An Integrated Management Model of Patients With Atrial Fibrillation: The Experience of the Local Health Unit Tuscany North-West
An Integrated Management Model of Patients With Atrial Fibrillation: The Experience of the Local Health Unit Tuscany North-West .......................................................... 3

Introduction ........................................................................................................... 5

The Management of Atrial Fibrillation in the Local Health Unit Tuscany North-West ................................................. 7

The Burden of Atrial Fibrillation: A Review of Italian and International Literature ......................................................... 9

Conclusions ............................................................................................................ 13

References ............................................................................................................. 15
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An Integrated Management Model of Patients With Atrial Fibrillation: The Experience of the Local Health Unit Tuscany North-West

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ABSTRACT

Atrial fibrillation (AF) is the most prevalent form of alteration in cardiac rhythm and is associated with a high economic burden resulting from both clinical consequences and impact on patients’ quality of life. Goals of treatment include symptom control and, in the high-risk patients, the prevention of thromboembolic complications. The advent of novel oral anticoagulant agents (NOACs) has improved the management of patients with non-valvular AF (NVAF) by overcoming limitations associated with traditional oral anticoagulation drugs. NOACs are associated with a lower risk of stroke, systemic embolism, and mortality compared to vitamin K antagonists (VKAs) and with a lower risk of fatal, major, and intracranial bleeding. This supplement aims at sharing the virtuous management model of AF patients in the Local Health Unit Tuscany North-West and promoting the importance of a multidisciplinary management, which involves cardiologists and general practitioners (GPs), not only in terms of clinical outcomes, but also of therapeutic appropriateness and economic sustainability.

Keywords

Non-valvular atrial fibrillation; Novel oral anticoagulant agents; Multidisciplinary management; Therapeutic appropriateness
Introduction

Atrial fibrillation (AF) is the most prevalent form of alteration in cardiac rhythm and is associated with severe episodes of stroke, with a high degree of residual disability, and mortality, particularly in patients ≥75 years.

The high economic burden of AF results from both clinical consequences (i.e., high number of cardiovascular events among which stroke is the most important one) and impact on patients’ quality of life [1]. It has been estimated that in European countries the total cost for the management of AF ranged from 0.28% to 2.6% of overall health expenditure [2-5] and the global prevalence and costs associated with AF are expected to increase in the next years due to progressive aging of the population and the increase in the prevalence of risk factors, such as obesity, hypertension, and diabetes mellitus [6,7]. An epidemiologic study estimated that in Europe in 2030 the prevalence of AF would be 2.7%-3.3% with about 280,000-340,000 new ischemic strokes, 3.5-6 million hospitalizations for AF, and 100-120 million outpatient visits [7]. In Italy, an observational study published in 2017 estimated a prevalence of AF equal to 1.7% for a total of 1,036,448 cases [8].

Due to the high prevalence and the association with cardiovascular comorbidities (especially stroke), AF is considered a pathology characterized by a great economic and social burden [9]. It has been estimated that the mean cost for the acute management of stroke was about 20,000 €/year per patient plus 30,000 €/year per patient due to the management of the associated disability, which involved about 40% of stroke survivors, and indirect costs associated with loss of productivity [10-12]. Similar results came from a study conducted in UK, in which costs per patient over the first years after stroke arose from the costs of acute treatment (1-year vs 5-year healthcare costs were £ 13,452 and £ 17,963, respectively), while social care costs accounted for a greater proportion of the total care costs over time (£ 8,977 vs £ 28,076, respectively) [9].

Goals of treatment in the management of AF patients include the symptom control and, in the high-risk patients, the prevention of thromboembolic complications [13]. Particularly, as reported in the current European Guidelines [13], oral anticoagulation (OAC) is not indicated in the absence of clinical risk factors (CHA2DS2-VASc = 0), while it is highly recommended in subjects with AF and CHA2DS2-VASc ≥ 2 (if men) or ≥ 3 (if women) and should be considered in men with CHA2DS2-VASc = 1 and women with CHA2DS2-VASc = 2 [13].

