

2019;20(Suppl1): 3-16



farmeconomia

— Health economics and therapeutic pathways

Trimestrale Poste italiane spa. Spedizione in A.P. DL 353/2003 (conv. in LEGGE 27/02/04 n. 46)
art. 1 comma 1 - Torino - Reg. Trib. TO n. 5436 del 13 ottobre 2000 ISSN 1721-6915 - Suppl 1 anno 2019

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



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Farmeconomia. Health economics and therapeutic pathways (ISSN 2240-256X) is published by:

SEEd Medical Publishers S.r.l.

Via Magenta, 35 – 10128 Torino, Italy

Tel +39-011.566.02.58

info@seedstm.com

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Registrazione del Tribunale di Torino:

n. 5436 del 13/10/2000

N. iscrizione ROC: 16323

Printed in February 2020 on acid-free paper by La Grafica Nuova, Torino

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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 (NVA) 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

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Received: 9 December 2019

Accepted: 13 December 2019

Published: 19 December 2019

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 ($\text{CHA}_2\text{DS}_2\text{-VASc} = 0$), while it is highly recommended in subjects with AF and $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ (if men) or ≥ 3 (if women) and should be considered in men with $\text{CHA}_2\text{DS}_2\text{-VASc} = 1$ and women with $\text{CHA}_2\text{DS}_2\text{-VASc} = 2$ [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 *Casa 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 cardiologic 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 patients' 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 pharmaceutical utilization 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 pharmacoutilization 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 cardiology 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 pharmacoutilization 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 pharmacoutilization 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 pharmacoutilization of OAC therapy. Between 2009 and 2012, the study enrolled 1,413 with AF (prevalence = 2.09%) and highlighted the

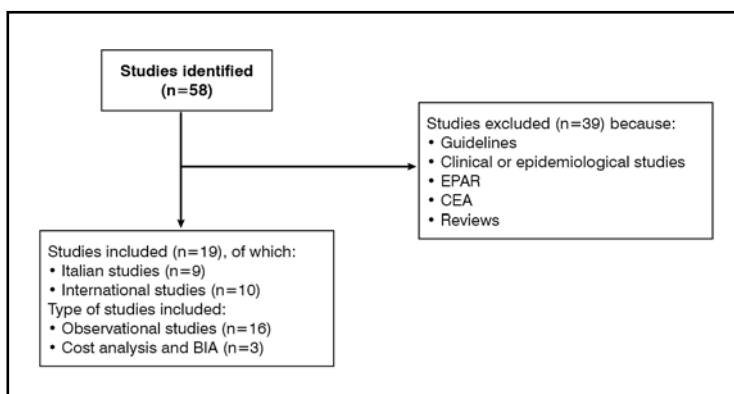


Figure 1. Flowchart of literature search

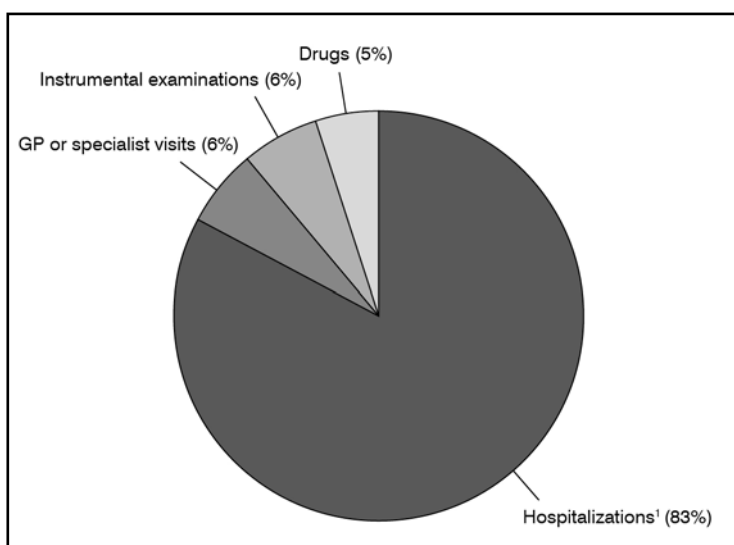


Figure 2. Distribution of costs per patient. Modified from [18]

¹Emergency room, day hospital, or hospital admission

Treatment at Index date	Health care resources (n)	Health care resource utilization	
		Mean, n (SD)	p
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]

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).

