XIX CONGRESSO NAZIONALE AMD

Roma, 30 Maggio 2013

Farmaci generici ed equivalenza terapeutica nelle malattie cardiovascolari

Prof. Alberto Margonato

Dipartimento Cardio-Toraco-Vascolare

Ospedale San Raffaele di Milano

Key Points

- Aspetti Economici
- Efficacia Terapeutica e Sicurezza
- Concetto di Intersostituibilità e di Interazione tra farmaci generici e non

Spesa Farmaceutica

Spesa farmaceutica in Italia gennaio-settembre 2010

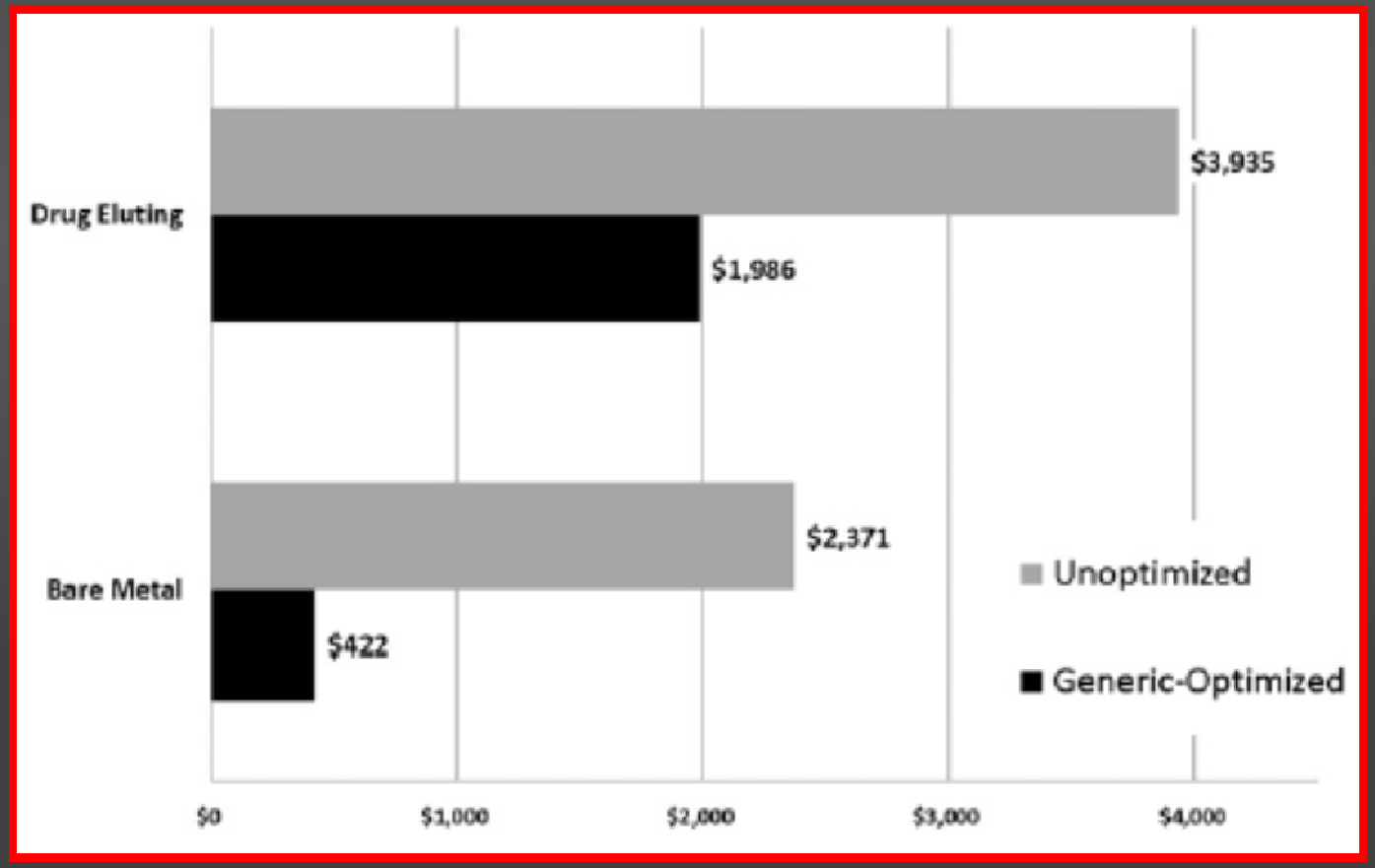
I farmaci del sistema cardiovascolare occupano saldamente il primo posto per spesa (58,1 euro pro capite), con un ulteriore incremento del 3,6% delle quantità prescritte rispetto al 2009; mentre il costo medio DDD registra una riduzione del 4,3%, tale dato è spiegabile dall'elevato numero di principi attivi a brevetto scaduto disponibili

Nel 2009 ogni 1000 italiani si è registrata una spesa farmaceutica cardiovascolare di 68.000 € su circa 185.000 € totali

L'atorvastatina si conferma il principio attivo con la spesa più elevata (399 milioni di euro) seguita da rosuvastatina (232 milioni)

I farmaci equivalenti rappresentano oramai il 30% della spesa farmaceutica e il 50% delle DDD

Spesa Farmaceutica



Garner G, Am J Cardiol 2010

The Cost Effectiveness of Statin Therapies in Spain in 2010, after the Introduction of Generics and Reference Prices

Variation in the cost effectiveness of HMG-CoA reductase inhibitors (statins) in Spain between 2003 and 2010

Statin	Dose/day (mg)	Cost (€) per percentage point reduction in LDL-C		
		2003[5]	2010 (95% CI)	% variation
Atorvastatin	10	11	12.8 (12.4, 13.2)	+16.4
	20	16	16.1 (12.9, 21.1)	+0.6
	40	23	15.5 (14.3, 16.9)	−32.6
	80	N/A	13.8 (12.2, 15.8)	
	Mean	16.7	14.5	−13.2
Simvastatin	10	12	6.5 (5.8, 7.4)	−45.8
	20	15	6.3 (6.1, 6.5)	−58.0
	40	21	6.7 (6.3, 7.2)	−68.1
	Mean	16.0	6.5	−59.4
Lovastatin	20	14	10.0 (9.5, 10.6)	−28.6
	40	17	10.2 (9.8–10.6)	−40.0
	Mean	15.5	10.1	−34.8

Statin	Dose/day (mg)	Cost (€) per percentage point reduction in LDL-C		
		2003[5]	2010 (95% CI)	% variation
Fluvastatin	20	15	13.6 (12.2, 15.0)	−9.3
	40	19	12.9 (12.4, 13.5)	−32.1
	80	24	14.0 (12.9, 15.4)	−41.7
	Mean	19.3	13.5	−30.0
Pravastatin	10	21	13.6 (11.6, 16.2)	−30.8
	20	26	13.7 (12.3, 15.5)	−47.3
	40	42	19.8 (19.4, 20.1)	−52.9
	Mean	29.7	15.7	−47.1
Rosuvastatin	10	N/A	10.4 (9.3, 11.8)	
	20	N/A	11.2 (10.1, 12.5)	
	40	N/A	12.5 (11.8, 13.6)	
	Mean		11.4	

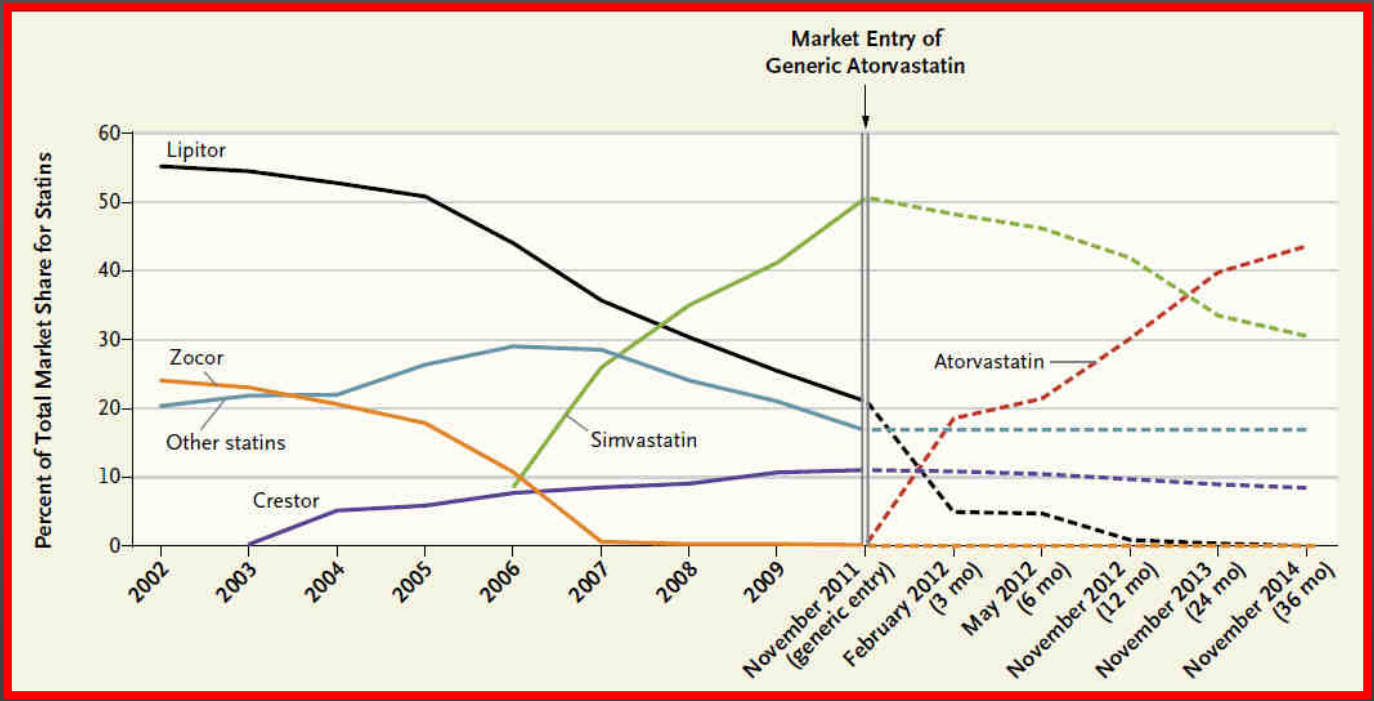
Am J Cardiovasc Drugs 2010; 10 (6): 369-382

Generic Atorvastatin and Health Care Costs

Cynthia A. Jackevicius, Pharm.D., Mindy M. Chou, Pharm.D., Joseph S. Ross, M.D., M.H.S., Nilay D. Shah, Ph.D., and Harlan M. Krumholz, M.D.

U.S. Statin Market Share before and Projected Market Share after entry of Generic ATV

Data for 2002 through 2009 are from IMS Health National Prescription Audit



Projected Cost Savings after the Market Entry of Generic Atorvastatin.*

Variable	2012	2013	2014
Total statin expenditure without entry of a generic	$17,544,160,000	$18,469,690,000	$19,395,220,000
Cost savings from entry of generic atorvastatin (%)	$2,058,470,000 (12)	$4,074,470,000 (22)	$4,536,520,000 (23)

NEJM, 366;3.202 january 19, 2012

Spesa Farmaceutica/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

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.

J. Alexander Cole et al. Pharmacotherapy 2006

Spesa Farmaceutica/Aderenza

Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-LoweringArm (ASCOT-LLA)

Pazienti con 20% di aderenza a terapia antipertensiva e statine

manifestavano il doppio degli eventi quali stroke, IMA ed angina

Se tale aderenza aumenta dal 20% all'80% (ideale) si eviterebbero 800

IMA e 600 strokes per 100.000 pazienti, ovvero circa 1 evento/70 pts

Garner G, Am J Cardiol 2010

Generic Substitution of Antihypertensive Drugs: Does It Affect Adherence?

