



Systematic review

Quality of anticoagulation with vitamin K antagonists in Spain: A systematic review with meta-analysis of national registries



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ABSTRACT

Background: Vitamin K antagonists (VKAs) depend on appropriate time in therapeutic range (TTR). We reviewed studies in Spain providing data on the quality of oral anticoagulation with VKA in atrial fibrillation (AF) patients, to present an overview of the quality of this therapy in our country.

Methods: Systematic review and meta-analysis of national studies. We searched PubMed, Web of Science and Google Scholar databases for studies published in the last 10 years, until June 2024. We reported the mean pooled TTR and proportion of international normalized ratios (INRs) in range (PINRR), as well as the pooled prevalence of poor quality of VKA therapy.

Results: Seven studies were included in the analysis, for an overall cohort of 6953 patients (mean age 73.6–83 years). The pooled analysis gave a mean TTR of 63.22% (95% confidence interval [CI] 46.55–79.89) and a mean PINRR of 60.53% (95% CI 44.40–76.65). Accordingly, the pooled prevalence of a TTR <65% was 50.01% (95% CI 45.36–54.65), and the pooled prevalence of a PINRR <60% was 46.90% (95% CI 41.56–52.31). Similar results were observed in a sensitivity analysis performed including only those studies fulfilling very similar inclusion/exclusion criteria ($n = 5$).

Conclusion: The mean TTR and PINRR of AF patients on VKAs in Spain were below the recommended standards. Nearly 50% of patients showed poor anticoagulation control, remaining exposed to low-quality therapy and complications related to AF.

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Calidad de la anticoagulación con antagonistas de la vitamina K en España: una revisión sistemática con metaanálisis de registros nacionales

RESUMEN

Introducción: Los antagonistas de la vitamina K (AVK) dependen de un tiempo en rango terapéutico (TRT) apropiado. Se han revisado estudios en España que proporcionan datos sobre la calidad de la anticoagulación oral con AVK en los pacientes con fibrilación auricular (FA), para presentar una visión general de la calidad de esta terapia en nuestro país.

Palabras clave:

Fibrilación auricular

Antagonistas de la vitamina K

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Tiempo en rango terapéutico
Calidad de la anticoagulación

Métodos: Revisión sistemática y metaanálisis de estudios nacionales. Buscamos en las bases de datos PubMed®, Web of Science® y Google® Scholar estudios publicados en los últimos 10 años, hasta junio de 2024. Reportamos el TRT medio agrupado y la proporción de razones internacionales normalizadas (INRs) en rango (PINRR), así como la prevalencia agrupada de una baja calidad de la terapia con los AVK.

Resultados: Se incluyeron 7 estudios en el análisis, con 6.953 pacientes (edad media: 73,6-83 años). El análisis agrupado arrojó un TRT medio del 63,22% (intervalo de confianza [IC] 95%: 46,55-79,89) y un PINRR medio del 60,53% (IC 95%: 44,40-76,65). En consecuencia, la prevalencia agrupada de TRT < 65% fue del 50,01% (IC 95%: 45,36-54,65) y la prevalencia agrupada de PINRR < 60% fue del 46,90% (IC 95%: 41,56-52,31). Se observaron resultados similares en un análisis de sensibilidad que incluyó solo aquellos estudios con criterios de inclusión/exclusión muy similares (n = 5).

Conclusión: El TRT medio y el PINRR de los pacientes con FA que recibían AVK en España estaban por debajo de los estándares recomendados. Casi el 50% de los pacientes mostraron un control deficiente de la anticoagulación, permaneciendo expuestos a una terapia de baja calidad, y a complicaciones relacionadas con la FA.

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Introduction

Atrial fibrillation (AF) is associated with an increased risk of stroke, hence most patients require the use of oral anticoagulation (OAC).¹ During more than 60 years, vitamin K antagonists (VKAs) were the therapy of choice for thromboprophylaxis in these patients. However, the introduction of direct-acting OACs (DOACs) solved several disadvantages of VKAs and completely changed the management of AF, being now the most frequently prescribed OACs in developed countries.

