensin-converting enzyme.

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J. Alexander Cole et al. Pharmacotherapy 2006

# Alcune ragioni della Non-aderenza

Reasons for nonadherence in patients with heart failure

| Reason | Frequency |
|---|---|
| Cannot remember to take on time | 20% |
| Too expensive | 16% |
| Too many medications | 10% |
| Don't know how or when to take | 9% |
| Side effects | 8% |
| Other patient education–related issues | 15% |
| Physically unable or too ill | 10% |

Garner G, Am J Cardiol 2010

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# Major Predictors of Poor Adherence to Medication, According to Studies of Predictors

| Predictor | Study |
|---|---|
| Presence of psychological problems, particularly depression | van Servellen et al.,[51] Ammassari et al.,[52] Stilley et al.[53] |
| Presence of cognitive impairment | Stilley et al.,[53] Okuno et al.[54] |
| Treatment of asymptomatic disease | Sewitch et al.,[55] |
| Inadequate follow-up or discharge planning | Sewitch et al.,[55] Lacro et al.[56] |
| Side effects of medication | van Servellen et al.[51] |
| Patient's lack of belief in benefit of treatment | Okuno et al.,[54] Lacro et al.[56] |
| Patient's lack of insight into the illness | Lacro et al.,[56] Perkins[57] |
| Poor provider–patient relationship | Okuno et al.,[54] Lacro et al.[56] |
| Presence of barriers to care or medications | van Servellen et al.,[51] Perkins[57] |
| Missed appointments | van Servellen et al.,[51] Farley et al.[58] |
| Complexity of treatment | Ammassari et al.[52] |
| Cost of medication, copayment, or both | Balkrishnan,[59] Ellis et al.[60] |

Osterberg L. Blaschke T. Adherence to Medication. N Engl J Med 2005;353:487-97.

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# Numero di pazienti in trattamento antidiabetico aderenti al trattamento [numeratore], sul totale dei pazienti in trattamento antidiabetico [denominatore]

| | 2014 N = 807.185 | | 2013 N = 780.577 | | 2012 N = 761.936 | |
|---|---|---|---|---|---|---|
| | % | Var. % | % | Var. % | % | Var. % |
| **TOTALE** | **62,2** | **-0,4** | **62,5** | **1,1** | **61,8** | **/** |
| Area geografica | | | | | | |
| Nord | 65,6 | 0,4 | 65,4 | 2,1 | 64,0 | / |
| Centro | 59,2 | -4,6 | 62,1 | 0,4 | 61,8 | / |
| Sud | 56,9 | 1,1 | 56,3 | -0,4 | 56,5 | / |
| Genere | | | | | | |
| Maschio | 63,7 | -0,1 | 63,8 | 1,1 | 63,1 | / |
| Femmina | 60,5 | -0,8 | 61,0 | 1,1 | 60,4 | / |
| Classi di età | | | | | | |
| ≤45 | 44,7 | 1,5 | 44,0 | 5,4 | 41,7 | / |
| 46-65 | 64,1 | -0,1 | 64,1 | 1,7 | 63,1 | / |
| 66-75 | 66,1 | -0,3 | 66,3 | 1,2 | 65,6 | / |
| >75 | 58,2 | -0,9 | 58,8 | -0,2 | 58,8 | / |
| Pregresso trattamento§ | | | | | | |
| Nuovi trattati | 29,8 | 5,1 | 28,3 | 4,2 | 27,2 | / |
| Già in trattamento | 67,7 | -1,0 | 68,4 | 0,1 | 68,4 | / |
| Comorbidità | | | | | | |
| Senza pregresso evento CV | 62,3 | -0,4 | 62,6 | 1,2 | 61,9 | / |
| Con pregresso evento CV | 58,9 | -0,6 | 59,3 | -0,7 | 59,7 | / |
| TOTALE senza occasionali° | 67,0 | -0,4 | 67,3 | 0,4 | 67,0 | |

L'aderenza al trattamento con ipoglicemizzanti è stata valutata nei 365 giorni successivi alla data della prima prescrizione nell'anno di inclusione (data indice). Aderenti al trattamento sono stati definiti i pazienti con una proporzione di giorni coperti uguale o superiore all'80%.

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Numero di pazienti trattati con farmaci antiipertensivi aderenti al trattamento [numeratore], sul totale dei pazienti trattati con antiipertensivi [denominatore].

| | 2014 N = 4.354.334 | | 2013 N = 4.253.410 | | 2012 N = 4.163.262 | |
|---|---|---|---|---|---|---|
| | % | Var. % | % | Var. % | % | Var. % |
| **TOTALE** | **55,5** | **0,2** | **55,3** | **1,3** | **54,7** | **/** |
| Area geografica | | | | | | |
| Nord | 56,8 | 1,7 | 55,8 | 0,9 | 55,3 | / |
| Centro | 50,4 | -7,7 | 54,6 | 0,4 | 54,4 | / |
| Sud | 56,2 | 3,0 | 54,5 | 3,4 | 52,7 | / |
| Genere | | | | | | |
| Maschio | 57,4 | -0,1 | 57,4 | 1,1 | 56,8 | / |
| Femmina | 53,9 | 0,5 | 53,6 | 1,3 | 52,9 | / |
| Classi di età | | | | | | |
| ≤45 | 33,1 | 0,7 | 32,8 | 2,4 | 32,1 | / |
| 46-65 | 50,6 | -0,4 | 50,8 | 0,8 | 50,4 | / |
| 66-75 | 60,1 | -0,1 | 60,2 | 0,8 | 59,7 | / |
| >75 | 60,1 | 0,4 | 59,8 | 1,1 | 59,2 | / |
| Pregresso trattamento§ | | | | | | |
| Nuovi trattati | 24,0 | 2,1 | 23,5 | 0,2 | 23,4 | / |
| Già in trattamento | 59,7 | 0,0 | 59,7 | 1,0 | 59,1 | / |
| Comorbidità | | | | | | |
| Senza pregresso evento CV o diabete | 53,2 | 0,3 | 53,0 | 1,3 | 52,3 | |
| Con pregresso evento CV o diabete | 66,6 | -0,5 | 66,9 | 0,9 | 66,3 | |
| TOTALE senza occasionali[a] | 58,8 | 0,0 | 58,8 | 1,0 | 58,2 | |

Numero di pazienti trattati aderenti al trattamento con statine [numeratore], sul totale dei pazienti trattati con statine [denominatore].

