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CENTRI PER LA DIAGNOSI
DELLA TROMBOSI E LA
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Aderenza e persistenza alle terapie anticoagulanti orali

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Dichiarazione di conflitto d'interesse

Partecipazione a Convegni come relatore e finanziamenti

1 ASPEN
2 BAYER
3 BMC Pfizer
4 NOVO Nordisk
5 Roche
5 WERFEN

Simili ?

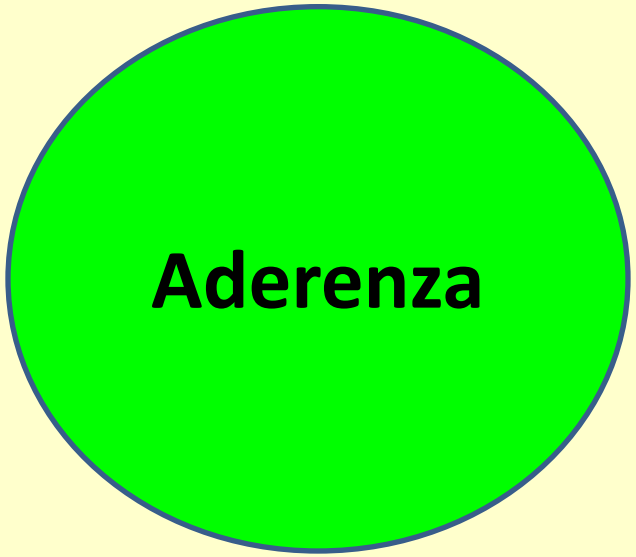
Aderenza

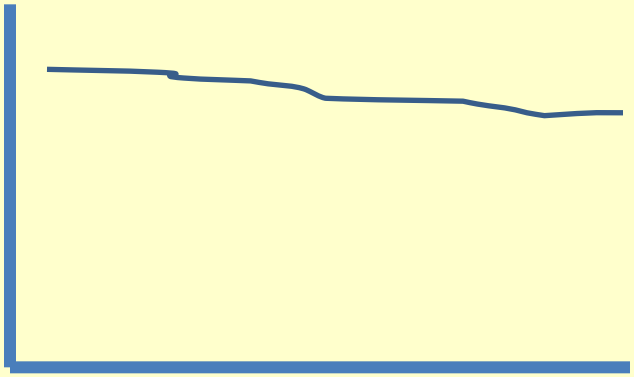
Atteggiamento cooperante da parte del paziente

Compliance

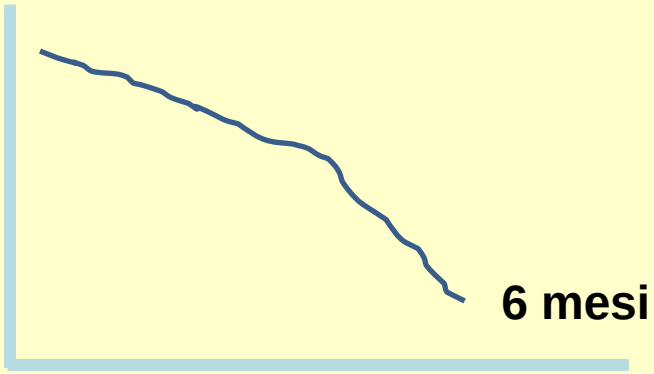
Atteggiamento passivo del paziente

In generale





Condizioni acute



Condizioni croniche

Il valore medio dell'aderenza negli studi clinici può essere elevato.

