Internal and Emergency Medicine (2019) 14:1307–1315
https://doi.org/10.1007/s11739-019-02148-7

IM - ORIGINAL

The effect of management models on thromboembolic and bleeding rates in anticoagulated patients: an ecological study

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Received: 23 April 2019 / Accepted: 4 July 2019 / Published online: 15 July 2019

Abstract

The primary study objective is to compare the outcomes of patients taking oral anticoagulant medications in two distinct populations treated according to different management models (comprehensive vs. usual care). (Design: regional prospective cohort study; setting: hospital admission data from two regions). Eligible partecipants were patients taking oral anticoagulant drugs (vitamin K antagonist or direct oral anticoagulants), residents in the Vicenza and Cremona districts from February 1st, 2016 to June 30th, 2017. Patients were identified by accessing the administrative databases of patient drug prescriptions. The primary study outcome was admission to the Emergency Department for stroke, systemic arterial embolism, recurrence of venous thromboembolism or major bleeding. The study evaluated outcomes in 14,226 patients taking oral anticoagulants, of whom 6725 being followed in Cremona with a comprehensive management model. There were 19 and 45 thromboembolic events over 6205 and 6530 patient-years in the Cremona and Vicenza cohort, respectively (IRR 0.44, 95% CI 0.24–0.77). The reduction of events in the Cremona cohort was almost entirely explained by a decrease of events in patients taking VKA (IRR 0.41, 95% CI 0.20–0.78) but not DOACs (IRR 1.08, 95% CI 0.25–5.24). The rate of major bleeding was non-significantly higher in Cremona than in Vicenza (IRI 1.32; 95% CI 0.74–2.40). Across the two cohorts, the risk of bleeding was lower in patients being treated with DOACs rather than warfarin (10/4574 vs. 42/8161 event/person-years, respectively, IRR 0.42 95% CI 0.19–0.86). We conclude that a comprehensive management model providing centralized dose prescription and follow-up may significantly reduce the rate of thromboembolic complications, without substantially increasing the number of bleeding complications. Patients treated with direct oral anticoagulants appear to have a rate of thromboembolic complications comparable to VKA patients under the best management model, with a reduction of major bleeding.

Keywords Vitamin K antagonists · Direct oral anticoagulants · Complications

This article is part of the topical collection "Direct Oral Anticoagulants".

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Introduction

In most western countries, the number of patients taking oral anticoagulants (either vitamin K antagonists, VKA, or direct oral anticoagulants, DOACs) is steadily increasing, with an estimated prevalence of oral anticoagulant therapy (OAT) use around 1.5% of the general population [1]. A recent survey has demonstrated that the use of anticoagulant drugs is the leading cause for access to an emergency department because of outpatient adverse drug events [2]. Patients treated with oral anticoagulants have specific health care needs that should be fulfilled to optimize the risk/benefit ratio of oral anticoagulants [3, 4], but the choice of the optimal healthcare model is uncertain. Earlier studies, performed in limited series of patients taking VKA, have suggested that anticoagulation clinics may improve the incidence of bleeding and thromboembolic complications when compared to patients managed by general practitioners (GPs, "usual care" management model) [5–9]. Improved patient education and a higher proportion of time spent within the therapeutic range (TTR) are the likely explanation for the improved outcomes observed in patients comprehensively followed by anticoagulation clinics [8, 10–13].

Direct oral anticoagulants have the potential of offering a more straightforward therapy, as their laboratory monitoring is usually not required. Meta-analyses of phase 3 randomized clinical trials suggest the use of DOACs results in a reduction of thromboembolism and major bleeding as compared with VKA [14]. The improved benefit-to-risk ratio observed for DOACs may be actually lower, however, in VKA patients followed by specialized anticoagulation clinics as compared to patients under a "usual care" model. Additionally, whether the availability of a comprehensive management model may promote the use of anticoagulant drugs in the frail, elderly population is unknown.