Traditional OAC therapy with vitamin K antagonists (VKAs) demonstrated to reduce the risk of stroke by 64% vs placebo [14], but it is associated with some limitations, such as the need for regular dosage adjustment based on INR monitoring, the interaction with drugs and food, and the risk of major bleedings [15]. In the last years, the class of novel oral anticoagulant agents (NOACs) has been introduced for the treatment of non-valvular AF (NVAF, which involves about 70% of all AF cases), resulting in an improvement in the prevention therapy of thromboembolic events in these patients. Indeed, NOACs are associated with a lower risk of stroke, systemic embolism, and mortality compared to VKAs [16]. Also, safety outcomes are improved with a lower risk of fatal, major, and intracranial bleeding [16].

As reported in the European Society of Cardiology (ESC) Guidelines [13], in patients with AF an integrated and multidisciplinary approach should be considered, in order to increase detection of AF, ensure adequate management and follow up, improve treatment adherence, and reduce hospitalizations and mortality. This supplement aims at sharing the virtuous management model of AF patients in the Local Health Unit Tuscany North-West and promoting the importance of a multidisciplinary management, which involves cardiologists and general practitioners (GPs), not only in terms of clinical outcomes, but also of therapeutic appropriateness and economic sustainability.
The Management of Atrial Fibrillation in the Local Health Unit Tuscany North-West

In the last seven years, several initiatives have been undertaken in the Local Health Unit Tuscany North-West to improve the management of patients with NVAF and reduce the relevant adverse events and comorbidities.

Since 2012, a close collaboration has been established between cardiologists and GPs and this cooperation has allowed, not only to better manage the patients and improve communication between cardiologists and GPs, but also to collect and explore data about epidemiology, clinical practice, and populations state of health.

Furthermore, about five years ago the cardiology department of Versilia Hospital (Lido di Camaiore, Lucca, Italy) decided to implement a new management pathway for patients with AF discharged from emergency room (ER), in order to reduce mortality, hospital, and ER admissions and improve the use of appropriate and innovative treatments such as oral anticoagulant drugs.

THE INTEGRATED MANAGEMENT MODEL

Over the years, several actions have been carried out in the Tuscany Region to increase the integration between hospital and GPs, such as grouping GPs (AFTs – Territorial Functional Aggregates), the Sanità d’iniziativa and, finally, the establishment of Case della Salute.

Sanità d’iniziativa is a model of care which involves GPs and specialists with the aim of early intercepting patients with chronic diseases (i.e. diabetes, heart failure, hypertension, diabetes, etc.) and preventing the condition’s exacerbation. Casa della salute is a place where citizens find social and health services charged to the Italian National Health Service. A multidisciplinary team works in the Casa della Salute, which includes GPs, pediatricians, nurses, specialists, administrative figures, and social workers, and guarantees the patients’ overall management (medical records are shared), the continuity of care, and the integration between health and social assistance.

In 2012, the implementation of Sanità d’iniziativa allowed the beginning of the collaboration between the Casa della Salute in Querceta (Lucca, Italy), which refers to AFT 6, and Dr Giancarlo Casolo, cardiologist at the Versilia Hospital. This integrated management model provides that, two mornings a month, Dr Casolo visits patients, referred by GPs, in the cardiological consulting room at Casa della Salute. Furthermore, he has access to the same source of information of GPs in terms of patients’ medical records, medical history, pharmaceutical prescriptions, and comorbidities.

Working together, in the same place, is a great opportunity for both specialists and GPs: cardiologists have the chance to leave the hospital context and to have a closer relationship with patients; furthermore the interaction with GPs is helpful to better understand the patient’s characteristics and prescribe treatment and schedule follow-up accordingly. In the same way, from the GPs’ point of view, the presence of the cardiologist is a valuable diagnostic and therapeutic support that allows healthcare professionals, to share decisions, thus guaranteeing the best treatment to the patient and improving the use of available resources.