Tuttavia l'aderenza può variare molto anche negli studi clinci (43-78 %)

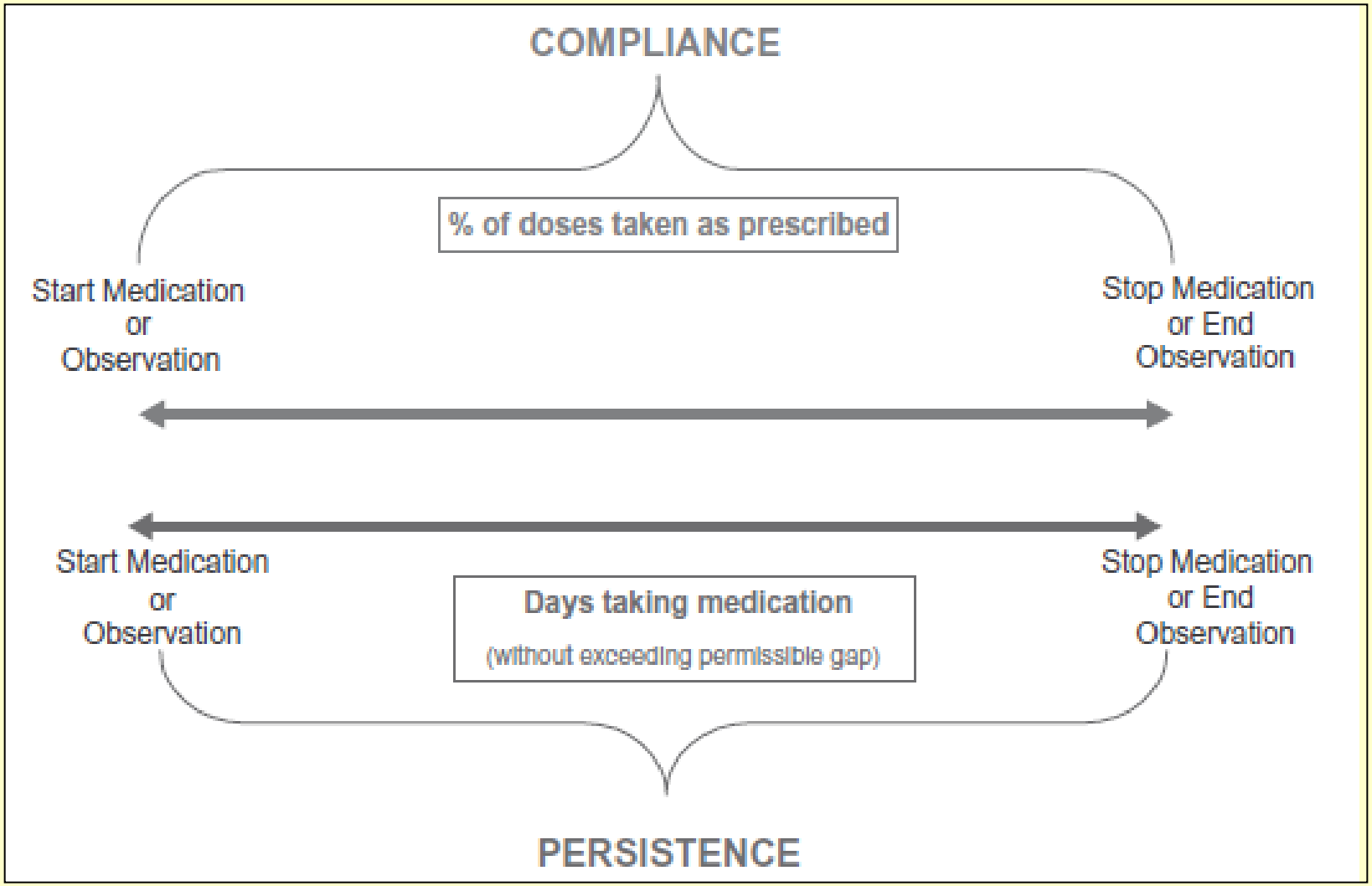
Non c'è accordo sulla percentuale.

Per alcuni l'aderenza può essere soddisfacente se non scende sotto l'80 %.