Boris LG Van Wijk, Olaf H Klungel, Eibert R Heerdink, and Anthonius de Boer

Table 2. Association Between Substitution and Nonadherence

Characteristic	Adherent/Nonadherent Pts., n (%)[a]		OR (95% CI)[b]	
	Substituted	Non-substituted	Crude	Adjusted
Overall	63/463 (13.6)	111/595 (18.7)	0.69 (0.49 to 0.96)	0.68 (0.48 to 0.96)
Gender				
male	38/228 (16.7)	47/282 (16.7)	1.00 (0.63 to 1.60)	0.97 (0.60 to 1.58)
female	25/235 (10.6)	64/313 (20.4)	0.46 (0.28 to 0.76)	0.46 (0.28 to 0.77)
Antihypertensive agent				
diuretic	9/70 (12.9)	25/117 (21.4)	0.54 (0.24 to 1.24)	0.41 (0.17 to 1.02)
β-blocker	39/253 (15.4)	60/319 (18.8)	0.79 (0.51 to 1.22)	0.82 (0.52 to 1.30)
calcium-channel blocker	1/27 (3.7)	4/35 (11.4)	0.30 (0.031 to 2.84)	0.44 (0.41 to 4.70)
ACE inhibitor	13/110 (11.8)	22/121 (18.2)	0.60 (0.29 to 1.27)	0.61 (0.29 to 1.29)
angiotensin II receptor antagonist	0/0	0/0		
other	1/3 (33.3)	0/3		
Age (y)				
≤39	5/36 (13.9)	5/49 (10.2)	1.75 (0.42 to 7.34)	1.95 (0.43 to 8.89)
40–59	20/189 (10.6)	45/224 (20.1)	0.49 (0.28 to 0.88)	0.49 (0.27 to 0.90)
60–79	30/208 (14.4)	43/278 (15.5)	0.87 (0.82 to 1.43)	0.85 (0.50 to 1.44)
≥80	8/30 (26.7)	18/44 (40.9)	0.60 (0.24 to 1.50)	0.50 (0.18 to 1.41)
Duration of use (days)				
0–90	20/143 (14.0)	34/207 (16.4)	0.83 (0.46 to 1.51)	0.85 (0.46 to 1.57)
91–180	17/103 (16.5)	26/128 (20.3)	0.78 (0.40 to 1.52)	0.80 (0.40 to 1.61)
181–270	12/79 (15.2)	18/91 (19.8)	0.73 (0.33 to 1.62)	0.62 (0.25 to 1.53)
≥271	14/138 (10.1)	33/169 (19.5)	0.47 (0.24 to 0.91)	0.42 (0.21 to 0.86)

"Generic substitution of antihypertensive drugs does not lead to lower adherence or more discontinuation and cardiovascular disease–related hospitalizations compared with brand-name therapy. When a less-expensive antihypertensive generic equivalent becomes available, generic substitution should be considered to achieve economic benefits"

Boris LG Van Wijk et al. Ann Pharmacother 2006;40:15-20

In generale, il basso costo dei farmaci generici ha popolarizzato il loro uso. Tuttavia, il basso costo di per sé giustifica il loro utilizzo come scelta preferenziale?

Bioequivalenza

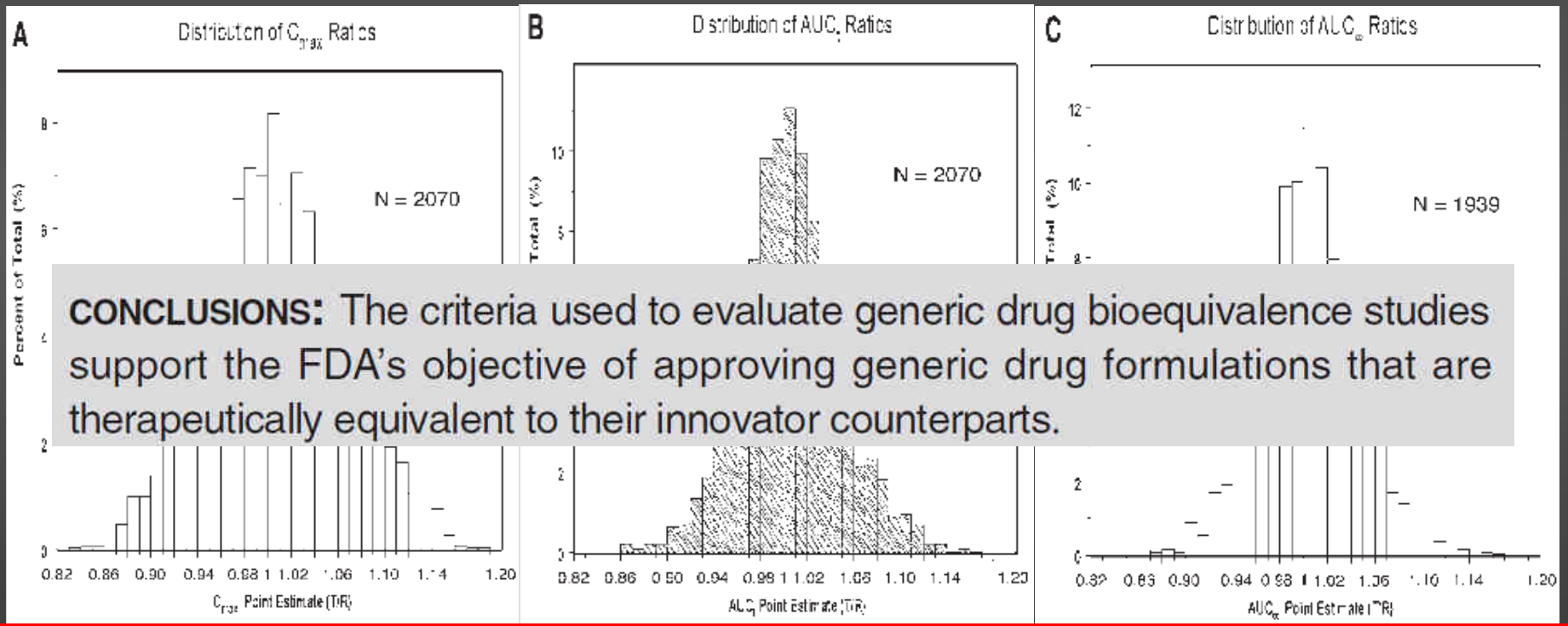
In 127 generic drug applications to the FDA, the difference in bioequivalence between branded and generic drugs was 3.3% for AUC (area under the concentration - time curve) and 4.3% for Cmax (peak plasma concentration)

Henney J. JAMA 1999;21:1995 Abstract

“On scientific grounds there is no reason to be concerned about substituting a generic product for a branded product that is flagged as bioequivalent.”

McLachlan AJ et al. Australian Prescriber 2007;30(2): 41-43

Bioequivalenza



CONCLUSIONS: The criteria used to evaluate generic drug bioequivalence studies support the FDA's objective of approving generic drug formulations that are therapeutically equivalent to their innovator counterparts.

AUC° = area under the drug plasma concentration versus time curve extrapolated to infinity
AUCt = area under the drug plasma concentration versus time curve until the last sampling time (t)
Cmax = peak drug plasma concentration
T/R = test/reference

Davit BM et al. Ann Pharmacother 2009;43:1583-97

Efficacia Terapeutica e Sicurezza

Metoprololo generico o di marca (49.673 pazienti)

Table 5. Incidence rates per 10 000 patient days (IR) and relative risks (RR) of hospitalization events among patients receiving the generic formulation of metoprolol compared with the original formulation (RR = incidence of group B/incidence of group A) in the study population

	Bremen					TK-North				
	A Beloc-ZOK		B Generics		RR	A Beloc-ZOK		B Generics		RR
	N	IR	*N*	IR		*N*	IR	*N*	IR	
Patient days of intake	2 203 934		770 783			6 613 171		1 962 358		
Myocardial infarction	95	0.431	50	0.649	1.51	112	0.169	42	0.214	1.26
Hypertensive crisis	57	0.259	26	0.337	1.30	174	0.263	43	0.219	0.83
Stroke	131	0.594	67	0.869	1.46	186	0.281	74	0.377	1.34
Index events	283	1.284	143	1.855	1.45	472	0.714	159	0.810	1.14
Cardiac dysrhythmia	130	0.590	50	0.649	1.10	503	0.761	162	0.826	1.09
Unstable angina pectoris	103	0.467	46	0.597	1.28	393	0.594	109	0.555	0.94
Cardiac syncope	26	0.118	10	0.130	1.10	38	0.057	23	0.117	2.04
Congestive heart failure	67	0.304	44	0.571	1.88	112	0.169	28	0.143	0.84
Orthostatic hypotension	5	0.023	0	0.000	0.00	5	0.008	3	0.015	2.02
All cardiovascular events	614	2.786	293	3.801	1.36	1 523	2.303	484	2.466	1.07
Other	2 713	12.310	980	12.714	1.03	6 898	10.431	1 898	9.672	0.93
Overall	3 327	15.096	1 273	16.516	1.09	8 421	12.734	2 382	12.138	0.95

Ahrens W, Pharmacoepidem Drug Saf 2007

Efficacia Terapeutica e Sicurezza

Metoprololo generico o di marca (49.673 pazienti)

Table 10. Odds ratio for index events, all cardiovascular events and hospitalizations overall adjusted for all co-variates listed in Tables 6 to 9

	Bremen		TK-North	
	OR	95%CI	OR	95%CI
Index events				
Male	0.97	0.78–1.17	1.11	0.92–1.30
Female	1.15	0.90–1.42	0.93	0.64–1.21
Total	1.06	0.89–1.24	1.04	0.89–1.19
Cardiovascular events				
Male	0.98	0.79–1.18	0.99	0.88–1.09
Female	1.03	0.83–1.23	0.97	0.82–1.13
Total	1.01	0.88–1.14	0.98	0.90–1.07
All hospitalization events				
Male	0.90	0.81–0.99	0.93	0.87–0.98
Female	0.99	0.91–1.06	0.91	0.85–0.98
Total	0.94	0.88–1.00	0.92	0.88–0.96

Ahrens W, Pharmacoepidem Drug Saf 2007

Equivalenza clinica dei Farmaci Generici

Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease

A Systematic Review and Meta-analysis

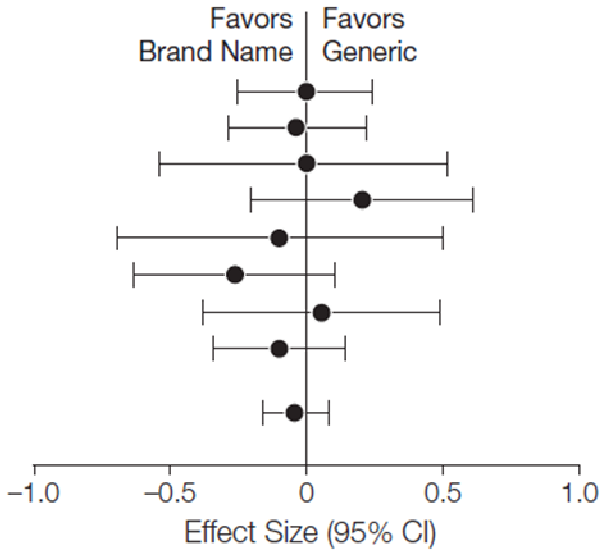
Tale studio ha analizzato, infatti, molti lavori pubblicati tra il 1984 e il 2008 dimostrando l'equivalenza clinica in 7/7 studi per i beta-bloccanti; 10/11 per i diuretici; 5/7 per i calcio-antagonisti; 3/3 per i farmaci antipiastrinici

Kesselheim AS, JAMA 2008

Equivalenza clinica dei Farmaci Generici

Drug Class and Aggregate Meta-analyses of Trials Comparing Generic and Brand-Name Drugs Used in Cardiovascular Disease

Drug Class	No. Studies	No. Subjects	Effect Size (95% CI)
β-Blockers	6	135	0.00 (–0.24 to 0.25)
Diuretics	10	135	–0.03 (–0.28 to 0.22)
Calcium channel blockers	4	242	0.00 (–0.53 to 0.53)
Antiplatelet agents	2	50	0.21 (–0.19 to 0.61)
ACE inhibitors	1	23	–0.09 (–0.68 to 0.50)
Statins	2	71	–0.25 (–0.62 to 0.12)
α-Blockers	1	43	0.06 (–0.37 to 0.50)
Warfarin	4	138	–0.09 (–0.33 to 0.15)
Overall	30	837	–0.03 (–0.15 to 0.08)



ACE indicates angiotensin-converting enzyme; CI, confidence interval.

