Tools to manage the introduction of new drugs in Italy: administrative databases, registries and risk-sharing schemes.

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HTA & Efficient Management of Basic Benefit Package

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Summary

- Background
- Horizon Scanning: a managed introduction of emerging drugs
- Registries
- Risk-sharing schemes

Background

Pharmaceutical expenditure has risen rapidly in Europe during the last decades. This has principally been driven by the introduction of new expensive drugs and has emphasized the need to develop new models to introduce medicines in healthcare to maintain an equitable and sustainable healthcare system.

Summary

- Background
- Horizon Scanning: a managed introduction of emerging drugs
- Registries
- Risk-sharing schemes

Horizon Scanning:
A managed introduction of emerging drugs

- ✓ To produce timeliness Assessment of emerging drugs
- ✓ To compare "real world" patients with those included into RCTs
- ✓ To identify the potential target population for the new drugs

The example of the New Anticoagulants

The New Product Information Report

NPIR

(-12 months to M.A.)

"Drug Name"
"Drug Indication"

- **general information**
  - *Active substance*
  - *Brand name*
  - *Company*
  - *ATC Group*
  - *Dosage*
  - *Route of administration*
  - *Development state*
  - *.....*

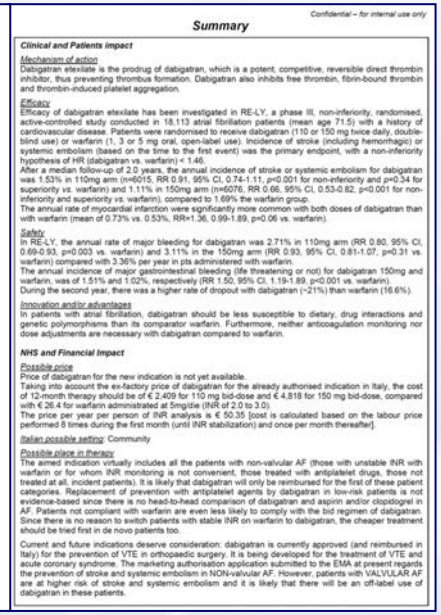
- **possible submission date of the MAA**
- **proposed indication**
- **clinical need and burden of disease**
- **summary of efficacy/safety data from available clinical trials**
- **clinical critical assessment**
- **overview of all ongoing trials and completed studies not published**
- **possible price economic / social impact**
- **ongoing trial(s) for other indication(s)**
- **alternative(s) already on the market**
- **possible competitors in development**

New Product Information Report

Dabigatran

Stroke prevention and systemic thromboembolism in AF

PG: 03-10-2008
Update: June 2010



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Summary

Clinical and Patients impact

Mechanism of action
Dabigatran etexilate is the prodrug of dabigatran, which is a potent, competitive, reversible direct thrombin inhibitor, thus preventing thrombus formation. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

Efficacy
Efficacy of dabigatran etexilate has been investigated in RE-LY, a phase III, non-inferiority, randomised, active-controlled study conducted in 18,113 atrial fibrillation patients (mean age 71.5) with a history of cardiovascular disease. Patients were randomised to receive dabigatran (110 or 150 mg twice daily, double-blind use) or warfarin (1, 3 or 5 mg oral, open-label use). Incidence of stroke (including hemorrhagic) or systemic embolism (based on the time to the first event) was the primary endpoint, with a non-inferiority hypothesis of HR (dabigatran vs. warfarin) < 1.46.
After a median follow-up of 2.0 years, the annual incidence of stroke or systemic embolism for dabigatran was 1.53% in 110mg arm (n=6015; RR 0.91, 95% CI, 0.74-1.11, p<0.001 for non-inferiority and p=0.34 for superiority vs. warfarin) and 1.11% in 150mg arm (n=6076, RR 0.66, 95% CI, 0.53-0.82, p<0.001 for non-inferiority and superiority vs. warfarin), compared to 1.69% the warfarin group.
The annual rate of myocardial infarction were significantly more common with both doses of dabigatran than with warfarin (mean of 0.73% vs. 0.53%; RR=1.36, 0.99-1.89, p=0.06 vs. warfarin).

Safety
In RE-LY, the annual rate of major bleeding for dabigatran was 2.71% in 110mg arm (RR 0.80, 95% CI, 0.69-0.93, p=0.003 vs. warfarin) and 3.11% in the 150mg arm (RR 0.93, 95% CI, 0.81-1.07, p=0.31 vs. warfarin) compared with 3.36% per year in pts administered with warfarin.
The annual incidence of major gastrointestinal bleeding (life threatening or not) for dabigatran 150mg and warfarin, was of 1.51% and 1.02%, respectively (RR 1.50, 95% CI, 1.19-1.89, p<0.001 vs. warfarin).
During the second year, there was a higher rate of dropout with dabigatran (~21%) than warfarin (16.6%).