EPIDEMIOLOGY OF ATRIAL FIBRILLATION IN THE LOCAL HEALTH UNIT TUSCANY NORTH-WEST

In the AFTs, GPs work with the same medical practice management software, which collects electronic health records in a common database. Using these data an observational study was carried out with the aim of investigating the prevalence of NVAF and the pharmacoutilization of anticoagulant drugs in the Local Health Unit Tuscany North-West. The study, which analyzed health records of 42,545 patients from three out of six Tuscan AFTs, was presented at the ESC Congress 2016 [17].
Results, which refer to 2015, showed the presence of NVAF in 1,260 patients, thus resulting in a prevalence of 2.95%, with percentages ranging from 2.5% (677 NVAF/26,797 total population) in AFTs 1+3, to 3.7% (583/15,748) in the AFT 6. Age and sex distribution of NVAF revealed a greater number of cases in the 80-85 (21.4%) and >85 (21%) age groups, while a similar prevalence was reported for males and females (52.4% vs 47.6%). Finally, the pharmacoutilizaton analysis highlighted that, overall, only 52% of patients with NVAF were treated with an oral anticoagulant drug (VKA and NOAC). A 2019 update of these data showed a greater number of patients (1,787 NVAF/44,000 total population), a consequent higher prevalence of NVAF (4.06%), and a higher percentage of patients treated with VKA and NOAC (61%).

This increase in the prevalence of NVAF are probably due to a greater awareness of atrial fibrillation through the implementation of regional health policies (i.e., Sanità d’iniziativa and Health goals), and initiatives of individual AFTs (i.e. screening during the flu vaccination campaign) and hospitals (i.e. the close collaboration between GPs and cardiologists).

THE MANAGEMENT OF ATRIAL FIBRILLATION IN THE VERSILIA HOSPITAL

In the Versilia Hospital, patients who come to the ER with a first episode of NVAF, or with an increase in heart rate due to a pre-existing AF, or to a comorbid condition (i.e. pneumonia), are visited by emergency room physicians, who manage pharmaceutical and electrical therapy, while cardiology consultation is only required in the most severe cases.

According to clinicians experience, it emerged that 1) there was a time gap between discharge and start of anticoagulant therapy, and 2) most patients had a relapse a few days after discharge. For these reasons and with the aim to reduce adverse events due to the first episode of NVAF, a cardiologic consulting room for patients with AF discharged from ER was established and a new management pathway has been implemented.

The new pathway provides that emergency room physicians act according to a protocol shared with cardiology, assess the type of AF (i.e. first episode or persistent), calculate CHADS-VASc score, and, if necessary, start anticoagulation therapy (i.e. low molecular weight heparin). Afterwards, patients refer to the cardiology consulting room and are called back to schedule a visit within 3-4 days.

During the visit, cardiologists perform an overall assessment of the patient, investigate potential causes of AF, perform an ECG, and calculate CHADS2-VASc and HAS BLED scores. If eligible for treatment with anticoagulant drugs, patients are sent to the GP with a treatment plan and a summary report.

A first assessment of this new management pathway showed that about half of patients accessing ER with an episode of AF are intercepted by the cardiology consulting room and a decrease in the readmissions to ER and non-programmed hospital admissions has been observed. Furthermore, all patients with AF who were visited in the consulting room and were eligible for treatment, received prescription for anticoagulant therapy.
The Burden of Atrial Fibrillation: A Review of Italian and International Literature

AIM

A review of the literature has been performed with the aim of estimating the clinical and economic impact of AF, the pharmaceutic utilization of NOACs, and the role of prescriptive appropriateness on clinical and economic outcomes.

METHODS

The literature search was conducted using MEDLINE/PubMed and Google Scholar (time interval from 2015 to 2019) with no limitations on languages or geographical origin. The electronic search was supplemented by manual check of reference lists of included and not included studies. The keywords used for the search included: NVAF; AF; stroke; new oral anti-coagulant (NOAC); vitamin K antagonists (VKA); burden of illness; economic burden; RWD; registry; health care resource use; indirect and direct costs; compliance; adherence. Real world data and economic studies on costs, resources utilization, and pharmaceutic utilization in patients with AF have been included, while review and cost-effective analyses have been excluded.