| | 2014 N = 1.768.218 | | 2013 N = 1.690.168 | | 2012 N = 1.597.006 | |
|---|---|---|---|---|---|---|
| | % | Var. % | % | Var. % | % | Var. % |
| **TOTALE** | **43,1** | **0,0** | **43,1** | **3,9** | **41,5** | **/** |
| Area geografica | | | | | | |
| Nord | 47,6 | 0,9 | 47,2 | 4,0 | 45,4 | / |
| Centro | 35,2 | -8,1 | 38,4 | 2,9 | 37,3 | / |
| Sud | 38,3 | 5,0 | 36,5 | 5,0 | 34,8 | / |
| Genere | | | | | | |
| Maschio | 46,4 | -0,5 | 46,6 | 3,3 | 45,1 | / |
| Femmina | 40,0 | 0,5 | 39,8 | 4,5 | 38,1 | / |
| Classi di età | | | | | | |
| ≤45 | 26,2 | -0,6 | 26,3 | 2,9 | 25,6 | / |
| 46-65 | 40,8 | -1,0 | 41,2 | 2,9 | 40,0 | / |
| 66-75 | 46,1 | 0,0 | 46,1 | 4,4 | 44,2 | / |
| >75 | 43,7 | 0,4 | 43,5 | 3,8 | 41,9 | / |
| Pregresso trattamento§ | | | | | | |
| Nuovi trattati | 24,1 | -3,7 | 25,0 | 0,7 | 24,8 | / |
| Già in trattamento | 47,2 | -0,5 | 47,5 | 3,8 | 45,7 | / |
| Comorbidità | | | | | | |
| Senza pregresso evento CV o diabete | 41,6 | 0,0 | 41,5 | 4,1 | 39,9 | / |
| Con pregresso evento CV o diabete | 48,5 | -0,4 | 48,7 | 3,0 | 47,3 | / |
| TOTALE senza occasionali[a] | 47,1 | -0,2 | 47,2 | 3,3 | 45,7 | / |

AIFA, Agenzia Italiana del Farmaco, Roma, 2015. Osservatorio Nazionale sull'impiego dei Medicinali.
L'uso dei farmaci in Italia. Rapporto Nazionale 2014.

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# Adherence to Medication

Lars Osterberg and Terrence Blaschke, n engl j med 353;5 august 4, 2005

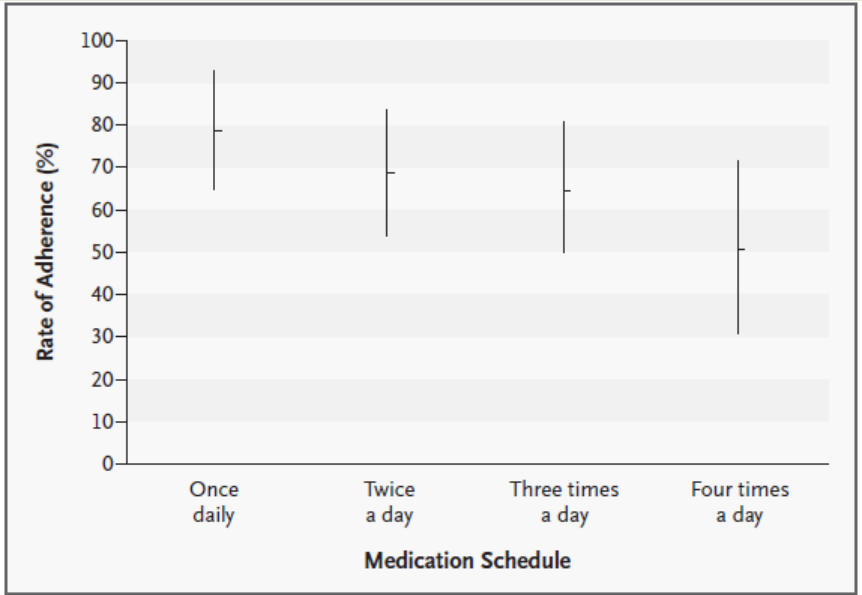


**Figure 1. Adherence to Medication According to Frequency of Doses.**
Vertical lines represent 1 SD on either side of the mean rate of adherence (horizontal bars). Data are from Claxton et al.[7]

*Drugs don't work in patients who don't take them.*

— C. Everett Koop, M.D.

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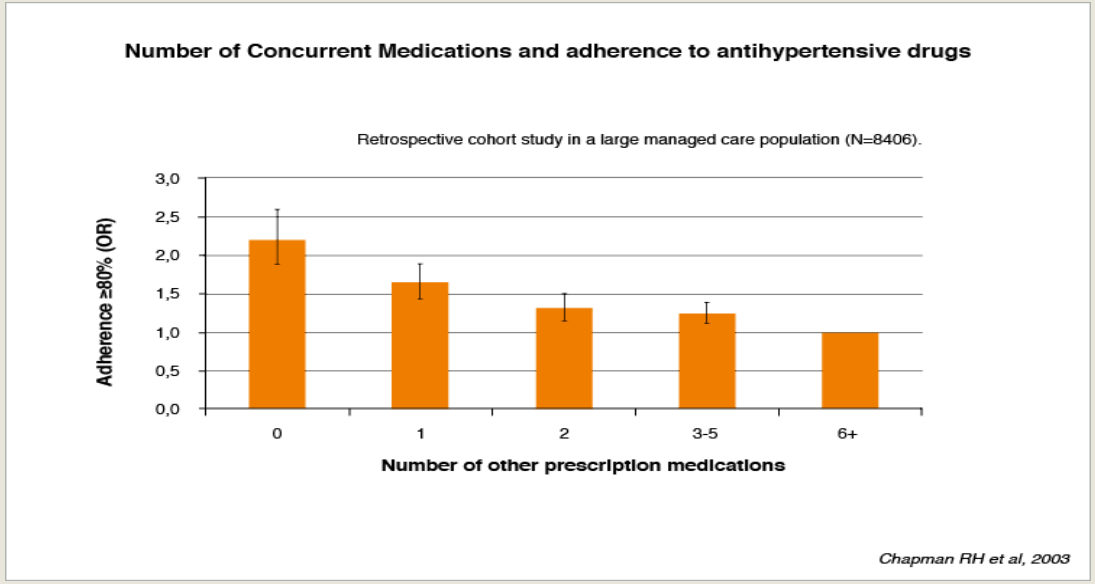
# Relazione fra aderenza e numero di prescrizioni

- **Quanto maggiore è il numero di farmaci tanto maggiore è la probabilità che il paziente non li assuma in maniera corretta**
- L'aderenza al trattamento infatti diminuisce all'aumentare del numero dei farmaci antipertensivi prescritti

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# Il concetto di aderenza e l'uso efficiente delle terapie

- L'organizzazione Mondiale della Sanità riconosce che **l'aderenza** nelle malattie croniche è uno dei fattori fondamentali che contribuiscono ad un **uso efficiente delle terapie** (Serup et al 2006)
  - Il successo di una terapia non dipende solo dalla correttezza della diagnosi e della scelta terapeutica da parte del medico; è fondamentale che il paziente "aderisca" alla cura, ovvero che segua esattamente le indicazioni fornitegli e per il tempo necessario
- La **mancata aderenza** può infatti compromettere l'efficacia di una terapia e determinare:
  - un aggravamento delle condizioni di salute
  - la necessità di esami o di ulteriori farmaci
  - l'aumento della morbilità e della mortalità
  - un peggioramento della qualità della vita del paziente
  - contestuale **aumento del costo** per paziente trattato

