Safety and efficacy of treatment with vitamin K antagonists in patients managed in a network of anticoagulation services or as routine general care

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ABSTRACT

This is a retrospective, record-linkage study aimed at comparing the effectiveness and safety of two management models of vitamin K antagonists: a Network model (NAS), in which anticoagulation clinics and general practitioners (GP) share the same management software and database, and an individual General Practitioners model. Main outcomes were thromboembolic events (TE), major bleeding (MB) and all-cause mortality. Crude incidence rate and sub-distribution hazard ratio were calculated. Fine and Grey models were used to calculate SHR in multi-variable analysis. 9,418 patients in the NAS and 5,508 in the Routine General Care (RGC) cohort were included. Patients in the NAS cohort had a lower incidence of TE and mortality in respect to the RGC (sHR 0.76%, 95% CI 0.64-0.90 and 0.82%, 95% CI 0.75-0.89, respectively). More patients in the NAS than in the RGC cohort attained a Time in Therapeutic Range >60% (62.2% *vs* 35.7%, p<0.001). No statistically significant difference was found in MB incidence. This study shows that the NAS model for vitamin K antagonist oral anticoagulants management significantly improves the TTR and reduces the incidence of TE and mortality, without affecting the MB rate.

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Key words: Vitamin k antagonists, Oral anticoagulants, Anticoagulation clinics, Management model.

Contributions: The authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by GDG, LS, KB. The first draft of the manuscript was written by GDG, LS and GP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest: The authors declare no potential conflict of interest.

Funding: None.

Availability of data and material: data from the database included in the study are available for consultation, according to the Italian law on the personal data protection.

Code availability: PARMA® software for the VKA management; STATA 15 software for statistical analyses.

Ethics approval: approval was obtained by Modena Ethics Committee on 11.8.2017, protocol n. 3050.

Consent to participate informed consent from all individual participants to the study was waived by the local Ethics Committee, according to the Italian law about the personal data protection on retrospective studies.

Received for publication: 7 December 2021.
Accepted for publication: 21 March 2022.

Bleeding, Thrombosis and Vascular Biology 2022; 1:9
doi:10.4081/btvb.2022.9

INTRODUCTION

Vitamin K antagonist oral anticoagulants (VKA) for over 50 years have been the only drugs available for chronic anticoagulation, exhibiting a good efficacy and an acceptable safety.[1]

Starting from 2009, oral anticoagulant directly inhibiting thrombin (dabigatran) or activated factor X (apixaban, edoxaban and rivaroxaban) (DOAC) have been authorized for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and for the treatment of venous thromboembolism (VTE).[2-6] VKA have been progressively replaced by DOACs in a large proportion of patients, whilst remaining the only suitable anticoagulants in some clinical situations, such as mechanical heart valve prostheses or severe renal impairment.[7,8] Currently, it is estimated that about 50,000 patients in the Emilia-Romagna, a region of Italy, still receive VKAs.

A major concern on the VKA's use is the need for a careful dose titration to maintain the anticoagulant effect within the narrow therapeutic range, as it has been shown that the quality of anticoagulation control strongly impacts on patients' outcome.[9,10]

These needs can be addressed by different management models, usually defined as anticoagulation clinic (AC) or general practitioner-based model (GP).

Nonrandomized, retrospective studies have reported better outcomes in patients whose anticoagulant therapy is managed by an AC compared with a GP model.[11,12] The AC model is widely adopted in the Emilia-Romagna region, ensuring a good quality of VKA treatment, as showed by a mean Time in Therapeutic Range (TTR) of 74% reported in a recent prospective study.[13]

Since 2010 in the Modena province the AC and GP models have been integrated in a network model (Network Anticoagulation Services, NAS) in which both specialists of hospital-based AC and GPs share the same management software and patients' database. The NAS model encompasses almost 60% of VKA treated patients in the Modena province, a province of the Emilia-Romagna region, the remaining being managed by GPs using either manual dosing or individual software for VKAs management (Routine General Care, RGC) outside of this network.

The aim of this study is to compare the effectiveness and safety of the NAS and RGC models for the management of VKA therapy in the Modena province.

MATERIALS AND METHODS

Setting

The Modena province is located in Northern Italy and has an incident population of about 700,000 inhabitants.[14]

The health care service in this area is provided by the Azienda Unità Sanitaria Locale (AUSL)-Modena, a structure of the Regional Health Care System. The AUSL directly manages 6 general hospitals and several primary care services, and coordinates about 470 GPs. A University Hospital situated in two locations completes the healthcare network of the Province.

