Interpretazione degli studi del mondo reale

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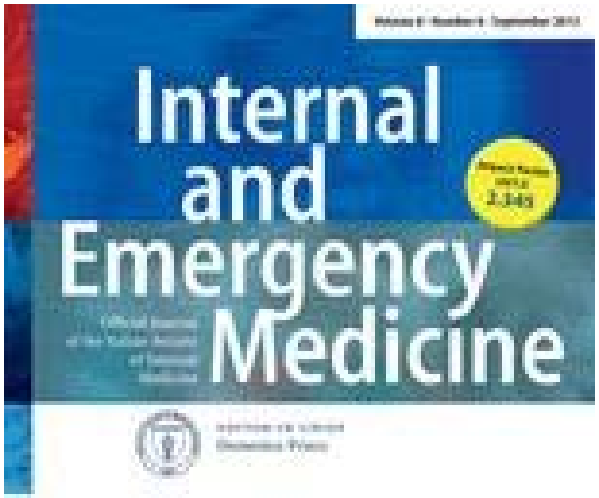
Conflitti di interesse

GrAM

(Gruppo di Autoformazione Metodologica)



- Cutting edge
- Corsi di formazione

Studi del mondo reale
Sommario

- ✓ Cosa sono?
- ✓ Perché?
- ✓ Trial pragmatici
- ✓ Studi osservazionali
- ✓ Conclusioni

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Il mondo reale…

Il mondo ideale…

Studi del mondo reale

Gli studi del «mondo reale» esaminano gli interventi in circostanze che si avvicinano maggiormente alla pratica del mondo reale con popolazioni di pazienti più eterogenei, protocolli di trattamento meno standardizzati e somministrazione in contesti clinici di routine

REAL WORLD STUDIES

INTERVENTIONAL STUDIES

- Pragmatic clinical trials

OBSERVATIONAL STUDIES: *PROSPECTIVE*

- Traditional cohort studies
- Patient surveys
- Disease registries

OBSERVATIONAL STUDIES: RETROSPECTIVE

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- Medical claims data
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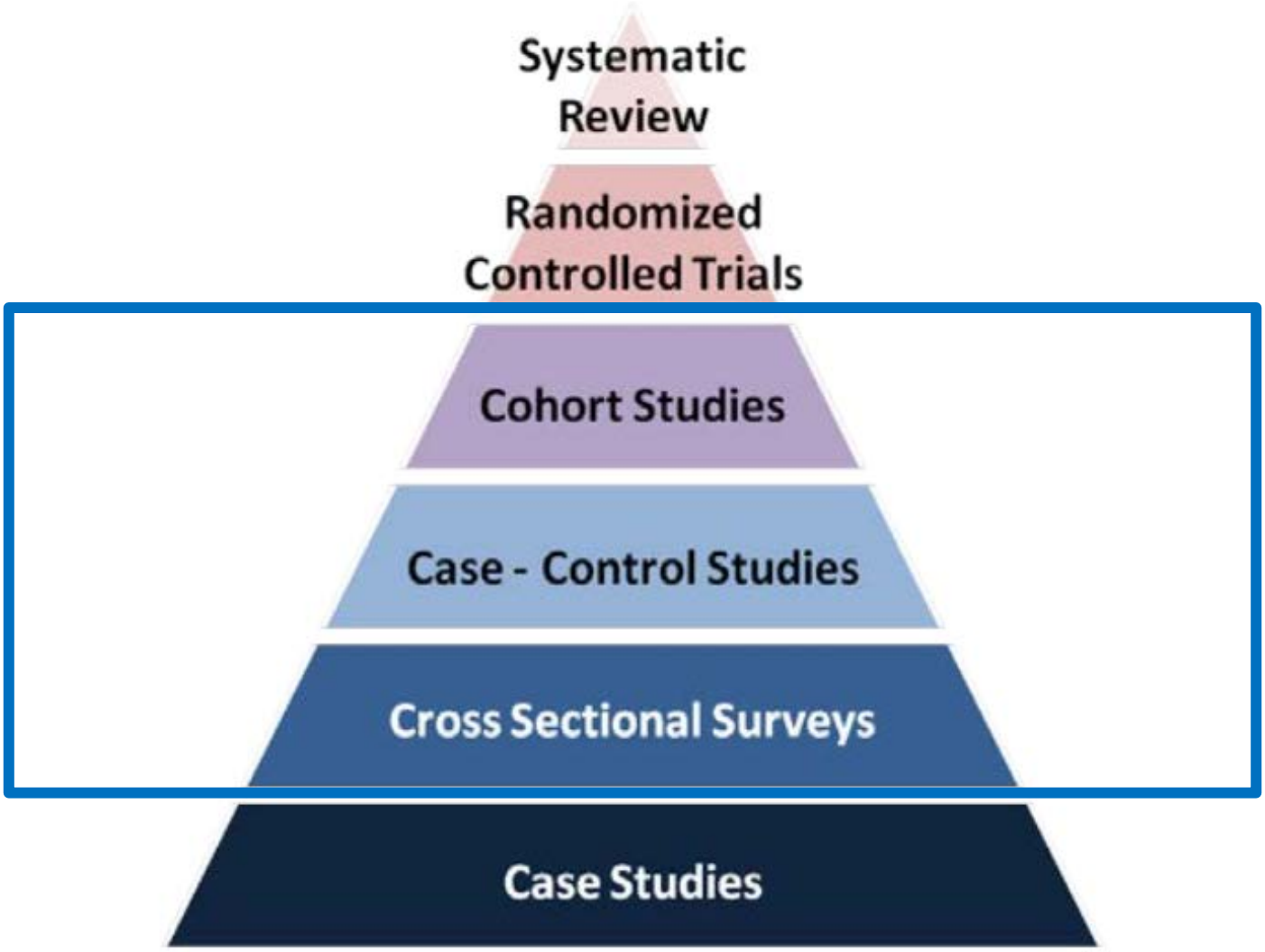
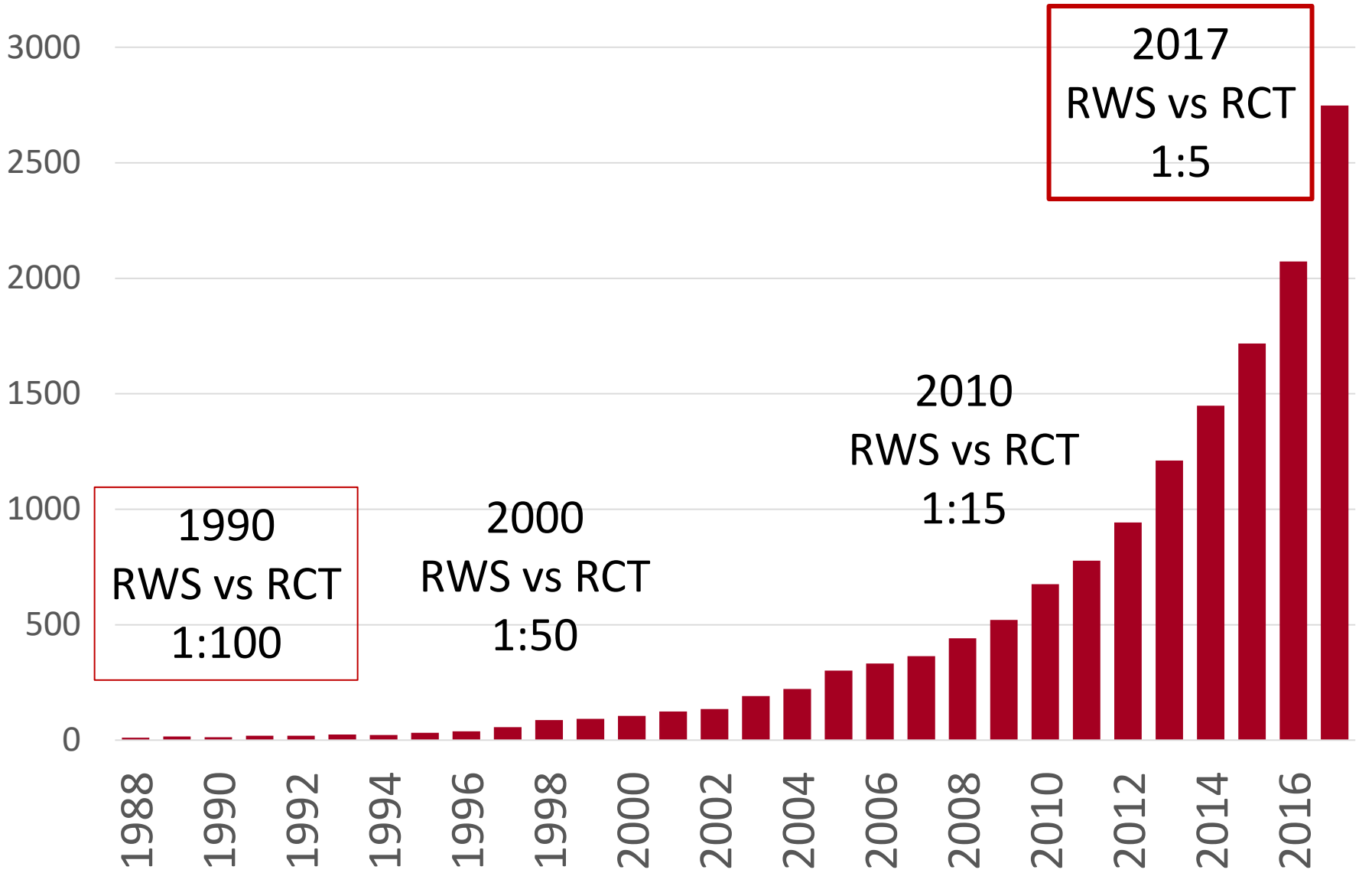
LA PIRAMIDE DELL'EVIDENZA