Despite the increasing use of DOACs in Spain, VKAs are still the most used anticoagulant yet their efficacy and safety depend on the time in therapeutic range (TTR) of international normalized ratio (INR) 2.0–3.0, that reflects of the overall quality of anticoagulation control.² Recent European Guidelines for the management of AF recommend DOACs over VKAs as first-line therapy, and a TTR >70% if VKAs are prescribed.³ Indeed, a high TTR translates into a lower risk of adverse events.^{4–6}

Notwithstanding, data on TTR in AF patients under VKA therapy in Spain from different studies remain consistent and disheartening across time and contexts. In this systematic review and meta-analysis, we reviewed national registries and observational studies in Spain informing about the TTR in patients with AF taking VKAs, to provide a contemporary picture of the quality of OAC therapy in our country.

Methods

Searches strategy and study selection

We conducted a systematic review and meta-analysis according to PRISMA guidelines⁷ (Supplementary Fig. 1). From 1st December 2023 to 30th June 2024, we searched MEDLINE (PubMed), Web of Science and Google Scholar databases to identify relevant studies. The search strategy, detailed in Supplementary Table 1, included keywords like “atrial fibrillation,” “TTR” and “PINRR” (proportion of INRs in range). The reference lists of relevant articles were scanned for studies missed by the databases search.

The initial inclusion criteria were¹: articles in English or Spanish,² national studies involving adult AF patients on VKA therapy,³ studies reporting the quality of VKA therapy at least in terms of TTR, and⁴ studies published in the last 10 years. We excluded studies based only on a single centre or single regions/areas, as well as case reports/series, reviews, and editorials/letters.

Two investigators (Eva Soler-Espejo and María Asunción Esteve-Pastor) independently reviewed titles and abstracts, to select studies for further assessment. A third investigator (José Miguel Rivera-Caravaca) evaluated the eligible studies for suitability and completeness based on the inclusion and exclusion criteria, with disagreements resolved through investigators discussion. This study was registered in PROSPERO under identification code CRD42024548912.

Data extraction

From the included studies, we recorded author names, year of publication, study design and setting, total number of patients, mean age, gender distribution, comorbidities and TTR/PINRR. All study data and outcomes were compiled into an electronic dataset (Microsoft Excel, Office 365).

TTR and PINRR definitions

The primary endpoint was the quality of anticoagulation with VKAs by using the TTR calculated by the method of Rosendaal.⁸ This method assumes that moving from one INR to another (higher or lower) in two different determinations separated by a certain number of days occur in a linear way, crossing the difference between the two INR values during those days. When reported, we also captured the PINRR (the so-called direct method). This simple method estimates the quality of anticoagulation by considering how many INRs were within the therapeutic range (INR 2.0–3.0) over the total INRs measured.⁹ For the definition of suboptimally controlled VKA therapy or poor-quality anticoagulation, we used two cut-off points (TTR <65% and PINRR <60%).

Risk-of-bias assessment

Two investigators (Danilo Menichelli and Daniele Pastori) independently evaluated the risk of bias (RoB) using the New Castle-Ottawa scale for observational studies¹⁰ and the RoB Assessment Tool for Nonrandomized Studies (RoBANS) for cross-sectional studies.¹¹ The New Castle-Ottawa include the selection, comparability and outcome domains, whereas the RoBANS assesses the following domains: selection of participants, confounding variables, intervention (exposure) measurement, blinding of outcome assessment, incomplete outcome data, selective outcome reporting. RoBANS figures were generated using the *robvis* online tool.¹² Publication bias was estimated through funnel plots.

Ethical review, patient, and public involvement

Ethical approval was not required given the study type (systematic review and meta-analysis article). Patients were not involved in study design and/or the development.

