Effects of the availability of *n*ew oral *a*nticoagulants *i*n patients with non-valvular atrial *f*ibrillation in the real world: the NAIF study

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ABSTRACT

Guidelines recommend anticoagulation to prevent stroke in patients with non-valvular atrial fibrillation (NVAF). In the real world, this treatment is underused, probably for pharmacologic limitations of vitamin-K-antagonist (VKA). The new oral anticoagulants (NOAC) overcome many limitations of VKA. The aim of this study is to assess if, after introduction of NOAC, anticoagulated patients are increased. We performed an observational retrospective cohort study about patients with NVAF, hospitalized in Internal Medicine or Geriatrics for any cause in two years, before and after the marketing of NOAC. The results showed: 640 patients enrolled (289 in 2012, 351 in 2015), elderly population (83±7), males 42% females 58%, high morbidity, high thromboembolic (CHA_2DS_2VASc 5±1.6) and hemorrhagic (HASBLED 2.7±1.2) risks, with frequent chronic renal disease (51% stage ≥3) and contraindications to anticoagulants (21.6%). Therapy at discharge 2012 *vs* 2015: VKA 124/289 (43%) *vs* VKA or NOAC 187/351 (53%) (P<0.01); antiplatelet 114/289 (39%) *vs* 70/351 (20%) (P<0.0001). For the high comorbidity, frequent use of low-molecular-weight heparin: 42/289 (15%) in 2012 *vs* 77/351 (22%) in 2015. NOAC have increased the adherence to guidelines in prescribing oral anticoagulants in patients with NVAF.

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Contributions: FV conception and design of study, analysis and interpretation of data, writing and drafting of manuscript, references search, statistical analysis, coordination and supervision. FM conception and design of study, data collection, analysis and interpretation of data, statistical analysis, revising manuscript. SC, LI, SE data collection, revising manuscript. ME coordination and supervision, revising manuscript for important intellectual content.

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Introduction

International guidelines recommend oral anticoagulation for stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation (NVAF) at high thromboembolic risk.

Nevertheless, in the real world this treatment has been widely and significantly underused.

The causes are several: i) usual limited impact of guidelines in the real world (common to all areas of medicine);[1-3] ii) resistance of physicians to prescribe a high hemorrhagic risk therapy especially in elderly patients and/or those at high risk of falls;[4,5] iii) lack of attention of physicians to the quantification of the thromboembolic risk of AF and its balance with the hemorrhagic risk; iv) important limitations related to the use of vitamin K antagonists (VKA),[6] which were, until a few years ago, the only drugs used for this indication (unpredictable response, requiring periodic and constant laboratory monitoring and frequent dose adjustments, narrow therapeutic window, slowly in onset and cessation of the effect, many interactions with food and other drugs, resulting in poor adherence by patients).

The new oral anticoagulants (NOAC), also called direct oral anticoagulants (DOAC), have overcome many of the typical limitations of VKA; therefore, the actual availability of such drugs should facilitate the

management of oral anticoagulant therapy and improve adherence to guidelines in the prescription of anticoagulant prophylaxis in patients with NVAF at high risk of thromboembolism.

Type and aim of the study

Retrospective cohort observational study on patients with NVAF hospitalized for any cause in Internal Medicine or Geriatrics Departments in two different years, 2012 and 2015, respectively before and after the marketing of NOAC.

Aim of the study is to assess whether the availability of NOAC really increased the proportion of patients with NVAF at high risk of thromboembolism, treated with anticoagulant therapy, and therefore support the hypothesis that a major cause of underuse of oral anticoagulant therapy was due to objective limitations of VKA.

Materials and Methods

This study was carried out in Italy, in two hospitals in Apulia: Internal Medicine Department of G. Tatarella Hospital in Cerignola (FG) and Geriatrics Department of Miulli Regional Hospital in Acquaviva delle Fonti (BA). We enrolled all patients with NVAF, without any exclusion criteria, including those hospitalized for bleeding or for the execution of invasive procedures. For each patient, based on clinical documentation, we recorded the type of AF (paroxysmal, persistent or permanent), calculated the thromboembolic and hemorrhagic risks using CHA_2DS_2VASc and HASBLED scores, assessed renal function by eGFR (estimated according to the 4-variable MDRD equation),[7,8] using GFR calculator/app of the National Kidney Foundation - version 2.3.[9]

It was searched for the presence of contraindications to anticoagulation: i) active bleeding; ii) current or recent gastrointestinal ulcer; esophageal varices or suspected ones; iii) presence of cancer at high risk of bleeding; iv) recent brain or spinal injury, recent neurosurgery or ophthalmic surgery; v) recent intracranial hemorrhage; vi) arteriovenous malformation, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities; vii) other impediments (dysphagia, frequent falls, invasive procedures, acute liver failure, severe thrombocytopenia, patient refusal to anticoagulant therapy, *etc*.).