Innovation and/or advantages
In patients with atrial fibrillation, dabigatran should be less susceptible to dietary, drug interactions and genetic polymorphisms than its comparator warfarin. Furthermore, neither anticoagulation monitoring nor dose adjustments are necessary with dabigatran compared to warfarin.

NHS and Financial Impact

Possible price
Price of dabigatran for the new indication is not yet available.
Taking into account the ex-factory price of dabigatran for the already authorised indication in Italy, the cost of 12-month therapy should be of € 2,409 for 110 mg bid-dose and € 4,818 for 150 mg bid-dose, compared with € 26.4 for warfarin administrated at 5mg/die (INR of 2.0 to 3.0).
The price per year per person of INR analysis is € 50.35 [cost is calculated based on the labour price performed 8 times during the first month (until INR stabilization) and once per month thereafter].

Italian possible setting: Community

Possible place in therapy
The aimed indication virtually includes all the patients with non-valvular AF (those with unstable INR with warfarin or for whom INR monitoring is not convenient, those treated with antiplatelet drugs, those not treated at all, incident patients). It is likely that dabigatran will only be reimbursed for the first of these patient categories. Replacement of prevention with antiplatelet agents by dabigatran in low-risk patients is not evidence-based since there is no head-to-head comparison of dabigatran and aspirin and/or clopidogrel in AF. Patients not compliant with warfarin are even less likely to comply with the bid regimen of dabigatran. Since there is no reason to switch patients with stable INR on warfarin to dabigatran, the cheaper treatment should be tried first in de novo patients too.

Current and future indications deserve consideration: dabigatran is currently approved (and reimbursed in Italy) for the prevention of VTE in orthopaedic surgery. It is being developed for the treatment of VTE and acute coronary syndrome. The marketing authorisation application submitted to the EMA at present regards the prevention of stroke and systemic embolism in NON-valvular AF. However, patients with VALVULAR AF are at higher risk of stroke and systemic embolism and it is likely that there will be an off-label use of dabigatran in these patients.

New Product Information Report

Rivaroxaban

Stroke prevention and systemic thromboembolism in AF

PG: 17-12-2010
Update: December 2011

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Summary

Clinical and Patients impact

Mechanism of action
Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability

Efficacy
In ROCKET-AF (randomised, double-blind, double-dummy, non-inferiority phase III trial) 14,264 patients with AF and *CHADS2-score* ≥2 were randomised to receive oral rivaroxaban (20 mg/day) or warfarin (dose adjusted to INR 2-3). After a median follow-up of 590 days, annual rate of stroke - ischemic or hemorrhagic- or systemic embolism (primary endpoint) in PP population was 1.7 % vs. 2.2% [rivaroxaban vs. warfarin; HR 0.79, 95% CI (0.66;0.96), p<0.001 for non-inferiority]. In the safety population, annual rate of ischemic stroke was 1.34% vs. 1.42% [HR 0.94, p=0.581] and annual rate of all-cause death was 1.87% vs. 2.21% [HR 0.85, p=0.073].

Safety
Annual rate of primary safety endpoint major + non-major bleeding was 14.9% vs. 14.5% [rivaroxaban vs. warfarin, HR 1.03 (0.96–1.11), p=0.44]. Annual rate of major bleeding (including clinically overt bleeding accompanied by a decrease in the haemoglobin level of ≥2 g/dL or transfusion of ≥2 units of packed red cells, occurring at a critical site, or resulting in death) was 3.6% vs. 3.4% [HR 1.04, 95% CI (0.90;1.20), p=0.58]. Among major bleeding, rivaroxaban augmented the annual frequency of transfusion (1.6% vs. 1.3%, p=0.04) and of decrease in haemoglobin of ≥2 g/dL (2.8% vs. 2.3%, p=0.02). During the trial, rate of treatment-emergent adverse events was 81.44% vs. 81.54% (rivaroxaban vs. warfarin). Total discontinuations were 23.7% vs. 22.2% and discontinuations due to AEs: 8.3% vs. 7.0%.

Innovation and/or advantages
Advantage of rivaroxaban over standard anticoagulation therapy (e.g. warfarin) is pharmacokinetics stability.

NHS and Financial Impact

Possible price
Price of apixaban is not yet available. One-month therapy with warfarin (dose-adjusted to INR 2.0-3.0) costs € 2.17. In addition, annual INR monitoring, according to standard laboratory protocol, costs € 50.35.