VKA-anticoagulated patients are managed in the Modena province by two different models.

The NAS model integrates eight AC, located in the hospitals in the area, and about two hundred GPs, adequately formed on anticoagulant treatments. Both AC and GP share the same management software (PARMA®, Werfen, Italy) in a tightly connected network for the management of VKA therapy.

Anticoagulated patients included in the NAS model have blood sampled for INR determination in one of the 40 blood sampling facilities, spread over the whole province of Modena; blood samples are then concentrated in the Modena Central laboratory, where INR tests are performed, and the results are electronically sent to the treating physicians by the PARMA® software.

On the other model (RGC), which includes about 40% of VKA-anticoagulated patients, each patient's trusted doctor (either GPs or private specialist) receives INR results (performed in either public or private laboratories) from the patient and manage anticoagulation conduction in full autonomy, outside of the previously described network.

Study design

This was a multicentre, retrospective, observational study by record-linkage of administrative healthcare datasets.

This study design provides only the observation of the clinical practice in a defined setting, not allowing *a priori* definition of the sample size.

Rather, the optimal balance of demographic and clinical characteristics between the two cohorts were obtained by applying the covariate balancing propensity score (CBPS) methodology and the Fine and Grey competitive risk models with Inverse Probability of Treatment Weighting (IPTW), as reported in the Statistical analysis paragraph of the Methods.

Accordingly, the effect size measures were assessed by means of standardized difference, before and after CBPS-weighting.

The 95% CI provide a standard esteem of the statistic reliability of the study's findings, being clearly dependent on the number of included subjects.

The study obtained ethics approval by the local Institutional Review Board (protocol number 3050 of 11.8.2017).

Data sources

Data about VKA patients were collected by record-linkage of the following Emilia-Romagna Regional Healthcare System databases:

i. Drug prescription database (Assistenza Farmaceutica Territoriale, AFT).
ii. Regional inpatient register (Schede di Dimissione Ospedaliera, SDO).
iii. Modena Local Health Unit registry.
iv. Laboratory Information System (LIS).
v. PARMA® dataset.
vi. Diabetes register of Modena province.
vii. Mortality register of the Modena province.

For a detailed description of databases, please refer to Supplementary Methods S1.

All record-linkage operations among databases were performed in accordance with the Italian law, by anonymized identification codes.

Study population and follow-up

From the start of the observation period (1st January 2011) to its end (31st December 2014), all citizens of the AUSL-Modena were eligible to participate.

Inclusion criteria were:

i. age 30-99 years having had one prescription of either warfarin (Coumadin®) or acenocoumarol (Sintrom®), the two VKAs commercially available in Italy, followed by at least another prescription or by two INR determinations within 90 days, irrespective of the clinical indication;
ii. do not having had any prescription of a DOAC during the observation period.

Patients reported in any of the available datasets having had a surgery for mechanical prosthetic heart valve substitution (excluding bio-prosthesis) where excluded from the study.

The beginning of the observation period for each patient was the date of the first VKA prescription.

Patients were classified into two cohorts, according to the current management of VKA treatment:

i. NAS cohort: included patients who were monitored exclusively through the PARMA® software
ii. RGC cohort: included patients who had received prescription for VKAs but did not have any control in the PARMA® database.

Patients were referred to NAS or RGC cohort according to their preference and to the GP's willingness to adhere to the local network for VKA management.

Patients included in both cohorts, because of a mixed management approach, were excluded from analysis.

Patients having had at least one VKA prescription from 2010 to the beginning of observation were defined as "experienced", whereas those starting VKA therapy-at the beginning of individual observation were defined as "naïve".

Patients' follow-up was stopped at the occurrence of any of the following events, whichever came first:

i. primary outcome achievement;
ii. exclusion from the list of all subjects assisted by the AUSL-Modena (usually because of transfer to another area),
iii. A time lapse of more than 90 days from:
    a. the last available INR test
    b. the last VKA prescription
    c. the last control recorded in the PARMA® database
    d. the end of study observation period (31st December 2014)

The individual patient's follow-up time was calculated after exclusion of the days spent during a hospital stay.