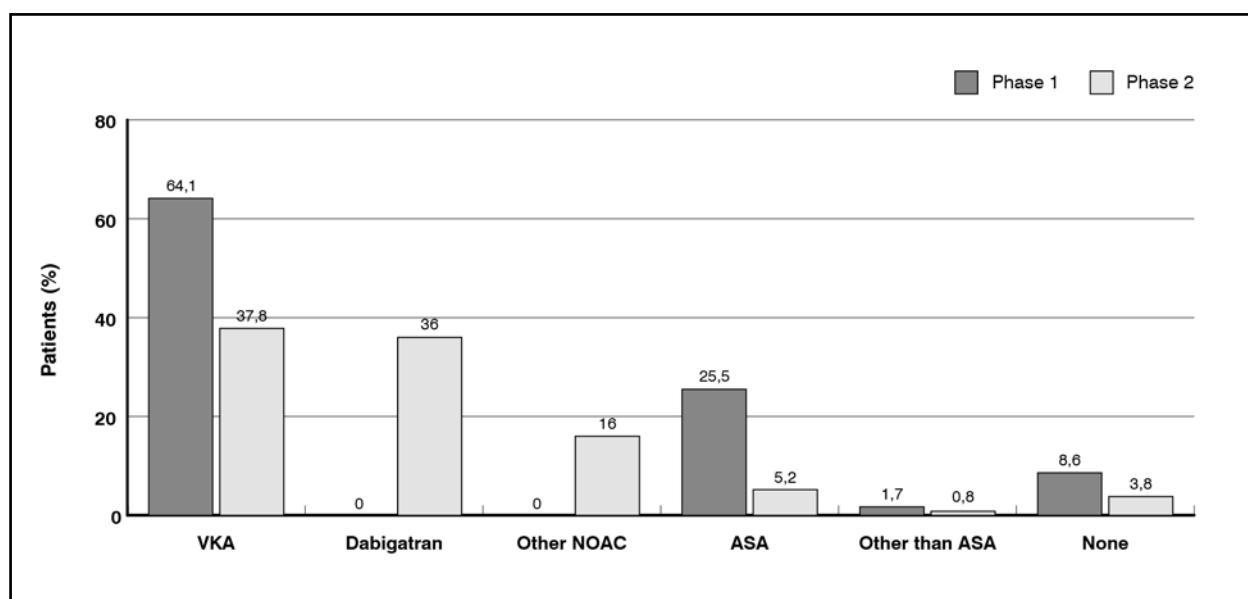


Figure 3. Antithrombotic treatment patterns in Europe. Modified from [21]