Italian possible setting: Community

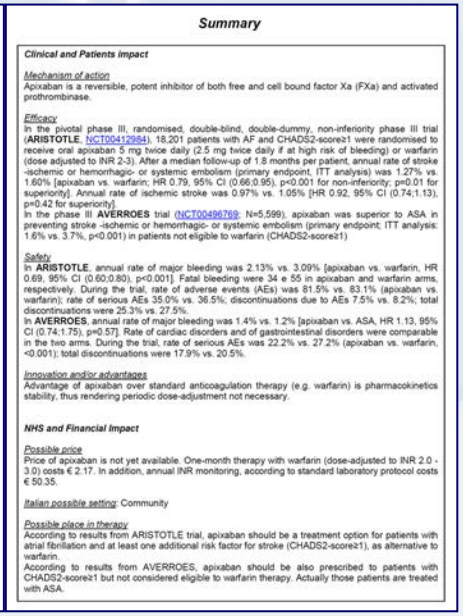
Possible place in therapy
According to trial results from ROCKET-AF and considering its inclusion/exclusion criteria, rivaroxaban should become a treatment option for patients with atrial fibrillation and presenting with CHADS2-score ≥2 (with history of stroke/TIA or systemic embolism or with at least two additional risk factors of stroke among age≥75; chronic heart failure, diabetes mellitus, hypertension or risk for future stroke).

New Product Information Report

Apixaban

Stroke prevention and systemic thromboembolism in AF

PG: 17-12-2010
Update: December 2011



Summary

Clinical and Patients impact

Mechanism of action
Apixaban is a reversible, potent inhibitor of both free and cell bound factor Xa (FXa) and activated prothrombinase.

Efficacy
In the pivotal phase III, randomised, double-blind, double-dummy, non-inferiority phase III trial (**ARISTOTLE**, NCT00412984), 18,201 patients with AF and CHADS2-score≥1 were randomised to receive oral apixaban 5 mg twice daily (2.5 mg twice daily if at high risk of bleeding) or warfarin (dose adjusted to INR 2-3). After a median follow-up of 1.8 months per patient, annual rate of stroke -ischemic or hemorrhagic- or systemic embolism (primary endpoint, ITT analysis) was 1.27% vs. 1.60% [apixaban vs. warfarin; HR 0.79, 95% CI (0.66;0.95), p<0.001 for non-inferiority; p=0.01 for superiority]. Annual rate of ischemic stroke was 0.97% vs. 1.05% [HR 0.92, 95% CI (0.74;1.13), p=0.42 for superiority].
In the phase III **AVERROES** trial (NCT00496769; N=5,599), apixaban was superior to ASA in preventing stroke -ischemic or hemorrhagic- or systemic embolism (primary endpoint; ITT analysis: 1.6% vs. 3.7%, p<0.001) in patients not eligible to warfarin (CHADS2-score≥1)

Safety
In **ARISTOTLE**, annual rate of major bleeding was 2.13% vs. 3.09% [apixaban vs. warfarin, HR 0.69, 95% CI (0.60;0.80), p<0.001]. Fatal bleeding were 34 e 55 in apixaban and warfarin arms, respectively. During the trial, rate of adverse events (AEs) was 81.5% vs. 83.1% (apixaban vs. warfarin); rate of serious AEs 35.0% vs. 36.5%; discontinuations due to AEs 7.5% vs. 8.2%; total discontinuations were 25.3% vs. 27.5%.
In **AVERROES**, annual rate of major bleeding was 1.4% vs. 1.2% [apixaban vs. ASA, HR 1.13, 95% CI (0.74;1.75), p=0.57]. Rate of cardiac disorders and of gastrointestinal disorders were comparable in the two arms. During the trial, rate of serious AEs was 22.2% vs. 27.2% (apixaban vs. warfarin, <0.001); total discontinuations were 17.9% vs. 20.5%.

Innovation and/or advantages
Advantage of apixaban over standard anticoagulation therapy (e.g. warfarin) is pharmacokinetics stability, thus rendering periodic dose-adjustment not necessary.

NHS and Financial Impact

Possible price
Price of apixaban is not yet available. One-month therapy with warfarin (dose-adjusted to INR 2.0 - 3.0) costs € 2.17. In addition, annual INR monitoring, according to standard laboratory protocol costs € 50.35.

Italian possible setting: Community

Possible place in therapy
According to results from ARISTOTLE trial, apixaban should be a treatment option for patients with atrial fibrillation and at least one additional risk factor for stroke (CHADS2-score≥1), as alternative to warfarin.
According to results from AVERROES, apixaban should be also prescribed to patients with CHADS2-score≥1 but not considered eligible to warfarin therapy. Actually those patients are treated with ASA.