Kesselheim AS, JAMA 2008

Efficacia Terapeutica e Sicurezza

Studi coinvolgenti i Betabloccanti

Source	Drugs Studied[a]	No. of Patients (Age Mean or Range, y)/ Duration	Study Design	Population (Setting)	Jadad or Newcastle-Ottawa Score[b]	Results	Listed Source of Funding
Ahrens et al,[25] 2007	Toprol XL vs 8 versions of long-acting metoprolol	49673 (56)/4 y	Retrospective cohort study	Patients affiliated with 3 German health insurers (non-US)	8	No excess risk of hospitalization for cardiovascular events after adjustment for confounding (OR, 1.04–1.06; 95% CI, 0.89–1.21)	Generic manufacturers
Portoles et al,[26] 2005	Coreg vs carvedilol	24 (22.8)/1 dose of each with washout	RCT with crossover	Healthy subjects (non-US)	2	No significant differences in HR, BP, PR length, tolerability	Not listed
Mirfazaelian et al,[27] 2003	Tenormin vs atenolol	12 (NA)/1 dose of each with washout	Bioequivalency study: double-blind RCT with crossover	Healthy subjects (non-US)	2	No significant differences in reductions of HR, BP	Not listed
Bongers and Sabin,[28] 1999	Toprol XL vs long-acting metoprolol	52 (62)/4 wk for each product	Double-blind RCT with crossover	Outpatients with stable angina and 6 proven ST-segment depressions on ambulatory ECG (non-US)	3	Both significantly reduced ischemic events; no significant difference in reductions of HR or BP, signs of ischemia on telemetry ($P = .21$), anginal attacks ($P = .34$), nitrate use ($P = .13$), or adverse events ($P = .08$); median HR slightly less for brand-name ($P = .05$)	Brand-name manufacturer
Chiang et al,[29] 1995	Tenormin vs atenolol	23 (59)/4 wk of each with washout	Double-blind RCT with crossover	Outpatients with hypertension (non-US)	3	No significant differences in reductions of HR, BP	Not listed
Sarkar et al,[30] 1995	Tenormin vs atenolol	31 (NA)/1 dose of each with washout	Bioequivalency study: RCT with crossover	Healthy subjects (US)	2	No significant differences in reductions of HR, BP	Generic manufacturer
Carter et al,[31] 1989	Inderal vs Inderal LA (long-acting) vs propranolol	15 (46)/4 wk of each with washout	Single-blind RCT with crossover	Outpatients with hypertension (US)	3	No significant differences in reductions of HR, reductions of BP, tolerability	National Institutes of Health
el-Sayed and Davies,[32] 1989	Inderal vs propranolol vs placebo	12 (NA)/1 dose of each with washout	Double-blind RCT with crossover	Healthy subjects (non-US)	2	No significant differences in change in resting HR, SBP, postexercise values	Not listed
Sanderson and Lewis,[33] 1986	Inderal vs propranolol	1700 (68)/Half switched to Inderal LA for 4 wk; then all switched for 4 wk	Retrospective cohort study	Outpatients with multiple indications for β-blocker (non-US)	3	Increased incidence of self-reported adverse effects among group taking generic at initiation of study ($P < .001$) (difference extinguished after all switched to Inderal LA, $P = .15$)	Not listed

Kesselheim AS, JAMA 2008

Efficacia Terapeutica e Sicurezza

Studi coinvolgenti i Diuretici

Source	Drugs Studied[a]	No. of Patients (Age Mean or Range, y)/ Duration	Study Design	Population (Setting)	Jadad or Newcastle-Ottawa Score[b]	Results	Source of Funding
Murray et al,[34] 1997	Lasix vs 3 versions of furosemide vs intravenous Lasix	17 (65)/1 wk of each product	Bioequivalency study: open-label RCT with crossover	Outpatients with CHF (US)	3	Statistically nonsignificant differences in urine electrolytes (P = .37–.45) but wide intraindividual variability	Brand-name manufacturer
Awad et al,[35] 1992	Lasix vs furosemide	20 (21–32)/1 dose of each with washout	Bioequivalency study: RCT with crossover	Healthy subjects (non-US)	0	Statistically nonsignificant differences in urine electrolytes, urine volume (P > .05)	Not listed
Kaojarern et al,[36] 1990	Lasix vs 3 versions of furosemide	8 (25–39)/1 dose of each with washout	Bioequivalency study: RCT with crossover	Healthy subjects (non-US)	1	Statistically nonsignificant differences in 6-h urine output, urine electrolytes (P > .05)	Medical center, brand-name manufacturer
Sharoky et al,[37] 1989	Dyazide vs triamterene-hydrochlorothiazide	30 (55)/3 wk of brand and 3 wk of generic	Bioequivalency study: RCT with crossover	Outpatients with hypertension taking brand-name Dyazide (US)	4	Statistically nonsignificant differences in electrolytes, CBC, BP, tolerability (P > .05)	Generic manufacturer
Singh et al,[38] 1987	Intravenous Lasix vs intravenous furosemide	5 (20–51)/1 dose of each with washout	Bioequivalency study: double-blind RCT	Inpatients with edema of renal origin (non-US)	2	Statistically nonsignificant differences in urine electrolytes, standing and recumbent BP, urine output, tolerability (P > .05)	Not listed
Meyer et al,[39] 1985	Lasix vs 3 versions of furosemide	12 (NA)/1 dose of each with washout	Bioequivalency study: double-blind RCT with crossover	Healthy subjects (non-US)	2	Statistically significant differences in 6-h urine output (P < .05)	Not listed
Grahnen et al,[40] 1984	Lasix vs furosemide vs intravenous furosemide	8 (26)/2 doses of each with washout	Bioequivalency study: double-blind RCT with crossover	Healthy subjects (non-US)	2	Statistically nonsignificant differences in urine output (P > .05)	Not listed
Garg et al,[41] 1984	Lasix vs furosemide	16 (NA)/1 dose of each with washout	Bioequivalency study: double-blind RCT with crossover	Healthy subjects (non-US)	2	Statistically nonsignificant differences in serum and urine electrolytes, HR, BP, urine output (P > .05)	Not listed
Pan et al[42] 1984	Lasix vs furosemide	5 (NA)/2 d of each	Bioequivalency study: double-blind RCT with crossover	Outpatients with CHF (non-US)	1	Statistically nonsignificant differences in electrolytes, urine output, weight, urine electrolytes (P > .2)	Not listed
Maitai et al,[43] 1984	Lasix vs 6 versions of furosemide	6 (NA)/1 dose of each with washout	Bioequivalency study: RCT with crossover	Healthy subjects (non-US)	0	"Acceptable level of diuresis" in self-reported urine output (no statistical tests done)	Government
Martin et al,[44] 1984	Lasix vs furosemide	12 (18–42)/1 dose of each with washout	Bioequivalency study: RCT with crossover	Healthy subjects (non-US)	0	Statistically nonsignificant trend of lower urine output (P = .07–.08), statistically nonsignificant differences in urine electrolytes	Medical center

Kesselheim AS, JAMA 2008

Efficacia Terapeutica e Sicurezza

Studi coinvolgenti i Calcio-Antagonisti

Source	Drugs Studied[a]	No. of Patients (Age Mean or Range, y)/Duration	Study Design	Population (Setting)	Jadad or Newcastle-Ottawa Score[b]	Results	Source of Funding
Kim et al,[45] 2007	Norvasc vs amlodipine camsylate	189 (53)/8 wk with dose increase after 4 wk if BP still elevated	Multicenter double-blind parallel group RCT	Outpatients with uncomplicated essential hypertension (non-US)	3	Significant BP improvement in both groups; statistically nonsignificant differences in tolerability ($P > .05$)	Generic manufacturer, government
Mignini et al,[46] 2007	Norvasc vs amlodipine maleate	24 (34.8)/1 dose of each with washout	Single-blind RCT with crossover	Healthy subjects (non-US)	2	Decrease in SBP, increase in HR, decrease in PR and QRS intervals, with statistically nonsignificant differences between the 2 groups	Not listed
Park et al,[47] 2004	Norvasc vs amlodipine camsylate	18 (22)/1 dose of each with washout	Bioequivalency study: open-label RCT with crossover	Healthy subjects (non-US)	4	Significant improvements in BP in both groups; statistically nonsignificant differences in electrolytes, CBC, UA, HR, ECG changes ($P > .05$)	Not listed
Saseen et al,[48] 1997	Calan vs verapamil	8 (70)/2 wk of each with washout	Bioequivalency study: double-blind RCT with crossover	Elderly outpatients with hypertension (US)	3	Generics associated with a marginally greater BP reduction than brand; statistically nonsignificant differences in HR, ECG changes ($P > .05$)	Not listed
Usha et al,[49] 1997	Cardizem vs long-acting diltiazem	12 (27)/1 dose of each with washout	Bioequivalency study: double-blind RCT with crossover	Healthy subjects (non-US)	3	Statistically nonsignificant differences in BP, HR, ECG changes ($P > .05$)	Generic manufacturer
Waldman and Morganroth,[50] 1995	Calan SR or Isoptin SR vs sustained-release verapamil	24 (NA)/1 dose of each with washout	Bioequivalency study (both fasting and after a meal): open-label RCT	Healthy subjects (US)	1	In fasting patients, statistically nonsignificant difference in BP, HR, or ECG changes; in fed patients, increased PR interval on ECG with generic ($P < .05$)	Brand-name manufacturer; brand-name, industry-affiliated foundation
Carter et al,[51] 1993	Isoptin vs 1 of 2 versions of verapamil	Youth cohort: 8 (27)/1 wk of each with washout; elderly cohort: 8 (73)/3 wk of each with no washout	Double-blind randomized 3-way RCT with crossover	Healthy subjects and elderly outpatients with hypertension (US)	2	Statistically nonsignificant differences in HR, BP, or PR intervals for youth cohort; statistically insignificant differences in elderly cohort also, except 1 generic associated with increased PR interval and (paradoxically) higher supine BP	American College of Clinical Pharmacy, medical center

Kesselheim AS, JAMA 2008

Efficacia Terapeutica e Sicurezza

Studi coinvolgenti Antipiastrinici, statine, ACE-inibitori, alfa-bloccanti

Source	Drugs Studied[a]	No. of Patients (Age Mean or Range, y)/Duration	Study Design	Population (Setting)	Jadad or Newcastle-Ottawa Score[b]	Results	Source of Funding
				Antiplatelet Agents			
Ashraf et al,[52] 2005	Plavix vs clopidogrel	30 (49)/1 dose of each with washout	Double-blind RCT with crossover	Patients with suspected ischemic heart disease (non-US)	3	Statistically nonsignificant differences in reduction in platelet aggregation blood tests (57.8% vs 60.7%, *P* = .72)	Generic manufacturer, government
Rao et al,[53] 2003	Plavix vs clopidogrel	20 (27)/10 d	Bioequivalency study: open-label parallel group RCT	Healthy subjects (non-US)	2	Statistically nonsignificant differences in bleeding time, tolerability (*P* > .05)	Not listed
Merali et al,[54] 1996	Enteric-coated aspirin vs 3 versions of enteric-coated acetylsalicylic acid	12 (18–45)/1 dose of each with washout	Bioequivalency study: RCT with crossover	Healthy subjects (non-US)	2	Statistically nonsignificant differences in platelet function assay (*P* > .05)	Internal funding
				Angiotensin-Converting Enzyme Inhibitors			
Portoles et al,[55] 2004	Vasotec vs enalapril	24 (23)/1 dose of each with washout	Bioequivalency study: open-label RCT with crossover	Healthy subjects (non-US)	3	Statistically nonsignificant differences in BP reductions, changes in HR, effect on CBC, UA (*P* > .05)	Not listed
				Statins			
Assawawitoontip and Wiwanitkit,[56] 2002	Zocor vs simvastatin	48 (37)/8 wk of each with washout	Double-blind RCT with crossover	Outpatients with hypercholes-terolemia not previously treated (non-US)	4	Reductions in LDL in both groups; statistically nonsignificant differences in cholesterol measurements, LFTs, creatine kinase levels (unpaired *t* test, α = .05)	Generic manufacturer
Wiwanitkit et al,[57] 2002	Zocor vs simvastatin	43 (49)/16 wk of each with washout	Double-blind RCT with crossover	Outpatients with hypercholes-terolemia not previously treated (non-US)	4	Reductions in LDL in both groups; statistically nonsignificant differences in cholesterol measurements, LFTs, adverse effects (*P* > .05)	Generic manufacturer
				α-Blockers			
Tsai et al,[58] 2007	Hytrin vs terazosin	43 (63)/6 wk of each with washout (dose change allowed at week 2)	Open-label RCT with crossover	Outpatients with BPH (non-US)	3	Improvements in urine flow and quality of life indices in both; statistically nonsignificant differences in effects on BP, HR, CBC, symptom scales (*P* > .05)	Generic manufacturer