It was finally registered the prescribed therapy for prophylaxis of stroke and systemic embolism, and the remaining drug therapy taken by patients.

In ten patients treated with dual and triple therapy (anticoagulant + acetylsalicylic acid and/or clopidogrel), it was recorded oral anticoagulation for stroke prevention and antiplatelet for the associated ischemic heart disease.

Statistical analysis was performed using the chi-square test for comparing frequencies and the Student's *t*-test for comparison between means.

Results

The departments that conducted the study, carried out in total: i) in the year 2012 No. 2000 inpatient admissions, of which No. 289 had NVAF, with a prevalence of 14.4%; ii) in the year 2015 No. 2149 inpatient admissions, of which No. 351 had NVAF, with a prevalence of 16.3%.

Therefore, in the two years of study, 640 patients with NVAF were enrolled on 4149 inpatients (prevalence of 15.4%). Figure 1 shows, relative to the total number of admissions, the distribution of patients enrolled between the departments of Internal Medicine and Geriatrics in the years 2012 and 2015, and the differentiation by sex.

Table 1 summarizes the demographic and clinical characteristics of the study population.

This is an elderly population (aged 83±7 years), with a proportion of *very elderly* (≥90 years) of 16% (103 patients), while only 2% (11 patients) are aged <65 years. 92% have a reduction of eGFR <90 mL/min, in 51% of patients this reduction was <60 mL/min, concentrated primarily in the range of 59-30 mL/min (44%), while the IV-V stage of chronic renal failure was present in only 7%. Almost all the patients are at high risk of thromboembolism: 99% have a CHA_2DS_2VASc score ≥2 (with an average value of 5±1.6); only 3 patients have a CHA_2DS_2VASc of 1 (none is low risk with score of 0). Table 1 shows the distribution of each item of CHA_2DS_2VASc score in the population, which indicates the high comorbidity present in the study sample.

The high co-morbidity of this population is also confirmed by the polypharmacy, prescribed at discharge (in addition to anticoagulants or antiplatelet agents), and by the presence of frequent contraindications/impediments to anticoagulation (Table 2).

The two cohorts of the 2012 and 2015 show some differences: the one of year 2015 is considerably more numerous, it has a higher average age of 3 years, a greater presence of very elderly (≥85 years) and a higher prevalence of heart failure. They are almost identical with regard to the risk of thromboembolism (CHA_2DS_2VASc score) and hemorrhagic risk (HAS-BLED score).

Therefore, as regards the indications for anticoagulant therapy according to the guidelines, the two populations are overlapping.

The comparison of the therapy prescribed at discharge between the two years shows important differences (Figure 2).

In the year 2012, the anticoagulant therapy with

VKA was prescribed in 43% of cases (124/289), almost all with warfarin (acenocoumarol only 2 patients). The antiplatelet therapy was prescribed in 39% of cases (114/289): acetylsalicylic acid (ASA) in 30% (87 patients), clopidogrel in 7% (20 patients), ASA plus clopidogrel in 1% (3 patients), ticlopidine in 1% (4 patients). In 15% of cases (42/289) low-molecular-weight heparin (LMWH) was prescribed. In 3% of patients (9/289) no anticoagulant or antiplatelet drug was prescribed.

In the year 2015, there are important variations. The oral anticoagulant therapy (VKA or NOAC) was prescribed in 53% of cases (187/351), with statistically significant difference compared to 2012 (chi-square test P<0.01) (Figure 3). Considering the two anticoagulant treatments separately, VKA were prescribed in 27% (95/351), NOAC in 26% (92/351). So VKA and NOAC were used in nearly identical rates (respectively 50.8% *vs* 49.2% of all 187 patients under oral anticoagulant treatment).

Antiplatelet therapy was prescribed in 20% of cases (70/351), with statistically significant difference compared to 2012 (chi-square test P<0.0001) (Figure 3). As regards the antiplatelet drugs, were used: ASA in 12% (41 patients), clopidogrel in 6% (20 patients), ASA + clopidogrel in 2% (8 patients), ticlopidine in one patient.