The primary aim of the study is to compare the incidence of major bleeding and thromboembolic complications in patients on anticoagulant therapy (VKAs and DOACs) in two demographically similar geographical areas but having two different territorial organization and management. We hypothesized that a comprehensive, decentralized clinic-based management model could reduce the number of major thromboembolic and bleeding complications as compared with a "usual care" model backed up by a second level Haemostasis and Thrombosis Centre (H&TC), thereby providing a useful health model for a patient taking oral anticoagulant drugs. A secondary study aim was the evaluation of the prevalence of use or oral anticoagulants in the two communities, with a special focus in elderly and female patients, where disparities were reported to occur [15–17].

Methods

Study design and source population

ITEM (Incidence of Thromboembolic and hEMorrhagic complications in patients on anticoagulant therapy) is a dynamic cohort, ecological study [18] in which all patients living in the towns of Cremona and Vicenza and receiving at least one dose of oral anticoagulant treatment during the period February 1st, 2016 to June 30th, 2017 were followed up for drug use and incidence of major thromboembolic and bleeding complications during their exposure time to oral anticoagulants. The two towns are close to each other (< 150 km distance) and share common demography and health facilities. In both cities, a single major hospital provides primary and secondary care to all resident inhabitants, with free access to emergency departments under the coverage of the Italian national health system; an H&TC is active both in Cremona and in Vicenza with free access granted to all patients taking anticoagulants. General Practitioners provide universal health coverage in both towns. Administrative data show that the two hospitals offer > 97% of all the hospital admissions of residents. The study obtained ethics approval by the local Institutional Review Board (IRB) in Cremona and Vicenza. No patients were involved in setting the research question or the outcome measures. No patients were asked to advise on the interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient population.

Anticoagulation management models in the two communities

The management models offered to patients on oral anticoagulant treatment is different in the two considered cohorts (Fig. 1). In Cremona, a telemedicine network connects the H&TC with the peripheral spokes ("Health Units"). (e.g., nursing homes and GPs' offices). Point-of-care coagulometers (Coaguchek™, Roche, Basel, Switzerland) are used to check prothrombin time (as INR) in VKA patients and monitoring of VKA therapies is provided by centralized clinical patient management using a telemedicine software [19]. The network also manages patients who cannot leave their homes due to severe physical impairment, illness or age, as well as self-managed patients. Trained physicians offer prescriptions of individualized VKA doses in the peripheral spokes. In the 2017 quality review roundup, performed by the Italian Federation of Anticoagulation Clinics (FCSA), the mean patient TTR in all VKA patients followed in Cremona was 69.6% [20]. Patients starting DOACs are followed up with a