RESULTS

The literature search identified 58 studies; of these 39 were excluded and 19 met the inclusion criteria and were analyzed (Figure 1).

Overview of the main studies

Direct cost associated with AF

The EPICARDIA study [18] is an observational, prospective, and multicenter study which evaluated direct costs associated with patients with NVAF admitted to the emergency rooms of two Italian hospitals between November 2004 and January 2005. The study followed 86 patients (mean age 69.2 years; 50% males) with NVAF for a year after discharge from the ER and recorded the consumption of health resources (new emergency room visits, hospital admissions, GPs or specialists visits, consumption of drugs, instrumental examinations). The results showed that the mean annual cost is about € 2,685 per patient, of which 83% is due to hospitalizations (Figure 2).

Pharmacoutilization of anticoagulant therapy

The observational study of Ermini et al. [19] used data collected by databases of GPs of a Local Health Unit in Italy aiming at assessing prevalence of AF and pharmaceutic utilization of OAC therapy. Between 2009 and 2012, the study enrolled 1,413 with AF (prevalence = 2.09%) and highlighted the

Figure 1. Flowchart of literature search

Figure 2. Distribution of costs per patient. Modified from [18]

1 Emergency room, day hospital, or hospital admission
underuse of OAC therapy: only 39.56% of patients received oral anticoagulant, 30% received antiplatelet therapy, and 16.28% received prescriptions for both therapies (only 4.17% received them at the same time). Furthermore, about 14% of patients did not receive any prescription of antithrombotic drug.

The retrospective study of Cataldo et al. [20] aimed at comparing the discontinuation risk and health care resource consumption between VKAs and NOACs in newly treated patients with NVAF. Based on administrative databases of five Italian Local Healthcare Units, 2,909 patients treated with VKA and 765 patients treated with NOAC with a discharge diagnosis of NVAF between 2011 and 2014 were included.

All patients included were followed from the first prescription date to the occurrence of any of the following events: a 90-day gap in therapy, switch to a different molecule or add-on of a different molecule into the regimen, death of patient, end of follow-up, all-cause hospitalizations, outpatient visits, and examinations.

Cox regression to model time to non-persistence within 12 months showed a 62% reduction in the risk of drug discontinuation in NOAC patients compared to VKA patients (HR: 0.38 [0.33-0.44]). Furthermore, NOACs were associated with less mean total number of all-cause hospitalizations, all-cause visits and examinations, compared to VKA (Table I).

GLORIA-AF is a prospective registry program describing antithrombotic treatment patterns in patients with newly diagnosed NVAF at risk of stroke. It comprises three phases: phase 1, before the introduction of NOACs; phase 2, during the time of the introduction of dabigatran, the first NOAC; and phase 3, once NOACs have been established in clinical practice (still ongoing). Phase 1 involved 1,063 patients, of whom 32.8% received VKA, 41.7% acetylsalicylic acid, and 20.2% did not receive any antithrombotic therapy. The phase 2 aim was to describe the effectiveness and safety of dabigatran etexilate over 2 years from routine clinical practice in GLORIA-AF patients who are newly diagnosed with NVAF and at risk of stroke. In phase 2 (n = 15,092), the prescription of oral anticoagulant drugs has increased (79.9% of patients, of whom 47.6% received NOAC and 32.3% VKA) while 7.9% of patients remain undertreated. Europe-related data (Figure 3) confirm the improvement of anticoagulation therapy (64.1% in phase 1 vs 89.8% in phase 2): particularly in phase 2, treatment with NOAC was more common than VKA (52.3% and 37.8%, respectively).

| Treatment at Index date | Health care resources (n) | Health care resource utilization Mean, n (SD) | p |
|------------------------|--------------------------|---------------------------------------------|---|
|                        |                          | n                                           |   |
| Outpatient visit       |                          |                                             |   |
| NOAC                   | 955                      | 1.84 (0.09)                                 | 0.0002 |
| VKA                    | 2,524                    | 2.33 (0.09)                                 |   |
| Laboratory examination |                          |                                             |   |
| NOAC                   | 4,796                    | 9.24 (7.90)                                 | < 0.0001 |
| VKA                    | 26,347                   | 24.35 (16.59)                               |   |
| Hospitalization        |                          |                                             |   |
| NOAC                   | 189                      | 0.36 (0.66)                                 | 0.0058 |
| VKA                    | 507                      | 0.47 (0.80)                                 |   |