In 22% of cases (77/351) LMWH was prescribed. In 5% of patients (17/351) no anticoagulant or antiplatelet drug was prescribed.

It should be emphasized that the fairly high rate of patients treated with LMWH, generally prescribed in prophylactic doses (*e.g.*, 4000 U/day of enoxaparin), both in 2012 and in 2015 (respectively 15% and 22%) should be related to the high rate of contraindications or objective impediments to oral anticoagulant therapy, already reported in Table 2: in many of these clinical situations, LMWH is the only possible *choice of compromise*.

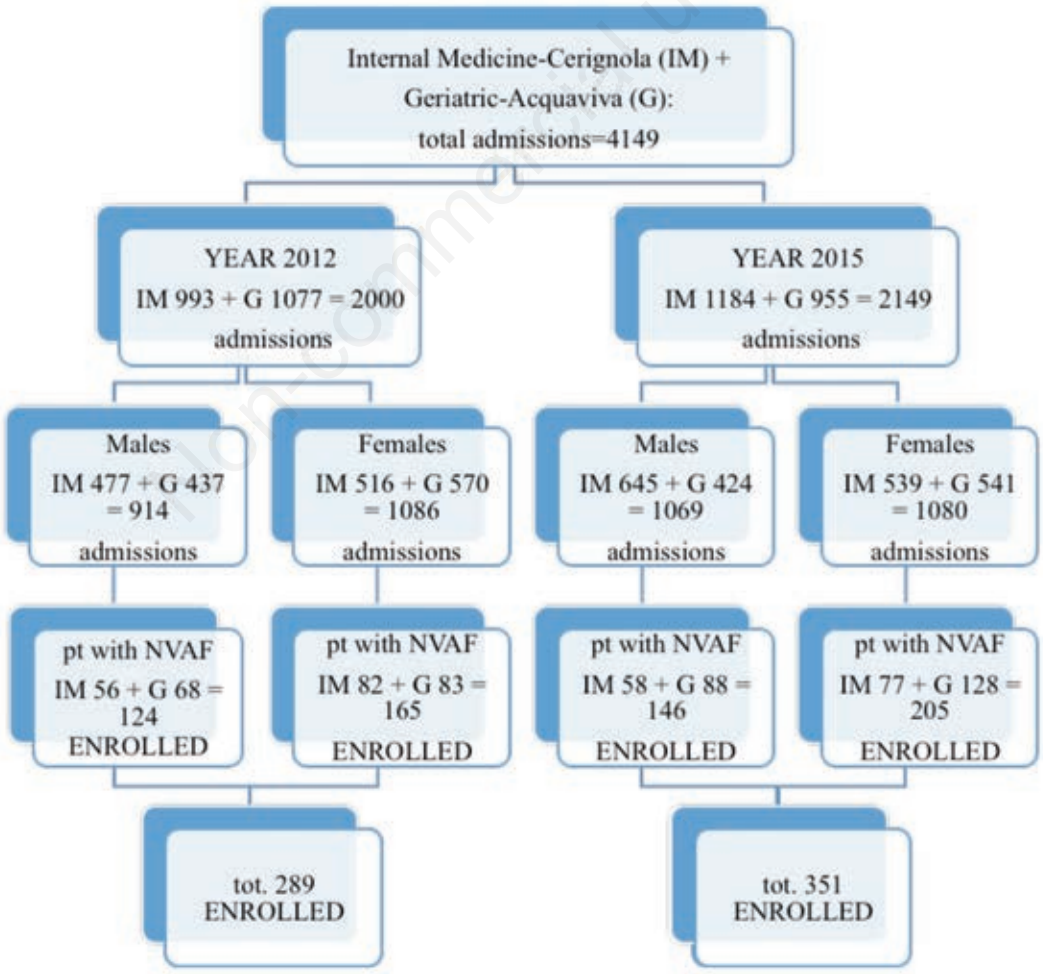

Figure 1. Flow-chart of enrolment of patients with non-valvular atrial fibrillation. pt, patients; NVAF, non-valvular atrial fibrillation.

Discussion

Anticoagulant therapy is highly recommended by all guidelines for stroke and systemic prevention in patients with NVAF with high thromboembolic risk.