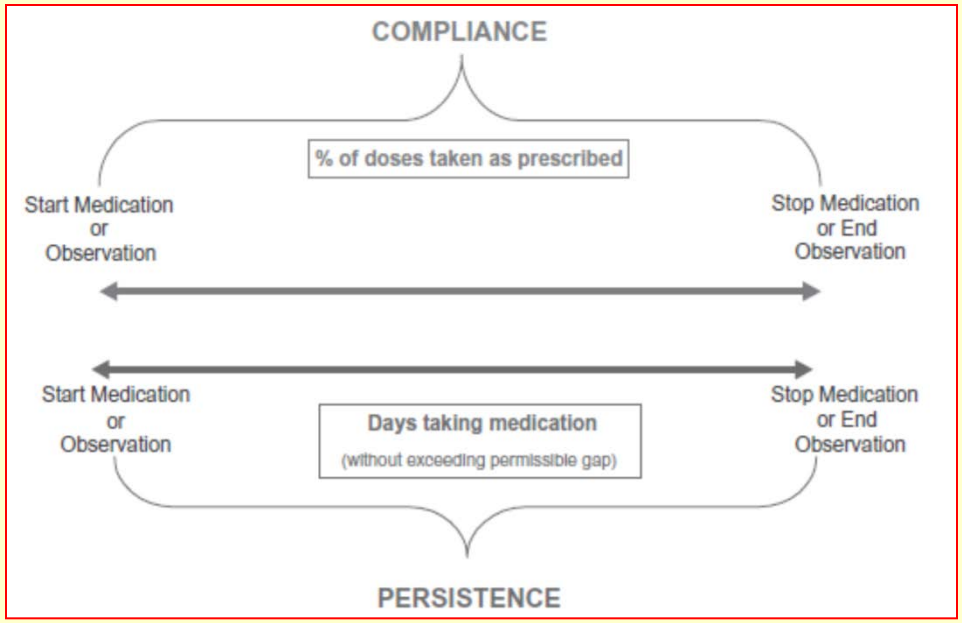
Per altri deve stare sopra il 95 %.

Differenze tra i *Clinical Trials* e la pratica quotidiana:

a) *Hawthorne effect* (sentirsi controllati)
b) Assenza di un *follow-up*
c) Comorbilità
d) Politerapia



Volume 11 • Number 1 • 2008
VA L U E I N H E A LT H



Compliance (Adherence):
timing, dosing and frequency (the extent to which the patient follows medical instructions).

Persistence:
the duration of time from starting to discontinuation of therapy.

Esempio di buona e cattiva aderenza (*compliance*)

Dom	Lun	Mar	Mer	Gio	Ven	Sab
x	x	x	x	x	x	x
x	x	x	x	x	x	x
x	x	x	x	x	x	x
x	x	x	x	x	x	x
x				x		
x		x				x
	x					
x			x	x		

Aderenza:

100 % (28/28) nelle prime 4 settimane

36 % (10/28) nelle seconde 4 settimane

Media: 68 % (28+10/56 giorni)

La scarsa aderenza è un fenomeno generale

Condizione	Aderenza
Ipertensione	26-51 %
Depressione	40-70 %
Asma	43 %
HIV	37-83 %

PDC: proportion of days covered

The PDC was defined as the number of doses dispensed in relation to the dispensing period. The numerator was based on the prescription fill dates and number of pills dispensed to determine the number of outpatient days for which each drug was supplied.

$$PDC = \left\{ \frac{\text{number of days covered}}{\text{number of days in period}} \right\} \times 100\ \%$$

PDC $\geq$ 0.80: good adherence

Non-persistence was defined as the presence of a ≥60-day gap in medication use.

28 384 patients with AF were identified; 16 036 (56.5%) had a warfarin prescription following AF hospitalization. 53.5% of warfarin users were persistent for at least 1 year, similar to other long-term medications commonly prescribed to the AF population.

42.6% of warfarin users permanently discontinued warfarin within 1 year, also consistent with the discontinuation rate of 32.9-52.0% of other long-term medications.

1 older age
2 history of ischemic stroke
3 warfarin use before hospitalization

All these figures significantly increased warfarin persistence and decreased the likelihood of discontinuation.

Adherence of od and bid medications was similar.