Table I. Health care resource utilization on 12-month persistent users. Modified from [20]

Figure 3. Antithrombotic treatment patterns in Europe. Modified from [21]
Pharmacoutilization and clinical and economic outcomes

Cowan et al. [22] estimated the correlation between stroke rates and OAC use in England using data of patients with AF from 2006 to 2016. Results showed an increase in the prevalence of AF (from 1.29% to 1.71%) and in the hospitalization rate due to AF-related stroke/100,000 AF patients from 80/week in 2006 to 98/week in 2011. Afterwards, hospital episodes of AF-related stroke/100,000 AF patients decreased to 86/week in 2016. The use of anticoagulant drugs in patients at risk of stroke increased from 48.0% to 78.6% while the use of antiplatelet agents declined from 42.9% to 16.1%. Finally, after adjustment for AF prevalence, a 1% increase in the anticoagulant use was associated with a 0.8% decrease in the weekly rate of AF-related stroke.

The study of Maggioni et al. [23] aimed at assessing rates of hospitalization for AF, ischemic strokes, and major hemorrhages and prescriptions for VKAs, NOACs, and antiplatelet agents. Furthermore, yearly cost per patient with AF has been assessed. The study used the longitudinal “Ricerca e salute” database, which involves over 12 million inhabitants, and followed 194,030 patients who was discharged alive with primary or secondary diagnosis of AF between January 2012 and December 2013 for one year. The results showed an increase in

Figure 4. Yearly trends in antithrombotic drug use and in admissions for strokes and bleeds. Modified from [23]

Figure 5. Integrated yearly costs per AF patients from 2012 to 2015. Modified from [23]
admissions for AF from 2012 (3.98 per 1,000 subjects) to 2015 (4.35 per 1,000 subjects), an increase in the use of OACs (from 56.7% to 64.4%), largely due to NOACs uptake (from 0.8% to 27.7%), and a decrease in the prescriptions of antiplatelet agents. Figure 4, which reports the yearly trends in the antithrombotic drug use and in the admissions for ischemic or hemorrhagic stroke and major bleedings, shows a reduction in the rate of admissions for ischemic stroke, concomitant to the increased uptake of NOACs, while the rate of admissions for hemorrhagic stroke or major bleedings did not change substantially. Yearly cost per patient has decreased from 2012 to 2015 thanks to reduced costs for hospitalizations that offset the increase in drug costs (Figure 5).

Finally, a costing report published by NICE [24] aimed at assessing the economic impact of implementing the NICE guideline on atrial fibrillation in UK. In particular, the report focused on the recommendations that are deemed to have the greatest impact, such as:

- Do not offer aspirin monotherapy solely for stroke prevention to people with AF.
- Use the CHA\textsubscript{2}DS\textsubscript{2}-VASc stroke risk score to assess stroke risk in people with symptomatic or asymptomatic paroxysmal, persistent or permanent AF; atrial flutter; a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm.
- Refer people promptly at any stage if treatment fails to control the symptoms of AFR and referral for more specialized management is needed.

The report estimated that the effect of not offering aspirin to reduce stroke risk and assessing stroke risk using CHA\textsubscript{2}DS\textsubscript{2}-VASc may result in an increase in the pharmaceutical costs which, however, would be compensated by the reduction of strokes (Table II).
Conclusions

The advent of NOACs has improved the management of patients with NV AF by overcoming the limitations associated with traditional OAC drugs. Safety, efficacy, and effectiveness of NOACs have been confirmed by meta-analyses of randomized trials [16,25-29] and real-world studies [30-33]. In addition to the effects on clinical outcomes (decreased risk of stroke, bleedings, and death compared to warfarin), NOACs are associated with rapid onset of action, fixed dosing, no need for INR monitoring, and fewer food and drug interactions.