Statistical analyses

For all studies, we extracted means and standard deviation (SD) of the variables of interest. When median and interquartile range (IQR) were reported, we manually calculated the SD by dividing the IQR with 1.35, as detailed in the Cochrane handbook of systematic reviews.¹³

Due to the high probability of relevant heterogeneity between the studies in the meta-analysis, random-effects models were used when appropriate. Heterogeneity was assessed through *I*² statistics. Results were expressed by forest plots with pooled TTR/PINRR or proportion (%) of poor quality of VKA therapy, and their 95% confidence intervals (CI).

In the primary analysis, we included all studies involved in this systematic review and meta-analysis. Additionally, we performed a sensitivity analysis including only those studies with almost identical inclusion/exclusion criteria.

Data management and statistical analyses were performed in MedCalc v. 16.4.3 (MedCalc Software bvba, Ostend, Belgium) and R software (R Development Core Team, 2021) version 4.1.2.

Results

We identified 140 results from the literature search. After the initial title and abstract screening, 24 full texts were analyzed, and 7 studies were finally included in the systematic review and meta-analysis (Supplementary Fig. 1).^{7,14-19} All the studies included were national, multicentre, and observational, although 5 of them were cross-sectional studies and 2 were prospective studies.

Study characteristics

We included 6953 patients, with a mean age ranging from 73.6 to 83.0 years. The proportion of females ranged from 42.0% to 51.3% (~45% of females overall). Hypertension was present in ~80% of patients and diabetes in ~30%. The prevalence of other risk factors was highly variable, being 3.9–76.7% for coronary artery disease, 0.59–29.52% for heart failure, 1.05–22.2% for stroke/TIA/thromboembolism, 0.13–100% for chronic kidney disease, and 1.05–22.2% for previous bleeding. Characteristics of the included studies are summarized in Table 1. Of the 6953 patients included from the 7 studies, quality of OAC with VKAs was available in 6709 patients (because only 593 patients from 837 in the ESPARTA study were on VKAs).⁷

Quality of OAC and prevalence of poor anticoagulation management

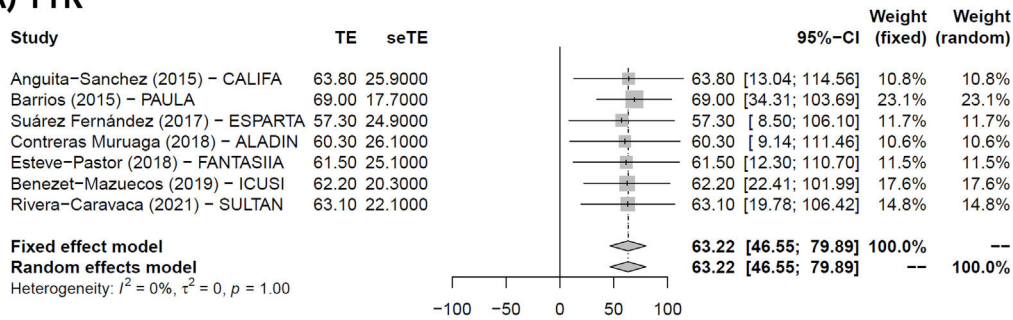
Combining those patients on VKAs from all studies, our meta-analysis showed that the mean TTR was 63.22% (95% CI 46.55–79.89) whereas the mean PINRR was 60.53% (95% CI 44.40–76.65) (Fig. 1A and B). The pooled prevalence of poor anticoagulation management (i.e. TTR <65%) was 50.01% (95% CI 45.36–54.65), with a high heterogeneity (*I*² = 93%) (Fig. 2A). Regarding PINRR, data for estimating the prevalence of poor anticoagulation management (i.e. PINRR <60%) was only available in three studies (PAULA, ALADIN and ICUSI) and the pooled prevalence of inappropriate quality of OAC with VKAs according to these studies

Table 1
Main characteristics of the included studies.