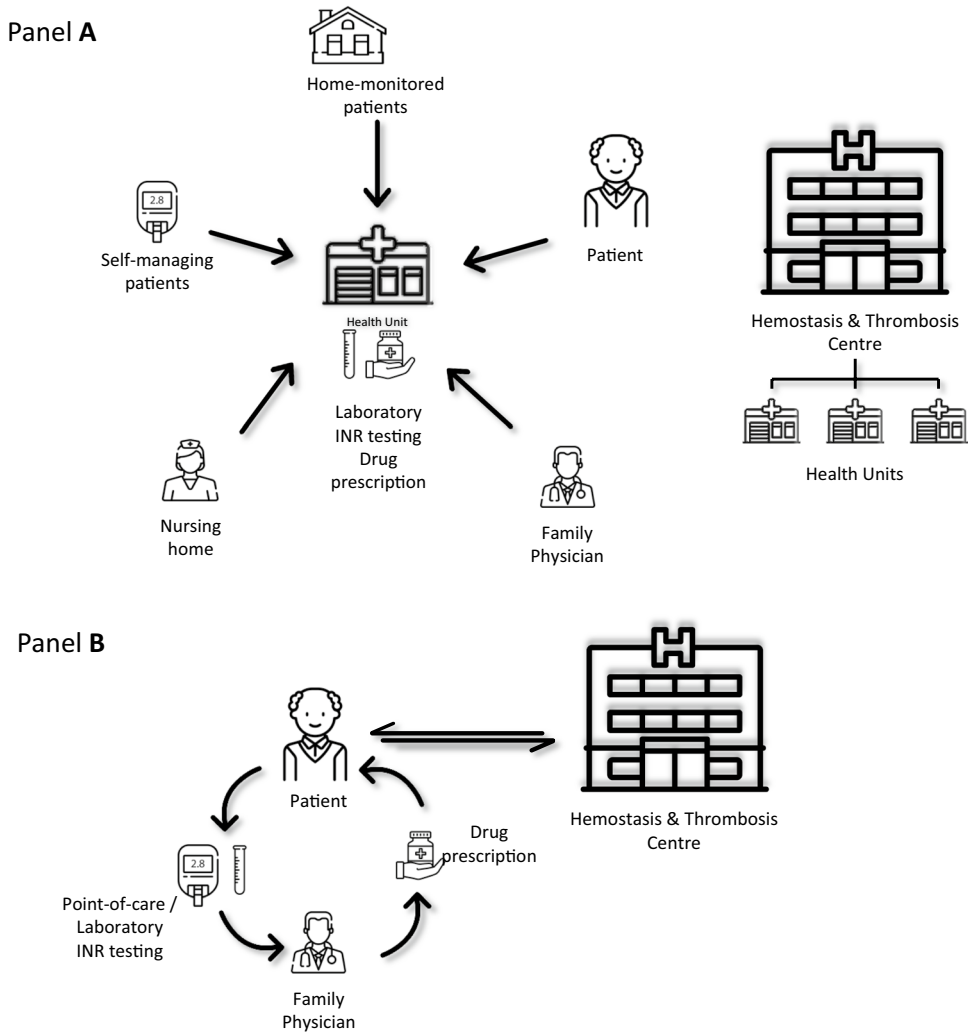

Fig. 1 **a**, **b** The management models adopted in Cremona and Vicenza, respectively. In Cremona, peripheral spokes ("Health units") provide laboratory facilities and drug prescription to all anticoagulated patients, with telemedicine support from the central Haemostasis and Thrombosis Centre

first follow-up visit at 3 months in the Cremona H&TC, and every 6 months thereafter.

In contrast, in Vicenza, the H&TC manages only a limited number of patients with current or previous comorbidities or risk factors (e.g., thrombocytopenia, myeloproliferative disorders, past major bleeding events, severe inherited thrombophilia). GPs routinely follow patients taking VKA or DOACs and refer them to the Vicenza H&TC in case of a personal TTR below 50% in the last 3 months, of bleeding or thrombotic complications. The Vicenza H&TC offers annual educational events and telephone support to local GPs general practitioners.

Demographic data and use of oral anticoagulants

Demographic data for residents in the two towns during the considered period were obtained by querying the National Statistics (ISTAT) website [21]. We obtained the number of patients using oral anticoagulants (either VKA or DOACs) by accessing the local administrative databases of patients' claimed drug prescriptions. For each patient, we computed the number of exposure times by dividing the number of claimed prescription pills by the daily pill consumption (e.g., if a patient received a prescription for 60 dabigatran pills, then the exposure time was 30 days). In Italy, drug prescriptions cannot span for more than 60 days; the mean average warfarin dose was set at 5 mg each day, corresponding to one Coumadin pill per day. Furthermore, since prescription of direct oral anticoagulants in Italy is regulated by the national drug agency (Agenzia Italiana del Farmaco, AIFA) all patients in Cremona and Vicenza shared the same criteria for drug and dose prescription. We considered patients as having been exposed to anticoagulant if they claimed a prescription covering at least 30 days of anticoagulant therapy with either warfarin, acenocoumarol, dabigatran, rivaroxaban, apixaban, or edoxaban. We computed the total cohort exposure years to each anticoagulant as the sum of all the individuals' exposure days divided by 364.25. Those patients who switched anticoagulant therapy (e.g.,

changing from warfarin to rivaroxaban) accounted to the global exposure time with their number of days spent within each drug.

Outcomes

We reviewed all admission charts to the Emergency Departments of patients taking oral anticoagulants of the Cremona and Vicenza hospitals during the considered observation interval. An adjudication panel (MS and GC) independently reviewed the charts of patients discharged with a diagnosis suggestive of cerebral or peripheral thromboembolism (MS) or major hemorrhage (GC). The primary study outcomes were stroke, systemic arterial embolism, or recurrence of venous thromboembolism. We defined stroke as the sudden onset of a neurologic deficit with imaging consistent with presenting symptoms, systemic arterial embolism or recurrent venous thromboembolism as an objectively documented acute arterial or venous occlusion of an extremity or organ, and major bleeding as a hemoglobin loss of at least 20 g per liter, transfusion of at least two units of blood, or symptomatic bleeding in a critical area or organ. Data regarding clinical complications were collected using the Redcap data entry software [22].