Studi del mondo reale (RWS)



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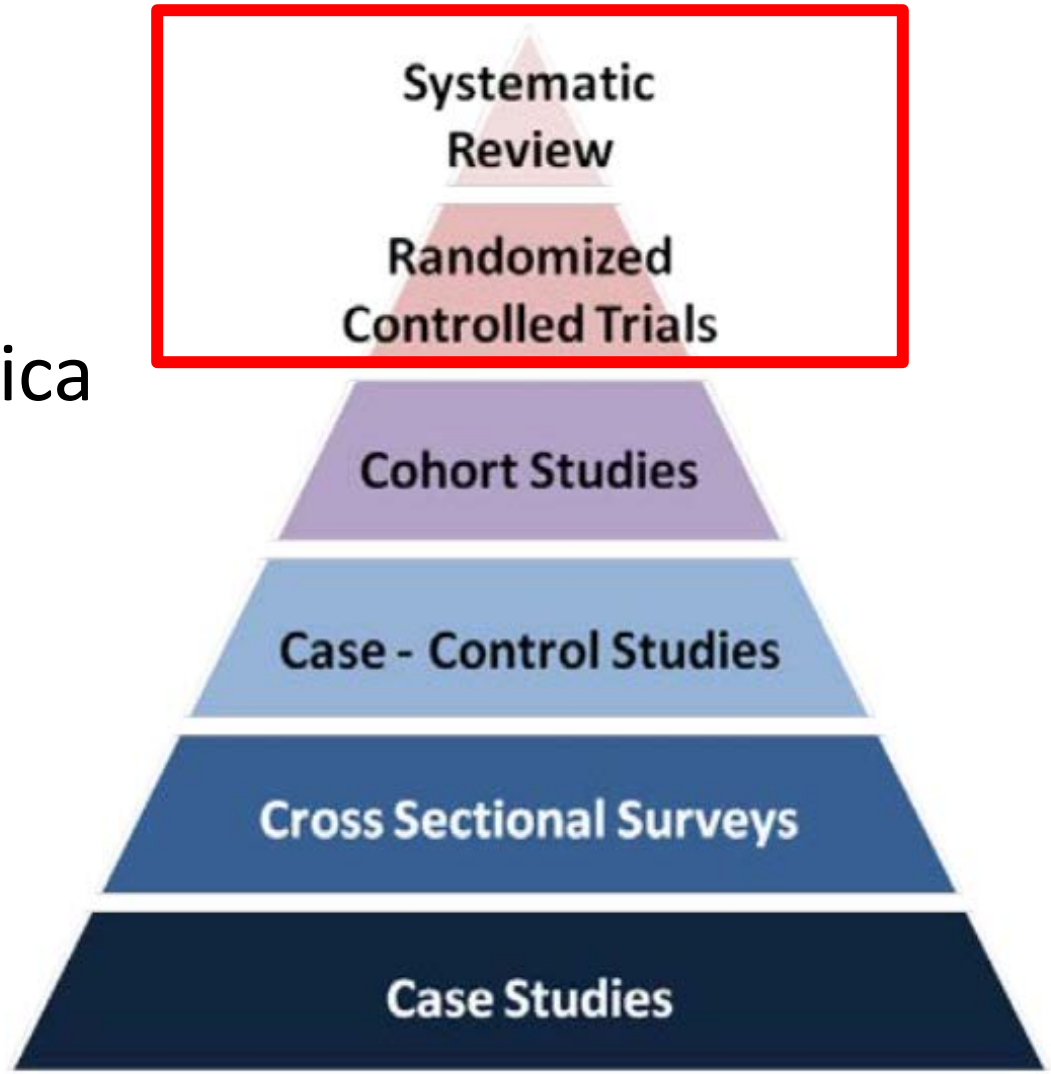
Studi del mondo ideale: RCT: randomised controlled trial

RCT:
gold standard
della ricerca clinica



RCT: il mondo ideale

- End point
- Randomizzazione
- Cecità
- Follow up
- Intention to treat analysis (anche per protocol)
- Significatività e limiti di confidenza
- NNT
- Criteri di inclusione
- Criteri di esclusione
- Conflitto d'interesse

Limiti degli RCT

- Efficacia in pazienti con numerose comorbilità e politerapie
- Aderenza «ideale»
- Follow up brevi
- Effetti collaterali: sottostostimati, specie:
  - se non vi sono confronti di dosi di farmaci
  - se end point primario significativo
  - in giornali ad alto Impact Factor
- RCT non sono «disegnati» per ricercare una differenza negli effetti collaterali

Cosa vorremmo da studi del «mondo reale»

- Efficacia in pazienti con numerose comorbilità e politerapie
- Aderenza reale
- Follow up lunghi
- Effetti collaterali

Studi del mondo reale
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- ✓ Perché?
- ✓ Trial clinici pragmatici
- ✓ Studi osservazionali
- ✓ Conclusioni

Trial clinici pragmatici

Sono studi **randomizzati** che confrontano l'efficacia di due o più interventi in situazioni reali