Possible place in therapy

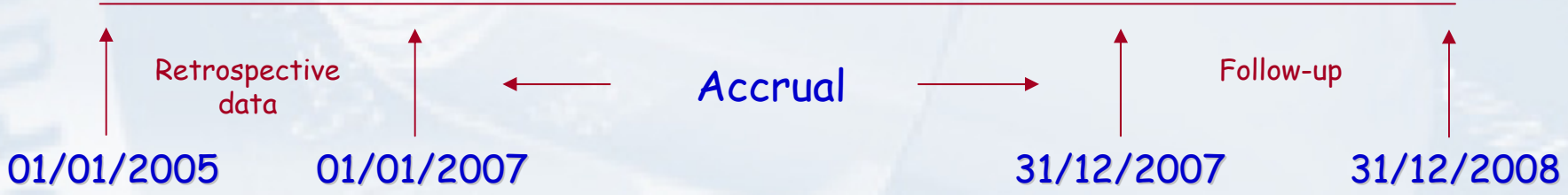
Alternative to warfarin in patients with AF, untreated and with CHADS2-score≥2, or unstable (2<INR<3)

Horizon Scanning:
A managed introduction of emerging drugs

- ✓ To produce timeliness Assessment of emerging drugs
- ✓ To compare "real world" patients with those included into RCTs
- ✓ To identify the potential target population for the new drugs