Statistical analysis and sample size

Based on previous reports [23], we conservatively estimated a rate of thromboembolic complications around 0.5 per 100 patient-years. We determined that our study had an alpha and beta error 5 and 20%, respectively, (power 80%) to detect an absolute risk difference equal to 0.023 per 100 patient-years (i.e., a risk above 0.73 per 100 patient-years in case of increased thromboembolic risk) for a follow-up of at least 3000 patient-years in both cohorts. Given the expected number of patients taking anticoagulants in the two groups, we, therefore, planned observation for 16 months. We used the χ^2 tests for categorical variables and Kruskal–Wallis test for continuous variables to test for differences between the Cremona and Vicenza cohorts. We examined differences in the use rates of anticoagulant use by direct standardization using the WHO Standard Population [24], and we computed incidence rate ratios (IRR) as the ratio of absolute risks, and 95% CI calculated with the exact method. Similarly, the standardized mortality rates in the two cohorts were obtained by direct standardization using the WHO Standard Population, and considering mortality rates obtained by querying the National Statistics (ISTAT) website [21]. All analyses were performed using the R software package [25] and the *epitools* package [26].

Ethics, funding and data sharing

The study was approved by the local IRB of the Cremona and Vicenza Hospitals, and was supported by the Cremona section of AIPA (Italian Association of Anticoagulated Patients) and partially funded by an unrestricted grant from Roche Diagnostic, Italy. Additional data are available for data sharing upon request to the authors.

Results

Prevalence of anticoagulant use in the two communities

Data regarding the demographic structure and the use of oral anticoagulants in the Cremona and Vicenza cohorts are presented in Table 1. The standardized mortality rate in persons > 65 years was similar in Cremona and in Vicenza (0.129 and 0.122, respectively). The standardized prevalence of anticoagulant use was higher in Cremona than in Vicenza

Table 1 Characteristics of the included cohorts

	Cremona	Vicenza	*p*
Residents	197,221	317,191	
Female/male	101,174/96,047	162,735/154,456	0.97
Age distribution, *n* (%)			
< 40 years	75,746 (38.4)	130,887 (41.3)	< 0.001
40–60 years	60,071 (30.5)	101,645 (32.0)	
60–80 years	45,119 (22.8)	65,238 (20.6)	
> 80 years	16,285 (8.3)	19,421 (6.1)	
OAC users (age-specific prevalence, %)[a]	6725 (3.4)	7501 (2.4)	
Female/male	3225/3500	3387/4114	< 0.001
< 40	369 (0.5)	78 (0.06)	< 0.0001
40–60	600 (1.0)	594 (0.6)	< 0.0001
60–80	3111 (6.9)	3887 (5.9)	< 0.0001
> 80	2645 (16.2)	2942 (15.1)	0.016
Prescribed anticoagulants (%)[b]			
VKA (warfarin or acenocoumarol)	5005 (71.3)	5700 (70.2)	0.17
Rivaroxaban	744 (10.5)	1087 (13.4)	
Apixaban	639 (9.3)	789 (9.7)	
Dabigatran	545 (7.7)	422 (5.2)	
Edoxaban	87 (1.2)	114 (1.4)	

[a]Percentage reporting the proportion of persons who used at least one oral anticoagulant drug during the observation time

[b]Number of persons taking the considered anticoagulant at least once during the considered period. Warfarin and acenocoumarol are listed together because warfarin accounted for > 90% of all prescriptions

(1.51% [95% CI 1.46–1.55] vs. 1.02% [95% CI 0.99–1.04]), and this was mainly related to the high prevalence of female users in the Cremona cohort. There were minimal differences in the type of anticoagulants used in the two towns, without a significant difference in the proportion of VKA or DOAC use in the two cohorts.