- strettamente integrati con la pratica clinica
- incorporano risultati rilevanti per i pazienti
- includono un'ampia gamma di situazioni cliniche
- hanno criteri di esclusione minimi

Questi studi cercano evidenze clinicamente applicabili sui relativi vantaggi e svantaggi degli interventi

Wichler et al, Clin Trial 2015

	RCT	Trial pragmatici
Popolazione	Selezionata, omogenea	Eterogenea
Setting	Centri terziari/universitari	Centri Ospedalieri di II livello
Provider	Molta esperienza, training	Medici mondo reale
End point	Hard o surrogati	Hard
Comparatore	Placebo/standard of care	Alternative clinicamente rilevanti
Cecità	Ove possibile	Normalmente assente
Randomizzazione	Individuale	Individuale o a «cluster»
Compliance	Normalmente alta	Variabile
Follow up	Visite	Registri

The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial

*The IST-3 collaborative group**

Methods:

In this **pragmatic** international, multicentre, randomised-controlled, open-treatment trial, patients were allocated to 0·9 mg/kg intravenous recombinant tissue plasminogen activator (rt-PA) or to control.

The IST-3 collaborative group Lancet 2012

The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial

*The IST-3 collaborative group**

…greater benefit in those older than 80 years of age, contrary to expectation

Interpretation:

For the types of patient recruited in IST-3, despite the early hazards, thrombolysis within 6 h improved functional outcome.

The IST-3 collaborative group Lancet 2012

End point

End point primario

- rappresentano eventi che possono essere misurati in maniera oggettiva per determinare ad esempio se un trattamento in esame è efficace.
- semplice o composito?
- hard o surrogato?

End point secondari

- Sono altre misure di esito che possono essere valutate in uno studio

Articles

Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE)

This risk reduction was primarily due to a decrease in all-cause mortality (4·8% vs 8·7%; risk reduction 46% [95% CI 5–69%], p=0·035)

Lancet 1997; **349**: 747–52

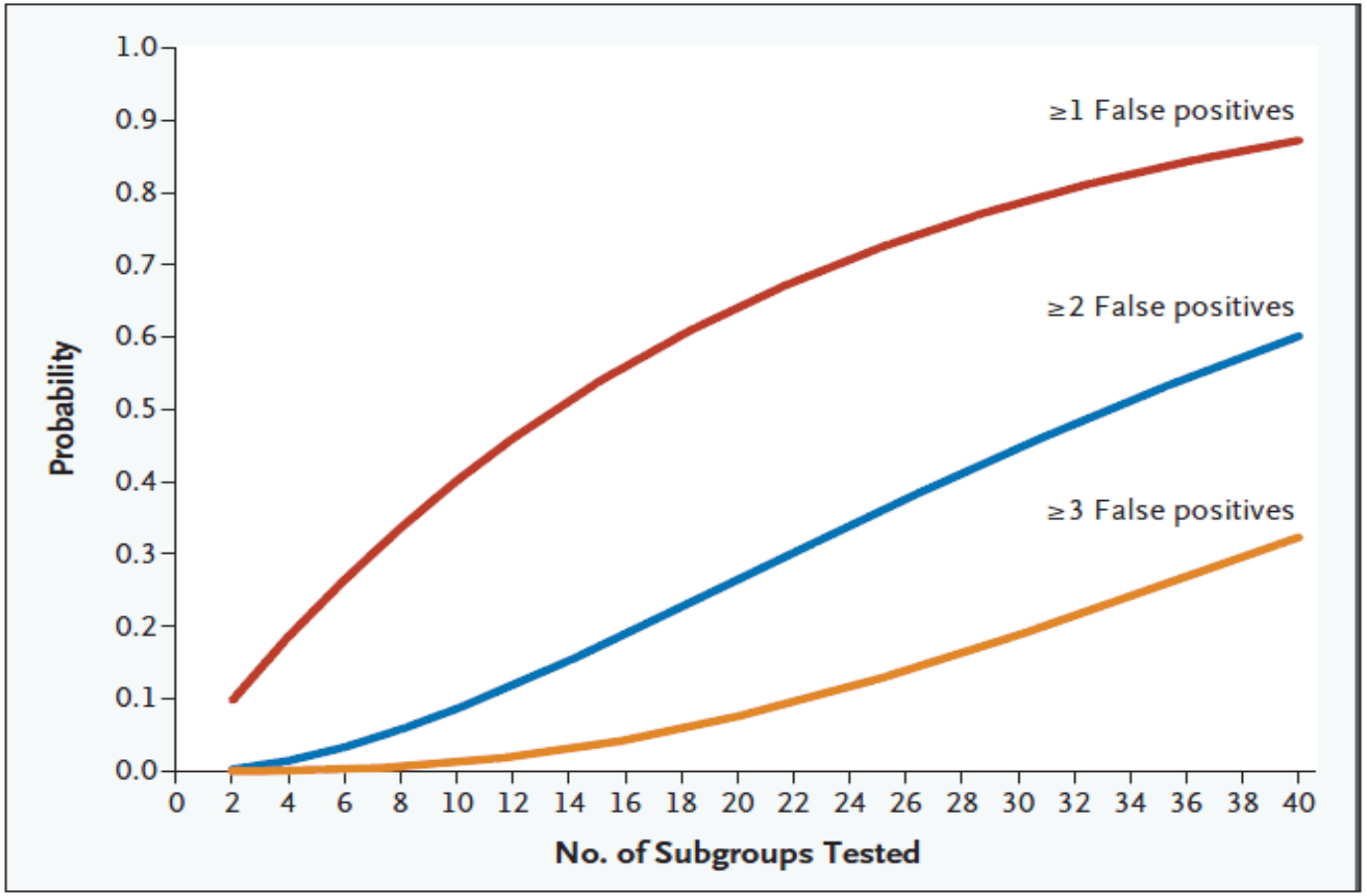
Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II

Interpretation Losartan was not superior to captopril in improving survival in elderly heart-failure patients, but was

Analisi per sottogruppi

- Analisi fatte in un sottogruppo di pazienti definito dalle sue caratteristiche di base
- Servono a esplorare se il risultato dello studio varia a seconda delle caratteristiche dei pazienti
- Dovrebbero essere decisi a priori e non a posteriori solo per cercare un sottogruppo in cui il risultato venga significativo
- La randomizzazione dovrebbe essere “stratificata”, permettendo una eguale distribuzione nei due bracci dei vari sottogruppi

Analisi per sottogruppi



Probability That Multiple Subgroup Analyses Will Yield at Least One (Red), Two (Blue), or Three (Yellow) False Positive Results.

The Challenge of Subgroup Analyses — reporting without distorting. NEJM 2006. 354(16):1667

Analisi per sottogruppi

Tabella II. Differente mortalità vascolare nei pazienti infartuati nati sotto il segno della Bilancia o dei Gemelli nello studio ISIS-2.