# Malattie cardiovascolari: aderenza subottimale alle terapie

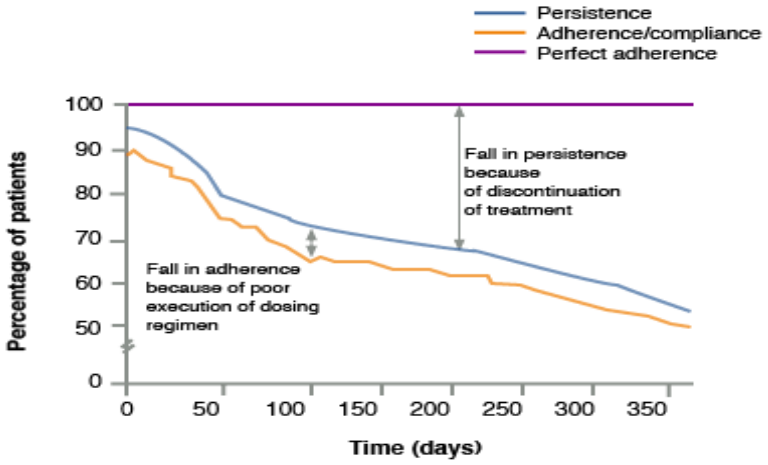
Dati di letteratura riportano che:

- **l'aderenza al trattamento è subottimale in Europa** per le patologie cardiovascolari risultando del 57%, considerando il valore ideale al 80%
- l'elevata **mancanza di aderenza nei pazienti affetti da cardiopatia ischemica** è preoccupante: tra i pazienti dimessi dopo infarto miocardico acuto in terapia con aspirina, beta bloccanti e statine, circa il 34% dei pazienti sospende almeno uno dei tre trattamenti e il 12% sospende tutti e tre entro il primo mese dalla dimissione
- **l'aderenza a 6 e 12 mesi, dopo diagnosi di cardiopatia ischemica,** è risultata del **71%** per la terapia con **aspirina, 46**% per la **terapia con beta-bloccanti e 44% per ipolipemizzanti e di solo il 21% con tutte e tre le categorie**
- la **continuità alla terapia con statine risulta di solo 40% a due anni dopo l'ospedalizzazione per sindrome coronarica acuta**, con dati di aderenza ancora minore nei pazienti con cardiopatia ischemica cronica
- esiste una diretta **correlazione fra mancata aderenza e rischio incrementato di morbilità e mortalità**: pazienti che hanno subito un infarto miocardico e che nei primi 120 giorni in seguito alla dimissione non assumono alcuna terapia prescritta presentano un **rischio di mortalità più alto dell'80%**, mentre **in caso di assunzione solo parziale** della terapia il rischio di mortalità **è maggiore del 44**% rispetto agli aderenti alla terapia
- per quanto concerne le statine, secondo un altro studio, l'interruzione di assunzione durante l'anno successivo all'ospedalizzazione comporta un aumento della mortalità variabile fra il 12% e il 25%

# Andamento declinante dell'aderenza dei pazienti ipertesi

**Adherence/compliance in hypertensive patients typically falls over time**

Study of hypertensive patients in clinical studies 4783 patients in 21 Phase IV trials Evaluated by medication event monitoring system




| No of patientsremaining in study | 3108 | 980 | 828 | 618 | 474 | 400 | 331 |
|---|---|---|---|---|---|---|---|

*Vrijens, Vincze, Kristanto, et al. BMJ 2008;336:1114–7*

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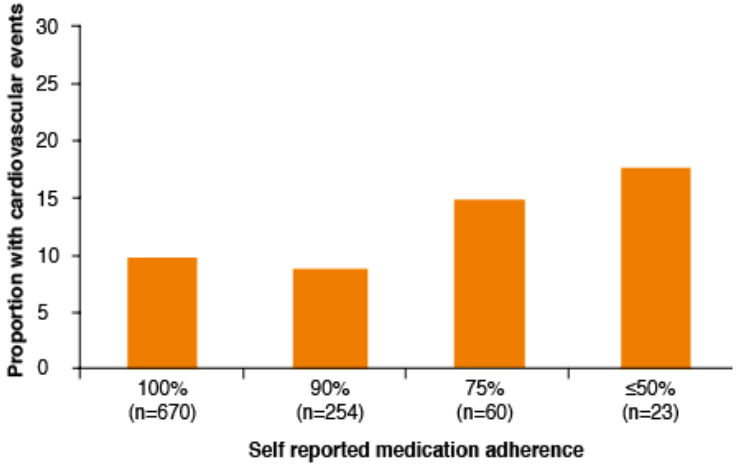
# Relazione fra aderenza ed eventi avversi CV

**Proportion with subsequent CV event**
**(myocardial infarction,stroke, or coronary heart disease death)**
**by the percentage of time reported as taking medications as prescribed**




P = 0.20 for proportion with events across all 4 adherence categories;
P = 0.03 for proportion with events in patients with adherence ≤75% vs >75% of the time

*Gehi AK et al. Arch Intern Med. 2007; 167(16): 1798-1803*

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# Correlazione tra compliance, ospedalizzazioni e costi

## Bramlage et al 2009

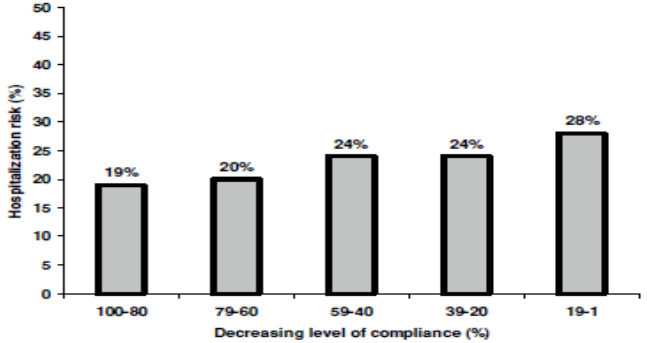


**Figure 4**
**Risk of hospitalisation (%) in relation to the level of compliance for hypertension** [24]. Level of compliance grouped into quintiles vs. risk of hospitalization. Patients with a high degree of compliance (of between 80 and 100%) have a 19% risk of hospitalization as compared to 28% in patients with a compliance between 1 and 19%.

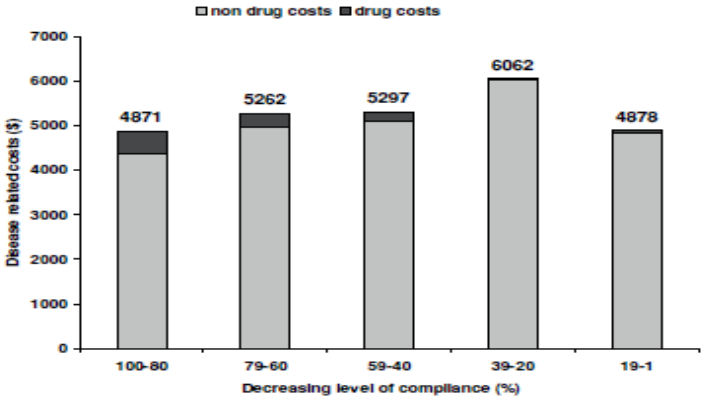


**Figure 5**
**Disease-related healthcare costs in relation to the level of compliance for hypertension** [24]. Costs are in $.