The example of the New Anticoagulants

Study design



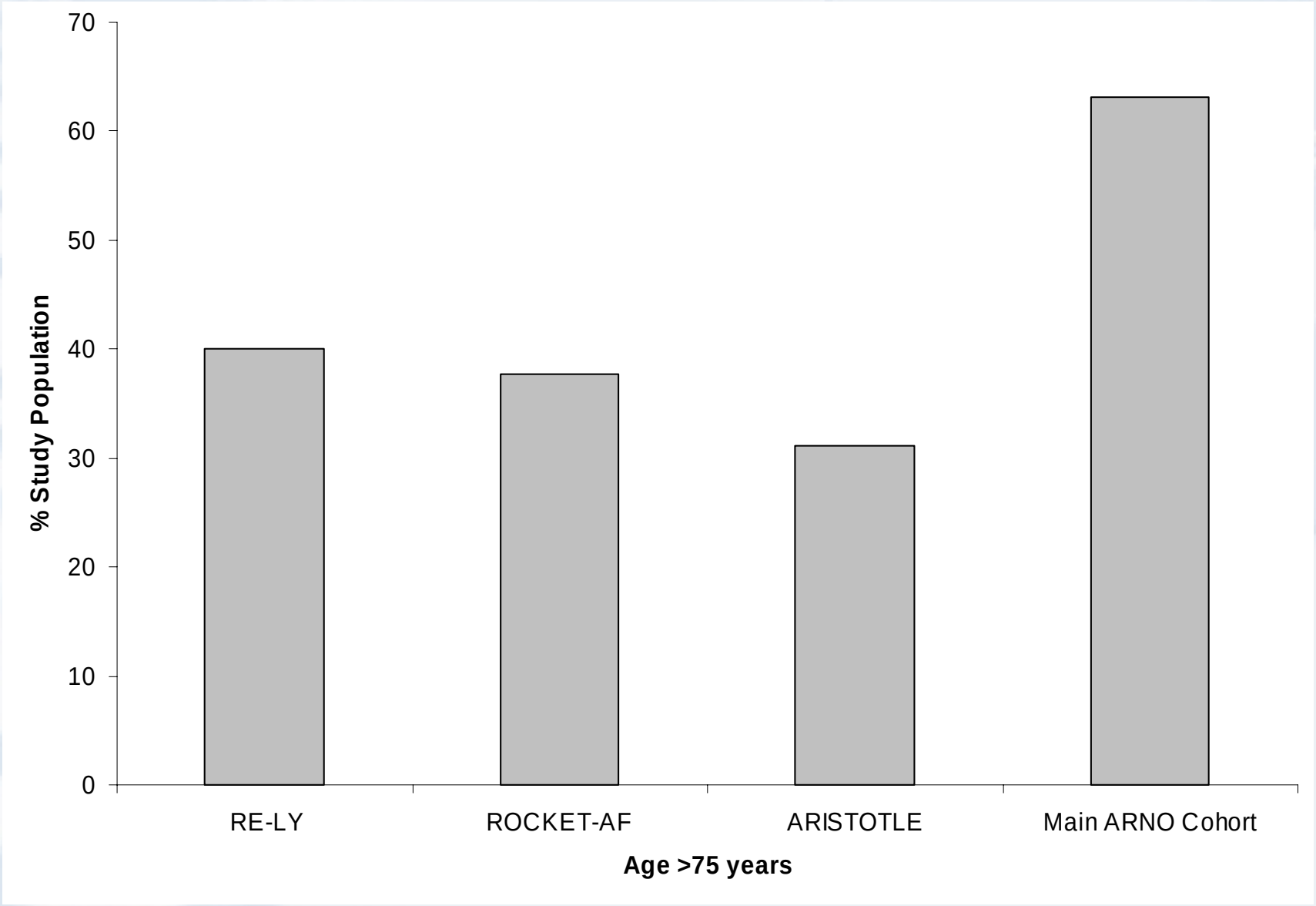
Cohort aged ≥18 years

2,862,264 subjects

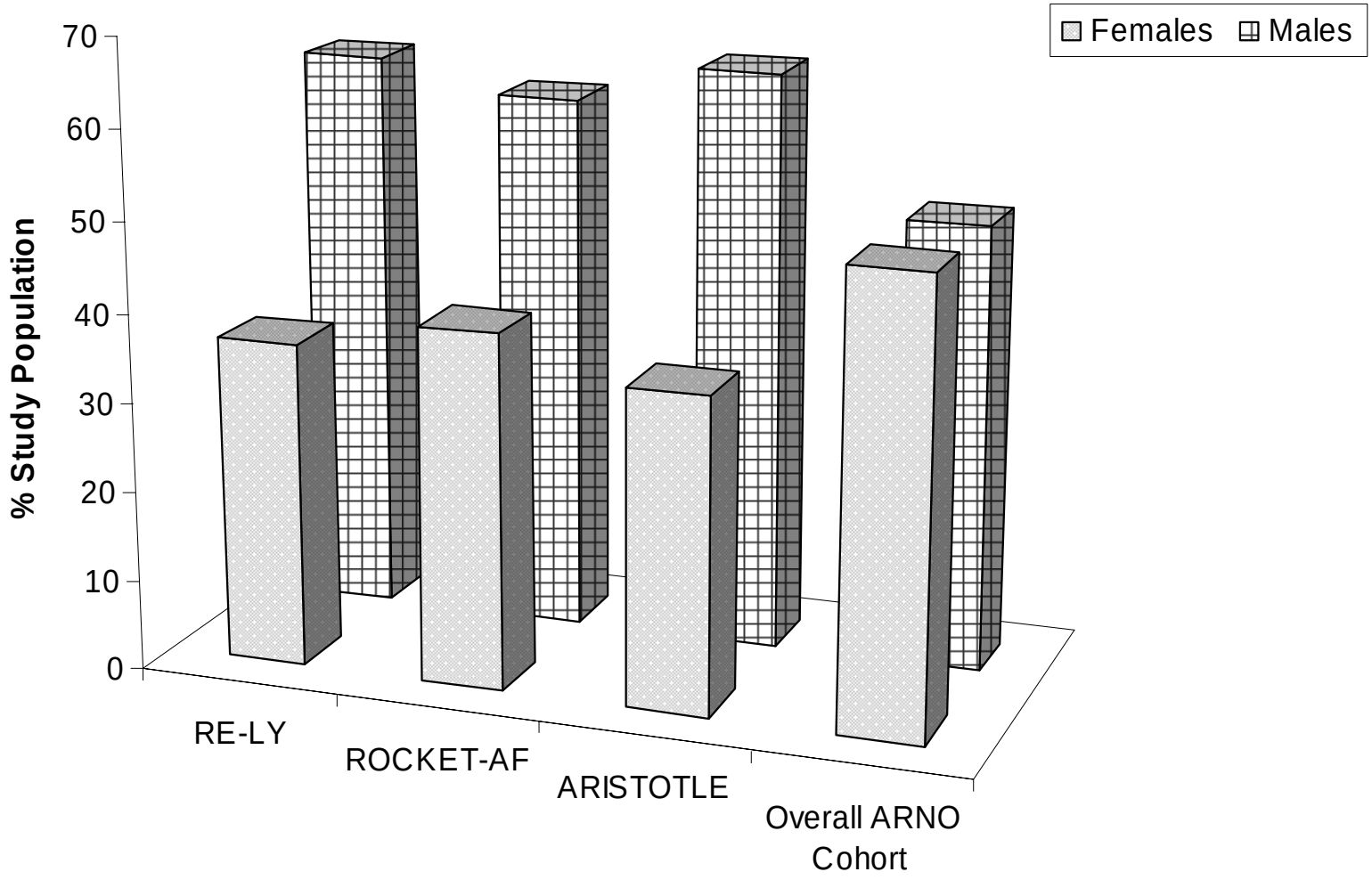
ARNO Cohort discharged with a diagnosis of non-valvular AF