Mortalità vascolare alla 5 settimana	Aspirina (%)	Placebo (%)	RR
Pazienti nati sotto il segno della Bilancia o dei Gemelli	150/1357 (11,1)	147/1442 (10,2)	1,09 NS
Pazienti nati sotto altri segni zodiacali	654/7228 (9,0)	868/7157 (12,1)	0,72 p<0,0001
Test of Interaction: P<0,00001			
Overall results	804/8587 (9,4)	1016/8600 (11,8)	0,79 p<0,0001

Analisi per sottogruppi

Month of birth	Events/patients: Surgical	Medical	ARR (%)	95% CI
May–Jun	6/83	18/47	33·4	18·2 to 48·6
Jul–Aug	8/84	16/58	20·7	7·0 to 34·4
Sept–Oct	10/87	7/34	9·6	−6·2 to 25·3
Nov–Dec	6/56	9/39	11·2	−5·2 to 27·6
Jan–Feb	9/73	6/43	0·1	−13·1 to 13·2
Mar–Apr	12/64	6/53	−7·7	−20·8 to 5·3
Total	51/447	62/274	11·6	5·6 to 17·6

Heterogeneity: p<0·0001

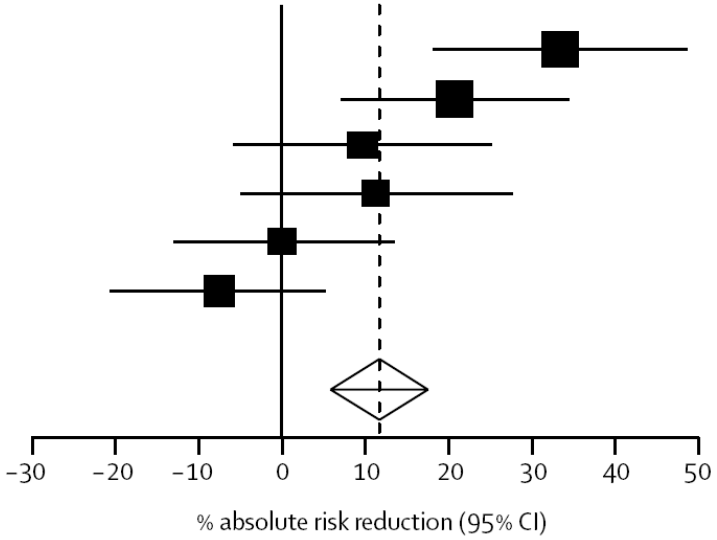


Figure 3: Effect of carotid endarterectomy in patients with ⩾70% symptomatic stenosis in ECST[126] according to month of birth in six 2 month periods

RCT vs trial pragmatici

	RCT	Trial pragmatico
Validità interna	alta	Variabile
Validità esterna	bassa	alta

Conclusioni: trial pragmatici

- ✓ Elevato rischio bias con possibile bassa validità interna
- ✓ Se buona validità interna, possono fornire le evidenze per cambiare la nostra pratica clinica

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Studio di coorte

Valutano *prospetticamente* l'effetto di un presunto fattore di rischio confrontando l'*outcome* di un gruppo di soggetti esposti con quello di un gruppo di soggetti *non* esposti a tale fattore.

Esposizione → **Outcome**

Grimes D et al Lancet 2002

Studi prospettici di coorte

Global Anticoagulant Registry in the Field (GARFIELD-AF)

Study Design Go to

Study Type :	Observational
Estimated Enrollment :	55000 participants
Observational Model:	Cohort
Time Perspective:	Prospective
Official Title:	Prospective, Multi Centre, International Registry of Male and Female Patients Newly

Outcome Measures Go to

Primary Outcome Measures :

1. Death [Time Frame: 4 monthly for 24 mths then annually until 2018]

Secondary Outcome Measures :

1. Systemic embolism [Time Frame: 4 monthly for 24 mths then annually until 2018]
2. Heart failure [Time Frame: 4 monthly for 24 mths then annually until 2018]
3. Acute coronary syndromes [Time Frame: 4 monthly for 24 mths then annually until 2018]
4. Therapy persistence [Time Frame: 4 monthly for 24 mths then annually until 2018]
5. Patient satisfaction with oral anticoagulant treatment [Time Frame: 4, 8, 12 and 24 months]
6. Bleeding Events [Time Frame: 4 monthly for 24 mths then annually until 2018]
7. Strokes (Haemorrhagic and thrombotic) [Time Frame: 4 monthly for 24 mths then annually until 2018]

Studi prospettici di coorte

Global Anticoagulant Registry in the Field (GARFIELD-AF)

Criteria

Inclusion Criteria:

Prospective Cohort

- Written informed consent
- Age 18 years and older
- New diagnosis of non-valvular atrial fibrillation (diagnosed within the last 6 weeks) with at least one additional risk factor for stroke and regardless of therapy.

Exclusion criteria:

- No further follow-up envisaged or possible within enrolling hospital or with associated family practitioner.
- Patients with transient AF secondary to a reversible cause.
- Patients recruited in controlled clinical trials.

Studi prospettici di coorte

Global Anticoagulant Registry in the Field (GARFIELD-AF)

Table 2 **Event rates (per 100 person-years) for selected clinical outcomes at 2 years of follow-up[a]**

	Rate (95% CI)
Death	3.83 (3.62; 4.05)
Cardiovascular death	1.55 (1.42; 1.70)
Non-cardiovascular death	1.37 (1.25; 1.51)
Undetermined cause	0.91 (0.81; 1.02)
Stroke/SE	1.25 (1.13; 1.38)
Major bleeding	0.70 (0.62; 0.81)
Acute coronary syndromes	0.63 (0.55; 0.73)
Congestive heart failure[b]	2.41 (2.24; 2.59)

Studi prospettici di coorte

Punti di forza:

- Disegno ideale per la valutazione di esposizioni rare;
- Permettono la stima di incidenza, rischio relativo (RR);
- Permettono la valutazione di *outcomes* multipli che possono derivare da una singola esposizione.
- Permettono di valutare gli effetti collaterali di farmaci

Punti di debolezza:

- Disegno non appropriato nel caso di malattia rara (bassa incidenza);
- Data la solitamente lunga durata dello studio, si possono avere cambiamenti dello stato di esposizione di alcuni soggetti o perdite rilevanti al follow up;
- La lunga durata dello studio può determinare costi elevati
- Fattori confondenti

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The New England
Journal of Medicine

VOLUME 341 SEPTEMBER 2, 1999 NUMBER 10

THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

BERTRAM PITT, M.D., FAIEZ ZANNAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAIGNE, M.D., ALFONSO PEREZ, M.D., JOLIE PALENSKY, M.S., AND JANET WITTES, PH.D., FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*

RCT: 1663 patients, 2 years follow up spironolactone substantially reduced morbidity and mortality in patients with severe heart

Pitt et al NEJM 1999

ORIGINAL ARTICLE

Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study

Polulation based study:
prescription claims data and hospital-admission records for more than 1.3 million adults 66 years of age or older in Ontario

The publication of RALES was associated with abrupt increases in the rate of prescriptions for spironolactone and in hyperkalemia-associated morbidity and mortality.