Study	Year of publication	Setting	n	Age	Female	HT	Diabetes	CAD	HF	Stroke/TIA/TE	Dyslipidemia	CKD	COPD	Smoking	Alcohol consumption	Previous bleeding
CALIFA	2015	Cardiology Clinics	1056	73.6 (9.8)	42	83.7	30.4	20.3	22.2	14.2	55.8	14.5	16.7	7.2	3	5.3
PAULA	2015	Primary Care	1524	77.4 (8.7)	48.6	80.2	31.0	9.6	23.9	13.7*	57.2	6.0	-	5.1	4.3	8.8**
ESPARTA	2017	Internal Medicine Clinics	837	83.0 (5.0)	51.3	84.3	39.1	14.6	62.7	19.2***	52.8	9.6	-	2.9	-	17.6
ALADIN	2018	Neurology and Internal Medicine Clinics	383	75.8 (8.7)	44.1	83	31.9	-	-	50.7	-	38.9	-	-	-	12
FANTASIA	2018	Cardiology Clinics, Internal Medicine Clinics and Primary Care	1470	74.1 (9.5)	43.6	80.7	29.8	19.1	30.9	9.1***	52.6	21.2	17.8	5.1	3.6	3.1
ICUSI	2019	Cardiology Clinics	813	75 (9)	45	82.5	29.4	-	42.2	13.8	-	12.3	-	-	2.1	-
SULTAN	2021	Cardiology Clinics	870	73.6 (9.2)	46.1	78.2	27.2	13.2	12.9	9.0	47.5	16.2	18.3	13.3	11.7	5.3

Data are presented as mean (standard deviation) or as percentage (%). CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HF: heart failure; HT: hypertension; TE: thromboembolism; TIA: transient ischemic attack.
* Does not include history of thromboembolism.
** Recorded as bleeding, anemia, or predisposition to bleeding.
*** Does not include history of TIA or thromboembolism.

A) TTR



B) PINRR

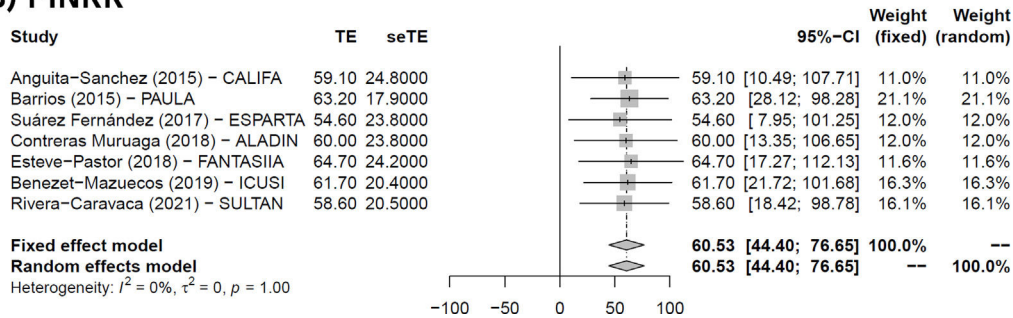
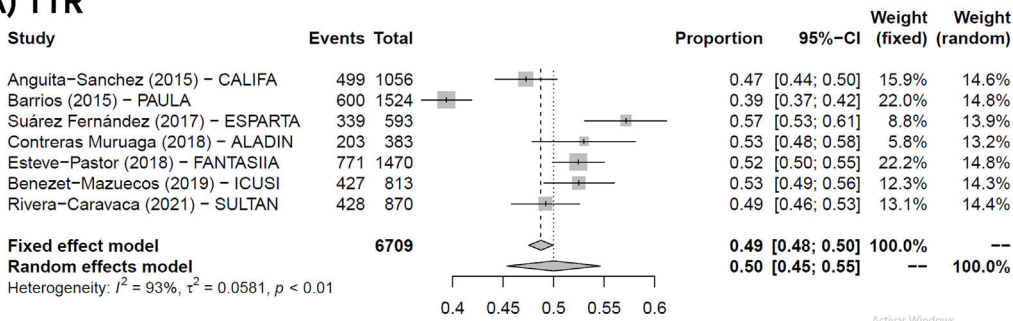


Fig. 1. Forest plot for the pooled quality of anticoagulation with vitamin K antagonists in all studies. Panel A. Quality of anticoagulation reported as TTR. Panel B. Quality of anticoagulation reported as PINRR.