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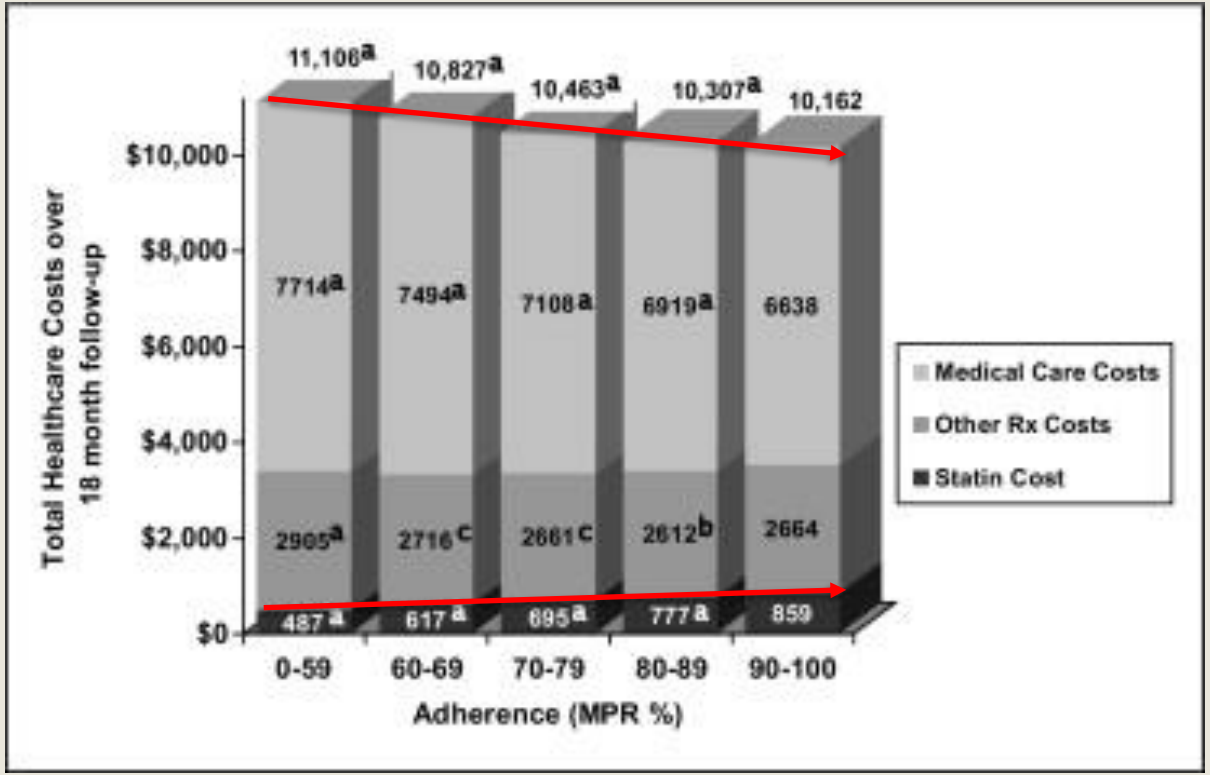
# Adherence to Statins, Subsequent Healthcare Costs, and Cardiovascular Hospitalizations

Pittman Am J Cardiol 2011;107:1662–1666

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Original Article Journal of Hypertension, Volume 32 Number 1 2014

# Medication persistence and the use of generic and brand-name blood pressure-lowering agents

Giovanni Corrao[a], Davide Soranna[a], Carlo La Vecchia[b,c,d], Alberico Catapano[e,f], Enrico A. Rosei[g], Gianfranco Gensini[h], Luca Merlino[i], and Giuseppe Mancia[j,k]

**Background:** Because of their lower cost, healthcare systems recommend physicians to prefer generic products, rather than brand-name medicaments. There is then considerable interest and debate concerning safety and effectiveness of generic products. Few studies have compared patients treated with brand-name and generic drugs for adherence to treatment, with somewhat inconsistent results. The primary objective of this study was to compare the risk of discontinuing antihypertensive drug therapy in patients treated with generic or brand-name agents.

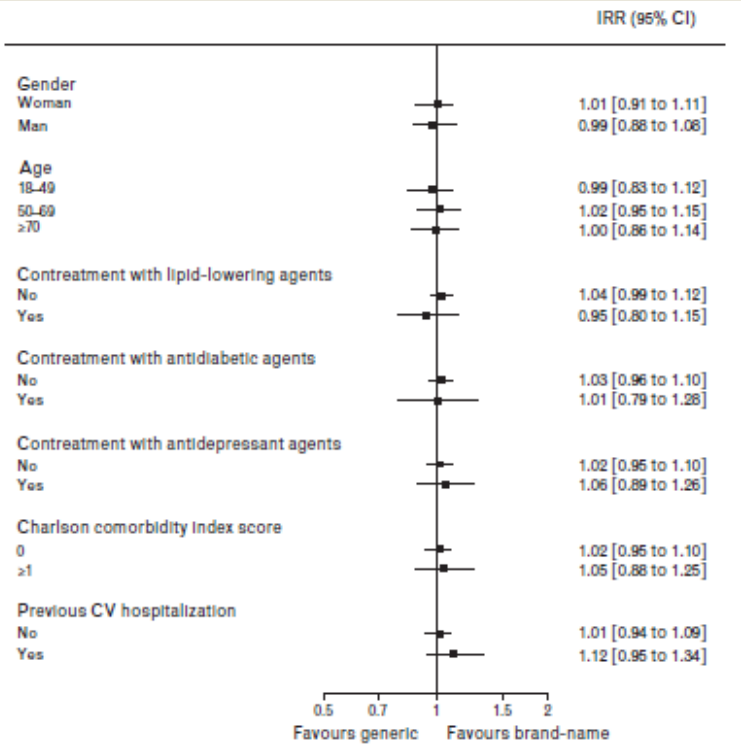
**Methods:** The 101 618 beneficiaries of the Healthcare system of Lombardy, Italy, aged 18 years or older who were newly treated on monotherapy with antihypertensive generic or brand-name drugs during 2008, were followed until the earliest date among those of the occurrence of treatment discontinuation to whatever antihypertensive drug therapy (outcome), or censoring (death, emigration, 12 months after treatment initiation). Hazard ratios of discontinuation associated with starting on generic or brand-name products (intention-to-treat analysis), and incidence rate ratio of discontinuation during periods on generic and brand-name products (as-treated analysis) were respectively estimated from a cohort and self-controlled case series analyses.

**Results:** Patients who started on generics did not experience a different risk of discontinuation compared with those starting on brand-name agents (hazard ratio: 1.00; 95% confidence interval 0.98–1.02). Discontinuation did not occur with different rates during periods covered by generics or brand-name agents (incidence rate ratio: 1.01; 95% confidence interval 0.96–1.11) within the same individuals. A number of sensitivity and subgroup analyses confirmed the robustness of these findings.

**Conclusion:** Generic products are not responsible for the high rate of discontinuation from antihypertensive drug therapy. Assuming therapeutic equivalence, clinical implication is of prescribing generic drug therapies.

**Perspectives**

This study offers one of the first uniform assessments of the impact of generic use on persistence with antihypertensive drugs. We conclude that generic products are not responsible for the high rate of discontinuation from antihypertensive therapy. Under assumption of therapeutic equivalence, the clinical implication of these findings is to encourage prescribing practices and formulary designs that promote generic drug therapies.