Jurrlink et al NEJM 2004

Use of Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation Who Have a History of Intracranial Hemorrhage

Tze-Fan Chao, MD*; Chia-Jen Liu, MD*; Jo-Nan Liao, MD; Kang-Ling Wang, MD; Yenn-Jiang Lin, MD; Shih-Lin Chang, MD; Li-Wei Lo, MD; Yu-Feng Hu, MD; Ta-Chuan Tuan, MD; Fa-Po Chung, MD; Tzeng-Ji Chen, MD; Gregory Y. H. Lip, MD†; Shih-Ann Chen, MD†

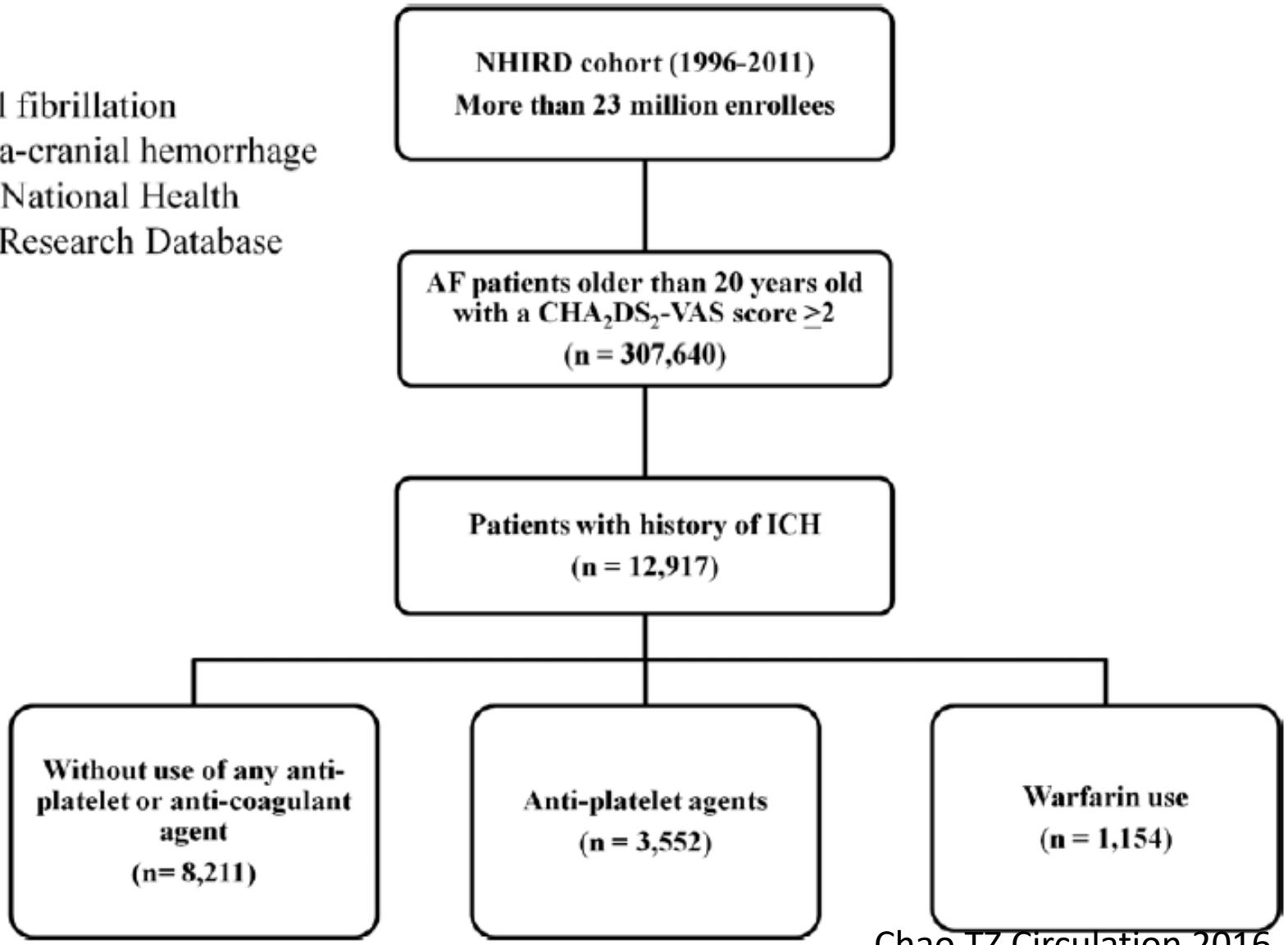
We aimed to investigate the risks and benefits in patients who have atrial fibrillation with a previous ICH treated with warfarin or antiplatelet drugs in comparison with no antithrombotic therapies.

Methods:
Cohort study
Data were collected from the Taiwanese National Insurance Research Database that accounts for more than 99% of the Taiwanese population. Inclusion criteria were a diagnosis of atrial fibrillation and a CHA2DS2VASc score of 2 or more.

Chao TZ Circulation 2016

Use of Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation Who Have a History of Intracranial Hemorrhage

AF = atrial fibrillation
ICH = intra-cranial hemorrhage
NHIRD = National Health Insurance Research Database



Chao TZ Circulation 2016

Validità esterna elevata

- Pazienti con pregressa ICH:
  - 4.9% hanno avuto trauma
  - 6.8% in terapia antiaggregante
  - 0.5% in terapia con Warfain
- Pazienti con FA con CHA2DS2VASc score ≥ 2

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The primary outcome was the occurrence of ischemic stroke, with radiological confirmation.

The safety end point was the occurrence of ICH necessitating admission to intensive care units; this diagnosis was based on codes registered on the database and no detailed results of imaging studies were available.

Chao TZ Circulation 2016

Use of Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation Who Have a History of Intracranial Hemorrhage

Table 5. Risk of Ischemic Stroke and ICH in Patients With History of ICH (n= Prevention

Stroke Prevention Strategy	n	Ischemic Stroke				
		No. of Events	Crude Incidence*	Adjusted Incidence†	Adjusted HR† (95% CI)	*P* Value
No antithrombotic therapy (reference group)	8211	964	5.8	5.7	Reference	–
Antiplatelet agents	3552	581	5.2	5.1	0.90 (0.81–1.01)	0.060
Warfarin	1154	130	3.4	3.6	0.66 (0.55–0.79)	<0.001

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio

Chao TZ Circulation 2016

Use of Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation Who Have a History of Intracranial Hemorrhage

Table 5. Risk of Isch12917) Stratified Based on the Strategies for Stroke Prevention

Stroke Prevention Strategy	n	ICH				
		No. of Events	Crude Incidence*	Adjusted Incidence†	Adjusted HR† (95% CI)	*P* Value
No antithrombotic therapy (reference group)	8211	730	4.2	4.2	Reference	–
Antiplatelet agents	3552	628	5.3	5.2	1.35 (1.21–1.51)	<0.001
Warfarin	1154	241	5.9	6.2	1.60 (1.38–1.86)	<0.001

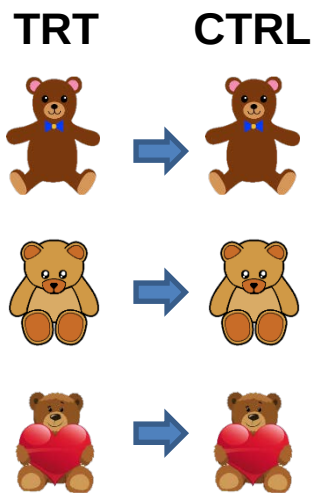
CI indicates confidence ib; and ICH, intracranial hemorrhage.

Chao TZ Circulation 2016

Come confrontare i due gruppi?