A) TTR



B) PINRR

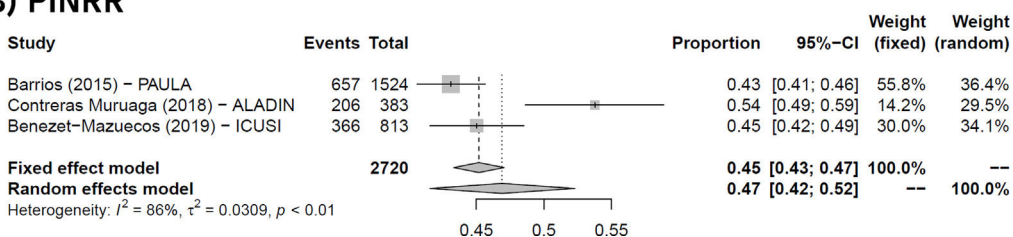


Fig. 2. Forest plot for the pooled proportion of poor anticoagulation quality with vitamin K antagonists in all studies. Panel A. TTR <65%. Panel B. PINRR <60%.

was 46.90% (95% CI 41.56–52.31), again with a high heterogeneity ($I^2 = 86\%$) (Fig. 2B).

Sensitivity analysis

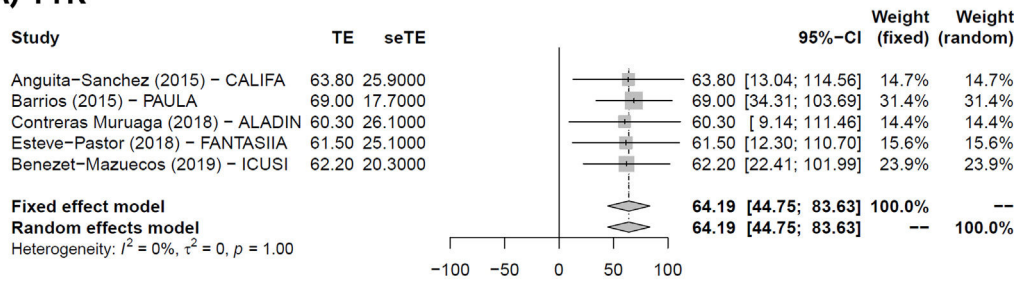
A sensitivity analysis was performed including only those studies fulfilling very similar inclusion/exclusion criteria ($n=5$), i.e. we excluded the ESPARTA study because it was performed only in patients >75 years, and the SULTAN since it included only patients naïve for VKAs. Hence, the mean TTR was 64.19% (95% CI 44.75–83.63) and the mean PINRR was 61.94% (95% CI 42.93–80.96) (Fig. 3A and B). The pooled prevalence of TTR <65% in the remained

five studies was 48.78% (95% CI 43.09–54.50; $I^2 = 94\%$) (Fig. 4), whereas the pooled prevalence of PINRR <60% was the same than the main analysis 46.90% (95% CI 41.56–52.31, $I^2 = 86\%$).

Quality and risk-of-bias (RoB) assessment

All cohort studies were considered of good quality regarding the selection of participants, and the overall quality was judged as fair to good (Supplementary Table 2). For cross-sectional studies, all presented low RoB in terms of selection of participants, whereas the RoB in the confounding and intervention measurement domains were unclear in two studies and low in three studies. Other domains