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Ann Ist Super Sanità 2014 | Vol. 50, No. 4: 333-340
DOI: 10.4415/ANN_14_04_07

# Generic substitution of antidiabetic drugs in the elderly does not affect adherence

**Francesco Trotta, [a,b], Roberto Da Cas[a], Marina Maggini[a], Mariangela Rossi[c] and Giuseppe Traversa[a]**

[a] *Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Istituto Superiore di Sanità, Rome, Italy*
[b] *Agenzia Italiana del Farmaco, Rome, Italy*
[c] *Direzione Regionale Salute, Coesione Sociale e Società della Conoscenza, Regione Umbria, Perugia, Italy*

**Abstract**

***Introduction.*** The possibility that variation in packaging and pill appearance may reduce adherence is a reason for concern, especially for chronic diseases. The objectives of the study were to quantify the extent of switches between generic antidiabetics and to verify whether switching between different products of the same substance affects adherence.

***Materials and methods.*** All elderly residents of the Umbria Region who received at least 2 prescriptions of antidiabetics in 2010 and 2011 were included in the study. Switching was defined as the dispensing of two different products of the same substance in a series of two prescriptions. Single and multiple switchers were identified according to the number of switches during 2011. Switching relevant to the three off-patent substances with generic use ≥ 5% (metformin, gliclazide and repaglinide) was quantified. The effect of switching on adherence, defined as the proportion of days in 2011 covered by prescriptions (Medication Possession Ratio, MPR), was estimated.

***Results.*** Among the 15 964 patients receiving antidiabetics (14.4% of the elderly population) 9211 were prescribed at least one of the generic substances. Of these patients, 23.3% experienced a single switch and 15.7% were multiple switchers (61.0% never switched). The proportion of multiple switchers increased with the number of prescriptions, reaching 26% among patients with ≥ 11 prescriptions. MPR was 62%, 62% and 72%, respectively among non-switchers, single and multiple switchers.

***Conclusions.*** In elderly patients treated with antidiabetics, the substitution between branded and unbranded products (as well as between generics) of the same substance, did not negatively affect adherence.

**Key words**
- adherence to medications
- generic substitution
- anti-diabetic drugs

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# Off-Patent Generic Medicines vs. Off-Patent Brand Medicines for Six Reference Drugs: A Retrospective Claims Data Study from Five Local Healthcare Units in the Lombardy Region of Italy

**Giorgio L. Colombo[1,2]*, Enrico Agabiti-Rosei[3], Alberto Margonato[4], Claudio Mencacci[5], Carlo Maurizio Montecucco[6], Roberto Trevisan[7]**

**1** Department of Drug Sciences, University of Pavia, Pavia, Italy, **2** S.A.V.E. Studi Analisi Valutazioni Economiche, Milan, Italy, **3** Division of Medicine and Surgery, Spedali Civili, Brescia, Italy, **4** Division of Cardiology, San Raffaele University Hospital, Milan, Italy, **5** Department of Neuroscience, A.O. Fatebenefratelli e Oftalmico, Milan, Italy, **6** Division of Rheumatology, IRCCS Policlinico S Matteo, University of Pavia, Pavia, Italy, **7** Unit of Diabetology, Ospedali Riuniti di Bergamo, Bergamo, Italy

## Abstract

The scientific documentation supporting the potential clinical and economic benefits of a growing use of off-patent generic drugs in clinical practice seems to be limited in Italy as yet.

***Methods:*** We compared differences in outcomes between off-patent generic drugs and off-patent brand drugs in real clinical practice. The outcomes were: persistence and compliance with therapy, mortality, and other health resources consumption (hospitalizations, specialist examinations, other drugs) and total costs. Retrospective analysis was carried out by using the administrative databases of five Local Healthcare Units (ASLs - Aziende Sanitarie Locali) in the Lombardy Region of Italy. Data from the five ASLs were aggregated through a meta-analysis, which produced an estimate indicator of the mean or percentage difference between the two groups (branded vs. generic) and their respective significance tests. The therapeutic areas and studied drugs were: diabetes: metformin - A10BA02; hypertension: amlodipine - C08CA01; dyslipidemia: simvastatin - C10AA01; psychiatry: sertraline - N06AB06; cardiology: propafenone - C01BC03; osteoporosis: alendronate - M05BA04.

***Results:*** The 5 Local Healthcare Units (ASL) represent a population of 3,847,004 inhabitants. The selected sample included 347,073 patients, or 9.02% of the total ASL population; 67% of the patients were treated with off-patent brand drugs. The average age was 68 years, with no difference between the two groups. After 34 months of observation, compliance and persistence were in favor to generic drugs in all therapeutic areas and statistically significant in the metformin, amlodipine, simvastatin, and sertraline groups. The clinical outcomes (hospitalizations, mortality, and other health costs) show no statistically significant differences between off-patent generic vs. off-patent brand medicines.

***Conclusions:*** Off-patent generic drugs appear to be a therapy option of choice in Italy as well, based on clinical outcomes and economic consequences, both for the National Health Service and patients, considering that the price difference between brand and generic drugs is completely charged on patients.

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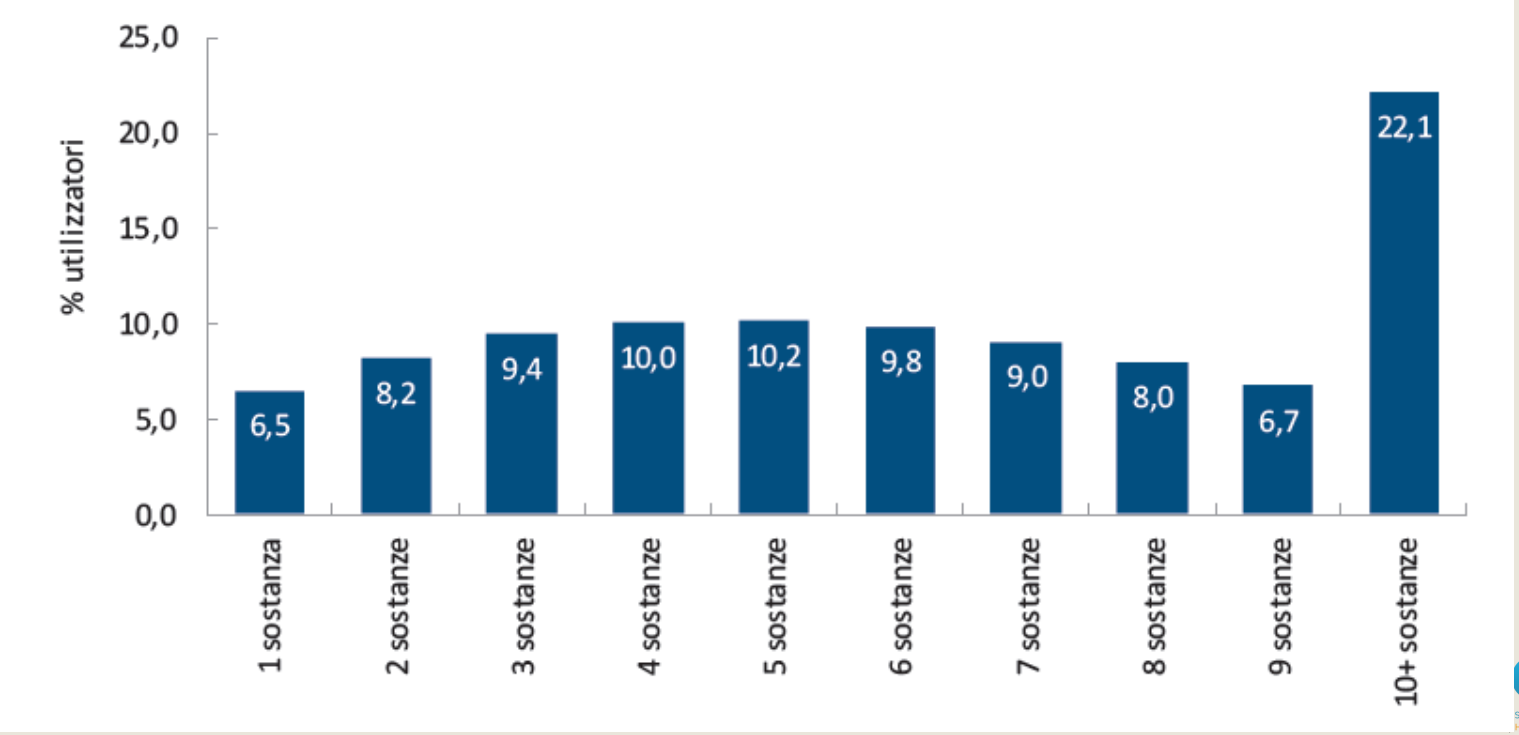
# Strategie per migliorare l'aderenza terapeutica