Propensity Score

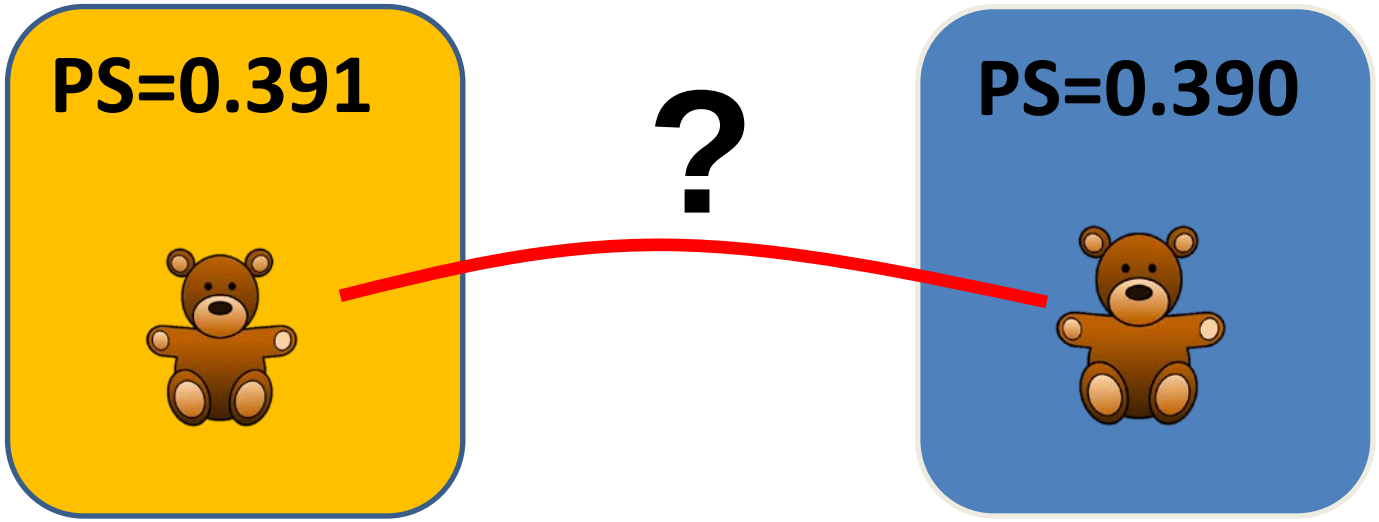
A partire dai dati osservati calcoliamo, per ogni paziente, uno score che indica quanto è probabile che quel pz (date le sue caratteristiche in termini di confondenti scelti da noi) appartenga al gruppo trattamento



Appaiando per Propensity Score, in teoria, eliminiamo l'effetto confondente delle variabili considerate.

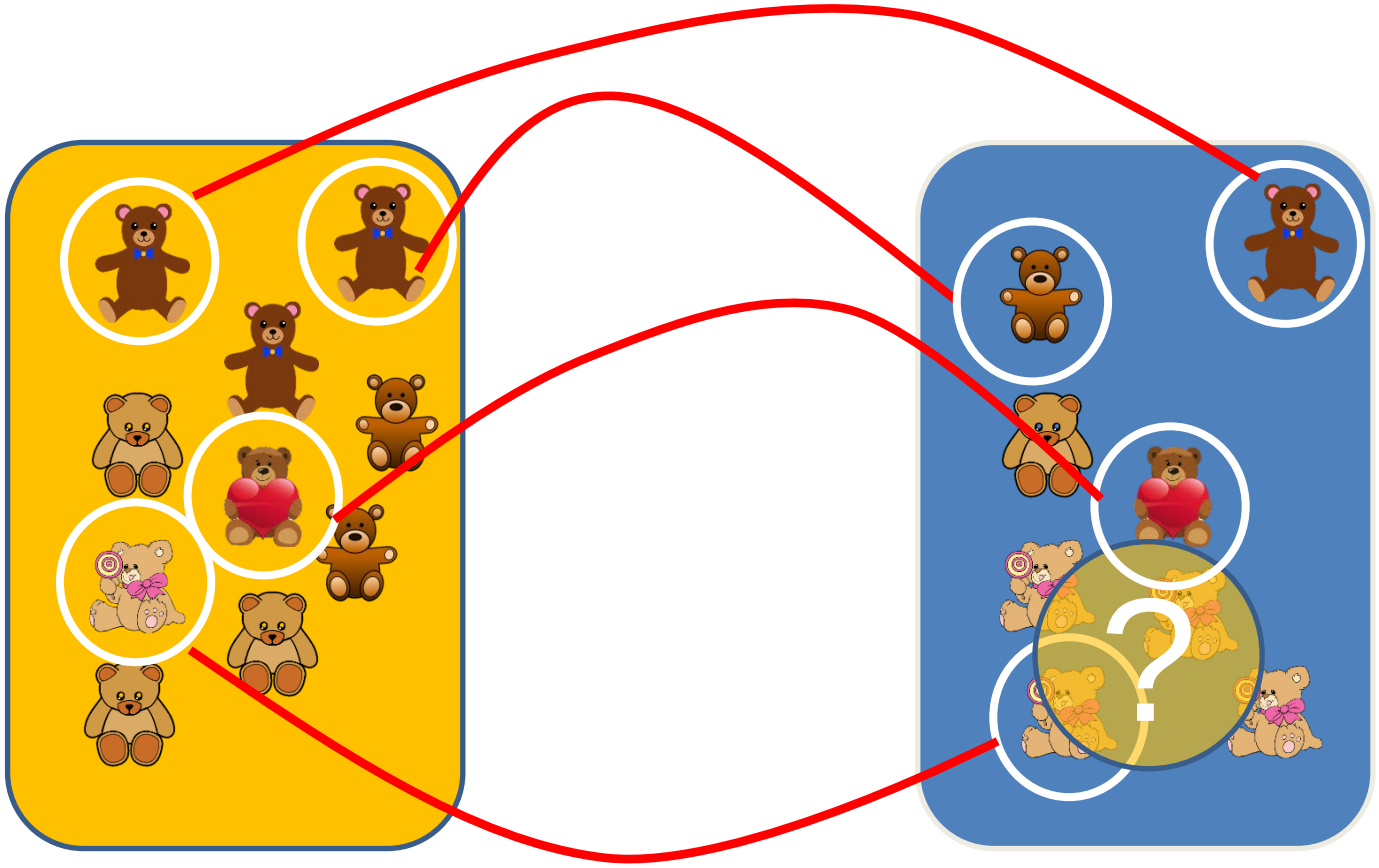
Punto critico: individuare tutti i principali fattori confondenti

Propensity Score, esempio



Sesso	Eta	BMI	ALT	AST	PLT	TTR	Propensity Score
M	66	28.4	35	27	110	0.58	0.39141
F	82	20.0	15	24	126	0.28	0.39023

Propensity Score



Use of Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation Who Have a History of Intracranial Hemorrhage