Collected baseline data

Demographic and clinical characteristics of patients and routine laboratory data were collected by the available databases (see Supplementary Methods S1).

A detailed description of comorbidities and concomitant drug therapies is provided in the Supplementary Table S1.

The follow-up data included all information regarding the management of VKA treatment, and events or complications occurring during treatment.

The quality of anticoagulation laboratory control was assessed using the percentage of time within (Time in Therapeutic Range, TTR), above or below the therapeutic range calculated according to Rosendaal *et al.*[15] Only INR values performed no more than 60 days apart were considered for this computation.

Because of exclusion of patients having had a mechanical prosthetic heart valve substitution, the INR range was assumed to be between 2 and 3 for all enrolled patients.

Outcomes

Primary outcomes were as follows.

Efficacy: the hospital admission rate for:

i. any thromboembolic event, including ischemic stroke, cerebral transitory ischemic attacks (TIA), peripheral arterial thromboembolism, pulmonary embolism and/or deep venous thrombosis
ii. ischemic stroke or TIA

Safety: the hospital admission rate for:

i. major bleeding (MB), defined as bleeding in critical sites such as intracranial, spinal, gastrointestinal or intraocular bleeding, or any bleeding resulting in hospital admission.
ii. intracerebral hemorrhage (ICH)

Mortality: the mortality rate for:

i. all-cause mortality
ii. cerebrovascular diseases

Secondary outcome was the percentage of patients achieving a TTR value equal or above 60%.

All outcomes were assessed by record-linkage of the described dataset, according to the ICD-9/ICD-10 codes reported in the Supplementary Methods S2 and S3.

Statistical analysis

Characteristics of patients at inclusion and drugs cotherapy were analyzed by descriptive statistics: percentages for categorical variables, mean and standard deviation for continuous variable. Comparisons between the NAS and RGC cohorts were performed by chi-square-test and t-test, respectively (Table 1).

Crude incidence of primary outcomes was calculated as number of events per 1,000 person-years. Time-to-event analysis was performed to calculate crude incidence rate ratio (IRR) and sub-distribution hazard ratio (SHR).

Due to the retrospective design of the study, the study populations might display some relevant unbalances in baseline characteristics. To account for these unbalances,

Fine and Grey competitive risk models,[16-18] with Inverse Probability of Treatment Weighting (IPWT) were performed.[19] Patients' weights were obtained by applying the covariate balancing propensity score (CBPS) methodology, to obtain an optimal balance of demographic and clinical characteristics between the two cohorts. Balance of the baseline characteristics, between cohorts, and the effect size measures were assessed by means of standardized difference, before and after CBPS-weighting.[20]

The 95% CIs provide a standard esteem of the statistic reliability of the study's findings, being clearly dependent on the number of included subjects.

Separate models were used to obtain estimates of SHR for each outcome, for all patients, experienced patients and naïve patients.

Models included co-therapy variables: anti-platelets, heparin derivatives, statins, non-steroidal anti-inflammatory drugs, proton pump inhibitors.

Statistical analyses were performed with STATA 15 software.

RESULTS

The flow-chart of patients' inclusion is shown in Figure 1.