The literature review reported in this supplement confirms the statistical correlation between the increase in the use of NOACs and the reduction of correlated adverse events and highlights the economic impact of these drugs on the total cost for the management of AF. NOACs are indeed more expensive than traditional OAC therapy, but the increase in the drug cost is compensated by the decrease in other cost items, such as hospitalizations and management of the consequences of stroke. Therefore, it can be concluded that a greater therapeutic appropriateness, in terms of increase in the use of NOACs, as recommended by clinical guidelines [13], would be associated with better clinical outcomes without increasing total management costs. Unfortunately, despite the clinical and economic advantages associated with NOACs, in Italy their use is still low, even in patients at high risk of stroke for which NOACs would be the most appropriate treatments.

Born with the aim of improving the management of patients with AF, the integrated model of care implemented in the Local Health Unit Tuscany North-West and described in this supplement has been associated with several advantages. First, the analysis of data collected by the medical practice management software showed an improvement in the number of cases diagnosed and in the percentage of patients treated with NOAC from 2014-2015 to 2019. Already in 2015 (and again in 2019), the prevalence of NV AF was higher than the national mean, thus reflecting a major awareness of AF in this context. Since AF is often asymptomatic, GPs, as the points of first contact with the healthcare system, have indeed a crucial role in the early detection of the disease and, in this sense, Local Health Unit Tuscany North-West, thanks to the implementation of regional health policies, initiatives of individual AFTs, and hospitals, has always been a virtuous example in the diagnosis and management of AF.

Furthermore, the close collaboration which has been established between cardiologist and GPs at Casa della Salute, which includes the sharing of patients’ medical records, has allowed expanding and sharing skills, education, and experiences to provide patients with early diagnosis and the best management. This integrated approach is reflected not only in better clinical outcomes, but also in greater appropriateness and economic sustainability.

Importance of integrated management of patients with AF is also acknowledged by ESC Guidelines, which suggest to involve non-specialists professionals in educating patients, coordinating care and, where appropriate, starting the treatment and improving adherence. A prompt access to specialist knowledge is also required to optimize care and, in all patients with newly diagnosed AF, to help overcome the current limitations of AF management, such as underuse of OAC therapy, improve cardiovascular risk reduction, and fully evaluate the effect of AF on cardiovascular health [13]. Furthermore, as reported by Perino et al. [34], when patients with newly diagnosed AF receive cardiology care, instead of primary care only, clinical outcomes in terms of strokes and death are improved, probably due to early prescription of OAC therapy.

Unfortunately, this virtuous model of integration is not applied in other AFTs due to the lack of cardiologists, absence of Casa della Salute, and political and economic decisions. In the future, it would be desirable to extend in every AFT the integration with the cardiologist (with the sharing of medical records), the training of GPs in the management of AF, and the extension of professionals authorized to prescribe NOACs or, at least, to renew the treatment plan. Also, indicators should be identified in order to evaluate efficacy and effectiveness of the integrated management model.
Finally, it should be interesting to assess if this new model of care is associated with an appropriate therapeutic taking care of AF patients which allows avoiding adverse events occurrence and a sustainable model according to Local Health Unit Tuscany North-West perspective in terms of reduction in resource utilization and disability.

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References

1. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol* 2000; 36: 1303-9; https://doi.org/10.1016/S0735-1097(00)00886-X

2. Cotte FE, Chaize G, Gaudin AF, et al. Burden of stroke and other cardiovascular complications in patients with atrial fibrillation hospitalized in France. *Europace* 2016; 18: 501-7; https://doi.org/10.1093/europace/euv248

3. McBride D, Mattenklotz AM, Willich SN, et al. The costs of care in atrial fibrillation and the effect of treatment modalities in Germany. *Value Health* 2009; 12: 293-301; https://doi.org/10.1111/j.1524-4733.2008.00416.x

4. Ball J, Carrington MJ, McMurray JJ, et al. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. *Int J Cardiol* 2013; 167: 1807-24; https://doi.org/10.1016/j.ijcard.2012.12.093