- Date le implicazioni cliniche ed economiche della **mancata aderenza**, risulta necessario **trovare e applicare strategie funzionali al suo miglioramento**
- Sono molteplici gli studi che hanno valutato l'impatto di differenti strategie volte a migliorare l'aderenza alle terapie, le principali risultano:
  - programmi di auto-monitoraggio e auto-gestione dei medicinali
  - maggiore spiegazione in merito all'utilità dei farmaci e ai danni dalla loro scorretta assunzione
  - coinvolgimento diretto dei farmacisti nella gestione dei farmaci
  - Adozione di **schemi terapeutici** quanto più possibile **semplificati**

***Ruolo delle single pill combination***

# Distribuzione degli utilizzatori nella popolazione di età ≥65 anni per numero di sostanze diverse (2018)




AIFA, Agenzia Italiana del Farmaco, Roma, 2019. Osservatorio Nazionale sull'impiego dei Medicinali. L'uso dei farmaci in Italia. Rapporto Nazionale 2019

# Effects of a Fixed-Dose Combination Strategy on Adherence and Risk Factors in Patients With or at High Risk of CVD
## The UMPIRE Randomized Clinical Trial

Simon Thom, *JAMA*. 2013;310(9):918-929. doi:10.1001/jama.2013.277064

**IMPORTANCE** Most patients with cardiovascular disease (CVD) do not take recommended medications long-term. The use of fixed-dose combinations (FDCs) improves adherence in several clinical areas. Previous trials of cardiovascular FDCs have assessed short-term effects compared with placebo or no treatment.

**OBJECTIVE** To assess whether FDC delivery of aspirin, statin, and 2 blood pressure-lowering agents vs usual care improves long-term adherence to indicated therapy and 2 major CVD risk factors, systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-C).

**DESIGN, SETTING, AND PARTICIPANTS** The UMPIRE trial, a randomized, open-label, blinded-end-point trial among 2004 participants with established CVD or at risk of CVD enrolled July 2010–July 2011 in India and Europe. The trial follow-up concluded in July 2012.

**INTERVENTIONS** Participants were randomly assigned (1:1) to an FDC-based strategy (n=1002) containing either (1) 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril, and 50 mg atenolol or (2) 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril, and 12.5 mg hydrochlorothiazide or to usual care (n=1002).

**MAIN OUTCOMES AND MEASURES** Adherence to medication (defined as self-reported use of antiplatelet, statin, and ≥2 BP-lowering medications) and changes in SBP and LDL-C from baseline.

**RESULTS** At baseline, mean BP was 137/78 mm Hg, LDL-C was 91.5 mg/dL, and 1233 (61.5%) of 2004 participants reported use of antiplatelet, statin, and 2 or more BP-lowering medications. Median follow-up was 15 months (interquartile range, 12-18 months). The FDC group had improved adherence vs usual care (86% vs 65%; relative risk [RR] of being adherent, 1.33; 95% CI, 1.26-1.41; $P < .001$) with concurrent reductions in SBP (−2.6 mm Hg; 95% CI, −4.0 to −1.1 mm Hg; $P < .001$) and LDL-C (−4.2 mg/dL; 95% CI, −6.6 to −1.9 mg/dL; $P < .001$) at the end of the study. Although there was consistency of effects across predefined subgroups, evidence existed of larger benefits in patients with lower adherence at baseline. In this subgroup of 727 participants (36%), adherence at the end of study was 77% vs 23% (RR, 3.35; 95% CI, 2.74-4.09; $P < .001$ for interaction), SBP was reduced by 4.9 mm Hg (95% CI 7.3-2.6 mm Hg; $P = .01$ for interaction), and LDL-C was reduced by 6.7 mg/dL (95% CI, 10.5-2.8 mg/dL; $P = .11$ for interaction). There were no significant differences in serious adverse events or cardiovascular events (50 [5%] in the FDC group and 35 [3.5%] in the usual care group; RR, 1.45; 95% CI, 0.94-2.24; $P=.09$) between the groups.

**CONCLUSIONS AND RELEVANCE** Among patients with or at high risk of CVD, use of an FDC strategy for blood pressure, cholesterol, and platelet control vs usual care resulted in significantly improved medication adherence at 15 months and statistically significant but small improvements in SBP and LDL-C.

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# Effects of a Fixed-Dose Combination Strategy on Adherence and Risk Factors in Patients With or at High Risk of CVD
## The UMPIRE Randomized Clinical Trial

Simon Thom, *JAMA*. 2013;310(9):918-929. doi:10.1001/jama.2013.277064

+21% aderenza

**Table 2. Effect of Treatment on Adherence to Primary and Secondary End Points**

| Outcomes | Fixed-Dose Combination (n = 1002) | Usual Care (n = 1002) | Treatment Effect (95% CI)[a] | *P* Value |
|---|---|---|---|---|
| Primary end points | | | | |
| Adherence, No./total (%)[b] | 829/961 (86) | 621/960 (65) | 1.33 (1.26 to 1.41) | <.001 |
| Systolic blood pressure, mm Hg | 129.2 (128.1-130.2) | 131.7 (130.7-132.8) | −2.6 (−4.0 to −1.1) | <.001 |
| Low-density lipoprotein cholesterol, mg/dL | 84.2 (82.5-85.8) | 88.4 (86.7-90.0) | −4.2 (−6.6 to −1.9) | <.001 |
| Secondary end points | | | | |
| Adherence at 12 mo, No./total (%) | 827/935 (88) | 602/925 (65) | 1.36 (1.29 to 1.43) | <.001 |
| Diastolic blood pressure, mm Hg | 72.8 (72.2-73.5) | 75.2 (74.7-75.8) | −2.5 (−3.3 to −1.6) | <.001 |
| Total cholesterol, mg/dL | 156.6 (154.6-158.5) | 159.1 (157.1-161.1) | −2.5 (−3.3 to 0.3) | .08 |
| High density lipoprotein cholesterol, mg/dL | 44.2 (43.7-44.6) | 43.7 (43.2-44.2) | 0.5 (−0.2 to 1.1) | .14 |
| Triglycerides, mg/dL | 142.3 (137.8-146.9) | 138.8 (134.2-143.4) | 3.6 (−2.9 to 10.0) | .28 |
| Plasma creatinine, mg/dL | 1.07 (1.06-1.08) | 1.04 (1.03-1.05) | 0.03 (0.01 to 0.05) | .002 |

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# Fixed-Dose Combinations Improve Medication Compliance: A Meta-Analysis

Bangalore, The American Journal of Medicine (2007) 120, 713-719

**BACKGROUND:** Compliance with treatment is a sine qua non for successful treatment of chronic conditions like hypertension. Fixed-dose combinations are designed to simplify the medication regimen and potentially improve compliance. However the data on comparison of fixed-dose combination with free-drug regimen to improve patient's medication compliance is limited.