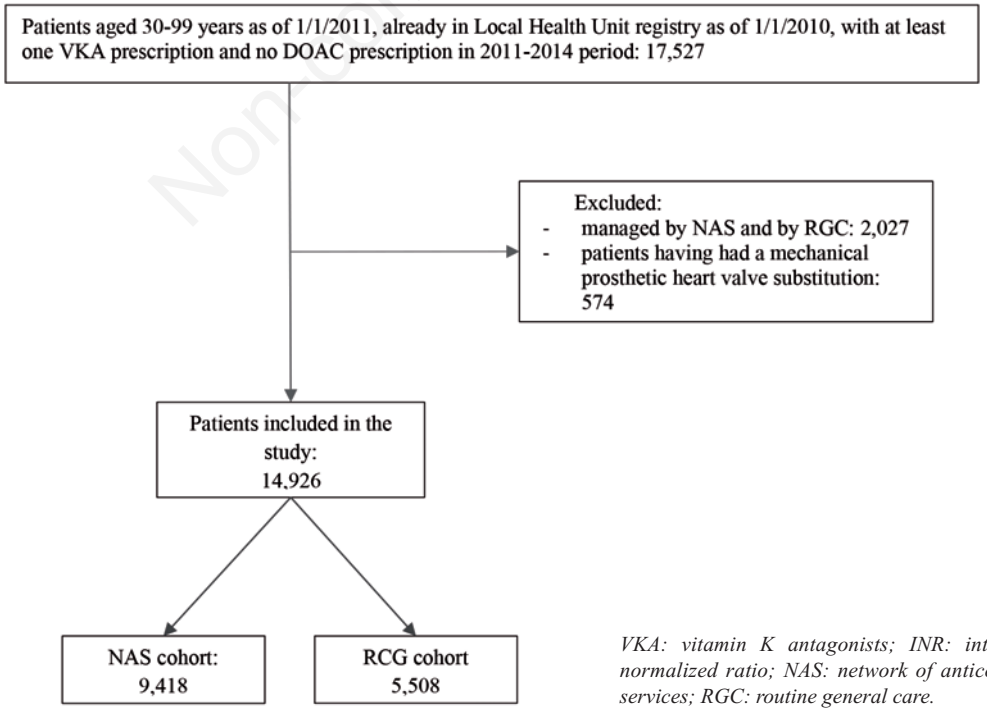
Among the initially selected 17,527 patients, 574 were excluded as being carriers of mechanical heart valve prostheses and 2,027 were excluded because recorded in both NAS and RGC cohorts. Of the remaining 14,926 patients, 5,597 (37.5%) were naïve to anticoagulation treatment at entry.

9,418 patients (63.1% of the total) were included in the NAS cohort and 5,508 (36.9%) the RGC one. The demographic and clinical characteristics of the two cohorts are summarized in the Table 1.

Analysis of standardized differences showed a fair balance between the two cohorts, excluding age at entry and naïve status for the whole sample, and renal failure among naïve patients only. These differences had only a small potential impact on the effect estimates. After weighing with IPTW, the two cohorts were well balanced, showing zero standardized differences for all variables at baseline (Supplementary Table S2).[21]

Five hundred eleven thromboembolic events (TE) were reported during follow-up, with a cumulative incidence of 14.75 per 1000 patient/years (‰p/ys).

The crude incidence rate of TE was 12.50 ‰p/ys in the NAS and 18.69 ‰ in the RGC cohort. Both non-adjusted IRR and adjusted SHR were significantly lower in the NAS than in the RGC cohort (IRR 0.67, 95%CI: 0.56-0.80, p=0.000; sHR 0.76%, 95%CI: 0.64-0.90, p=0.002). IRR and SHR were significantly lower in the NAS than in the RGC also when naïve and experienced patients were separately analyzed (Table 2).



VKA: vitamin K antagonists; INR: international normalized ratio; NAS: network of anticoagulation services; RGC: routine general care.

Figure 1. Flow-chart of patients analyzed and included in the study.

Table 1. Demographic and clinical characteristics of included patients.

	NAS cohort (n = 9,418) (py = 22,074)		RGC cohort (n = 5,508) (py = 12,575)		P value
	N	%	N	%	
Men	5,023	53.3	2,887	52.4	0.278
Age at entry (mean, SD)	74.9	10.07	75.9	10.09	*0.000*
Age classes (at entry)					*0.000*
<50	346	3,7	181	3.3	
50-64	1,067	11.3	557	10.1	
65-80	4,819	51.2	2,620	47.6	
>80	3,186	33,8	2,150	39.0	
Co-payment exemption for (at entry)					
Low-income	2,655	28.2	1,449	26.3	*0.013*
Disability	621	6.6	322	5.8	*0.013*
Naïve to anticoagulation (at entry)	3,728	39.6	1,869	33.9	0.070
Comorbidity (history of, at entry)					*0.000*
Diabetes	2,044	21.7	1,27	23.1	0.055
Hypertension	6,842	72.6	4,014	72.9	0.763
Kidney diseases	462	4.9	348	6.3	*0.000*
Liver diseases	131	1.4	87	1.6	0.354
Cancer	1,119	11.9	535	9.7	*0.000*
Myocardial infarction	436	4.6	239	4.3	0.410
Heart failure	3,813	40.5	2,407	43.7	*0.000*
Mitral stenosis	49	0.5	15	0.3	*0.025*
Pulmonary embolism	366	3.9	195	3.5	0.284
Ischemic stroke/TIA	789	8.4	481	8.7	0.453
Aortic plaque /arterial thromboembolism	98	1.0	74	1.3	0.094
Peripheral artery disease	140	1.5	102	1.9	0.088
Venous thromboembolism	237	2.5	168	3.1	0.053
Bleedings	469	5.0	300	5.4	0.213
Drugs co-therapy (during follow-up)					
Anti-platelets	1,845	19.6	1,012	18.4	0.068
NSAIDs	896	9.5	695	12.6	*0.000*
Heparin derivatives	3,708	39.4	1,672	30.4	*0.000*
Statins	3,779	40.1	1,931	35.1	*0.000*
PPIs	4,807	51.0	2,797	50.8	0.759