Among guidelines of the main scientific societies, there are some differences on how to assess the thromboembolic risk, and on the risk threshold for prescription of anticoagulant therapy.

European guidelines[10] and American ones[11] agree on the fact that the CHA_2DS_2-VASc score is the best tool for risk gradation. A survey of 2013 shows that, in the European real world, the CHA_2DS_2-VASc score is by far the most popular, used by 93.2% of the centers, while only 6.6% use the $CHADS_2$.[12]

However, European and American guidelines differ on the threshold for the indication to anticoagulant therapy. European Society of Cardiology recommend

Table 1. Characteristics of the study population.

	2012	2015	Difference 2012 *vs* 2015	2012 + 2015
Total admissions	2000 (M 914, F 1086)	2149 (M 1069, F 1080)	-	4149
Whole cohort with NVAF	289	351		640
Male	124 (43%)	146 (42%)	NS	270 (42%)
Female	165 (57%)	205 (58%)	NS	370 (58%)
Age (mean±SD)	81±7 year	84±7	P<0.001	83±7
Age (range)	49-96 year	60-103	-	49-103
Age ≥90	30 (10%)	73 (21%)	-	103 (16%)
Age 85-89	71 (25%)	84 (24%)		155 (24%)
Age 75-84	145 (50%)	156 (45%)		301 (47%)
Age 65-74	37 (13%)	33 (9%)		70 (11%)
Age <65	6 (2%)	5 (1%)		11 (2%)
Type of AF:				
Paroxysmal	59 (20%)	80 (23%)	NS	139 (22%)
Persistent	14 (5%)	11 (3%)	NS	25 (4%)
Permanent	216 (75%)	260 (74%)	NS	476 (74%)
CHA_2DS_2VASc score:				
mean±SD	5±1.6	5±1.6	NS	5±1.6
range	1-9	1-9	NS	1-9
0	0	0	NS	0
1	3 (1%)	14 (4%)	NS	17 (3%)
≥2	286 (99%)	337 (96%)	NS	623 (97%)
HASBLED score:				
mean±SD	2.7±1.2	2.6±0.9	NS	2.7±1
range	1-7	1-6		1-7
eGFR (mL/min):				
mean±SD	63±28	59±21	NS	62±23
range	9-137	12-129	NS	9-137
K-DOQI stages:				
≥90 mL/min	8%	8%	NS	8%
89-60 mL/min	48%	34%	NS	41%
59-30 mL/min	37%	52%	NS	44%
29-15 mL/min	5%	5%	NS	5%
<15 mL/min	2%	1%	NS	2%
Item CHA_2DS_2VASc:				
Congestive heart failure	153 (53%)	219 (62%)	P<0.05	372 (58%)
Hypertension	225 (78%)	273 (78%)	NS	498 (78%)
Age ≥75 year	246 (85%)	313 (89%)	NS	559 (87%)
Diabetes	102 (35%)	123 (35%)	NS	225 (35%)
Stroke/TIA	75 (26%)	86 (25%)	NS	161 (25%)
Vascular disease	109 (38%)	110 (31%)	NS	219 (34%)
Age 65-74 year	37 (13%)	33 (9%)	NS	70 (11%)
Sex category (F)	165 (57%)	205 (58%)	NS	370 (58%)

NVAF, non-valvular atrial fibrillation; NS, not significant; SD, standard deviation; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack.

anticoagulation in all patients with CHA_2DS_2-VASc ≥1, with the exception of female patients with CHA_2DS_2-VASc=1 aged <65 years, in which the female gender is the only risk factor. This position is substantially confirmed by guidelines of the Asia-Pacific Heart Rhythm Society,[13] by English guidelines of the National Institute for Health Care Excellence (NICE)[14] and by Italian guidelines of the Association of Arrhythmology and Cardiac-stimulation (AIAC).[15]

Instead the guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) have a slightly more restrictive approach: they recommend anticoagulation in patients with previous stroke or transient ischemic attack (TIA), or in those with CHA_2DS_2-VASc score ≥2, while in patients with CHA_2DS_2-VASc=1 they do not recommend any antithrombotic therapy, anticoagulants or ASA.[11]

Canadian guidelines differ from the previous in the thromboembolic risk assessment, proposing an algorithm based on age at first and then on the old $CHADS_2$ score.[16]

Beyond the above-described differences, all guidelines give a strong recommendation for use of oral anticoagulant therapy in patients with NVAF at high risk; nevertheless, in the real world this treatment has so far been widely underused.[17-21]

Even in very high-risk patients, such as those with previous TIA or stroke, oral anticoagulant therapy is prescribed, in the best case studies, only in about 60%. Underuse is particularly relevant in older patients. In a cohort of outpatients without contraindications for anticoagulation, the prescription of anticoagulant therapy was performed in 55% of the total population, but in the cohort of patients ≥85 years it decreased drastically to 35%.[22]

In Italy, the situation is much diversified. There are some studies finding very low rates of anticoagulation in patients with AF at high thromboembolic risk (29%[23] and 26%[24]).