Am J Cardiovasc Drugs 2012;12:245-53

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Warfarin discontinuation was defined as a gap of ≥ 45 days in warfarin prescription within 1 year after initiation

A total of 27,000 patients were included

Warfarin discontinuation was significantly associated with increased risk of ischemic stroke (hazard ratio [HR]: 2.04; 95% confidence interval [CI]: 1.47-2.84.

Warfarin discontinuation: double risk for stroke

Curr Med Res Opin 2015;31:2021-9

Warfarin use and stroke risk among patients with nonvalvular atrial fibrillation in a large managed care population.

Among warfarin initiators with NVAF (N = 16,253), 51.4% discontinued warfarin therapy at least once during a mean follow-up of 668 days.

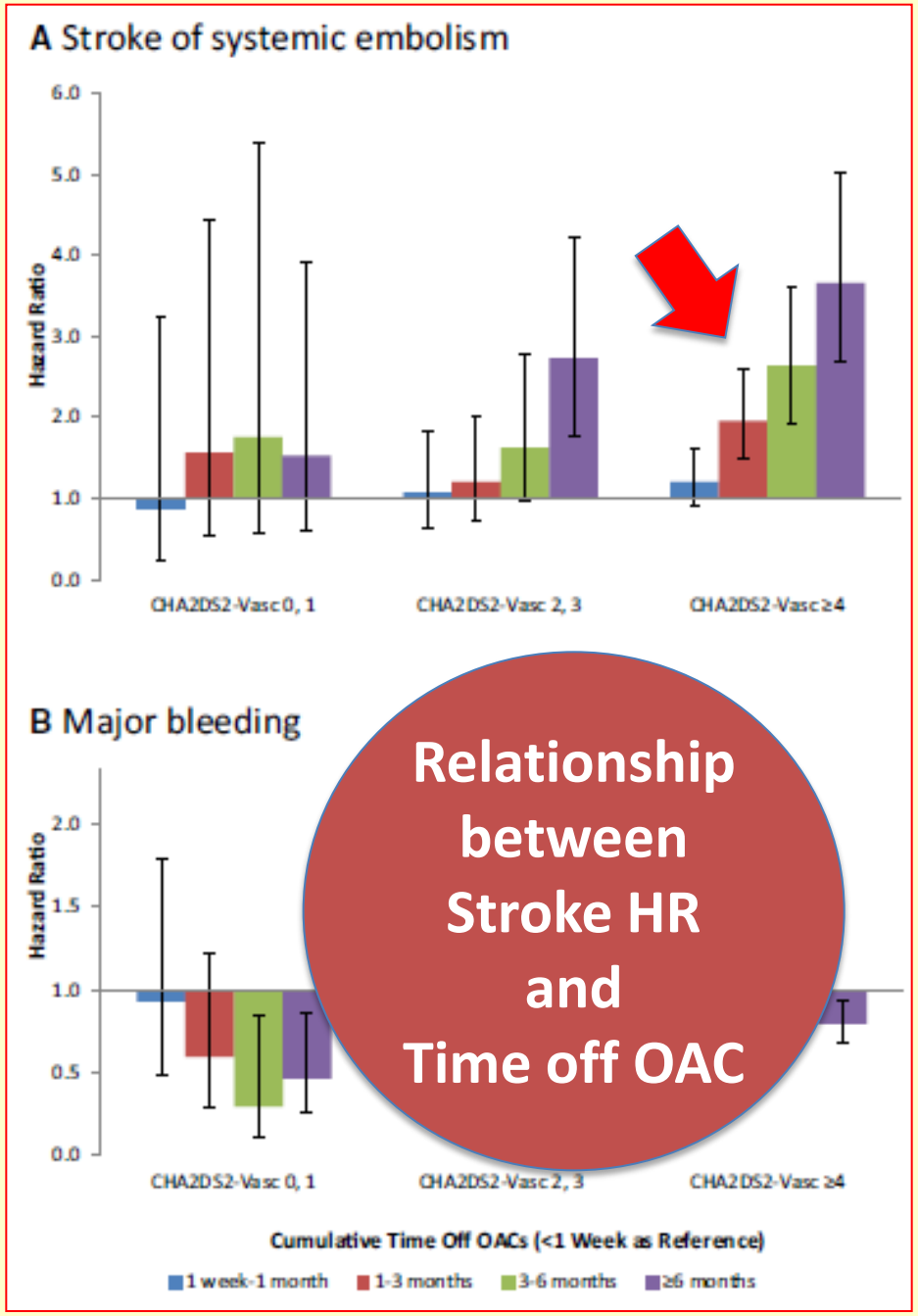
Stroke risk was significantly greater during warfarin discontinuation periods compared with therapy periods (hazard ratio = 1.60; 95% CI, 1.35-1.90; P < 0.001).