Kesselheim AS, JAMA 2008

Efficacia Terapeutica e Sicurezza

Studi coinvolgenti i Farmaci a stretto Indice Terapeutico

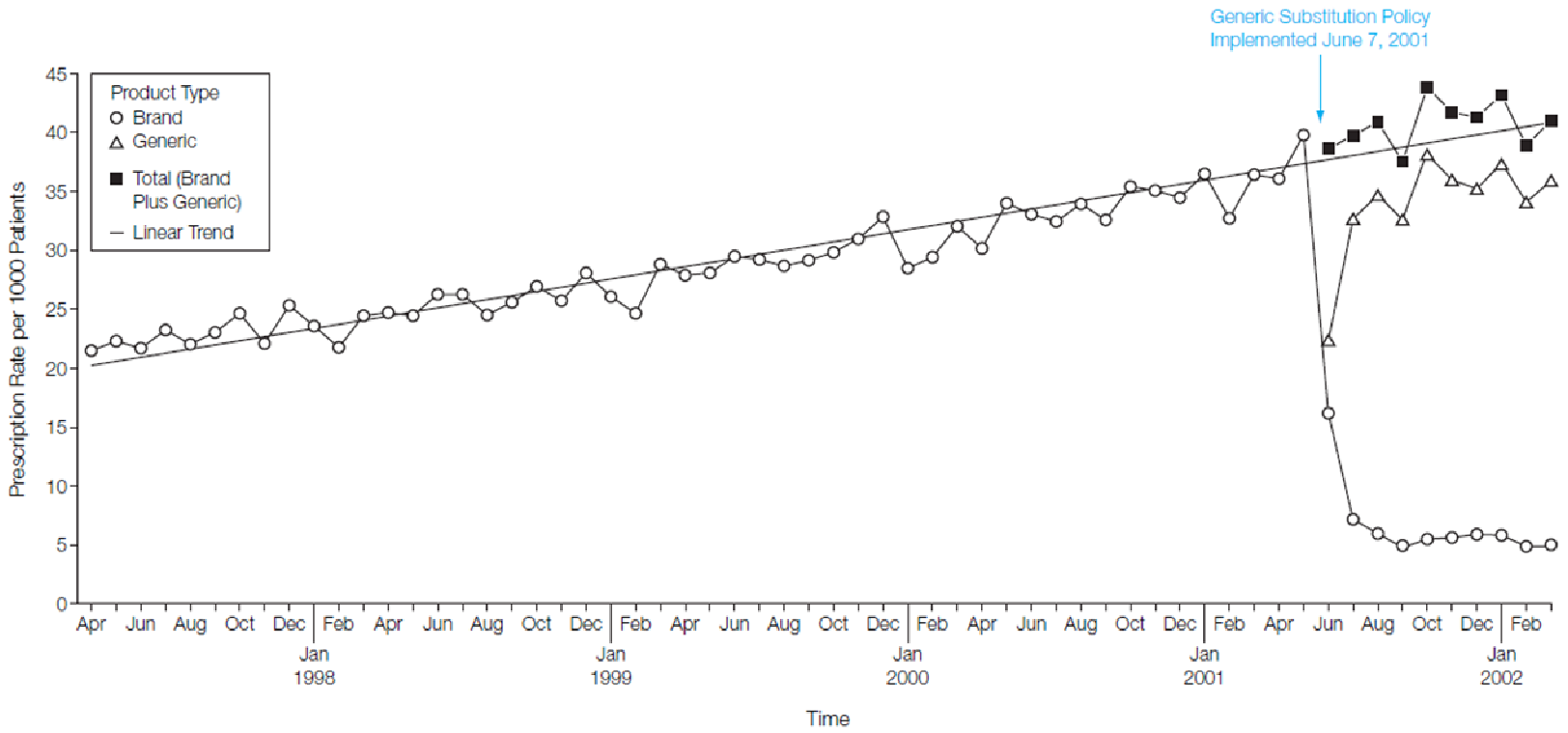
Source	Drugs Studied[a]	No. of Patients (Age Mean or Range, y)/Duration	Study Design	Population (Setting)	Jadad or Newcastle Ottawa Score[b]	Results	Source of Funding
				Antiarrhythmic Agents			
Amit et al,[59] 2004	Rythmex vs propafenone	119 (65)/18 mo	Retrospective cohort study (pre/post design without concurrent controls)	Patients with atrial fibrillation stable while receiving brand for ≥18 mo switched to generic (non-US)	4	Generic use associated with slight reduction in total ED discharges and ED visits for chest pain ($P < .01$); no significant differences in clinic visits, admissions, cardioversions, and rate of use of other cardiovascular medications ($P > .05$)	Generic manufacturer
Kasmer et al,[60] 1987	Pronestyl vs procainamide	10 (62)/6 doses of each separated by 1 wk of prior therapy	Bioequivalence study: single-blind RCT with crossover	Patients with ventricular dysrhythmias (US)	1	No significant change in type or frequency of VPBs on telemetry ($P > .05$)	Generic manufacturer, National Institutes of Health
				Warfarin Anticoagulant			
Handler et al,[61] 1998	Coumadin vs warfarin	57 (71)/4 wk of Coumadin and then 8 wk of warfarin vs 4 wk of warfarin and then 8 wk of Coumadin	Double-blind RCT with crossover	Outpatients with arrhythmia (US)	5	No significant differences in INR ($P = .40$), dose adjustments, adverse events ($P > .05$)	Generic manufacturer
Pereira et al,[62] 2005	Coumadin vs warfarin	7 (63)/Five 3-wk periods of each	Double-blind RCT with crossover	Outpatients with indications for anticoagulation (US)	4	No significant differences in INR measurements or variation ($P = .98$)	Not listed
Patterson et al,[63] 2006	Coumadin vs 1 of 2 versions of warfarin	36 724 (≥66)/40 mo before, 1 mo of transition, and 9 mo following switch	Population-based, cross-sectional time-series analysis	Elderly outpatients with numerous indications for anticoagulation taking Coumadin (non-US)	5	No significant differences in INR testing ($P = .93$) or hospitalization for hemorrhage ($P = .89$) or thromboembolism ($P = .97$)	Government
Lee et al,[64] 2005	Coumadin vs warfarin	35 (52)/4 wk of Coumadin and then 8 wk of warfarin vs 4 wk of warfarin and then 8 wk of Coumadin	Single-blind RCT with crossover	Patients with mechanical heart valves who received Coumadin for ≥2 mo (non-US)	3	Dose changes were rare; no significant differences in pooled INRs or frequency of adverse effects ($P > .05$)	Unknown
Halkin et al,[65] 2003	Coumadin vs warfarin	975 (70)/6 mo before and 6 mo after switch	Retrospective observational study (pre/post design)	Outpatients with numerous indications for anticoagulation taking Coumadin (non-US)	5	After the switch, INR values were lower and warfarin doses prescribed were higher, especially in those who were subtherapeutic when receiving Coumadin ($P < .01$)	Not listed
Witt et al,[66] 2003	Coumadin vs warfarin	2299 (69)/3 mo before and 3 mo after switch	Retrospective cohort study	Outpatients with numerous indications for anticoagulation taking Coumadin (US)	4	More INR values below therapeutic range with generic ($P < .001$); overall average INR decreased by 0.13 after switch; no significant differences in hospitalizations, ED use, outcomes (bleeding or thromboembolism)	Not listed
				Warfarin Anticoagulant			
Milligan et al,[67] 2002	Coumadin vs warfarin	182 (75)/6 mo before and 10 mo after switch	Retrospective cohort study	Outpatients with numerous indications for anticoagulation taking Coumadin (US)	5	No significant differences in INR ($P = .3$), dose adjustments ($P = .41$), adverse events	Insurance company
Weibert et al,[68] 2000	Coumadin vs warfarin	113 (70)/4 wk before and 10 wk after switch	Multicenter double-blind RCT with crossover	Outpatients with atrial fibrillation who received Coumadin for 1 mo (US)	4	No significant differences in daily dose (<0.5 mg/d), average INR difference ($P < .08$), adverse events ($P = .24$ for hemorrhagic)	Generic manufacturer
Swenson and Fundak,[69] 2000	Coumadin vs warfarin	210 (78)/6 wk	Prospective observational cohort study	Outpatients with indications for anticoagulation receiving Coumadin for ≥3 mo switched to warfarin (US)	6	No significant differences in INR between groups ($P = .15$); changes in INR of > 1.0 were rare; no adverse effects or adverse events	Not listed
Neutel and Smith,[70] 1998	Coumadin vs warfarin	39 (70)/3 wk of Coumadin and then 6 wk of warfarin vs 3 wk of warfarin and then 6 wk of Coumadin	Single-blind RCT with crossover	Outpatients with arrhythmia stably treated with Coumadin for 6 wk (US)	2	Changes in INR after switching were small and not significant ($P > .05$); no differences in adverse effect profiles between drugs	Not listed
Richton-Hewett et al,[71] 1988[c]	Coumadin vs warfarin	55 (57)/3 mo of warfarin and then 4 mo of Coumadin	Retrospective cohort study	Outpatients with indications for anticoagulation switched to warfarin in a single hospital (US)	5	Higher rate of INR out of range ($P < .001$), dose changes ($P < .05$), clinic utilization ($P < .03$) with generic group; no significant differences in morbidity/mortality	Not listed

Kesselheim AS, JAMA 2008

RESEARCH LETTER

Clinical Consequences of Generic Warfarin Substitution: An Ecological Study

Figure 1. Rate of Prescription for Warfarin by Product Type Among Patients Aged 66 Years and Older in Ontario



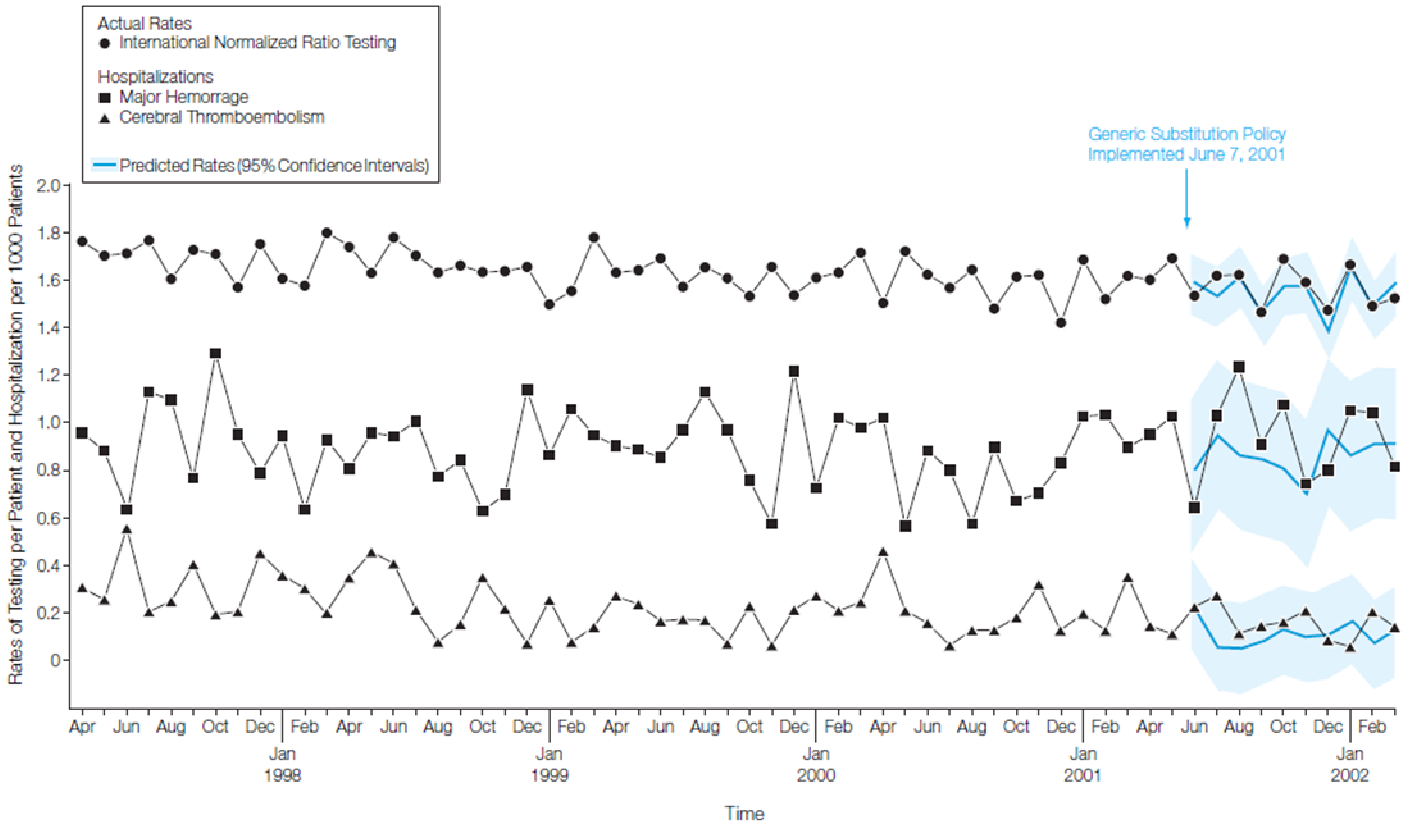
Dashed line indicates a linear trend line fit using the method of least squares.