A) TTR



B) PINRR

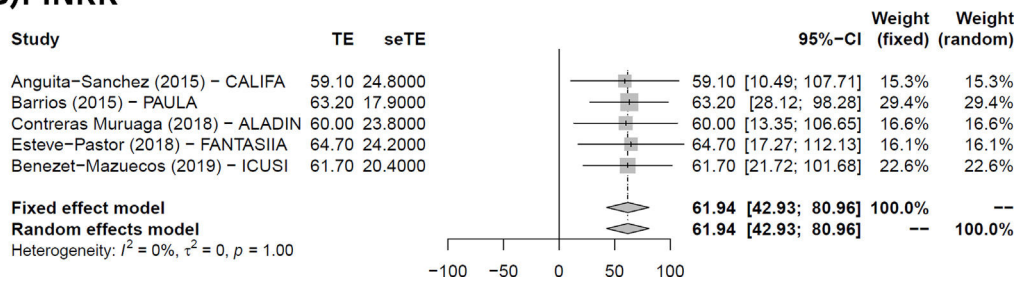


Fig. 3. Forest plot for the pooled quality of anticoagulation with vitamin K antagonists in the sensitivity analysis. Panel A. Quality of anticoagulation reported as TTR. Panel B. Quality of anticoagulation reported as PINRR.

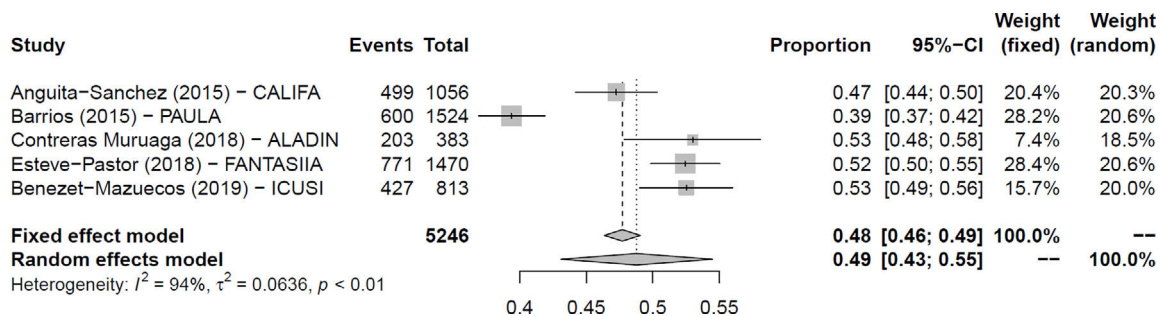


Fig. 4. Forest plot for the pooled proportion of poor anticoagulation quality with vitamin K antagonists (TTR <65%) in the sensitivity analysis.

were considered of lower relevance or not applicable for the aims of the present meta-analysis. The overall RoB assessment is shown in [Supplementary Fig. 2](#). Additionally, funnel plots for all the analyses are presented in the [Supplementary Figs. 3 and 4](#).

Discussion

In this systematic review including nearly 7000 AF patients, our principal findings are as follows: (1) the mean TTR or PINRR is below the recommended standards and (2) there was a pooled prevalence of 50% who were AF patients with poor quality of TTR (46.90% if using PINRR).

In Spain, prescribing DOACs requires an inspection visa based on specific clinical conditions. Although this has been toned down in the last Therapeutic Positioning Report of the Spanish Medicines Agency, DOACs are still only reimbursed if AF patients fulfill particular conditions.²⁰ It has been nearly 15 years since the introduction of the first DOAC in Spain, and the situation differs importantly from that in Europe, with considerable geographical heterogeneity.²¹ In the GLORIA-AF Phase III Registry, DOAC use in Europe was 62.6% and 46% of patients were prescribed DOACs at 30 days after AF diagnosis.²² When contrasting the first 4 years after DOAC approval, the proportion of prescriptions increased in Europe from 53.4% to 75.8%.²³

Regarding anticoagulation quality, the results from our meta-analysis are in accordance with previous papers from different Spanish regions. In the ANFAGAL study, poor VKA quality was reported in 42.7% and 41.5% of patients according to the TTR and PINRR, respectively.²⁴ In a large population-based study in the region of Valencia, the mean TTR was 63% whereas the mean PINRR was 59.2%, and 51.2% of patients had a TTR <65%.²⁵ These studies confirm that our national report is also align to the results reported in other single centre or single regions analyses. Nevertheless, we believe that the overall quality of anticoagulation with VKAs in Spain should be better nowadays than it was years ago. This assumption is based on a straightforward rationale: given the global experience gained from DOACs, most AF patients with poor TTR should have already switched to DOACs, leaving only those with appropriate TTR on VKAs. Consequently, most patients currently on VKAs would show a good TTR. Unfortunately, we are far from this ideal model. Actually, a study assessing the 6-month TTmMoR in VKA-treated patients before and after DOACs were recommended as first-line therapy by clinical guidelines showed no difference between these periods (TTR of 59% in 2015 vs. TTR of 63% in 2022; $p = 0.45$).²⁶