13,360 subjects

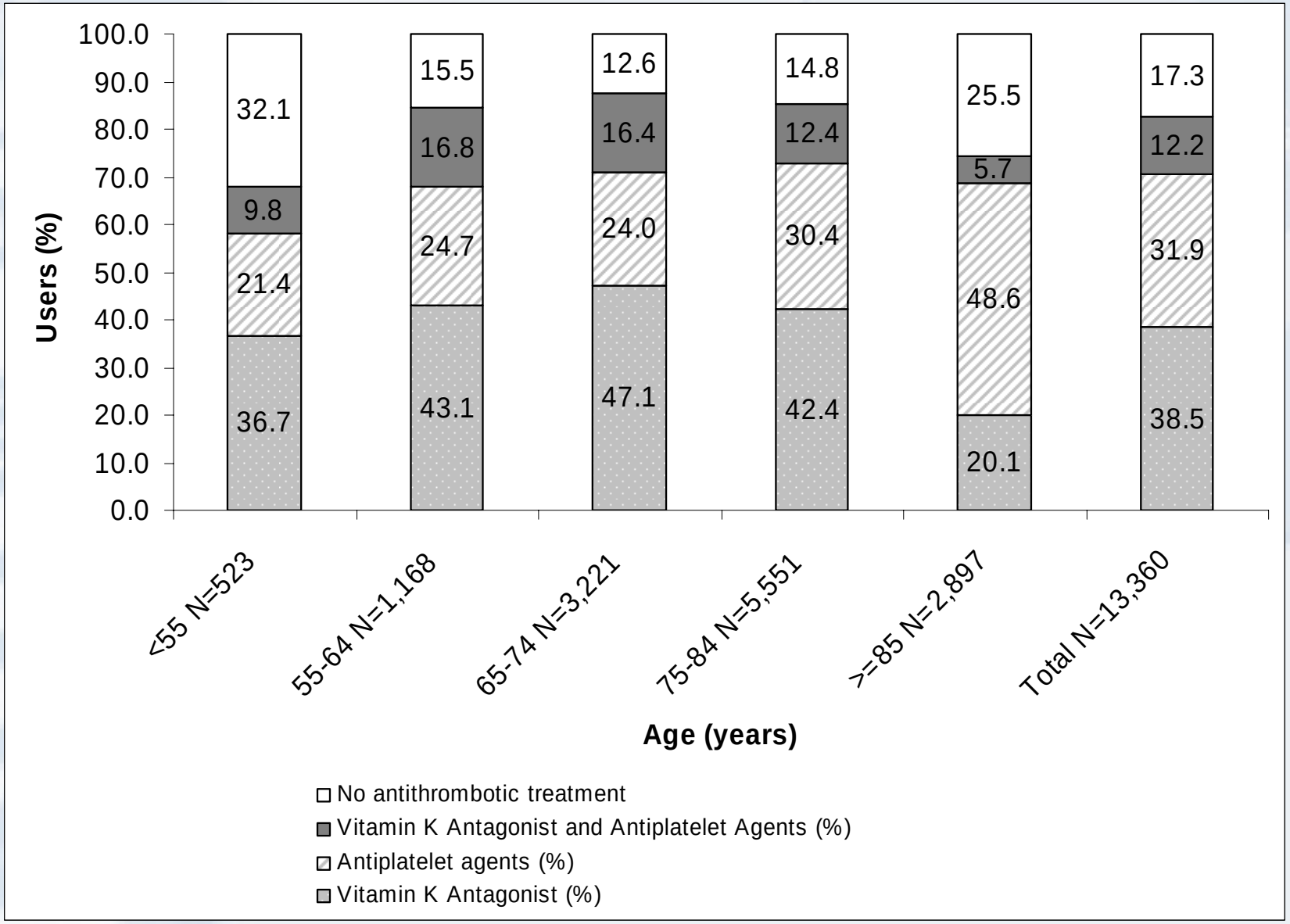
Distribution of patients aged >75 years in the ARNO cohort vs. RE-LY, ROCKET or ARISTOTLE studies



Gender distribution of the ARNO cohort vs. RE-LY, ROCKET or ARISTOTLE participants



Prevalence of antithrombotic treatments in the ARNO cohort according to age



Exclusion criteria

✓ Renal failure: 3.6% of the ARNO cohort was hospitalized in the previous 12 months

✓ Stroke: 2.2% (no inclusion into RE-LY and ROCKET-AF) of the ARNO cohort was hospitalized in the previous 6-12 months

Warnings

✓ Polipharmacy: 92.9% of the ARNO cohort treated with ≥3 associated drugs (mean 8 medicines/patient; range 1-28);

✓ Amiodarone: 20.1% of the ARNO cohort vs. 10.7% in RE-LY and 11.3% in ARISTOTLE, respectively ➡ to half the dose of dabigatran

Horizon Scanning:
A managed introduction of emerging drugs

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The example of the New Anticoagulants

Proposed Criteria for the treatment with the new anticoagulants

Patients with a diagnosis of non-valvular AF, no severe renal impairment, no severe stroke in the previous 6-12 months

AND

treated with ASA or no anti-thrombotic treatment and CHADS2 score ≥2 (UNTREATED)

OR

treated with Vitamin K antagonists but unstable (2<*INR*<3)

ARNO Cohort with non-valvular AF

13,360 subjects

Pts. hospitalized from renal failure
3.6%

Pts. hospitalized from stroke or TIA
2.2%

Potential eligible cohort

12,585 patients

UNTREATED

49.2%

UNTREATED

with CHADS2 score ≥2

62%

TREATED with

Vitamin k antagonists

38.5%

UNSTABLE (2<INR<3)

25%*

* Wallentin L. Lancet 2010 Sep 18;376(9745):975-83.