py: person-years; CVD: cerebrovascular diseases; NAS: network of anticoagulation services; NSAID: non-steroidal anti-inflammatory drugs; PPIs: proton pump inhibitors; RGC: routine general care.

Table 2. Clinical events recorded during follow-up in the two cohorts. Thromboembolic events.

	Cohorts	Events n.	Rate (x1000 p/y)	Non adjusted IRR 95% CI	Non adjusted IRR p-value	Adjusted SHR 95% CI	Adjusted SHR p-value
Thromboembolic events (all)							
All patients	ALL	511	14.75				
	RGC	235	18.69	1		1	
	NAS	276	12.50	0.67 (0.56-0.80)	0.000	0.76 (0.64-0.90)	0.002
Experienced	RGC	176	17.97	1		1	
	NAS	211	13.02	0.72 (0.59-0.89)	0.002	0.81 (0.67-1.00)	0.046
Naïve	RGC	59	21.21	1		1	
	NAS	65	11.07	0.52 (0.36-0.76)	0.000	0.61 (0.43-0.88)	0.008
Ischemic stroke or TIA							
All patients	ALL	390	11.26				
	RGC	171	13.60	1		1	
	NAS	219	9.92	0.73 (0.59-0.90)	0.002	0.84 (0.69-1.03)	0.096
Experienced	RGC	133	13.58	1		1	
	NAS	175	10.80	0.80 (0.63-1.00)	0.048	0.91 (0.72-1.14)	0.393
Naïve	RGC	38	13.66	1		1	
	NAS	44	7.50	0.55 (0.35-0.87)	0.008	0.66 (0.43-1.02)	0.062

IRR: incidence rate ratio; SHR: sub-distribution hazard ratio; RGC: routine general care; NAS: network of anticoagulation services.

Adjusted SHRs for ischemic stroke or TIA were found lower in the NAS cohort as compared to the RGC one, although the difference did not achieve statistical significance (0.84, 95%CI:0.69-1.03, p=0.096). The same trend was observed in naïve and experienced patients, with a SHR non-significantly lower in the NAS cohort (0.66; 95%CI: 0.43-1.02, p=0.062 and 0.91; 95%CI: 0.72-1.14, p=0.393, respectively).

Crude incidence rates and IRRs for major and intracranial hemorrhages did not differ significantly between NAS and RGC cohorts (18.17 *vs* 18.45 ‰p/ys, unadjusted IRR 0.98, 95%CI 0.84-1.16, P=0.85). A marginally non-significant trend toward an increased risk in the NAS cohort (sHR 1.14, 95%CI 0.97-1.34, P=0.121) for this endpoint was found (Table 3).

Crude incidence rate for all-cause mortality and mortality for cerebrovascular disease were 52.39 and 4.22 ‰p/ys in the NAS cohort and 72.50‰p/ys and 7.00 72.50‰p/ys in the RGC one, respectively. Non-adjusted IRR and adjusted SHR of all-cause mortality and mortality for cerebrovascular disease were significantly lower in the NAS than in the RGC cohort (Table 4).

Table 3. Clinical events recorded during follow-up in the two cohorts. Bleeding events.