Variables	Anti-platelet agents vs. no antithrombotic therapy			Warfarin vs. no antithrombotic therapy		
	No antithrombotic therapy (n = 3,432)	Anti-platelet agents (*n* = 3,432)	*P* value	No antithrombotic therapy (*n* = 1,134)	Warfarin (*n* = 1,134)	*P* value
Age, years	75.0 ± 10.9	74.7 ± 10.1	0.33	70.5 ± 12.3	69.5 ± 12.4	0.065
Age 65-74 years, n (%)	961 (28)	967 (28)	0.87	357 (32)	348 (31)	0.68
Age ≥ 75 years, n (%)	1,947 (57)	1,947 (57)	1.00	443 (39)	443 (39)	1.00
Gender (male), n (%)	1,965 (57)	1,965 (57)	1.00	613 (54)	613 (54)	1.00
CHA_2DS_2-VASc score , median value (25^{th}, 75^{th} percentiles)	6 (5-7)	6 (5-7)		6 (4-7)	6 (4-7)	
Medical history (components of the CHA_2DS_2-VASc score), n (%)						
Hypertension	3,146 (92)	3,129 (91)	0.46	946 (83)	931 (82)	0.40
Diabetes mellitus	1,396 (41)	1,373 (40)	0.57	430 (38)	420 (37)	0.66
Congestive heart failure	1,663 (49)	1,621 (47)	0.31	511 (45)	524 (46)	0.58
Previous stroke/TIA	2,188 (64)	2,230 (65)	0.29	737 (65)	748 (66)	0.63
Previous vascular disease	987 (29)	1,005 (29)	0.63	342 (30)	337 (30)	0.82
Medical history (other than the components of the CHA_2DS_2-VASc score), n (%)						
COPD	1,522 (44)	1,486 (43)	0.38	383 (34)	383 (34)	1.00
Hyperlipidemia	1,166 (34)	1,164 (34)	0.96	383 (34)	374 (33)	0.69
Malignancy	150 (4)	173 (5)	0.19	30 (3)	36 (3)	0.45
End-stage renal disease	94 (3)	100 (3)	0.66	14 (1)	14 (1)	1.00
Mean propensity score	0.33 ± 0.12	0.33 ± 0.12	1.00	0.17 ± 0.10	0.17 ± 0.10	0.99

Risk of ischemic stroke in patients with history of ICH with different strategies for stroke prevention after the propensity match

Stroke prevention strategy	n	Ischemic stroke				
		No. of event	Crude incidence*	Adjusted incidence+	Adjusted HR+ (95% CI)	P value
Anti-platelet agents versus no antithrombotic therapy						
No antithrombotic therapy (reference group)	3,432	425	6.2	6.2	Reference	-
Anti-platelet agents	3,432	567	5.2	5.2	0.89 (0.78–1.01)	0.060
Warfarin versus no antithrombotic therapy						
No antithrombotic therapy (reference group)	1,134	165	6.0	5.9	Reference	-
Warfarin	1,134	126	3.3	3.4	0.58 (0.46–0.73)	<.0001

Chao TZ Circulation 2016

Risk of ischemic ICH in patients with history of ICH with different strategies for stroke prevention after the propensity match

Stroke prevention strategy	n	ICH				
		No. of event	Crude incidence*	Adjusted incidence+	Adjusted HR+ (95% CI)	P value
Anti-platelet agents versus no anti						
No antithrombotic therapy (reference group)	3,432	298	4.1	4.1	Reference	-
Anti-platelet agents	3,432	612	5.3	5.3	1.36 (1.19–1.57)	<.0001
Warfarin versus no antithromboti						
No antithrombotic therapy (reference group)	1,134	116	4.0	4.0	Reference	-
Warfarin	1,134	240	6.0	6.0	1.58 (1.27–1.98)	<.0001

Chao TZ Circulation 2016

NNT for Preventing 1 Stroke and NNH for Producing 1 ICH With Warfarin for Patients With a CHA2DS2-VASc Score ≥ or < 6

Table 6. NNT for Preventing 1 Stroke and NNH for P Patients With a CHA_2DS_2-VASc Score ≥6

Groups	Number of Events	Number c Patients
Ischemic stroke		
Without antithrombotic agents	499	4467
With warfarin	59	604
NNT=37		
Intracranial hemorrhage		
Without antithrombotic agents	316	4467
With warfarin	97	604
NNH=56		

Table 7. NNT for Preventing 1 Stroke and NNH for Pro Patients With a CHA_2DS_2-VASc Score <6

Groups	Number of Events	Number of Patients
Ischemic stroke		
Without antithrombotic agents	465	3744
With warfarin	71	550
NNT=63		
Intracranial hemorrhage		
Without antithrombotic agents	414	3744
With warfarin	144	550
NNH=53		

Use of Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation Who Have a History of Intracranial Hemorrhage

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Conclusion

In this Asian cohort of AF patients with previous ICH, warfarin use may be beneficial for patients with a CHA2DS2-VASc score ≥ 6.

Patients receiving antiplatelet agents had a similar risk of ischemic stroke but higher risk of ICH in comparison with untreated patients.

Chao TZ Circulation 2016

Studi retrospettivi

Punti di forza:

- Disegno ideale per studi che intendono indagare malattie a bassa incidenza;
- Relativa economicità di esecuzione (tempi relativamente brevi)
- Permettono di valutare gli effetti collaterali di farmaci

Punti di debolezza:

- Non permettono la stima di rischio relativo ma solo di odds ratio (OR);
- Estrema cautela nel valutare efficacia di un farmaco per limitita validità interna dovuta all'elevato rischio di bias (principalmente di informazione, di selezione…)

Studi del mondo reale
Sommario

- ✓ Cosa sono?
- ✓ Perché?
- ✓ Trial pragmatici
- ✓ Studi osservazionali
- ✓ Conclusioni

Conclusioni: studi osservazionali

- ✓ Elevato rischio bias con possibile bassa validità interna
- ✓ Non possono fornire evidenze di efficacia di terapia
- ✓ Generatori di idee
- ✓ Complementari a RCT: la valutazione di effetti collaterali dei farmaci può cambiare la nostra pratica clinica

GRAZIE !

DOAC e AF: RCT

	RE-LY[4]	ROCKET AF[5]	ARISTOTLE[6]	ENGAGE AF-TIMI 48[7]
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Number of patients	18,113	14,264	18,201	21,105
Study design	Open (PROBE)	Double-blind	Double-blind	Double-blind
CHF or LVEF	32%[a]	62.6%[b]	35.5%[c]	58%
Hypertension	79%	91%	87%	94%
Age (years)	Mean 72	Median 73	Median 70	Median 72
Diabetes mellitus	23%	40%	25%	36%
Prior stroke, TIA	20%	55%	19%	28%
$CHADS_2$ score:	0/1: 31.9% 2: 35.6% ≥3: 32.4%	0/1: <1% 2: 13.0% ≥3: 86.9%	≤1: 34.0% 2: 35.8% ≥3: 30.2%	0/1: 0% 2: 48% ≥3: 52%
Mean $CHADS_2$ score	2.1	3.5	2.1	2.8
TTR (mean)	64%	55%	62%	68%

Primary outcome: stroke or systemic embolism

Safety end point was a composite of major and non major clinically relevant bleeding events.