Italian patients aged ≥18 years with non-valvular AF

716,837*

Excuded due to severe renal impairment

3.6%

Excluded due to stroke or TIA

2.2%

Potentially eligible patients

675,261

UNTREATED (49.2%)

332,228 pts

UNTREATED

with CHADS2 score ≥2 (62%)

205,981 pts

TREATED with

Vitamin k antagonists (38.5%)

259,976 pts

UNSTABLE [2<INR<3] (25%)

64,994 pts

* Health Search – ESC 2008 – Eur Heart (2008) 29 (suppl 1): 505-32

NHS sustainability

UNTREATED
with CHADS2 score ≥2
205,981 pts

UNSTABLE [2<INR<3]
64,994 pts

Eligible patients
270,975

Possible price
€2.10/die

1° year market share: 8%
€13,292,950

2° year market share: 30%
€49,848,561

Key messages

- Early warning systems were developed to support policymakers in their decisions since HTA could not provide them with timely information.
- The use of administrative database can offer a relevant support in predicting the impact of emerging technologies on the NHS.

Summary

- Background
- Horizon Scanning: a managed introduction of emerging drugs
- **Registries**
- Risk-sharing schemes

Definition

A patient registry is an organized system that uses observational research methods to collect data for the scientific assessment of patients outcome.

Aims

A registry that is appropriately designed, conducted, and analysed provides unique scientific information about the appropriateness, effectiveness, and safety of the technology/intervention that is being studied.

Type of registries

Registry aimed at the appropriateness of drug use

- *considered for high cost drugs (potential risk for patients' safety or for public expenditure, in using he drug outside the authorized indication)*
- *an extremely simplified data collection is required*

Registry aimed at acquiring new info on the risk profile

- *duration and regional extension of data coherent with the expected incidence of events of interest*
- *attention in preventing that pts. are lost to follow-up*

Registry focused on effectiveness (reasons for possible discrepancies between pre-marketing studies and clinical practice)

- *Quality controls*
- *Ascertainment of confounding factors*

Italian registries

- In Italy, over the past 10 years, several registers associated with the reimbursement of drugs by the NHS have been put in place by the Ministry of Health.
- The regulatory path that made them grow comes from the so-called "note limitative" and treatment plans associated with the use of certain drugs.
- From these experiences different types of registries have been created that collect, at the time of prescription, information about the safety and appropriateness of use of medication where a benefit-risk profile in the general population is still not well defined.

Post-marketing studies run by the Ministry of Health

Study	Drug / Disease	Beginning Duration / N. pts.	Population	Study carachteristics	Aims / results
IMPROVE	Interferone + ribavirina Epatite C	1999 2 anni 7340 pz	Pazienti affetti da epatite cronica C mai trattati o con recidiva dopo il primo trattamento con IFN	Studio osservazionale multicentrico	Valutare la risposta terapeutica e la tollerabilità: non emerge un profilo beneficio-rischio diverso dall'atteso
CRONOS	Anticolinesterasici Demenza di Alzheimer	2000 2 anni ½ 40.000 pz	Pazienti affetti da DA di grado lieve o moderato	Studio osservazionale multicentrico in Unità di Valutazione individuate dalle regioni	Monitoraggio prospettico della terapia e valutazione del profilo di «sicurezza attribuibile» al farmaco nei reali contesti di utilizzazione
ANTARES	Anti-TNFα Etanercept e Infliximab Artrite reumatoide	2001 2 anni 1892 pz	Artrite reumatoide in fase attiva non rispondente ad altre terapie	Studio osservazionale in centri ospedalieri individuati dalle regioni	Valutazione dell'efficacia e tollerabilità e dell'adeguatezza della rete assistenziale
GLITAZONI	Rosiglitazone e tioglitazone	2000 >1 anno ½ 2000 pz x studio	Diabete mellito tipo 2 in pazienti con insufficiente controllo metabolico	Due protocolli prospettici di verifica dell'appropriatezza d'impiego e della safety	Valutazione del rischio cardiovascolare e del tasso di morbilità/ mortalità in terapia combinata con sulfaniluree o metformina; appropriatezza d'impiego
SYNERCID® LINEZOLID®	Quinupristin - dalfopristin linezolid Infezioni nosocomiali severe	>1 anno 150 pz 200 pz	Pazienti ospedalizzati con infezioni da Gram+ severe e resistenti	Osservazionale multicentrico in setting ospedaliero	Studio delle resistenze batteriche, criteri della scelta terapeutica, tossicità venosa e tollerabilità