More recently, better performances were found in the ATA-AF study,[25] where anticoagulant therapy is prescribed in 58.8% of the total patients, although with differences between cardiologists (whose patients were anticoagulated in 67% of cases) and internists (49.1%). Conversely, internists use most often ASA (42.7%) compared to cardiologists (26.7%). 7.1% of patients in the study were not receiving anticoagulant therapy or either ASA.

Similar results are found in the ARAPACIS study,[26] where 55% of the total of enrolled patients are treated with anticoagulant therapy; considering only high-risk patients (CHA_2DS_2VASc ≥2) the rates of anticoagulated patients rise slightly with differences depending on the region (Nord 61%, Center 60% and South 53%).

Table 2. Factors indicative of comorbidity: main drugs prescribed at discharge and contraindications/impediments to anticoagulation (whole cohort: 2012=289, 2015=351).

	Other drugs prescribed at discharge											
Year	**Diuretics**	**β-blockers**	**Statin**	**ACE-i**	**ARBs**	**Digoxin**	**Oral antidiabetics**	**Insulin**	**Nitrates**	**Antiarrhythmic**	**Calcium channel blockers**	
2012	214 (74%)	127 (44%)	60 (21%)	82 (28%)	70 (24%)	87 (30%)	58 (20%)	42 (15%)	57 (20%)	33 (11%)	23 (8%)	
2015	267 (76%)	185 (53%)	95 (27%)	61 (17%)	69 (20%)	53 (15%)	62 (18%)	52 (15%)	37 (11%)	45 (13%)	35 (10%)	
Total	481 (75%)	312 (49%)	155 (24%)	143 (22%)	139 (22%)	140 (22%)	120 (19%)	94 (15%)	94 (15%)	78 (12%)	58 (9%)	
	Contraindications/impediments to anticoagulation											
Year	**Active bleeding**	**Current or recent gastro-intestinal ulcer; esophageal varices**	**Cancer at high risk of bleeding**	**Recent brain or spinal injury, recent neurosurgery or ophthalmic surgery**		**Recent intracranial hemorrhage**	**Arteriovenous malformation, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities**		**Other impediments (dysphagia, frequent falls, invasive procedures, acute liver failure, severe thrombocytopenia, patient refusal to anticoagulant therapy, *etc.*)**		**Total**	
2012	19 (6.6%)	17 (5.9%)	7 (2.4%)	0		1 (0.3%)	0		8 (2.8%)		52 (18%)	
2015	34 (9.7%)	13 (3.7%)	4 (1.1%)	0		9 (2.6%)	0		26 (7.4%)		86 (24.7%)	
Total	53 (8.3%)	30 (4.7%)	11 (1.7%)	0		10 (1.6%)	0		34 (5.3%)		138 (21.6%)	

ACE-i, angiotensin-converting-enzyme inhibitor; ARBs, angiotensin receptor blockers.

Compared to the ATA-AF study, which enrolled both inpatients and outpatients, with valvular AF or NVAF, our study enrolled only inpatients with NVAF. Except these important distinctions, the characteristics of the sample of our study are comparable to those of Internal Medicine of the ATA-AF study with a few minor differences. In our study, the average age is slightly higher, there is a greater prevalence of heart failure and kidney failure; furthermore, the presence of contraindications or impediments to oral anticoagulant therapy is more relevant. Regarding anticoagulant therapy, in the ATA-AF study 46.3% of Internal Medicine patients with NVAF take oral anticoagulant therapy, whereas in our study the oral anticoagulant therapy was prescribed in 43% of patients in 2012, rising to 53% in 2015.