JAMA, October 25, 2006

RESEARCH LETTER

Clinical Consequences of Generic Warfarin Substitution: An Ecological Study

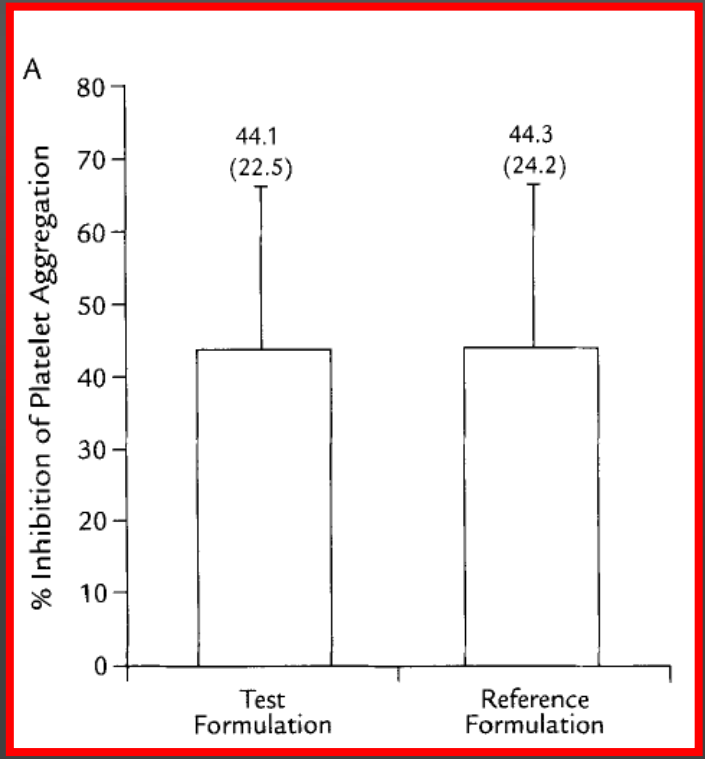
Figure 2. Rates of International Normalized Ratio Testing and Hospital Admission for Major Hemorrhage and Cerebral Thromboembolism Among Patients Treated With Warfarin



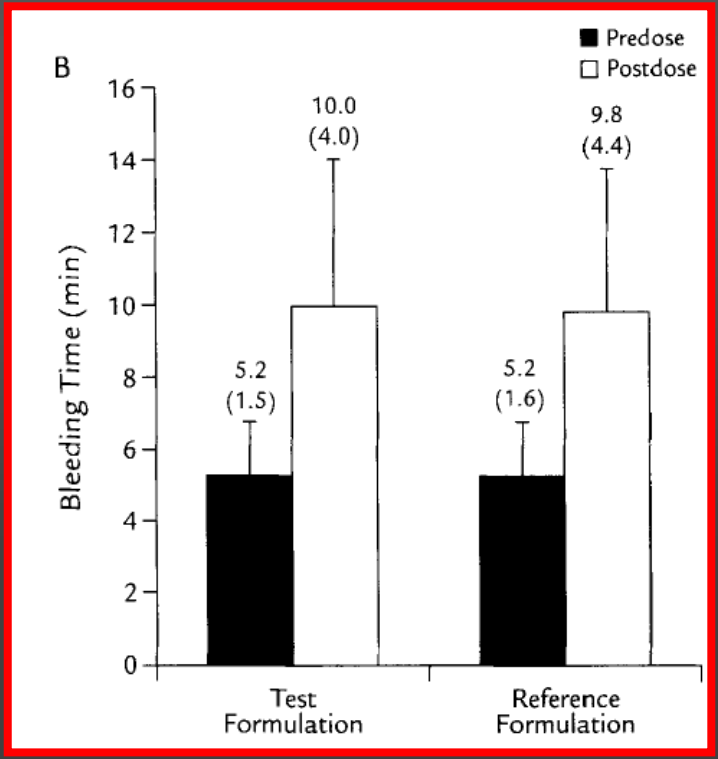
JAMA, October 25, 2006

Comparison of Effects of Two Different Formulations of Clopidogrel Bisulfate Tablets on Platelet Aggregation and Bleeding Time in Healthy Korean Volunteers: A Single-Dose, Randomized, Open-Label, 1-Week, Two-Period, Phase IV Crossover Study

Mean percent inhibition of plt aggregation after 7 days' administration of the test and the reference formulation



Changes in bleeding time afterafter 7 days' administration of the test and the reference formulation



Clinical Therapeutics/Volume 32, Number 9, 2010

Efficacia Terapeutica e Sicurezza

Amiodarone-induced thyroid dysfunction: brand-name versus generic formulations

Meytal A. Tsadok PhD, Cynthia A. Jackevicius PharmD MSc, Elham Rahme PhD, Vidal Essebag MD PhD, Mark J. Eisenberg MD MPH, Karin H. Humphries DSc, Jack V. Tu MD PhD, Hassan Behlouli PhD, Jennifer Joo BS, Louise Pilote MD PhD

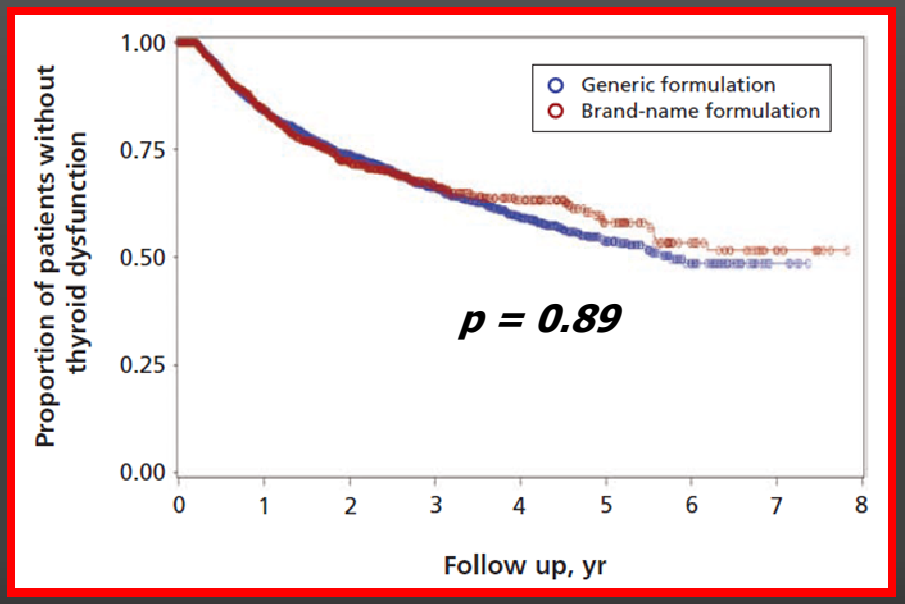


Table 3: Outcomes related to thyroid dysfunction among patients using brand-name and generic formulations of amiodarone

Variable or outcome	Brand name (n = 2804)	Generic (n = 6278)	p value*
Length of follow-up, y, mean ± SD	1.2 ± 0.2	1.3 ± 0.2	0.008
Patients with disorders of the thyroid, %	16.8	17.9	0.22
Hypothyroidism, %†	15.8	16.6	0.35
Hyperthyroidism, %†	2.6	2.5	0.75
Total rate of thyroid dysfunction, per 100 person-years	14.1	14.1	0.98
Hypothyroidism, per 100 person-years†	13.1	12.8	0.77
Hyperthyroidism, per 100 person-years†	1.9	1.6	0.40

Note: SD = standard deviation
*Continuous data were compared using Student t tests, and categorical data were compared using χ^2 tests.
†Some patients had both hypothyroidism and hyperthyroidism.

Meytal Tsadok et al. CMAJ 2011

Il farmaco equivalente nella pratica clinica. I risultati di una *survey* in area cardiovascolare presso cooperative di Medici di Medicina Generale

Obiettivo del lavoro: L'obiettivo del presente lavoro è stato quello di raccogliere, in modo consecutivo per due semestri di osservazione (2010 e 2011), le variabili cliniche e strumentali comunemente correlate all'area cardiovascolare e metabolica unite a quelle consistenti con la diagnosi della stessa, di pazienti assistiti presso un gruppo di ricercatori Medici di Medicina Generale - MMG. Questo al fine di valutare in pratica clinica eventuali differenze di outcome clinico ed economico tra farmaci con il brevetto (In patent) vs. farmaci a brevetto scaduto (Off patent) ed all'interno dell'Off patent fra brand ed unbranded.

Materiali e metodi: 50 MMG ricercatori, aderenti all'area-ricerca "MySearch" del Consorzio Sanità - Co.S, nell'arco di 18 mesi lavorativi (nei periodi da gennaio 2010 a giugno 2010 e da gennaio 2011 a giugno 2011) hanno arruolato 613 pazienti che si sono rivolti all'ambulatorio, utilizzatori di statine ad entrambe le rilevazioni, ed affetti da patologia cardiovascolare e metabolica (CCV e DM). Per individuare le eventuali differenze statisticamente significative tra il gruppo dei pazienti trattati con farmaco In patent e quello degli Off patent e tra il sottogruppo Off patent Brand vs. generico puro è stato impiegato il test $\chi 2$ che si basa sulla statistica di chiquadro e sulla sua relativa distribuzione di probabilità; il livello di significatività considerato è stato quello convenzionale dello 0,05%.

Risultati: Tra i gruppi di pazienti all'arruolamento (farmaci In patent vs. farmaci Off patent) e nel sottogruppo Off patent brand vs. generico puro, non si riscontrano differenze statisticamente significative per età, per sesso e per diagnosi principale. Dopo sei mesi di osservazione non si rilevano nei gruppi di osservazione differenze statisticamente significative negli esiti clinici; questo sia nel gruppo dei pazienti trattati con farmaco In patent vs. Off patent che nel confronto diretto tra pazienti trattati con Off patent Brand vs. generico puro. Le principali variabili cliniche impiegate in medicina generale nel controllo e monitoraggio dei pazienti non appaiono diverse in funzione della tipologia di trattamento somministrato nei gruppi di osservazione.

Conclusioni: La sostanziale sovrapponibilità dei parametri clinici all'arruolamento e al termine del periodo di osservazione suggerisce che l'impiego esclusivo di farmaci Off patent in medicina generale avrebbe consentito un risparmio del 38% dei costi complessivi a carico del SSN, aumentando potenzialmente il numero di pazienti trattati, senza sostanziali modifiche degli indicatori di esito clinico. L'impiego di farmaci generici puri avrebbe inoltre consentito un ulteriore risparmio di spesa a carico del cittadino. Alla luce dell'analisi proposta, il farmaco generico puro appare un'opportunità terapeutica di elezione in funzione degli esiti clinici e delle ricadute economiche sia per il SSN sia per il cittadino.