Incidence of thromboembolic and bleeding complications

Table 2 reports the characteristics of patients presenting with an incident thromboembolic or bleeding events in the two cohorts during the considered period. While patients were comparable regarding age and sex distribution, most patients presenting with a bleeding or thrombotic complication were anticoagulated for chronic atrial fibrillation. There was an excess of gastrointestinal bleeding events in the Cremona cohort as compared to the Vicenza Cohort.

Tables 3 and 4 report the incidence of thromboembolic and bleeding complications in the two cohorts. There were 19 and 45 thromboembolic events over 6205 and 6530 patient-years in the Cremona and Vicenza group (IRR 0.44, 95% CI 0.24–0.77). The decrease of events in patients taking VKA almost entirely explained the reduction of events

Table 2 Characteristics of patients with thromboembolic or bleeding complications

	Cremona $N=48$	Vicenza $N=68$
Sex		
Female	24 (50.0%)	27 (39.7%)
Male	24 (50.0%)	41 (60.3%)
Age, years [interquartile range]	79.0 [73.8; 84.0]	82.5 [75.0; 87.2]
Reason for anticoagulant use		
Mechanical prosthesis	8 (17.8%)	5 (7.81%)
NVAF	31 (68.9%)	59 (92.2%)
VTE	6 (13.3%)	0 (0.00%)
Events		
Major bleeding	29 (60.4%)	23 (33.8%)
Thromboembolism	19 (39.6%)	45 (66.2%)
Type of thromboembolic complications		
Recurrent venous thromboembolism	1 (5.26%)	1 (2.22%)
Ischemic stroke	16 (84.2%)	40 (88.9%)
Peripheral arterial thromboembolism	2 (10.5%)	4 (8.89%)
Type of major bleeding complication		
Intracranial (intracerebral and subdural)	11 (37.9%)	18 (78.1%)
Gastrointestinal bleeding	12 (41.3%)	2 (8.70%)
Hemoptysis/epistaxis	2 (6.8%)	2 (8.70%)
Hematuria	1 (3.45%)	1 (4.35%)
Muscular hematoma	3 (10.3%)	0 (0.00%)

NVAF non-valvular atrial fibrillation, *VTE* venous thromboembolism

Table 3 Incidence of thromboembolic complications

	Cremona			Vicenza			Incidence rate ratio (95% CI)
	N	Person/years	Incidence rate	*N*	Person/years	Incidence rate	
VKA, total	13	3555	0.36	41	4606	0.89	0.41 (0.20–0.78)
<40 years	0	160	–	0	53	–	–
40–60 years	0	340	0	1	414	0.24	0 (0–47.4)
60–80 years	10	1722	0.58	18	2551	0.70	0.82 (0.33–1.88)
>80 years	3	1333	0.22	22	1588	1.38	0.16 (0.03–0.54)
DOAC, total	6	2650	0.22	4	1924	0.20	1.08 (0.25–5.24)
<40 years	0	111	–	0	15	–	–
40–60 years	2	178	1.1	0	131	–	–
60–80 years	3	1783	0.16	0	1029	0	–
>80 years	1	578	0.17	4	749	0.53	0.3 (0.001–3.27)

Table 4 Incidence of bleeding complications

	Cremona			Vicenza			Incidence rate ratio (95% CI)
	N	Person/years	Incidence rate	*N*	Person/years	Incidence rate	
VKA, total	22	3555	0.61	20	4606	0.43	1.42 (0.74–2.45)
< 40 years	0	160	–	0	53	–	–
40–60 years	0	340	0	1	414	0.24	0 (0–47.4)
60–80 years	9	1722	0.52	8	2551	0.31	1.66 (0.57–4.96)
> 80 years	13	1333	0.97	11	1588	0.69	1.40 (0.58–3.47)
DOAC, total	7	2650	0.26	3	1924	0.15	1.69 (0.38–10.15)
< 40 years	0	111	–	0	15	–	–
40–60 years	0	178	–	0	131	–	–
60–80 years	6	1783	0.33	1	1029	0.09	3.46 (0.42–159.3)
> 80 years	1	578	0.17	2	749	0.26	0.64 (0.01–12.4)