**METHODS:** We conducted a MEDLINE search of studies using the words fixed-dose combinations, compliance and/or adherence. The inclusion criteria were studies which involved fixed-dose combination versus free-drug components of the regimen given separately. Only studies which reported patient's compliance were included.

**RESULTS:** Of the 68 studies on fixed-dose combinations, only 9 studies fulfilled the inclusion criteria. Two studies were in patients with tuberculosis, 4 in the hypertensive population, 1 in patients with human immunodeficiency virus (HIV) disease and 2 in the diabetic population. A total of 11,925 patients on fixed-dose combination were compared against 8317 patients on free-drug component regimen. Fixed-dose combination resulted in a 26% decrease in the risk of non-compliance compared with free-drug component regimen (pooled relative risk [RR] 0.74; 95% confidence interval [CI], 0.69-0.80; $P < .0001$). There was no evidence of heterogeneity in this analysis ($\chi^2 = 14.49$, df = 8; $P = .07$). A subgroup analysis of the 4 studies on hypertension showed that fixed-dose combination (pooled RR 0.76; 95% CI, 0.71-0.81; $P < .0001$) decreased the risk of medication non-compliance by 24% compared with free-drug combination regimen.

**CONCLUSIONS:** Fixed-dose combination decreases the risk of medication non-compliance and should be considered in patients with chronic conditions like hypertension for improving medication compliance which can translate into better clinical outcomes. © 2007 Elsevier Inc. All rights reserved.

**+26% compliance**

**+24% in ipertensione**

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# Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases (Review)

Cochrane Library
Cochrane Database of Systematic Reviews

Bahiru E, *Cochrane Database of Systematic Reviews* 2017, Issue 3. Art. No.: CD009868.

In the initial review, we identified nine randomised controlled trials with a total of 7047 participants and four additional trials (n = 2012 participants; mean age range 62 to 63 years; 30% to 37% women) were included in this update. Eight of the 13 trials evaluated the effects of fixed-dose combination (FDC) therapy in populations without prevalent ASCVD, and the median follow-up ranged from six weeks to 23 months. More recent trials were generally larger with longer follow-up and lower risk of bias. The main risk of bias was related to lack of blinding of participants and personnel, which was inherent to the intervention. Compared with the comparator groups (placebo, usual care, or active drug comparator), the effects of the fixed-dose combination treatment on mortality (FDC = 1.0% versus control = 1.0%, RR 1.10, 95% CI 0.64 to 1.89, $I^2$ = 0%, 5 studies, N = 5300) and fatal and non-fatal ASCVD events (FDC = 4.7% versus control = 3.7%, RR 1.26, 95% CI 0.95 to 1.66, $I^2$ = 0%, 6 studies, N = 4517) were uncertain (low-quality evidence). The low event rates for these outcomes and indirectness of evidence for comparing fixed-dose combination to usual care versus individual drugs suggest that these results should be viewed with caution. Adverse events were common in both the intervention (32%) and comparator (27%) groups, with participants randomised to fixed-dose combination therapy being 16% (RR 1.16, 95% CI 1.09 to 1.25, 11 studies, 6906 participants, moderate-quality evidence) more likely to report an adverse event . The mean differences in systolic blood pressure between the intervention and control arms was -6.34 mmHg (95% CI -9.03 to -3.64, 13 trials, 7638 participants, moderate-quality evidence). The mean differences (95% CI) in total and LDL cholesterol between the intervention and control arms were -0.61 mmol/L (95% CI -0.88 to -0.35, 11 trials, 6565 participants, low-quality evidence) and -0.70 mmol/L (95% CI -0.98 to -0.41, 12 trials, 7153 participants, moderate-quality evidence), respectively. There was a high degree of statistical heterogeneity in comparisons of blood pressure and lipids ($I^2 \geq 80\%$ for all) that could not be explained, so these results should be viewed with caution. Fixed-dose combination therapy improved adherence to a multidrug strategy by 44% (26% to 65%) compared with usual care (4 trials, 3835 participants, moderate-quality evidence).

**+44% compliance**

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**Table 1** Eligible studies for meta-analysis

| Study | Indication | No. of participants (SPC) | Age in years, mean (SPC/FCT) | Gender, % female (SPC/FCT) | Compounds | Class |
|---|---|---|---|---|---|---|
| **Combination with statins** | | | | | | |
| Hussein et al. (2010) [9] | Hyp/Dys | 35 430 (3136) | 50.0–55.2/54.4–56.9[a] | 34.4–44.0/41.0–54.6[a] | AML/ATOR | CCB/Statin |
| Patel et al. (2008) [10] | Hyp/Dys | 4703 (795) | 61.4/62.1–64.4[a] | 42.5/47.8–57.5[b] | AML/ATOR | CCB/Statin |
| Simons et al. (2011) [11] | Hyp/Dys | 10 350 (4146) | 70.7/71.2 | 54.0/54.0 | AML/ATOR | CCB/Statin |
| Balu et al. (2009) [12] | Dys | 8988 (6638) MPR | 51.9/56.0–56.1[a] | 26.9/77.7–83.0 | Niacin/Lovastatin | Niacin/Statin |
| Kamat et al (2011) [13] | Dys | 42460 (38847) | 56.4/54.8 | 44.8/37.7 | (Niacin or Ezetimibe)/Simvastatin Niacin/Lovastatin | (Niacin or Ezetimibe)/Statin |
| **Combination without statins** | | | | | | |
| Ram et al. (2012) [14] | Hyp | 46706 (32807) | Only numbers per age range are given | 64.4–65.9/59.5–63.5 | AML/OLM (& AML/VAL) | CCB/ARB |
| Levi et al. (2016) [15] | Hyp | 4890 (3057) | 66.6/68.1 | 52.2/50.8 | AML/OLM | CCB/ARB |
| Brixner et al. (2008) [16] | Hyp | 2189 (1628) | Only numbers per age range are given | 49/41.5 | VAL/HCTZ | ARB/HCTZ |
| Machnicki et al. (2015) [17] | Hyp | 3768 (1884) | 48.4/48.0 | 66.4/66.8 | AML/VAL/HCTZ | CCB/ARB/HCTZ |
| Jackson et al. (2008) [18] | Hyp | 908 (619) | Only numbers per age range are given | 57.6–58.5/55.4 | AML/VAL/HCTZ | CCB/ARB/HCTZ |
| Xie et al. (2014) [19] | Hyp | 17465 (8516) | 54.8/59.1–63.9[a] | 45.2/49.5–51.3 | AML/(VAL or OLM)/HCTZ | CCB/ARB/HCTZ |