Warfarin discontinuation:
~50 % off
Increased risk for stroke

Clin Ther 2013;35:1201-10.

A retrospective cohort analysis by using a large US commercial insurance database to identify 64 661 patients with atrial fibrillation who initiated warfarin, dabigatran, rivaroxaban, or apixaban treatment between November 1, 2010 and December 31 2014.

Follow-up median: 1.1 y



J Am Heart Assoc 2016;5:e003074

Time Not Taking OAC	Hazard Ratio (95% CI)
CHA_2DS_2-VASc score 0 or 1	
<1 wk	Ref
1 wk to 1 mo	0.87 (0.23–3.23)
1–3 mo	1.57 (0.55–4.44)
3–6 mo	1.76 (0.58–.37)
≥6 mo	1.53 (0.60–3.91)
CHA_2DS_2-VASc score 2 or 3	
<1 wk	Ref
1 wk to 1 mo	1.08 (0.64–1.82)
1–3 mo	1.21 (0.74–2.00)
3–6 mo	1.63 (0.96–2.78)
≥6 mo	2.73* (1.76–4.23)
CHA_2DS_2-VASc score ≥4	
<1 wk	Ref
1 wk to 1 mo	1.21 (0.91–1.60)
1–3 mo	1.96* (1.48–2.60)
3–6 mo	2.64* (1.93–3.61)
≥6 mo	3.66* (2.68–5.01)

High CHA2DS2-Vasc score: less time OAC off for increasing Stroke HR

J Am Heart Assoc 2016;5:e003074

Adherence to OACs (PDC ≥80%), Stratified by Index Medication (N=64 661)

	Apixaban n=3900	Dabigatran n=10235	Rivaroxabn n=12336	NOACs n=26471	Warfarin n=38190	P All vs W
All	52.1 %	45.9 %	47.6 %	47.5 %	38.7 %	<0.001
0-1*	40.6 %	28.6 %	30.8 %	30.8 %	25.2 %	<0.001
2-3*	51.9 %	46.9 %	48.8 %	48.3 %	37.3 %	<0.001
>4*	54.1 %	48.7 %	50.1 %	50.1 %	42.0 %	<0.001

*CHA_2DS_2-Vasc score

J Am Heart Assoc 2016;5:e003074

PDC: Proportion of days covered

Adherence to Rivaroxaban, Dabigatran, and Apixaban for Stroke Prevention for Newly Diagnosed and Treatment-Naive Atrial Fibrillation Patients: An Update Using 2013-2014 Data

Joshua D. Brown, PharmD, PhD; Anand R. Shewale, MS; and Jeffery C. Talbert, PhD

9 Months				
	Rivaroxaban n=7,969	Dabigatran n=2,456	Apixaban n=1,858	*P* Value
PDC[a]				
Mean (SD)	0.66 (0.34)	0.57 (0.35)	0.66 (0.33)	<0.001
≥ 0.80, n (%)	3,753 (47.1)	912 (37.1)	889 (47.9)	<0.001
0.50-0.79, n (%)	1,421 (17.8)	432 (17.6)	356 (19.2)	
<0.50, n (%)	2,795 (35.1)	1,112 (45.3)	613 (33.0)	
Gaps,[b] n (%)				
≥ 15 days	1,578 (20.8)	591 (25.3)	482 (27.3)	<0.001
≥ 30 days	902 (11.9)	335 (14.3)	280 (15.9)	<0.001
≥ 60 days	408 (5.4)	158 (6.8)	111 (6.3)	0.052
Switch,[c] n (%)				
Other OAC	719 (9.5)	440 (18.8)	185 (10.5)	<0.001
Antiplatelet	256 (3.4)	90 (3.9)	60 (3.4)	0.538