Cronos

- effectiveness/safety register
- started in September 2000-2002 (I^ semester)
- was implemented by the Ministry of Health and the National Institute of Health
- registration of pts. with mild to moderate Alzheimer's disease was mandatory to administer acetylcholinesterase inhibitors by the specialists (neurologists, geriatricians, and psychiatrist)
- aims:

  - to characterize the population of Alzheimer's disease patients treated with acetylcholinesterase inhibitors,
  - to analyse effectiveness and drug safety in the clinical practice
  - to identify variables that may predict the response to therapy

Psocare

- appropriateness/effectiveness register
- started in September 2005-2009
- funded by the AIFA
- pts. registration mandatory to administer conventional and new systemic psoriasis therapies to pts. with moderate to severe psorisis
- standardized follow-ups to ascertain demographic and lifestyle characteristics, treatment exposure, psoriasis severity and any medical event (i.e. new diagnoses, hospitalizations, outpatient specialist visits)

Key messages

- In recent years the use of registries has grown considerably, particularly as manufacturers, regulators and other decisionmakers seek objective info to augment what is known from RCTs and other research studies about the harms and benefits of therapies.
- In the set out of a register it is important:

✓ To clearly define its purposes

✓ To guarantee:

a) *ad hoc resources*

b) *adequacy of infrastructures*

c) *adequate qualification of researcher/clinician*

d) *independence in data analysis*

e) *freedom to publish all findings*

Summary

- Background
- Horizon Scanning: a managed introduction of emerging drugs
- Registries
- **Risk-sharing schemes**

Risk-sharing schemes have been proposed for handling interventions with limited therapeutic evidence.

Italian risk-sharing schemes (I)

- ✓ pricing and reimbursement agreements depending on patient outcomes
- ✓ actively supported by manufacturers willing both to shorten time to market access and to obtain a good price
- ✓ based on the rates of "non-responders," defined as disease progression or progression-related death, unacceptable toxicity not allowing continuation of treatment or toxicity-related death
- ✓ non-responders have to be identified within a pre-set time for each drug/indication (median,8 ws.)

Italian risk-sharing schemes (II)

- ✓ based on Web registries run by AIFA (vs. several specific product registries held by manufacturers)
- ✓ hospital doctors are required to fill in an e-prescription (patient's identification data, indication for use and dosages)
- ✓ the system validates each prescription and automatically requests the hospital pharmacy to release the drug
- ✓ every single prescription for each patient is tracked, to monitor appropriate use
- ✓ the registry requires the treating physician to record follow-up clinical data and outcomes
- ✓ if a patient meets non-responder criteria, the hospital pharmacist applies for pay-back to the manufacturer, who can accept or reject the proposal (requiring arbitration)

The first Italian performance-based arrangement was agreed in July 2006 and by October 2010, 18 contracts have been in force (two medicines for age-related macular degeneration (ranibizumab and pegaptanib), and 15 onco drugs: erlotinib, sunitinib, sorafenib-RCC and sorafenib-hepatocarcinoma, bevacizumab, dasatinib, lenalidomide, nilotinib, temsirolimus, panitumumab, trabectidine, lapatinib, cetuximab, bortezomib, gefitinib, everolimus)

Criticisms

- undocumented non-responders are paid as a success
- pre-set timing: time frames are not always appropriate to allow a reliable assessment (e.g. only a small proportion of CML pts resistant to nilotinib or dasatinib can be detected within 4 ws.)
- scientific rationale of non-responder criteria has not been made public (reliability and applicability?)
- focusing on performance vs. non-performance: premium prices only for innovations that actually improve health?
- if a drug is administered outside the registry, the product is reimbursed outside any outcome-based arrangement
- overall compliance with registry procedures still seems to vary widely between Italian regions
- Italian regions do not seem yet able to quantify the amount of pay-back matured

Key messages

Risk-sharing agreements are an opportunity for:

- companies to shorten time to market access;
- specific patients groups that can possibly benefit of new treatment options;
- Health Authorities, which can pay for those patients who respond to the new treatment(s) only.

However, the Italian experience seems to support concerns raised elsewhere. Risk-sharing schemes :

- seem to be a complicated way of discounting (burden ties mainly on payers)
- require a full transparency on the non-responder criteria and an adequate pre-set timing
- actual compliance with registry requirements is needed to understand whether they are a consistent tool for assessing cost-effectiveness

THANK YOU FOR YOUR ATTENTION!