in the Cremona cohort (13/3555 vs. 41/4606, IRR 0.41, 95% CI 0.20–0.78). Notably, the reduction of thromboembolic risk was particularly evident in patients taking VKA and > 80 years old (IRR 0.16, 95% CI 0.03–0.54). There was no reduction of thromboembolic events in the Cremona cohort in patients taking DOACs (IRR 1.08, 95% CI 0.25–5.24). In the Cremona cohort (i.e., the town having the lower absolute incidence of thromboembolic complications), DOACs had a lower rate of thromboembolism than VKA in terms of effect size (6/2650 vs. 13/3555, IRR 0.61, 95% CI 0.19–1.74); pooling data from the Cremona and Vicenza cohort, DOACs were associated with a reduction of thromboembolic risk vs. VKA (IRR 0.33, 95% CI 0.15–0.65).

As shown in Table 4, the incidence of major bleeding was non-significantly higher in Cremona than in Vicenza (IRR 1.32; 95% CI 0.74–2.40). Across the two cohorts, the risk of bleeding was lower in patients taking DOACs than in those taking warfarin (10 events vs. 42 per 4574 and 8161 person-years, respectively, IRR 0.42 95% CI 0.19–0.86), and slightly higher in elderly than in younger patients (IRR > 80 years vs. 40–60 years = 1.39; 95% CI 0.43–7.12). The incidence of intracranial bleeding was slightly, but not significantly, lower in Cremona (IRR 0.64, 95% CI 0.27–1.43), whereas the risk of major gastrointestinal bleeding was markedly higher in the Cremona cohort (IRR 6.31, 95% CI 1.40–58.1).

Discussion

The principal study finding is that a highly integrated telemedicine network joining an H&TC with peripheral spokes correlates with a lower incidence of thromboembolic complications in anticoagulated patients and with increased use of anticoagulant drugs in the referral population, highlighting that a telemedicine system can improve health care [27, 28]. Telemedicine applied to anticoagulated patients has the potential to facilitate accessibility to health care services for an increased number of patients, empowering management strategies, and to export quality procedures and competences outside specialized centers, increasing communications, not only between physician and patient, but also between different medical specialties and the H&TC [19]. Moreover, a telemedicine system applied to anticoagulation management can be adopted by either nursing care facilities, nursing homes, healthcare facilities equipped with a medical staff, hospitals or groups of general practitioners and patients [19, 29, 30].

In patients receiving VKA, the Cremona model was associated with an absolute risk reduction of thromboembolism equal to 0.53% events per year, or 1 event spared every 188 patients treated. Even conservatively assuming a standardized prevalence of anticoagulant use around 1% in the general population, or 1000 treated every 100,000 residents, the Cremona model may spare up to 5 cases of thromboembolism (mainly stroke) every 100,000 patients, each year. On the other side, our study does suggest no benefit of the Cremona model for patients taking DOACs. When pooling data from the Cremona and Vicenza cohort, DOAC use reduced the thromboembolic risk (67% relative risk reduction) as compared to VKA. These results confirm and emphasize the importance of an adequate monitoring of anticoagulant therapy in patients taking VKA to maximize its benefit-to-risk ratio. Conversely, the efficacy advantage of DOACs over VKA may be more relevant when a comprehensive management system is not available.

Another potential advantage of the Cremona model is the finding of a statistically significant 0.49% increased use of anticoagulants in the Cremona cohort, that was associated with a reduction of gender-related disparity. Albeit apparently low, the increase of anticoagulant use may result into an absolute increase of 490 persons receiving warfarin every 100.000, or 13 thromboembolic events prevented by the Cremona management model every 100,000 patient/year, assuming that the excess use is for patient having

non-valvular atrial fibrillation, the indication with the higher number of under-treated patients [31]. A likely explanation for this finding is that a better management model promotes the use of drugs perceived to be at increased bleeding risk and that this improvement may primarily benefit frail categories (such as female or elderly patients), relieving treatment disparities [16]. Taking together the increased use of anticoagulant drugs and the reduced thromboembolic risk, we may estimate that the Cremona comprehensive model may spare 18 (13 + 5) thromboembolic events annually every 100,000 inhabitants.