J Manag Care Spec Pharm. 2017;23(9):958-67

Low PDC in patients with low CHA_2DS_2-Vasc

9 Months				
OAC PDCs, mean (SD)	Rivaroxaban n = 7,969	Dabigatran n = 2,456	Apixaban n = 1,858	*P* Value
Overall	0.69 (0.33)	0.66 (0.32)	0.70 (0.31)	< 0.001
CHA_2DS_2-VASc = 0, 1	0.51 (0.33)	0.50 (0.33)	0.45 (0.31)	0.049
CHA_2DS_2-VASc = 2, 3	0.72 (0.32)	0.70 (0.31)	0.72 (0.30)	0.011
CHA_2DS_2-VASc ≥ 4	0.77 (0.29)	0.74 (0.29)	0.78 (0.27)	0.022

J Manag Care Spec Pharm. 2017;23(9):958-67

Only Charlson Comorbidity Index is associated to poor adherence

Multiple logisic regression	OR and 95 % CI		
Aged 65-74 years vs. <65 years	2.94	2.66	3.24
Aged ≥ 75 years vs. <65 years	2.70	2.45	2.97
Hypertension	1.23	1.14	1.33
Diabetes	1.24	1.11	1.39
Charlson Comorbidity Index	0.92	0.87	0.96
Hyperlipidemia	1.21	1.12	1.31
Cancer	1.28	1.12	1.48

Elderly patients show good adherence

J Manag Care Spec Pharm. 2017;23(9):958-67

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Between June 2012 and April 2014, 11,477 rivaroxaban and 2992 apixaban users were identified.

Relative to apixaban users, rivaroxaban users were more likely to have a PDC ≥0.80 at both 90 days (85.3% vs 79.9%; P < 0.001) and 180 days (75.8% vs 72.2%; P = 0.001).

The proportion of patients with at least one 5+ and 10+ day gap in prescriptions was significantly lower in the rivaroxaban versus apixaban cohorts: 54.2% versus 62.4% (P < 0.001) and 40.0% versus 49.2% (P < 0.001), respectively.

Clin Ther 2016;38:2477-2488

Retrospective cohort study using administrative data from Ontario, Canada, from January 1998 to March 2014 of patients with AF who were dispensed dabigatran or rivaroxaban.

Non-persistence was defined as a gap in dabigatran or rivaroxaban prescriptions ≥14 days.

The cohort consisted of 15 857 dabigatran (age 80.7±6.7 year) and 10 119 rivaroxaban users (age 77.0±7.1 year) with women com ach medication group.

At 6 months, 36.4% of patients were non-persis patients were non-persistent to rivaroxaban.

Stroke/TIA/death was significantly higher for t (HR 1.76 (95% CI 1.60 to 1.94); p<0.0001) or riva 2.19); p<0.0001) compared with those who were

Risk of stroke/TIA was markedly higher in non-persistent gatran (HR 3.75 (95% CI 2.59 to 5.43); p<0.0001) and rivaroxaban (HR 6.25 (95% CI 3.37 to 11.58); p<0.0001) than those persistent.