High Blood Pressure & Cardiovascular Prevention (2020) 27:157–164

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# Adherence to single-pill combination versus multiple-pill combination lipid-modifying therapy among patients with mixed dyslipidemia in a managed care population

*Kamat et al.* Current Medical Research & Opinion Vol. 27, No. 5, 2011, 961–968

| | SPC ($N = 38{,}847$) | | MPC ($N = 3613$) | | *P* Value |
|---|---|---|---|---|---|
| Index therapy, *N* (%) | | | | | |
| Simvastatin + ezetimibe | 35,240 | (90.71%) | 2768 | (76.61%) | |
| Lovastatin + niacin | 3332 | (8.58%) | 237 | (6.56%) | |
| Simvastatin + niacin | 275 | (0.71%) | 608 | (16.83%) | |
| Age, years, mean (±SD), median | 56.35 (±12.27) | 56 | 54.82 (±11.57) | 54 | <0.0001 |
| Men, *N* (%) | 21,442 | (55.20%) | 2251 | (62.30%) | <0.0001 |
| Duration of follow-up, months, mean (±SD), median) | 18.63 (±12.65) | 14.46 | 16.58 (±10.64) | 13.96 | <0.0001 |

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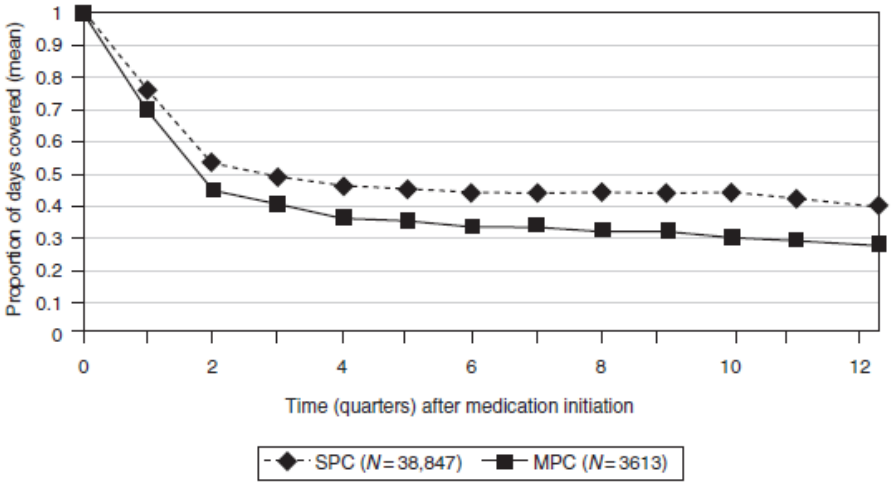
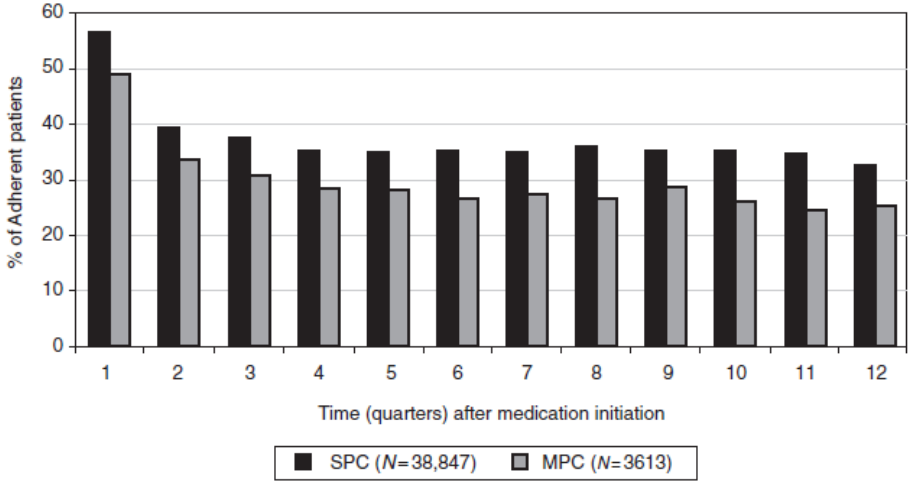
# Adherence to single-pill combination versus multiple-pill combination lipid-modifying therapy among patients with mixed dyslipidemia in a managed care population

*Kamat et al.* Current Medical Research & Opinion Vol. 27, No. 5, 2011, 961–968

Mean proportion of days covered over follow-up ($N = 42{,}460$).




Proportion of patients with optimal adherence ($N = 42{,}460$).

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# Ruolo delle SPC in ambito cardiovascolare

- L'attuale disponibilità di terapie costituite dalla combinazione di più principi attivi in un'unica compressa (**single pill combination, SPC**) è considerato uno **strumento** di rilievo su cui fare leva per il **miglioramento dell'aderenza**
- Queste formulazioni **consentono regimi terapeutici semplificati**, particolarmente utili in pazienti per cui sono previsti schemi di terapia complessi per eventuale presenza di patologie concomitanti, più tendenti a presentare bassi profili di aderenza
- In ambito cardiovascolare le **SPC consentono la somministrazione in unica compressa** di due principi attivi della **stessa categoria** (es. due antiipertensivi o due ipolipemizzanti) o unione di **due categorie differenti** ma agenti simbioticamente sulla riduzione del rischio CV esitando in maggior efficacia e aderenza
- La disponibilità di un **range variabile di dosaggi** rende **flessibile l'uso delle combinazioni**
- Il ricorso a terapie in grado di **ottimizzare l'aderenza** può comportare anche una **riduzione dei costi** associati all'assistenza, in virtù della maggiore efficacia e sicurezza del trattamento e alla conseguente **riduzione di eventi cardiovascolari e complicanze**

# Take home message

Nonostante [illegible] trattamenti, **il controllo dell'ipercolesterolemia resta subottimale** e una [illegible] **ssi profili di aderenza** alle cure con ripercussioni sulla prognosi del [illegible]

**È importante rivolgere l'attenzione alle nuove combinazioni di ipolipemizzanti alla luce della recente genericazione dei principi attivi ipolipemizzante ad elevata potenza**

**pprietezza** delle prescrizioni è **fondamentale per la sostenibilità del** [illegible] re l'onere economico dovuto alle diverse patologie.

**centivare** e far **aumentare** il tasso di **aderenza** alle terapie e il **controllo** [illegible] **dell'appropriatezza** delle prescrizioni.

L'uso delle single pill combinations (SPCs) rappresenta uno strumento importante per il perseguimento di tale obiettivo

**Flessibilità di dosaggio**

**Possibilità di ridurre il dosaggio rispetto a combinazioni libere**

**Miglioramento profilo di aderenza**

**Riduzione di spesa per miglior gestione e aderenza terapeutica**

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«[…] *In un momento in cui le risorse sono scarse, il mio suggerimento ai diversi Paesi è questo:* ***prima di tagliare la spesa per l'assistenza sanitaria, guardate*** *in primo luogo* ***alle opportunità per migliorare l'efficienza****.*

***Tutti i sistemi sanitari, ovunque, potrebbero ottenere un migliore utilizzo delle risorse****, attraverso migliori pratiche di acquisto, un uso più ampio di prodotti a brevetto scaduto, migliori incentivi per fornitori o procedure amministrative o di finanziamento semplificate* [...]»

Dr Margaret Chan
Director-General
World Health Organization

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