	Cohorts	Events n.	Rate (x1000 p/y)	Non adjusted IRR 95% CI	Non adjusted IRR p-value	Adjusted SHR 95% CI	Adjusted SHR p-value
Major bleedings							
All patients	ALL	633	18.27				
	RGC	232	18.45	1		1	
	NAS	401	18.17	0.98 (0.84-1.16)	0.848	1.14 (0.97-1.34)	0.121
Experienced	RGC	174	17.77	1		1	
	NAS	285	17.59	0.99 (0.82-1.20)	0.913	1.14 (0.94-1.38)	0.171
Naïve	RGC	58	20.85	1		1	
	NAS	116	19.76	0.95 (0.69-1.32)	0.733	1.10 (0.80-1.52)	0.542
Intracranial haemorrhages							
All patients	ALL	262	7.56				
	RGC	95	7.55	1		1	
	NAS	167	7.57	1.00 (0.77-1.30)	0.996	1.17 (0.91-1.51)	0.220
Experienced	RGC	72	7.35	1		1	
	NAS	118	7.28	0.99 (0.73-1.35)	0.944	1.14 (0.85-1.53)	0.377
Naïve	RGC	23	8.27	1		1	
	NAS	49	8.35	1.01 (0.60-1.74)	0.982	1.26 (0.75-2.10)	0.379

IRR: incidence rate ratio; SHR: sub-distribution hazard ratio; RGC: routine general care; NAS: network of anticoagulation services.

Table 4. Clinical events recorded during follow-up in the two cohorts. Mortality.

	Cohorts	Events n.	Rate (x1000 p/y)	Non adjusted IRR 95% CI	Non adjusted IRR p-value	Adjusted SHR 95% CI	Adjusted SHR p-value
All-cause mortality							
All patients	ALL	2171	60.69				
	RGC	978	75.20	1		1	
	NAS	1193	52.39	0.70 (0.64-0.76)	0.000	0.82 (0.75-0.89)	0.000
Experienced	RGC	755	74.61	1		1	
	NAS	929	55.46	0.74 (0.67-0.82)	0.000	0.84 (0.76-0.93)	0.001
Naïve	RGC	223	77.28	1		1	
	NAS	264	43.87	0.57 (0.47-0.68)	0.000	0.72 (0.60-0.86)	0.000
Deaths due to cerebrovascular events (ischemic/haemorrhagic)							
All patients	ALL	187	5.23				
	RGC	91	7.00	1		1	
	NAS	96	4.22	0.60 (0.45-0.81)	0.001	0.73 (0.54-0.98)	0.035
Experienced	RGC	65	6.42	1		1	
	NAS	77	4.60	0.72 (0.51-1.01)	0.049	0.85 (0.61-1.19)	0.342
Naïve	RGC	26	9.01	1		1	
	NAS	19	3.16	0.35 (0.18-0.66)	0.001	0.45 (0.24-0.83)	0.010

IRR: incidence rate ratio; SHR: sub-distribution hazard ratio; RGC: routine general care; NAS: network of anticoagulation services.

More patients in the NAS cohort achieved the secondary outcome of a TTR value equal or above 60% as compared to the RGC: 74.4% *vs* 52.1%, p<0.001. A similar significant difference was found when naïve and experienced subgroups were analyzed (Table 5).

Of note, data about TTR distribution below or above the range showed that in the RGC cohort more time was spent with INR below the assigned range in respect to the NAS one, in the whole population as well as in naïve and experienced subgroups. By the other side, percentage of days over therapeutic range was very similar in the three populations (Table 6).

DISCUSSION

In this retrospective study, we found that the NAS model, integrating AC laboratory and GP by the use of a shared management software, allows a better quality of VKA treatment on both clinical and laboratory outcomes, as compared to a routine general care model, outside of this network.

Indeed, we found that the NAS model adopted in the Modena province significantly reduces the incidence of thromboembolic events (sHR 0.76%, 95%CI: 0.64-0.90, p=0.002) as well as the mortality for any cause and for cerebrovascular events (sHR 0.82, 95% CI 0.75-0.89, p=0.000 and 0.73, 95% CI 0.54-0.98, p=0.035). Moreover, it allows more patients to attain an INR >60% (74.4% *vs* 52.1%, p<0.001), with no significant increase of major bleeding.

We found a greater proportion of days spent with INR below the assigned range in the RGC cohort in respect to the NAS one.

It can be assumed that this trend to a lower-intensity anticoagulation could account for both the statistically significant increase in TE events in the RGC cohort and the non-significant increase in MB rate in the NAS one. The different clinical impact of these two issues matches the finding of a lower SHR of mortality in the NAS cohort.

Although VKAs are used since as much as fifty years, the best healthcare model to fulfil the specific healthcare needs of those patients remains to be defined. Earlier studies have suggested that an AC management model may improve the outcome of anticoagulated patients compared to those managed by general practitioners. However, this "centrally based" model has some limits, first of all the struggle for some patients to gain access to INR monitor.