In the ARAPACIS study were enrolled both inpatients and outpatients, but only with NVAF, on average younger than those of our study; our population has an average age of about 10 years older than the ARAPACIS cohort of southern regions. In addition, enrolment in the ARAPACIS study excluded patients with active cancer or diseases with a life expectancy of less than three years, which are frequent conditions in our population and often represent contraindications to anticoagulation. This difference should be duly assessed in comparing our anticoagulation rates (43% in 2012 and 53% in 2015) vs those of the ARAPACIS study, whose anticoagulation rates are 55% on the entire population and 53% on the southern Italian population.

Another important aspect of our study, worthy of proper assessment, is the significant rate of our population treated with LMWH (15% in 2012 and 25% in 2015). It is known that LMWH is an anticoagulant treatment that has no indication in atrial fibrillation; nevertheless, in many cases it is the only antithrombotic treatment that can be administered, sometimes even only for limited periods (patients with swallowing deficiency, patients about to undergo invasive procedures, patients at very high risk of bleeding, *etc.*). LMWH was usually prescribed in prophylactic doses (*e.g.*, 4000 U/day of enoxaparin) in both cohorts.

A special emphasis deserves the assessment of usage preferences of VKA *vs* NOAC: in 2015 VKA and NOAC are used in almost identical rates (respectively 50.8% *vs* 49.2% of all patients on oral anticoagulant treatment). This finding appears significant in comparison with the results of the European Heart Rhythm Association survey of 2013, in which 73.3% of physicians, in the priority ranking of anticoagulants consider VKA the first choice,[27] and EORP-AF Pilot Survey, in which VKA were prescribed in 72.2% of cases *vs* 7.7% of NOAC.[28]

Similar to our balanced use of VKA and NOAC are the latest results of the European Heart Rhythm Association Survey, in which NOAC were preferred (33.3%) or considered equal (48.5%) to VKA.[29]

In our population, the choice between VKA and DOAC was carried out based on specific criteria, differentiated for naive patients (not previously taking any anticoagulant therapy) and patients already receiving VKA.

In naive patients, DOAC were prescribed if there were one or both of the following conditions of eligibility laid down by the Italian Drug Administration (AIFA): i) CHADSVASC score ≥1 and HASBLED score >3; or ii) impracticability of treatment with VKA for objective difficulties to ensure the monitoring of international normalized ratio (INR). VKA were prescribed in the absence of both of these conditions or in patients with contraindications to DOAC (*e.g.*, severe kidney or liver failure, need for concomitant use of drugs that cannot be associated with DOAC, *etc.*).

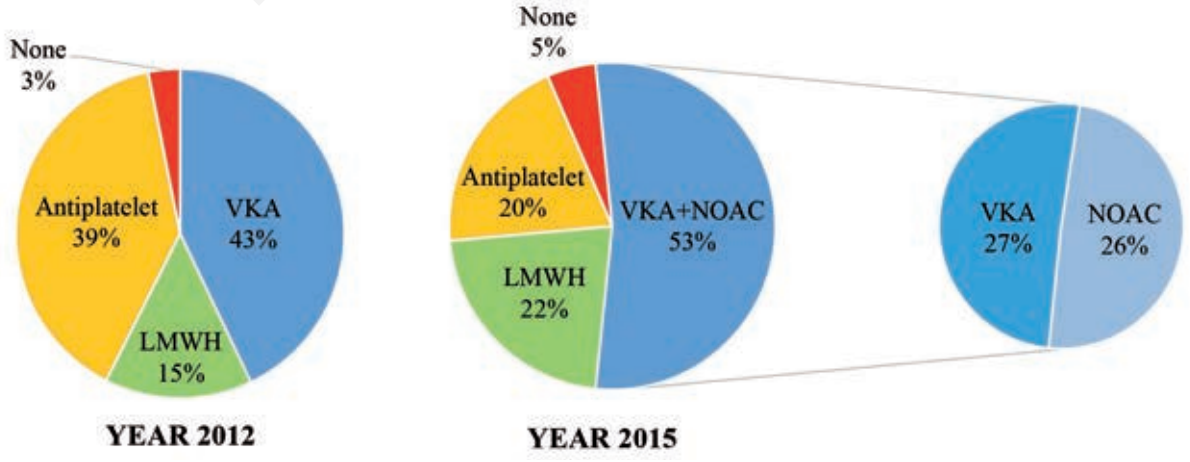

Figure 2. Antithrombotic therapy at discharge. VKA, vitamin-K-antagonist; LMWH, low-molecular-weight heparin; NOAC, new oral anticoagulants.