DOAC e tipo di sanguinamenti (safety outcome)

	Dabigatran		Rivaroxaban	Apixaban	Edoxaban	
	RE-LY (8–10)		ROCKET AF (7, 115)	ARISTOTLE (11)	ENGAGE AF-TIMI 48 (12)	
NOAC regimen	110 mg bid	150 mg bid	20 mg od[a]	5 mg bid[b]	30 mg od[c]	60 mg od[c]
Comparator arm	Warfarin		Warfarin	Warfarin	Warfarin	
Total number of patients randomised	18,113		14,264	18,201	21,105	
Major bleeding[d] NOAC vs warfarin (%/years) HR (95% CI) p-value	 2.92 vs 3.61 0.80 (0.70–0.93)[e] p=0.003	 3.40 vs 3.61 0.94 (0.82–1.08)[e] p=0.41	 3.6 vs 3.4 1.04 (0.90–1.20) p=0.58	 2.13 vs 3.09 0.69 (0.60–0.80) p<0.001	 1.61 vs 3.43 0.47 (0.41–0.55) p<0.001	 2.75 vs 3.43 0.80 (0.71–0.91) p<0.001
Intracranial bleeding NOAC vs warfarin (%/years) HR (95% CI) p-value	 0.23 vs 0.76 0.30 (0.19–0.45)[e] p<0.001	 0.32 vs 0.76 0.41 (0.28–0.45)[e] p<0.001	 0.50 vs 0.70 0.67 (0.47–0.93) p=0.02	 0.33 vs 0.80 0.42 (0.30–0.58) p<0.001	 0.26 vs 0.85 0.30 (0.21–0.43) p<0.001	 0.39 vs 0.85 0.47 (0.34–0.63) p<0.001
Gastrointestinal bleeding NOAC vs warfarin (%/years) HR (95% CI) p-value	 1.15 vs 1.07 1.08 (0.85–1.38)[e] p=0.52	 1.56 vs 1.07 1.48 (1.18–1.85)[e] p=0.001	 2.00 vs 1.24[f] 1.61 (1.30–1.99) p<0.001	 0.76 vs 0.86 0.89 (0.70–1.15) p=0.37	 0.82 vs 1.23 0.67 (0.53–0.83) p<0.001	 1.51 vs 1.23 1.23 (1.02–1.50) p=0.03
Fatal bleeding NOAC vs warfarin (%/years) HR (95% CI) p-value	 0.2 vs 0.3 0.70 (0.43–1.14)[e] p=0.15	 0.2 vs 0.3 0.58 (0.35–0.97)[e] p=0.039	 0.2 vs 0.5 0.50 (0.31–0.79) p=0.003	 34 vs 55 patients	 0.13 vs 0.38 0.35 (0.21–0.57) p<0.001	 0.21 vs 0.38 0.55 (0.36–0.84) p=0.006

Weitz H Thromb Haem 2015

Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study

Neena S Abraham,[1 2 3] Sonal Singh,[4 5] G Caleb Alexander,[4 5] Herbert Heien,[3] Lindsey R Haas,[3] William Crown,[6] Nilay D Shah[2 3]

Objective:
To determine the real world risk of gastrointestinal bleeding associated with the use of the novel oral anticoagulants dabigatran and rivaroxaban compared with warfarin.
Methods:
Retrospective, propensity matched cohort study.
Data were collected from Optum Labs Data Warehouse, a large database including administrative claims data on privately insured and Medicare Advantage enrollees.
New users of dabigatran, rivaroxaban, and warfarin from 1 November 2010 to 30 September 2013.

Abraham NS BJM 2015

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Outcome

Incidence rates (events/100 patient years) and propensity score matched Cox proportional hazards models were used to estimate **rates of total gastrointestinal bleeds**, upper gastrointestinal bleeds, and lower gastrointestinal bleeds **for the novel oral anticoagulants compared with warfarin in patients** with and without atrial fibrillation.

Abraham NS BJM 2015

Dabigatran & emorragia gastrointestinale (II)

	Events per 100 patient years (95% CI)		Hazard ratio* (95% CI) for bleeding: dabigatran *v* warfarin
	Dabigatran n=7749	Warfarin n=7749	
Atrial fibrillation			
Total bleeding events	2.29 (1.88 to 2.79)	2.87 (2.41 to 3.41)	0.79 (0.61 to1.03)
Upper GI bleeding events	1.42 (1.11 to 1.83)	1.81 (1.45 to 2.25)	0.78 (0.56 to 1.09)
Lower GI bleeding events	0.86 (0.63 to 1.19)	1.06 (0.80 to 1.41)	0.81 (0.53 to 1.24)
Non-atrial fibrillation			
Total bleeding events	4.10 (2.47 to 6.80)	3.71 (2.16 to 6.40)	1.14 (0.54 to 2.39)
Upper GI bleeding events	2.73 (1.47 to 5.08)	2.57 (1.34 to 4.94)	1.09 (0.44 to 2.69)
Lower GI bleeding events	1.37 (0.57 to 3.28)	1.14 (0.43 to 3.04)	1.23 (0.33 to 4.59)

Abraham et al. bmj 2015

Rivaroxaban & emorragia gastrointestinale (II)

	Events per 100 patient years (95% CI)		Hazard ratio* (95% CI) for bleeding: rivaroxaban *v* warfarin
	Rivaroxaban	Warfarin	
Atrial fibrillation	n=5146	n=5146	
Total bleeding events	2.84 (2.30 to 3.52)	3.06 (2.49 to 3.77)	0.93 (0.69 to 1.25)
Upper GI bleeding events	1.83 (1.40 to 2.39)	1.74 (1.32 to 2.28)	1.05 (0.72 to 1.54)
Lower GI bleeding events	1.02 (0.97 to1.82)	1.33 (0.97 to 1.82)	0.77 (0.48, 1.24)
Non-atrial fibrillation			
Total bleeding events	1.66 (1.23 to 2.24)	1.57 (1.25 to 1.99)	0.89 (0.60 to 1.32)
Upper GI bleeding events	1.03 (0.70 to 1.51)	0.99 (0.74 to 1.33)	0.87 (0.53 to 1.44)
Lower GI bleeding events	0.63 (0.39 to 1.03)	0.58 (0.40 to 0.86)	0.91 (0.48 to 1.73)

Abraham et al. bmj 2015

Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study

Neena S Abraham,[1 2 3] Sonal Singh,[4 5] G Caleb Alexander,[4 5] Herbert Heien,[3] Lindsey R Haas,[3] William Crown,[6] Nilay D Shah[2 3]

Objective:
The risk of gastrointestinal bleeding related to novel oral anticoagulants was similar to that for warfarin.
Caution should be used when prescribing novel oral anticoagulants to older people, particularly those over 75 years of age.

Abraham NS BJM 2015

NOAC & emorragia gastrointestinale maggiore

Metanalisi di 43 RCT, inclusi 166,289 pazienti

Rischio di emorragia GI vs Warfarin:

Dabigatran: 2.0% vs 1.4%; OR, 1.27; 95% CI, 1.04-1.55

Rivaroxaban: 1.7% vs 1.3%; OR, 1.40; 95% CI, 1.15-1.70

Apixaban: 0.6% vs 0.7%; OR, 0.81; 95% CI, 0.64–1.02

Edoxaban: 1.9% vs 1.6%; OR, 0.93; 95% CI, 0.78–1.11

Miller et al. Clinical Gastroenterology and Hepatology 2017

Use of Intravenous Recombinant Tissue Plasminogen Activator in Patients With Acute Ischemic Stroke Who Take Non–Vitamin K Antagonist Oral Anticoagulants Before Stroke

	No. Events/Total No. of Patients (%)			Adjusted OR* NOACs vs No (95% CI)	Adjusted OR* Warfarin vs No (95% CI)
	NOACs (n=251)	Warfarin With INR<1.7 (n=1500)	No Oral Anticoagulant (n=41 136)		
Primary outcomes					
Symptomatic intracranial hemorrhage <36 h	12/251 (4.8)	73/1500 (4.9)	1587/41 136 (3.9)	0.92 (0.51–1.65)	0.85 (0.66–1.10)
Life-threatening or serious systemic hemorrhage <36 h	1/251 (0.4)	14/1500 (0.9)	347/41 136 (0.8)	0.38 (0.05–2.71)	0.78 (0.45–1.37)

Nessuna informazione su

- ultima dose assunta
- somministrazione di antidoti

Xian Circulation 2017