Table 5. Percentages of patients with time in therapeutic range (TTR, 2.0-3.0 INR) ≥ 60%.

	Cohort	Patients	Mean of follow-up days percentage covered by useful INR[a]		Patients with TTR[b] ≥60% n (%)		Patients with TTR[c] ≥60% n (%)	
All patients	RGC	5,508	67.3		2,870 (52.1)		1,967 (35.7)	
	NAS	9,418	88.5	***	7,006 (74.4)	***	5,862 (62.2)	***
	Total	14,926	80.7		9,876 (66.2)		7,829 (52.5)	
Experienced	RGC	3,639	70.4		2,032 (55.8)		1,475 (40.5)	
	NAS	5,69	91.8	***	4,431 (77.9)	***	3,904 (68.6)	***
	Total	9,329	83.5		6,463 (69.3)		5,379 (57.7)	
Naïve	RGC	1,869	61.3		838 (44.8)		492 (26.3)	
	NAS	3,728	83.3	***	2,575 (69.1)	***	1,958 (52.5)	***
	Total	5,597	75.9		3,413 (61.0)		2,450 (43.8)	

*[a]INRs performed at no more than 60 days apart (useful for TTR calculus); [b]calculated on patient's valid follow-up days (covered by useful INR); [c]calculated on patient's total follow-up days. *p< 0.05, **p< 0.01, ***p< 0.001.*

Table 6. Percentages of days spent with TTR below or above the range.

	Cohort	TTR% mean	TbTR% mean	ToTR% mean
All patients	RGC	53.1	20.6	13.2
	NAS	68.3	18.4	13.0
	Total	62.7	19.2	13.1
Experienced	RGC	55.2	18.4	13.4
	NAS	70.2	15.5	14.0
	Total	64.4	16.7	13.8
Naïve	RGC	48.9	24.8	12.8
	NAS	65.5	22.8	11.4
	Total	60.0	23.5	11.9

TTR%: percentage of days in therapeutic range; TbTR%: percentage of days below therapeutic range; ToTR%: percentage of days over therapeutic range.

Moreover, a management model of VKA treatment mainly, or totally, delegated to hospital specialists could undermine a proper and timely sharing of information between hospital specialists and a comprehensive approach to the patient's care.

It has been shown that a comprehensive management model providing centralized dose prescription and follow-up may improve the outcome of VKA-treated patients.[22]

This integrated approach is granted also in our NAS model, which connect specialists and GPs by a common management software, and by a shared training process about the VKA treatment.

The main strength is the use of administrative healthcare databases to gather information about the study outcomes, ensuring a standardized data collection. Moreover, the use of several data sources and record-linkage techniques allowed to collect a wide range of demographic and clinical data, including those on quality of VKA treatment, such as TTR. Moreover, the large size of study population and the thorough statistical analysis plan, with a complete balance between the NAS and RGC cohorts after weighing with IPTW, led to achieve reliable estimates of the effects of the two management models on the main outcomes.

Some limitations of our work deserve discussion. First, we cannot exclude that more patients in the RGC cohort had INR controls performed in private laboratories or by portable coagulometers, therefore not included in the LIS database.

This bias could have affected the lower TTR of the RGC cohort, as only INRs values reported in the LIS database no more than 60 days apart were considered for this computation.

However, a significantly higher rate of patients with a TTR ≥60% was observed in the NAS cohort when either all the follow-up time or the follow-up time covered by INRs useful for TTR calculation were considered (74.4% *vs* 52.1% and 62.2% *vs* 35.7%, respectively).

Second, a selection bias in the referral of patients to the NAS or GP model cannot be excluded, because the choice of either model is left to patient's and GP's decision. Moreover, the quality of patient's education may change between the two models. Indeed, in the NAS model all VKA prescribers are adequately trained for the education and engagement of patients on anticoagulant therapy, whereas no formal training of GPs about such a crucial issue is routinely planned.

CONCLUSIONS

In conclusion, this study suggests that the use of an integrated management model between AC and GP may reduce thromboembolic events and favourably impact on mortality in patients treated with VKA.

Moreover, as the PARMA® software used in the NAS model has recently been updated to allow its use also in DOAC treatment, it is advisable that further studies will be carried out to explore the hypothesis that such a comprehensive management model may also improve outcomes in DOAC users.

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