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

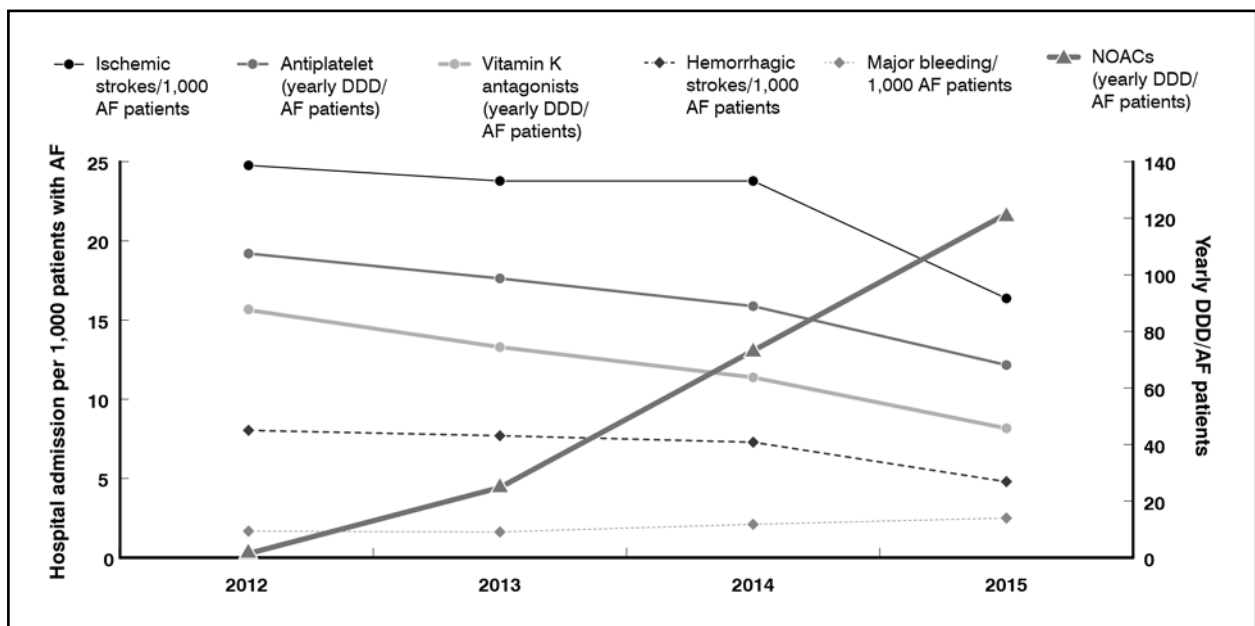


Figure 4. Yearly trends in antithrombotic drug use and in admissions for strokes and bleeds. Modified from [23]

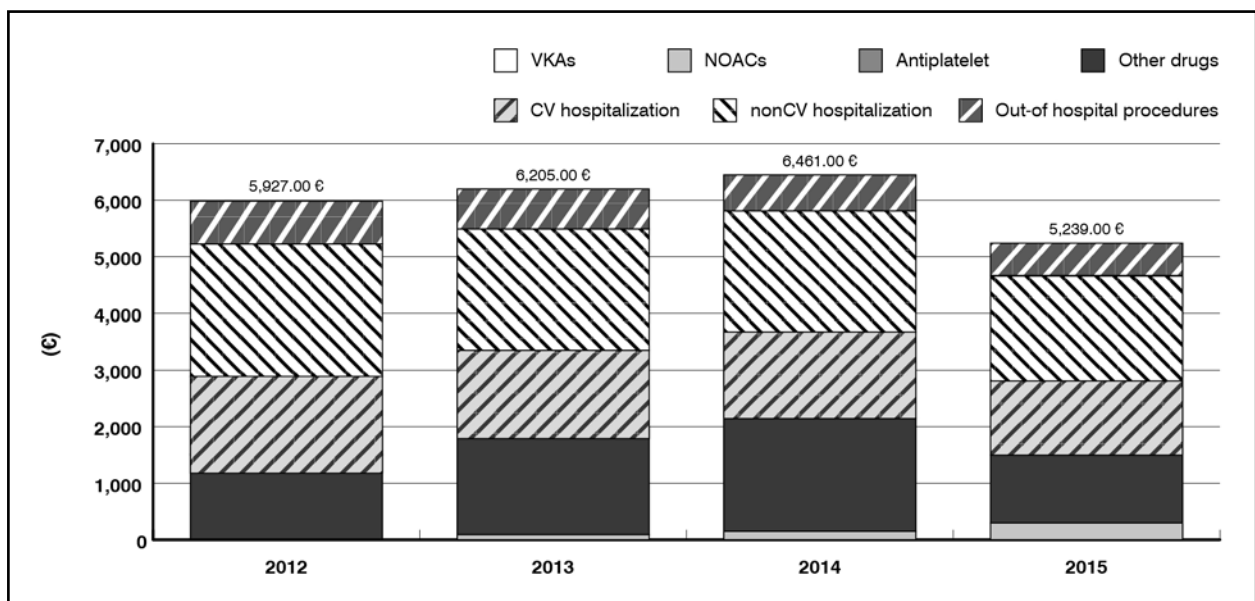


Figure 5. Integrated yearly costs per AF patients from 2012 to 2015. Modified from [23]

	Current treatment	Future treatment
Drugs		
Warfarin	34.32	46.76
Aspirin	22.49	2.50
Dabigatran etexilate	4.73	11.65
Rivaroxaban	4.73	11.65
Apixaban	4.73	11.65
No treatment	28.99	15.79
Estimated strokes (n x 100,000)	59	41
Costs (£ x 100,000)		
Drugs	347	654
Adverse events	733	513
Total	1,080	1,168

Table II. Overview of clinical and economic impact of implementing guidelines recommendations

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 CHA₂DS₂-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 CHA₂DS₂-VASc may result in an increase in the pharmaceutical costs which, however, would be compensated by the reduction of strokes (Table II).

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 anti-thrombotic 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

Conclusions

The advent of NOACs has improved the management of patients with NVAf 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 NVAf 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.

Funding

This supplement was realized with an unconditional contribution by Boehringer Ingelheim Italia S.p.A.

Conflict of interest

The Authors have nothing to disclose regarding the present work.



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This supplement was realized with an unconditional contribution by Boehringer Ingelheim Italia S.p.A.