Dabigatran and Rivaroxaban: poor persitence associated to high risk for stroke

Heart 2017;103:1331-1338

Cause della scarsa aderenza

1 Scarsa comunicazione medico-paziente

2 Assenza di visite di controllo periodiche

3 Difetti cognitivi

4 Giovane età

5 Complessità del trattamento (numero di cp/die)

6 Trattamento cronico in profilassi primaria (Ipertensione, FA)

7 Non conoscenza del perché si fa il trattamento.

Ho PM et al. Circulation 2009;119:3028-35
Barcellona D et al. Haematologica 2002;87:1081-6

Politerapia: 5 o più farmaci/die

Conseguenze:

a) Scarsa aderenza
b) Aumento degli eventi avversi

In caso di Politerapia

Drugs taken by patients over VKA	Patients *n* (%)	Patients who would forget to take DOACs *n* (%)
<6 tablets/die	309 (59 %)	59 (19.1 %)
≥6 tablets/die	214 (41 %)	69 (32.2 %)
	$p < 0.0001$	$p = 0.0009$

Alto rischio di scarsa aderenza

Barcellona D et al. Intern Emerg Med 2015;10:157-63.

La ruota

infernale

Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI study

Prevalenza massima della politerapia (≥ 5 farmaci/die):

70-84 anni

51.9 % al momento del ricovero

67 % alla dimissione

Nobili A et al. Eur J Clin Pharmacol 2011; 67:507–519

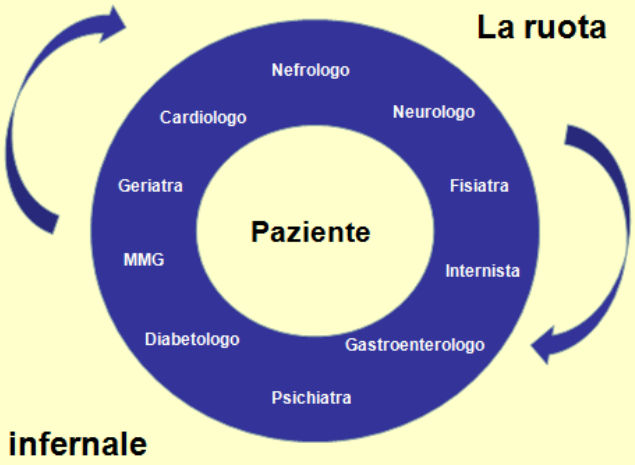
Spesso più di 10 farmaci al giorno

Molti farmaci

Conseguentemente

Circa il 30 % inutili

Hajjar ER et al. Am Geriatr Soc 2005;53:1518-23



Spesso più di 10 farmaci al giorno

Molti farmaci

Conseguentemente

Aderenza bassa

Sarebbe bene:

1 Osservare quanti farmaci assume il paziente

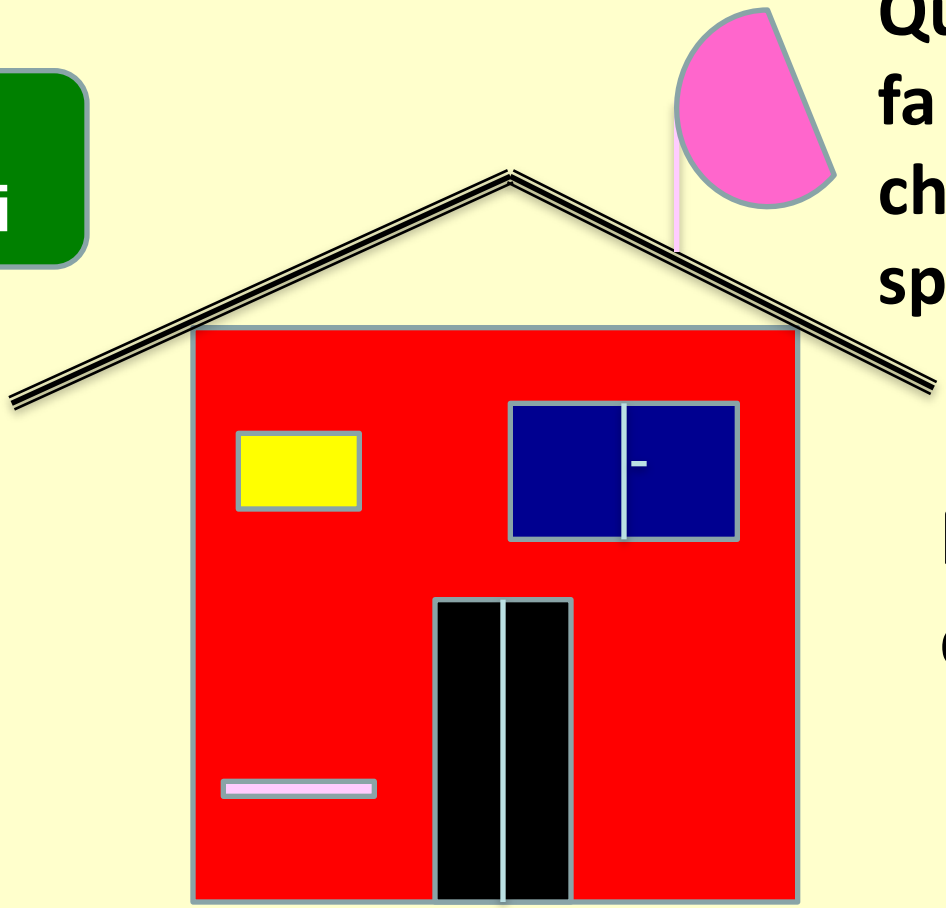
2 Eliminare i farmaci inutili (Fascia C) e senza indicazione