The most striking advantage provided by DOACs over VKAs, is the substantially lower risk of major bleeding, in particular intracranial haemorrhage (ICH), irrespective of the TTR.²⁷ For

example, in a comparative study of DOACs vs. VKAs with mean TTR of 70%, there were no differences in thromboembolic events, but DOACs caused fewer major bleedings.²⁸ Another study did not observe difference between DOACs and high TTR warfarin treatment regarding stroke, but fewer bleeding events were seen in DOAC users.²⁹ In a large observational registry-based cohort, even reduced dose DOACs were associated with lower risk of major bleeding and all-cause stroke than high quality VKA treatment (TTR $\geq 70\%$).³⁰ In the same line, in a systematic review and meta-analysis of randomized controlled trials, DOACs presented lower risk of stroke and ICH than warfarin, regardless of the TTR strata.³¹

However, the interest in the proper quality of anticoagulation when on VKAs is not trivial since TTR is associated with worse clinical outcomes.^{32–34} A study carried out in our country demonstrated that half of AF patients hospitalized because of a stroke/systemic embolism or major bleeding had inappropriate TTR,³⁵ and a large cohort study showed that well-managed VKA therapy was associated with a low risk of complications.³⁶ Indeed, previous studies demonstrated that every point of TTR matters and not only a pre-specified cut-off point (i.e. 70% or 65%).⁴ Even more, with a high TTR, differences between DOACs and VKAs in terms of efficacy and safety are importantly attenuated. In a nationwide study in Finland, differences in the risk of ischemic stroke, ICH and mortality between high TTR groups and standard dose DOACs were modest or even absent.³⁷ Similarly, in another study there was no difference in ischemic stroke/TIA, ICH, or mortality risks between DOAC-treated or VKA-treated AF patients with effective TTR.³⁸ In this context, some analyses demonstrated that VKAs are the most cost-effective treatment for patients who can achieve a TTR $\geq 70\%$ whereas DOACs are more likely to be cost-effective in settings with poor quality of VKA therapy.^{39,40} Therefore, one of the main reasons for switching to DOACs is the mean TTR, yet by guidelines, several patients are still not switched.⁴¹

The implication of TTR on patient prognosis is unquestionable but several factors affect the anticoagulant effect of VKAs (narrow therapeutic range, multiple food and drugs interactions, etc.), and they are influenced by an important inter- and intra-patient variability.⁴² Hence, routine monitoring is required to identify and modify potential variables of poor anticoagulation control. During the last years, several approaches have been investigated, including the use of multidose drug dispensing systems,⁴³ self-management of VKA therapy,^{44,45} Telehealth programs,⁴⁶ and specialized or mixed anticoagulation clinics,^{47,48} to improve adherence and TTR. Integrated and holistic care management is also key, as AF patients correctly managed and adherent to such an approach have higher TTR, independently of other comorbidities.⁴⁹

In addition, patient-centred education plays a central role in the appropriate anticoagulation quality. Investing in education and counselling lead to better quality of VKA therapy.⁵⁰ A brief educational intervention improves anticoagulation therapy knowledge, focused on patient's knowledge of the target INR and factors that may affect INR⁵¹; and higher baseline OAC knowledge is associated with better TTR.⁵² Indeed, OAC education is central since in AF patients switching from VKAs to DOACs due to a low pre-switch TTR have a worse persistence pattern to DOACs after the switch compared to patients with a high pre-switch TTR.⁵³ Despite patients with low TTR more consistently achieve treatment targets after DOAC switching, adherence-oriented interventions may be beneficial.⁵⁴ Thus, switching to DOACs in patients with poor TTR would not be good enough if it is not accompanied by counselling, education, and a patient-centred care.