The study was not able to demonstrate a comparable reduction of the bleeding risk in the Cremona cohort. There was a tendency for higher bleeding risk in Cremona than in Vicenza, that was comparable both for VKA and DOACs and particularly for gastrointestinal bleeding. Interestingly, the increased risk of major bleeding parallels the increased use of anticoagulants in the Cremona cohort, suggesting that practitioners need to be cautious when prescribing oral anticoagulants in patients at potentially higher bleeding risk. Similarly to their apparent higher efficacy, the use of DOACs seemed to be associated with a lower bleeding risk than VKA, with a 58% reduction of relative risk when pooling data from the Cremona and Vicenza cohort. Being bleeding an unwanted adverse effect, unaffected by selection bias, our study is, therefore, able to reaffirm the previously reported higher safety of DOACs [32, 33].

The study has both strengths and limitations. A major strength is that, based on administrative data, we were able to catch almost all major thromboembolic bleeding and thrombotic complications (at least > 97% of all significant complications) thanks to the distinctive health facilities in the two areas, with a single major hospital covering nearly all admissions for acute disease. Furthermore, since we abstracted bleeding and thromboembolic complications from a real-world population without any restriction to age categories or therapy indication, our results may be considered representative of the whole community at large. Finally, external assessors independently evaluated all bleeding and thromboembolic events.

Among potential limitations, we acknowledge that the present study is purely observational. Furthermore, given the ecological nature of the study, the quality of the evidence provided (in terms of avoidance of a possibly unmeasured bias) is limited [18], but nonetheless similar to the quality provided by case–control studies [34]. For instance, we were not able to adjust our findings for the effect of patients' time in therapeutic range, a indirect measure of the quality of VKA management likely to affect the rate of thromboembolic complications [10, 35], or for the median time since inception of anticoagulation in the two cohorts. We cannot exclude that a selection bias may influence the secondary sub-analysis of efficacy comparison between drug types (DOACs vs. warfarin). Another major study limitation is that, by design, we were not able to directly evaluate neither the number of thromboembolic events not prevented in subjects not using anticoagulants in the Vicenza cohort nor the number of fatal events. As we were not able to collect data on adherence to oral anticoagulant therapy, particularly for patients taking DOACs, we were not able to assess if the Cremona model may improve adherence-associated outcomes [36, 37]. Due to the relatively new introduction of DOACs in the clinical practice, exposure to DOACs is still limited when compared to VKA. In particular, the low number of exposure years in patients taking DOACs does not confer enough study power for secondary safety subanalyses. Finally, due to the relatively low number of bleeding complications, our study may have limited power to detect an increased bleeding risk in one of the two cohorts.

In conclusion, by comparing two different management models, this study suggests that the use of a highly integrated telemedicine management model may reduce thromboembolic events in patients treated with VKA agents and that it could increase the use of oral anticoagulants, particularly in frail population subsets. More extensive use of DOACs may mitigate the impact of different management model in the general population, but larger prospective studies are warranted to explore the hypothesis that a comprehensive management model may improve outcomes between DOAC users.

Author contributions AT and ST contributed equally to the manuscript. AT designed the study, analyzed the data, and wrote the manuscript. He has received travel funding from Bayer and Novo-Nordisk; lecture fees from Stago, Werfen, and Roche. ST designed the study and wrote the manuscript. She declares lecture fees from Bayer, Stago, Roche, Boheringer, Sobi, Daiichi, BMS Pfizer, and Sanofi. GP revised the manuscript for important intellectual content. He declares participation to advisory boards for Alfasigma, Pfizer, Roche; lectures fees from Werfen. FC, MP, PE, RM, IN, OP, and MT collected the data. FC, SM, and AM contributed to the study design and administrative data collection. MS and GC revised the data and critically revised the manuscript for important intellectual content and adjudicated events

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the Cremona and Vicenza Institutional Review Boards and with the 1964 Helsinki declaration and its later amendments (see also Ethics, funding and data sharing paragraph). This article does not contain any studies with animals performed by any of the author.

Informed consent For this type of observational study, formal consent is not required.

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