5. Stewart S, Murphy NF, Walker A, et al. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart* 2004; 90: 286-92; https://doi.org/10.1136/hrt.2002.008748

6. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol* 2014; 11: 639-54; https://doi.org/10.1038/nrcardio.2014.118

7. Zoni-Berisso M, Lercari F, Carazza T, et al. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2014; 6: 213-20; https://doi.org/10.2147/CLEP.S47385

8. Andreotti F, D'Angela D, Mancusi RL, et al. Prevalence of atrial fibrillation, treatment eligibility and consumption of oral anticoagulants in Italian Local Health Authorities: impact of non-vitamin K antagonist oral anticoagulants. *G Ital Cardiol* 2017; 18: 230-8; https://doi.org/10.1714/2674.27400

9. Xu XM, Vestesson E, Paley L, et al. The economic burden of stroke care in England, Wales and Northern Ireland: Using a national stroke register to estimate and report patient-level health economic outcomes in stroke. *Eur Stroke J* 2018; 3: 82-91; https://doi.org/10.1177/2396987317746516

10. Lucioni C, Mazzi S, Micieli G, et al. Valutazione economica del trattamento con alteplase di pazienti con ictus ischemico in fase acuta, con riferimento all'Italia. *PharmacoEconomics - Italian Research* 2010; 12: 91-103; https://doi.org/10.1007/BF03320667

11. Fondazione Censis, A.L.I.C.e. Italia Onlus. I costi sociali ed i bisogni assistenziali dei malati di ictus cerebrale. 2010

12. Il Sole 24ore Sanità. I Quaderni di Medicina. Marzo 2011

13. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016; 18: 1609-78; https://doi.org/10.1093/europace/euw295

14. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; 146: 857-67; http://dx.doi.org/10.7326/0003-4819-146-12-200706190-00007

15. Ansell J, Hirsh J, Hylek E, et al.; American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133: 160S-98S; https://doi.org/10.1378/chest.08-0670

16. Makam RCP, Hoaglin DC, McManus DD, et al. Efficacy and safety of direct oral anticoagulants approved for cardiovascular indications: Systematic review and meta-analysis. *PLoS One* 2018; 13: e0197583; https://doi.org/10.1371/journal.pone.0197583
17. Casolo G, Cavrini G, Pardini M, et al. Prevalence of non valvular atrial fibrillation and Anticoagulation treatment in a large outpatient population. Analyss of the personal health records from different general practicioner groups. *Eur Heart J* 2016; 37: 504; [https://doi.org/10.1093/eurheartj/ehw432](https://doi.org/10.1093/eurheartj/ehw432)

18. Occhetta E, Diotallevi P, Venegoni L, et al. I costi sanitari della Fibrillazione Atriale. Follow-up a un anno dello studio EPICARDIA. *Giac* 2010; 13: 232-42

19. Ermini G, Perrone V, Veronesi C, et al. Antithrombotic prophylaxis of atrial fibrillation in an Italian real-world setting: a retrospective study. *Vasc Health Risk Manag* 2017; 13: 239-46; [https://doi.org/10.2147/VHRM.S136009](https://doi.org/10.2147/VHRM.S136009)

20. Cataldo N, Pegoraro V, Ripellino C, et al. Non-persistence risk and health care resource utilization of Italian patients with non-valvular atrial fibrillation. *Recenti Prog Med* 2018; 109: 113-21; [https://doi.org/10.1701/2865.28904](https://doi.org/10.1701/2865.28904)

21. Huisman MV, Rothman KJ, Paquette M, et al. The Changing Landscape for Stroke Prevention in AF: Findings From the GLORIA-AF Registry Phase 2. *J Am Coll Cardiol* 2017; 69: 777-85; [https://doi.org/10.1016/j.jacc.2016.11.061](https://doi.org/10.1016/j.jacc.2016.11.061)