There are some limitations should be acknowledged. First, included studies were performed in different settings, including cardiology, internal medicine, neurology, and primary care clinics. Management and anticoagulation quality may differ importantly among these specialties, although this also brings a good overview

of the national context. Of note, many of the studies have retrospective or cross-sectional design. Regarding the statistical analysis, since we do not have a random selection process, the statistical measures we provide are unfounded and the overall uncertainty will be greater than that quantified by statistical measures that presume chance, known as random error.

Another limitation is the assessment of the mean TTR using the Rosendaal's method. In some studies, TTR was calculated considering INR controls in the 6 months prior to inclusion in the study, while in others it was calculated at 6 months following inclusion, and in one of them, at one year after inclusion. Furthermore, the threshold for poor quality of anticoagulation according to European clinical guidelines (TTR $< 70\%$) was only reported in two studies, so we were unable to provide the pooled proportion of poor TTR using this cut-off. We also noted a high statistical heterogeneity that should be considered.

Finally, we have no data about how many patients were on acenocoumarol and how many were on warfarin (or even in a little extend, how many were on other VKAs such as phenprocoumon). In Spain, the most used VKA is acenocoumarol, but there are regions where warfarin is also frequent. The half-life of warfarin is longer than that of acenocoumarol, which theoretically provides more stable anticoagulation. However, none of the studies included in this systematic review reported TTR (or PINRR) in patients on acenocoumarol and warfarin separately, so we could not include such analysis in our systematic review.

Conclusion

In this systematic review and meta-analysis of AF patients on VKA therapy from national studies in Spain, we found a mean TTR of 63.22%, and a mean PINRR of 60.53%, both below the recommended standards and far from optimal. The pooled prevalence of poor anticoagulation control according to the TTR was 50%, and 46.90% when using PINRR. Healthcare professionals should focus on patients with poor anticoagulation quality by implementing more careful and closer follow-up to identify potential variables of poor VKA therapy, exploring strategies to improve treatment quality, and switching to DOACs whenever possible.

CRediT authorship contribution statement

Eva Soler-Espejo and María Asunción Esteve-Pastor reviewed the titles and abstracts of identified manuscripts to select studies for further assessment. José Miguel Rivera-Caravaca evaluated suitability and completeness of the eligible studies based on the inclusion and exclusion criteria, resolved disagreements, performed statistical analyses and drafted the manuscript. Danilo Menichelli and Daniele Pastori independently evaluated the risk of bias and plotted the funnel plots. David Vivas, Inmaculada Roldán, Manuel Anguita, and José Luis Ferreira, made an in-deep critical revision. Francisco Marín and Vanessa Roldán conceived and supervised the study, and made a critical revision. All authors read and approved the final version of the manuscript.

Ethical considerations

Ethical approval was not required given the study type (systematic review and meta-analysis article). Patients were not involved in study design and/or the development.

Declaration of generative AI and AI-assisted technologies in the writing process

Artificial intelligence was not used in the preparation of this manuscript.

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Conflicts of interest

José Miguel Rivera-Caravaca: Consultant for Idorsia Pharmaceuticals LTD. Jose Luis Ferreiro: reports honoraria for lectures from Eli Lilly Co, Daiichi Sankyo, Inc., AstraZeneca, Pfizer, Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Rovi, Terumo and Ferrer; consulting fees from AstraZeneca, Eli Lilly Co., Ferrer, Boston Scientific, Pfizer, Boehringer-Ingelheim, Daiichi Sankyo, Inc., Bristol-Myers Squibb and Biotronik; and research grants from AstraZeneca. Francisco Marín is consultant and speaker for Boehringer-Ingelheim and BMS/Pfizer. There is nothing to disclose for other authors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.1016/j.medcli.2025.107031>.

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