VKA were also preferred in cases in which, after discussion with the patient and/or family members, in the opinion of the physician the frequent monitoring of INR was considered useful in order to motivate and improve patient adherence to therapy.

In patients already on therapy with VKA, this treatment was continued if there was a good time in therapeutic range (>60-70%) without complications or side effects, or if the patient and/or family members communicated the desire to continue VKA. In the absence of such conditions, the treatment was changed to DOAC, provided that there were no contraindications to these drugs.

Conclusions

Our real-life NAIF study shows as the prescription of antithrombotic therapy for prevention of stroke and systemic embolism in patients with NVAF has changed in two different years, 2012 and 2015, respectively, before and after the marketing of NOAC. The results demonstrate that, in patients admitted to internal medicine or geriatrics departments, characterized by difficult management for advanced age, high comorbidity, poly-therapy and high prevalence of contraindications/impediments to anticoagulation, the availability of NOAC has improved adherence to guidelines, increasing the prescription of oral anticoagulant therapy from 43% in 2012 to 53% in 2015 (P<0.01) and reducing the prescription of antiplatelet from 39% in 2012 to 20% in 2015 (P<0.001).

An important proportion of the enrolled sample was found to have contraindications/impediments to oral anticoagulant therapy (18% in 2012 *vs* 24.7% in 2015). This helps to explain not only the small rate of patients without prescription for any antithrombotic drug (2% in 2012 *vs* 5% in 2015), but also a significant rate of patients treated with LMWH (15% in 2012 *vs* 22% in 2015).

Our study supports the hypothesis that, among the various possible causes of the underuse of oral anticoagulant therapy for stroke prevention and systemic embolism in patients with NVAF, an important component is due to the pharmacological limitations of VKA. NOAC, which have not such limitations, allow us to offer the oral anticoagulant therapy even in patients of difficult management.

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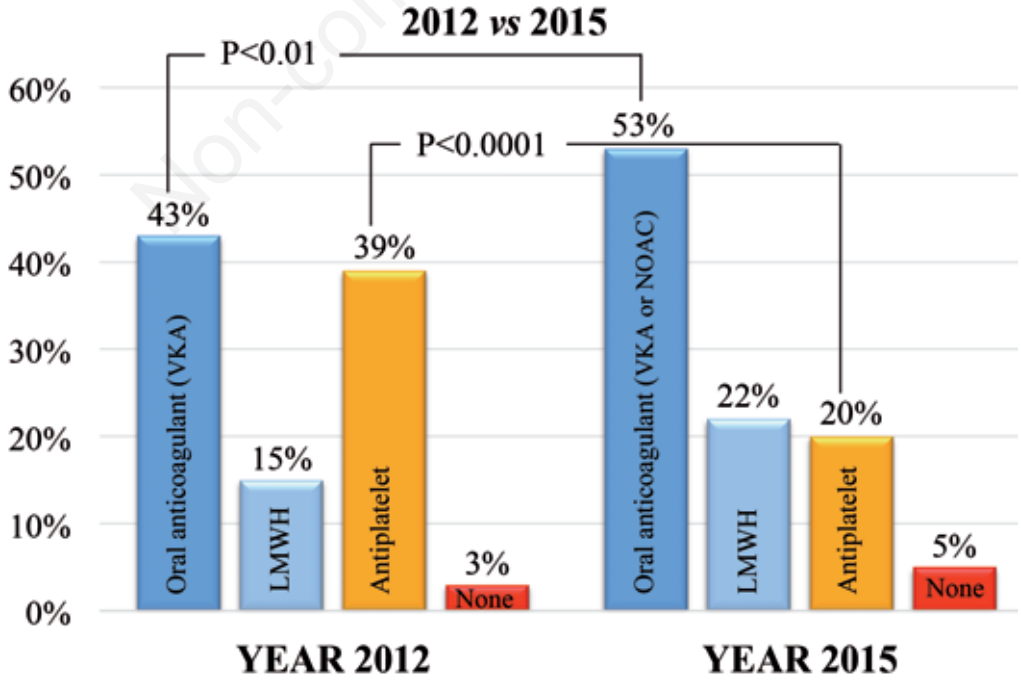

Figure 3. Statistical comparison 2012 *vs* 2015. VKA, vitamin-K-antagonist; LMWH, low-molecular-weight heparin; NOAC, new oral anticoagulants.

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