Aronica, et al. ClinicoEconomics - Italian Articles on Outcomes Research, 2011:6

Risultati indicatori di esito intermedio: confronto in Patent vs. Off Patent

Area cardiovascolare e metabolica	Periodo					
	I sem 2010			I sem 2011		
	Numero Pazienti					
CCV (HBP - CHD - STROKE - DM)	In Patent	Off Patent	p	In Patent	Off Patent	p
PA sis 120-140	55	60	0,98	68	74	0.69
PA sis 141-160	21	22		25	35	
PA sis mag 160	5	6		8	8	
PA dia 80-89	29	43	0,68	45	56	0,06
PA dia 90-99	5	7		14	9	
PA dia mag 100	5	2		0	4	
Col. Tot min 201	97	104	0,81	87	96	0,66
Col. Tot mag 200	34	39		32	40	
Col. HDL min 31	1	2	0,61	4	6	0,63
Col. HDL mag 30	127	136		117	128	
Glicemia min 126	91	108	0,44	95	110	0,77
Glicemia mag 125	47	46		31	39	
Microalbuminuria min 31	51	60	0,01	55	58	0,9
Microalbuminuria mag 30	12	3		13	13	
Creatinina min 1.6	105	110	0,89	103	121	0,72
Creatinina mag 1.5	8	9		11	15	
eGFR min 61	64	63	0,62	61	73	0,9
eGFR mag 60	48	54		51	59	

Aronica, et al. ClinicoEconomics - Italian Articles on Outcomes Research, 2011:6

Risultati indicatori di esito intermedio: confronto Off Patent Brand vs. Off Patent generici

Area cardiovascolare e metabolica	Periodo					
	I sem 2010			I sem 2011		
	Numero Pazienti					
CCV (HBP - CHD - STROKE - DM)	Off P. Brand	Off P. Gen.	p	Off P. Brand	Off P. Gen.	p
PA sis 120-140	36	24	0,46	48	26	0,74
PA sis 141-160	15	7		20	15	
PA sis mag 160	5	1		5	3	
PA dia 80-89	29	14	0,40	36	20	0,91
PA dia 90-99	6	1		6	3	
PA dia mag 100	2	0		3	1	
Col. Tot min 201	71	33	0,30	64	32	0,07
Col. Tot mag 200	23	16		20	20	
Col. HDL min 31	1	1	0,68	3	3	0,51
Col. HDL mag 30	87	49		81	47	
Glicemia min 126	73	35	0,77	72	38	0,20
Glicemia mag 125	30	16		21	18	
Microalbuminuria min 31	41	19	0,95	37	21	0,50
Microalbuminuria mag 30	2	1		7	6	
Creatinina min 1.6	71	39	0,90	70	51	0,25
Creatinina mag 1.5	6	3		11	4	
eGFR min 61	41	22	0,86	44	29	0,92
eGFR mag 60	36	18		35	24	

Aronica, et al. ClinicoEconomics - Italian Articles on Outcomes Research, 2011:6

Risultati: analisi dei costi e considerazioni farmacoeconomiche

	I sem 2010			I sem 2011			12 mesi
	In Patent	Off Patent	TOTALE	In Patent	Off Patent	TOTALE	TOTALE
Totale pazienti	279	334	613	282	331	613	
Giorni trattamento	180			180			
Costo trattamento per DDD (statine)	€ 1,16	€ 0,50		€ 1,16	€ 0,50		
Costo a carico del SSN	€ 58.255,20	€ 30.060,00	€ 88.315,20	€ 58.881,60	€ 29.790,00	€ 88.671,60	€ 176.986,80
Potenziale spesa per il SSN (100% farmaci off patent)			€ 55.170,00			€ 55.170,00	€ 110.340,00
Potenziale risparmio per il SSN (100% farmaci off patent)			€ 33.145,20			€ 33.501,60	€ 66.646,80

Aronica, et al. ClinicoEconomics - Italian Articles on Outcomes Research, 2011:6

Analisi dell'efficacia della terapia farmacologica con farmaci generici e farmaci branded in sette aree terapeutiche prevalenti attraverso l'utilizzo di indicatori surrogati

Un'analisi sui Database Amministrativi di 5 ASL Lombarde

GENERICI *vs* BRANDED

Lo studio utilizza i dati estratti dagli archivi sanitari automatizzati di 5 ASL della Regione Lombardia:

L'OBIETTIVO DELLO STUDIO E' QUELLO DI CONFRONTARE L'EFFICACIA DEI FARMACI GENERICI CON I FARMACI BRANDED ATTRAVERSO L'UTILIZZO DI INDICATORI SURROGATI.

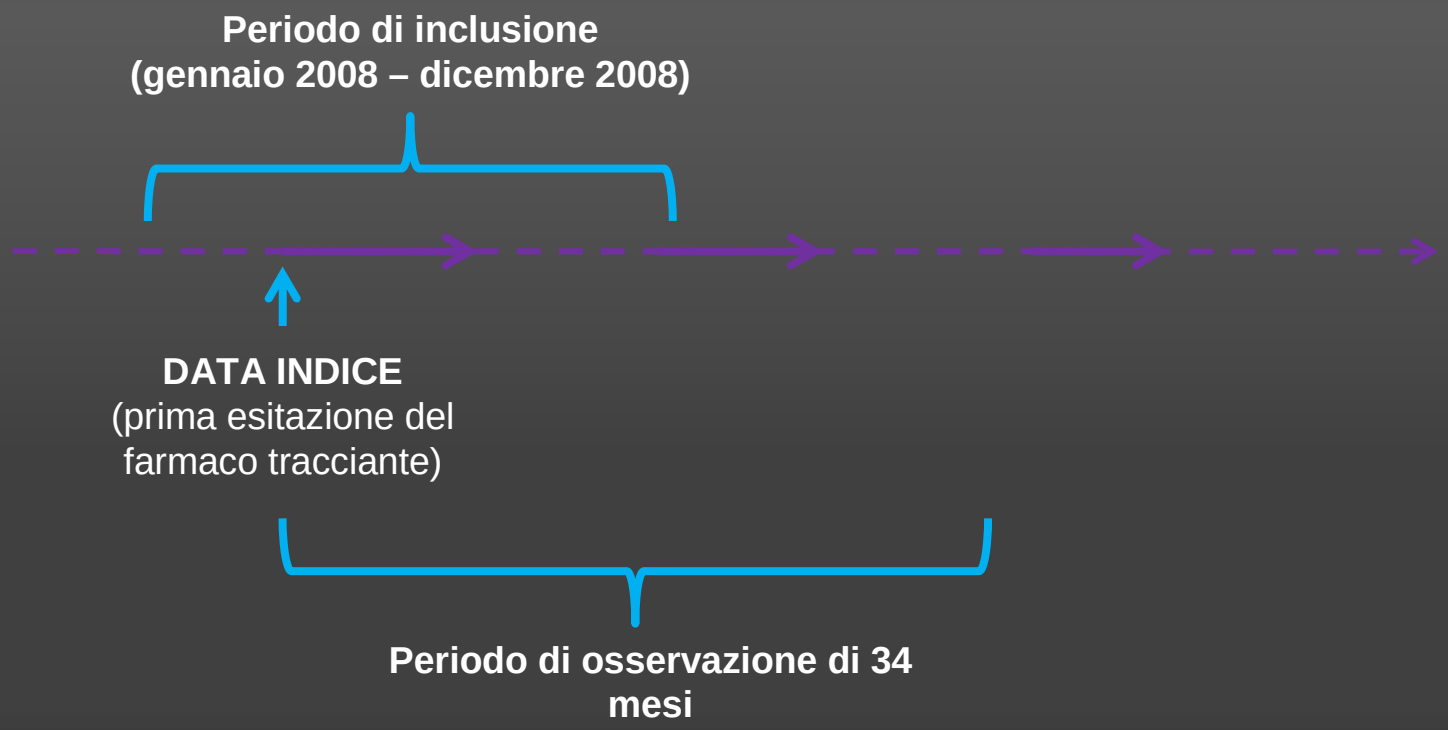
Questo strumento è stato disegnato per 6 aree terapeutiche dal seguente Board Scientifico:

DIABETE	*Prof. Trevisan (Bergamo)*
IPERTENSIONE	*Prof. Agabiti Rosei (Brescia)*
DISLIPIDEMIA	*Prof. Catapano (Milano)*
PSICHIATRIA	*Prof. Mencacci (Milano)*
CARDIOLOGIA	*Prof. Margonato (Milano)*
REUMATOLOGIA	*Prof. Montecucco (Pavia)*
FARMACOECONOMIA	*Prof. Colombo (Pavia)*

COORTI

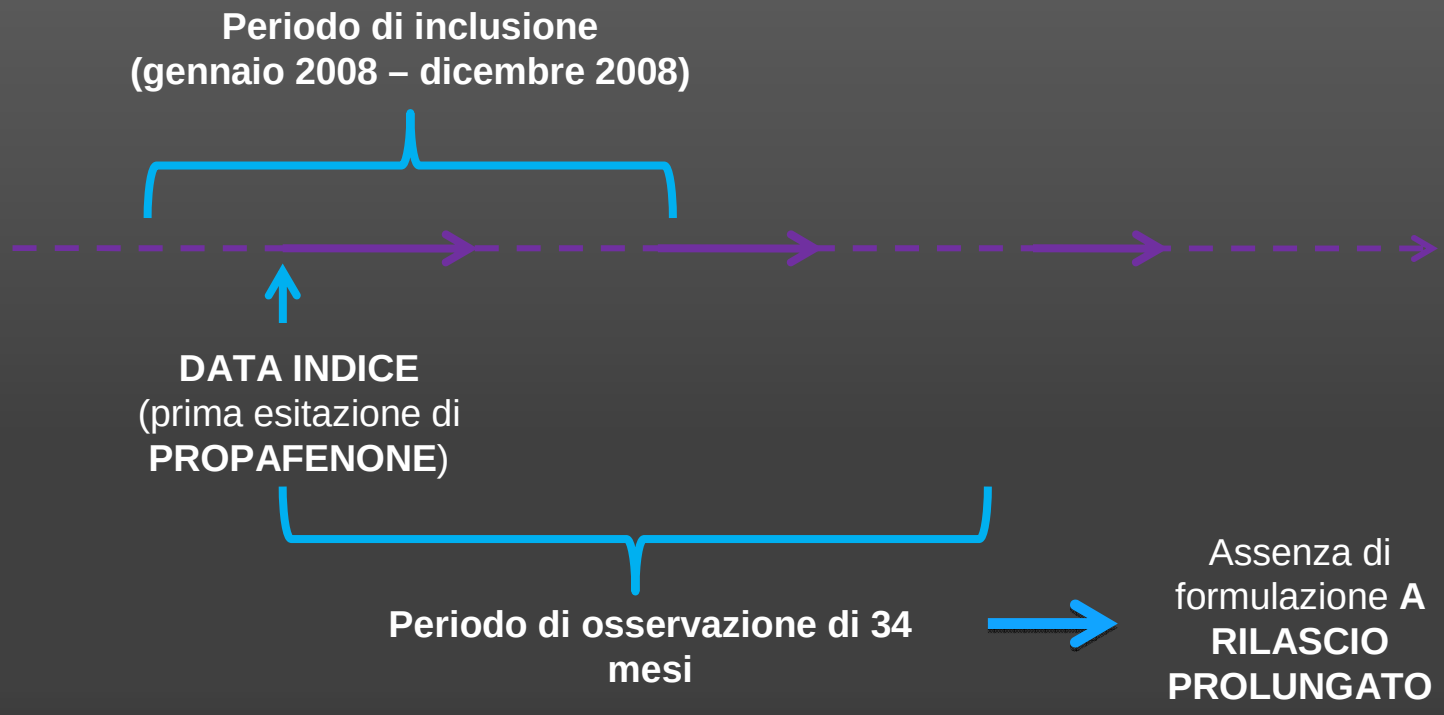
Criteri di Selezione dei Pazienti

Tutti i pazienti che abbiano ricevuto almeno una esitazione del FARMACO TRACCIANTE da gennaio 2008 a dicembre 2008.