3 Considerare che quanti più farmaci il paziente assume tanto più scarsa sarà l'aderenza e la persistenza.

Tutto questo non è facile.
Difficilmente si sospendono farmaci dati da altri.

Centro Trombosi

Qualche anno fa si pensava che sarebbero spariti



Dovrebbe proporsi per Il *follow-up* dei DOAC

Ma non è così

Aderenza e persistenza migliorerebbero

Possibile questionario da sottoporre, ad esempio, ogni 4 mesi (anche per via telematica)

1) Ha preso regolarmente le compresse ?
2) Ha praticato regolarmente l'iniezione sotto cute ?
3) Se ha dimenticato la terapia, quante volte è successo ?
4) Ha notato lividi sulla pelle, sangue con le urine, con le feci ?
5) Ha avuto perdita di coscienza, perdita di forza alle braccia ed alle gambe anche per poco tempo ?
6) Si è inceppata la parola anche per poco tempo ?
7) Ha avuto dolore alle gambe ?
8) Si sono gonfiate ?
9) Come giudica il suo stato di salute: stazionario, migliorato, peggiorato ?

+

Creatininemia, enzimi epatici,
Emocromo (soprattutto anziani)

Ricercare un *Hawthorne effect ?*

Quarters	Mean (%)	CI 95%	*P*
Interview (May)			
June–August 2004 vs February–April 2004	13	9.1/16.8	<0.001
Course, brochure, nothing (September)			
October–December 2004 vs June–August 2004	0.6	–2.9/4.1	0.73
January–March 2005 vs October–December 2004	0	–2.3/2.3	0.98
April–June 2005 vs January–March 2005	–0.2	–3.7/3.4	0.93

Negativo l'approccio «passivo»

Barcellona D et al. J Thromb Thrombolysis. 2006 Dec;22(3):185-90

It is diffucult to improve adherence and persistence

Across the body of evidence (182 RCTs), effects were inconsistent.

Current methods of improving medication adherence for chronic health problems are mostly complex (intense education, counseling including motivational interviewing or daily treatment support, and sometimes additional support from family or peers) and not very effective, so that the full benefits of treatment cannot be realized.

Cochrane Database Syst Rev 2014 Nov 20;(11):CD000011.

Conclusioni

1 Aderenza e persistenza sono due aspetti cruciali spesso sottovalutati.

2 Se scarse (e lo sono), hanno un impatto negativo sulla salute.

3 E' difficile migliorarle.

4 Gli anticoagulanti orali (vecchi e nuovi) non sfuggono al problema. I DOAC sembrano migliori del Warfarin.

5 La mono somministrazione dei DOAC non necessariamente incrementa l'aderenza e la persistenza.