22. Cowan JC, Wu J, Hall M, et al. A 10 year study of hospitalized atrial fibrillation-related stroke in England and its association with uptake of oral anticoagulation. *Eur Heart J* 2018; 39: 2975-83; [https://doi.org/10.1093/eurheartj/ehy411](https://doi.org/10.1093/eurheartj/ehy411)

23. Maggioni AP, Dondi L, Andreotti F, et al. Four-year trends in oral anticoagulant use and declining rates of ischemic stroke among 194,030 atrial fibrillation patients drawn from a sample of 12 million people. *Am Heart J* 2019; 220: 12-9; [https://doi.org/10.1016/j.ahj.2019.10.017](https://doi.org/10.1016/j.ahj.2019.10.017)

24. National Institute for Health and Care Excellence. Costing Report: atrial Fibrillation. Implementing the NICE guideline on atrial fibrillation (CG180). Published: June 2014

25. Miller CS, Grandi SM, Shimony A, et al. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. *Am J Cardiol* 2012; 110: 453-60; [https://doi.org/10.1016/j.amjcard.2012.03.049](https://doi.org/10.1016/j.amjcard.2012.03.049)

26. Liu T, Korantzopoulos P, Li L, et al. Survival benefit of new anticoagulants compared with warfarin in patients with atrial fibrillation: a meta-analysis. *Int J Cardiol* 2012; 156: 96-7; [https://doi.org/10.1016/j.ijcard.2011.12.093](https://doi.org/10.1016/j.ijcard.2011.12.093)

27. Dentali F, Riva N, Crowther M, et al. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation* 2012; 126: 2381-91; [https://doi.org/10.1161/CIRCULATIONAHA.112.115410](https://doi.org/10.1161/CIRCULATIONAHA.112.115410)

28. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. *Lancet* 2014; 383: 955-62; [https://doi.org/10.1016/S0140-6736(13)62343-0](https://doi.org/10.1016/S0140-6736(13)62343-0)

29. Lip GY, Mitchell SA, Liu X, et al. Relative efficacy and safety of non-vitamin k oral anticoagulants for nonvalvular atrial fibrillation: network meta-analysis comparing apixaban, dabigatran, rivaroxaban and edoxaban in three patient subgroups. *Int J Cardiol* 2016; 204: 88-94; [https://doi.org/10.1016/j.ijcard.2015.11.084](https://doi.org/10.1016/j.ijcard.2015.11.084)

30. Camm AJ, Amarenco P, Haas S, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J* 2016; 37: 1145-53; [https://doi.org/10.1093/eurheartj/ehv466](https://doi.org/10.1093/eurheartj/ehv466)

31. Steinberg BA, Holmes DN, Piccini JP, et al. Early adoption of dabigatran and its dosing in us patients with atrial fibrillation: results from the outcomes registry for better informed treatment of atrial fibrillation. *J Am Heart Assoc* 2013; 2: e000535; [https://doi.org/10.1161/JAHA.113.000535](https://doi.org/10.1161/JAHA.113.000535)

32. Yu AYX, Malo S, Svenson LW, et al. Temporal Trends in the Use and Comparative Effectiveness of Direct Oral Anticoagulant Agents Versus Warfarin for Nonvalvular Atrial Fibrillation: A Canadian Population-Based Study. *J Am Heart Assoc* 2017; 6: e007129; [https://doi.org/10.1161/JAHA.117.007129](https://doi.org/10.1161/JAHA.117.007129)

33. Datar M, Crivera C, Rozjabek H, et al. Comparison of real-world outcomes in patients with nonvalvular atrial fibrillation treated with direct oral anticoagulant agents or warfarin. *Am J Health Syst Pharm* 2019; 76: 275-85; [https://doi.org/10.1093/ajhp/zxy032](https://doi.org/10.1093/ajhp/zxy032)

34. Perino AC, Fan J, Schmitt SK, et al. Treating Specialty and Outcomes in Newly Diagnosed Atrial Fibrillation: From the TREAT-AF Study. *J Am Coll Cardiol* 2017; 70: 78-86; [https://doi.org/10.1016/j.jacc.2017.04.054](https://doi.org/10.1016/j.jacc.2017.04.054)
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