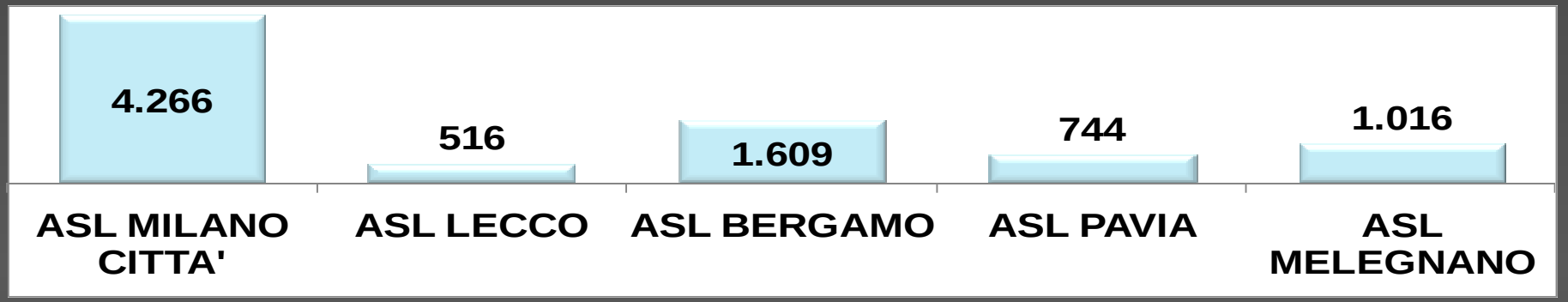
Criteri di Selezione dei Pazienti -CARDIOLOGIA

Tutti i pazienti che abbiano ricevuto almeno una esitazione di PROPAFENONE da gennaio 2008 a dicembre 2008 e senza la formulazione A RILASCIO PROLUNGATO per tutto il periodo di osservazione.



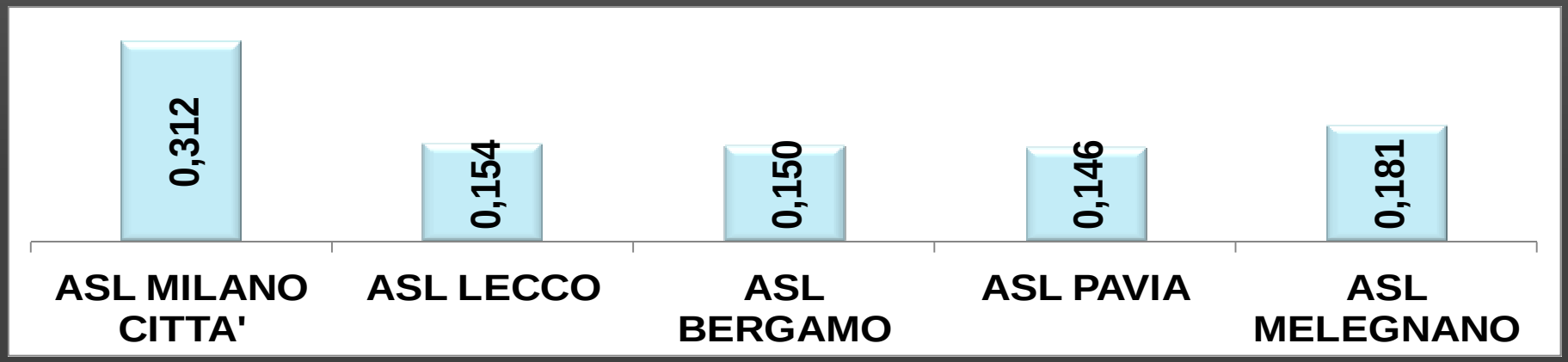
Caratteristiche della Coorte: CARDIOLOGIA

Numerosità della Coorte



Pazienti totali: **8.151**

Prevalenza della Coorte

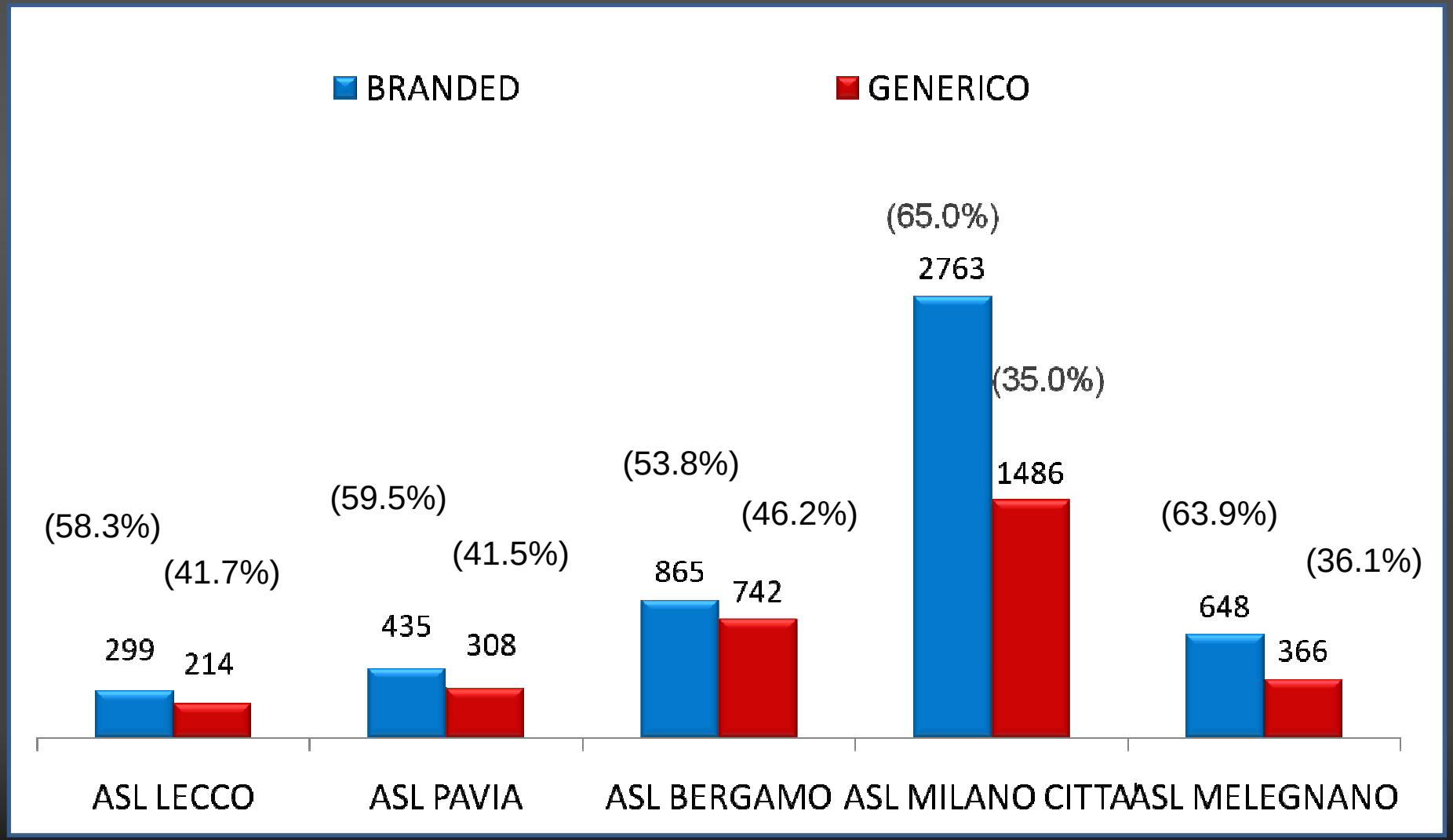


Significatività della prevalenza:

Chi-quadro < 0.0001

CARDIOLOGIA - PROPAFENONE

Numerosità delle Coorti



CARDIOLOGIA - PROPAFENONE

Parametri Analizzati

- Persistenza
- Compliance
- Ospedalizzazione
- Mortalità
- Visite specialistiche
- Sostituibilità

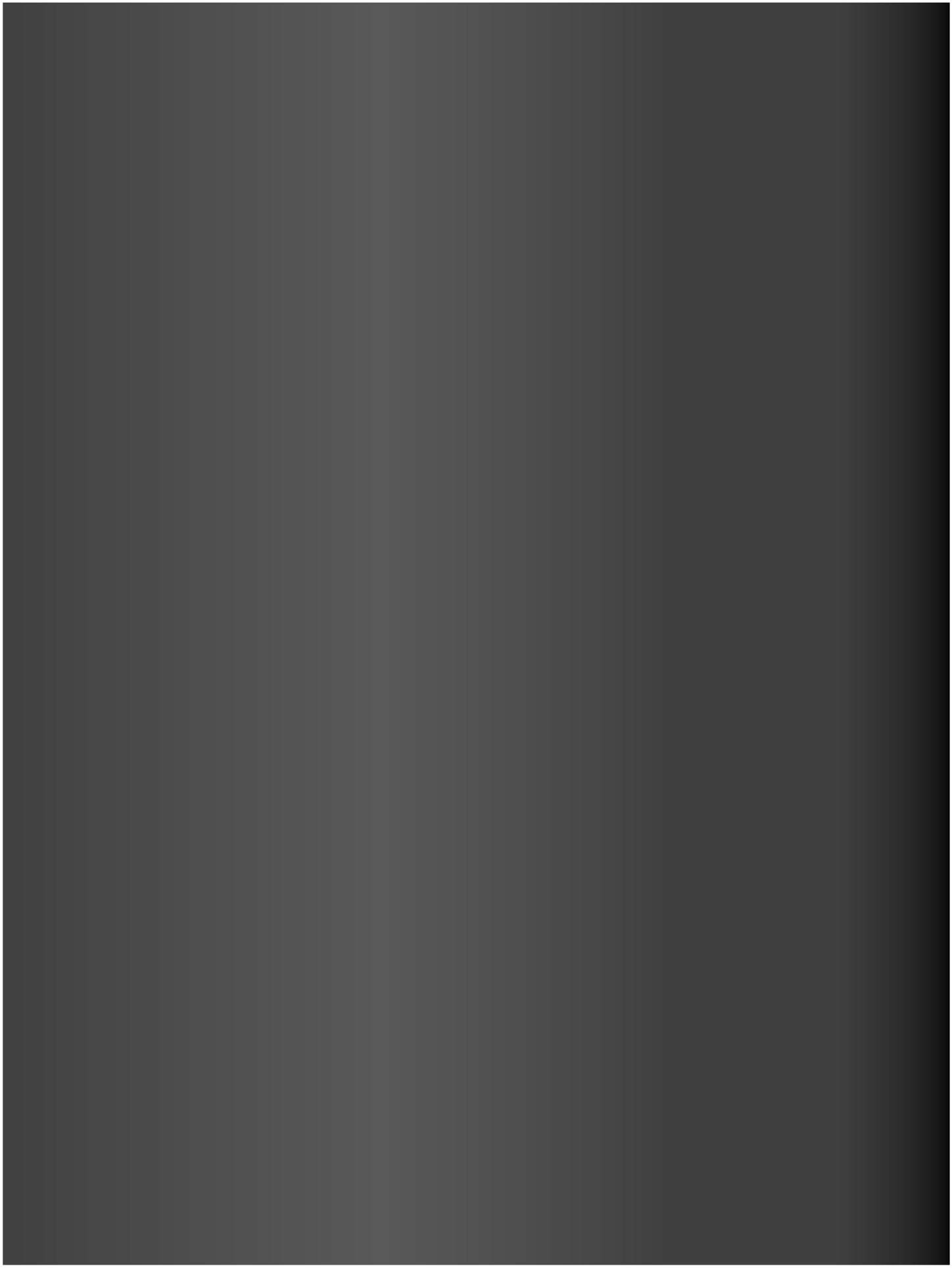
Conclusioni

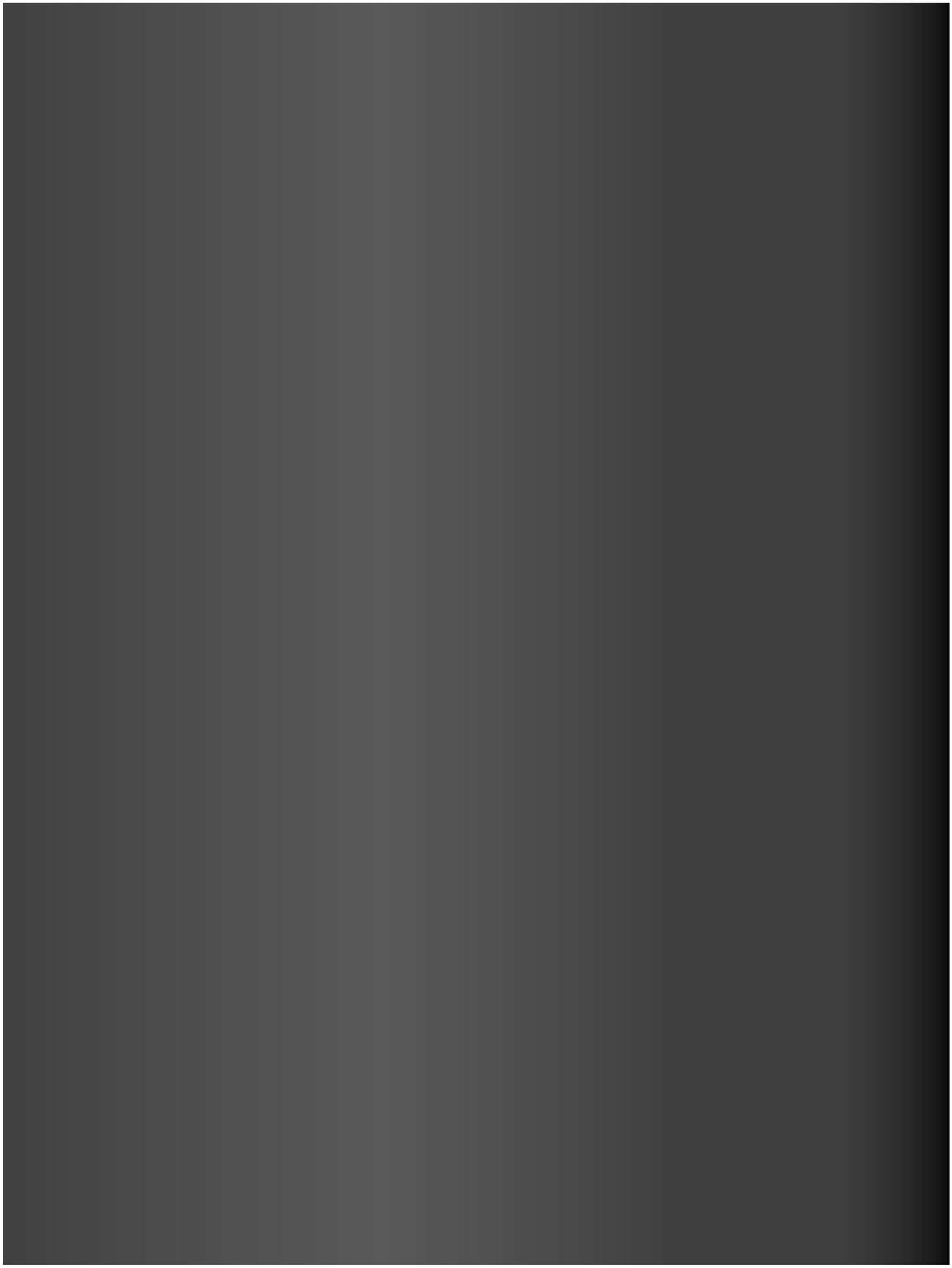
- I farmaci generici usati in ambito cardiovascolare hanno la stessa efficacia e sono ugualmente sicuri perché sottoposti agli stessi controlli a cui sono soggetti tutti i farmaci in commercio

- La valenza economica del medicinale generico è un fattore molto importante poichè permette notevoli risparmi sia ai cittadini che al Servizio Sanitario Nazionale comportando inoltre un aumento dell'aderenza terapeutica

- E' utile convincere prima di tutto i medici, ed in seconda istanza anche i pazienti, di potersi "fidare" nell'utilizzare i farmaci generici , con qualche cautela in più per i farmaci a stretto range terapeutico

- In particolare, sarebbe preferibile usare sempre lo stesso sostituto, così la farmacocinetica diventa quantomeno prevedibile per lo stesso farmaco





PERSISTENZA

Definizione di Persistenza: continuazione della terapia per il periodo di tempo consigliato.

PERSISTENZA

I GAP utilizzati sono:

DIABETE	*90 gg*
IPERTENSIONE	*90 gg*
DISLIPIDEMIA	*30 gg*
PSICHIATRIA	*30 gg*
CARDIOLOGIA	*30 gg*
REUMATOLOGIA	*60 gg*

CARDIOLOGIA – PROPAFENONE

	Persistenza							
	Tipologia	N	Mean	Median	SD	Min	Max	p-value (Wilcoxon)
ASL LECCO	Branded	48	271.7	62.5	360.4	15.0	1066.0	N.S.
	Generico	15	137.5	60.0	133.1	15.0	375.0	
ASL PAVIA	Branded	52	213.9	60.0	339.4	15.0	1031.0	N.S.
	Generico	39	214.9	89.0	290.3	15.0	1037.0	
ASL BERGAMO	Branded	113	291.9	99.0	373.6	15.0	1070.0	N.S.
	Generico	80	274.0	84.0	361.4	15.0	1093.0	

GAP : 30

CARDIOLOGIA – PROPAFENONE

	Persistenza							
	Tipologia	N	Mean	Median	SD	Min	Max	p-value (Wilcoxon)
ASL MILANO CITTA'	Branded	470	197.1	60.0	287.8	15.0	1113.0	N.S.
	Generico	157	230.4	81.0	314.5	15.0	1112.0	
ASL MELEGNANO	Branded	122	283.0	89.5	365.3	15.0	1106.0	N.S.
	Generico	37	264.9	105.0	328.1	15.0	1037.0	

GAP : 30

COMPLIANCE

Definizione di Compliance: assunzione del farmaco ai dosaggi indicati.

CARDIOLOGIA – MPR M1

	Tipologia	N	Mean	Median	SD	Min	Max	P-value (Wilcoxon)
LECCO	Branded	403	0.87	1.00	0.23	0.02	1.00	N.S.
	Generico	304	0.86	1.00	0.23	0.04	1.00	
PAVIA	Branded	593	0.83	1.00	0.25	0.03	1.00	N.S.
	Generico	471	0.86	1.00	0.23	0.02	1.00	
BERGAMO	Branded	197	0.46	0.34	0.38	0.01	1.00	N.S.
	Generico	191	0.52	0.45	0.37	0.01	1.00	
MILANO CITTA'	Branded	3758	0.82	1.00	0.26	0.01	1.00	0.0035
	Generico	2331	0.85	1.00	0.24	0.03	1.00	
MELEGNANO	Branded	1050	0.87	1.00	0.22	0.03	1.00	0.0001
	Generico	707	0.91	1.00	0.18	0.03	1.00	

CARDIOLOGIA – MPR M2

	Tipologia	N	Mean	Median	SD	Min	Max	P-value (Wilcoxon)
LECCO	Branded	48	0.71	0.94	0.34	0.02	1.00	N.S.
	Generico	15	0.65	0.74	0.36	0.08	1.00	
PAVIA	Branded	52	0.66	0.69	0.34	0.02	1.00	N.S.
	Generico	39	0.67	0.75	0.34	0.03	1.00	
BERGAMO	Branded	113	0.71	0.88	0.34	0.03	1.00	N.S.
	Generico	80	0.70	0.84	0.32	0.04	1.00	
MILANO CITTA'	Branded	470	0.62	0.70	0.35	0.02	1.00	N.S.
	Generico	157	0.67	0.75	0.33	0.01	1.00	
MELEGNANO	Branded	122	0.72	0.93	0.33	0.03	1.00	0.0365
	Generico	37	0.83	1.00	0.28	0.03	1.00	

OSPEDALIZZAZIONE

Indicatore 1: Numero medio di ricoveri ordinari o day hospital

Indicatore 2: Numero pazienti con ricovero ordinario o day hospital

OSPEDALIZZAZIONE

Sono stati considerati i pazienti persistenti per almeno:

DIABETE	*6 mesi*
IPERTENSIONE	*6 mesi*
DISLIPIDEMIA	*1 anno*
PSICHIATRIA	*6 mesi*
CARDIOLOGIA	*1 anno*
REUMATOLOGIA	*6 mesi*

CARDIOLOGIA - PROPAFENONE

Numero medio di ricoveri ordinari

OSPEDALIZZAZIONE

	Tipologia	N	Mean	Median	SD	Min	Max	P-value (Wilcoxon)
ASL LECCO	Branded	7	1.14	1.00	0.37	1.00	2.00	N.S.
	Generico	4	1.50	1.00	1.00	1.00	3.00	
ASL PAVIA	Branded	11	1.00	1.00	-	1.00	1.00	N.S.
	Generico	11	1.09	1.00	0.30	1.00	2.00	
ASL BERGAMO	Branded	32	1.21	1.00	0.49	1.00	3.000	N.S.
	Generico	32	1.15	1.00	0.36	1.00	2.00	

CARDIOLOGIA - PROPAFENONE

Numero medio di ricoveri ordinari

OSPEDALIZZAZIONE

	Tipologia	N	Mean	Median	SD	Min	Max	P-value (Wilcoxon)
ASL MILANO CITTA'	Branded	52	1.23	1.00	0.67	1.00	5.00	N.S.
	Generico	36	1.13	1.00	0.35	1.00	2.00	
ASL MELEGNANO	Branded	25	1.40	1.00	0.86	1.00	5.00	0.0209
	Generico	18	1.00	1.00	-	1.00	1.00	

CARDIOLOGIA - PROPAFENONE

Numero medio di ricoveri in day hospital

OSPEDALIZZAZIONE

	Tipologia	N	Mean	Median	SD	Min	Max	P-value (Wilcoxon)
ASL LECCO	Branded	2	1.50	1.50	0.70	1.00	2.00	N.S.
	Generico	1	1.00	1.00	.	1.00	1.00	
ASL PAVIA	Branded	3	1.00	1.00	-	1.00	1.00	N.S.
	Generico	2	1.50	1.50	0.70	1.00	2.00	
ASL BERGAMO	Branded	6	1.83	1.50	1.16	1.00	4.00	N.S.
	Generico	5	1.00	1.00	-	1.00	1.00	

CARDIOLOGIA - PROPAFENONE

Numero medio di ricoveri in day hospital

OSPEDALIZZAZIONE

	Tipologia	N	Mean	Median	SD	Min	Max	P-value (Wilcoxon)
ASL MILANO CITTA'	Branded	24	1.20	1.00	0.50	1.00	3.00	N.S.
	Generico	11	1.27	1.00	0.46	1.00	2.00	
ASL MELEGNANO	Branded	2	1.00	1.00	-	1.00	1.00	N.S.
	Generico	2	1.00	1.00	-	1.00	1.00	

CARDIOLOGIA - PROPAFENONE

Numero di pazienti con almeno un ricovero ordinario

OSPEDALIZZAZIONE

	Branded		Generico		p-value (Chi-quadro)
	N	%	N	%	
ASL LECCO	7/129	5.43	4/78	5.13	N.S.
ASL PAVIA	11/129	8.53	11/105	10.48	N.S.
ASL BERGAMO	32/293	10.92	32/299	10.70	N.S.
ASL MILANO CITTA'	52/648	8.02	36/392	9.18	N.S.
ASL MELEGNANO	25/209	11.96	18/128	14.06	N.S.

CARDIOLOGIA - PROPAFENONE

Numero di pazienti con almeno un ricovero in day hospital

OSPEDALIZZAZIONE

	Branded		Generico		p-value (Chi-quadro)
	N	%	N	%	
ASL LECCO	2/129	1.55	1/78	1.28	N.S.
ASL PAVIA	3/129	2.33	2/105	1.90	N.S.
ASL BERGAMO	6/293	2.05	5/299	1.67	N.S.
ASL MILANO CITTA'	24/648	3.70	11/392	2.81	N.S.
ASL MELEGNANO	2/209	0.96	2/128	1.56	N.S.

MORTALITA’

Indicatore: Numero pazienti deceduti

MORTALITA'

Sono stati considerati i pazienti persistenti per almeno:

DIABETE	*6 mesi*
IPERTENSIONE	*6 mesi*
DISLIPIDEMIA	*1 anno*
PSICHIATRIA	*6 mesi*
CARDIOLOGIA	*1 anno*
REUMATOLOGIA	*6 mesi*

CARDIOLOGIA - PROPAFENONE

Numero di pazienti deceduti

MORTALITA'

	Branded		Generico		p-value (Chi-quadro)
	N	%	N	%	
ASL LECCO	9/129	6.98	10/78	12.82	N.S.
ASL PAVIA	7/129	5.43	10/105	9.52	N.S.
ASL BERGAMO	24/293	8.19	38/299	12.71	N.S.
ASL MILANO CITTA'	58/648	8.95	35/392	8.93	N.S.
ASL MELEGNANO	16/209	7.66	23/128	17.97	0.0041

Grazie dell'attenzione

Un'analisi sui Database Amministrativi di 5 ASL Lombarde

PROGETTO CONSENSUS PAPER