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# Group-based Trajectory Models to Assess Quality of INR Control and Its Association With Clinical Outcomes

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**Background:** The Time in Therapeutic Range (TTR) is the gold-standard measure used to assess the quality of oral anticoagulation with vitamin K antagonists. However, TTR is a static measure, and International Normalized Ratio (INR) control is a dynamic process. Group-based Trajectory Models (GBTM) can address this dynamic nature by classifying patients into different trajectories of INR control over time.

**Objectives:** The objective of this study was to assess the quality of INR control in a population-based cohort of new users of vitamin K antagonist with a diagnosis of atrial fibrillation using GBTM.

**Methods:** We classified patients into different trajectories according to their propensity for being adequately anticoagulated over their first year of treatment using GBTM, and we evaluated the association between trajectories and relevant clinical outcomes over the following year.

**Results:** We included 8024 patients in the cohort who fulfilled the inclusion criteria; the mean number of INR determinations over the first year of treatment was 13.9. We identified 4 differential trajectories of INR control: Optimal (9.7% of patients, TTR: 83.8%), Improving (27.4% of patients, TTR: 61.2%), Worsening (28%; TTR: 69.1%), and Poor control (34.9%; TTR: 41.5%). In adjusted analysis, Poor and Worsening control patients had a higher risk of death than Optimal control patients (hazard ratio: 1.79; IC 95%, 1.36–2.36 and hazard ratio: 1.36; IC 95%, 1.02–1.81, respectively). Differences in other outcomes did not achieve statistical significance, except for a reduced risk of transient ischemic attack in the Improving Control group.

**Conclusions:** GBTM may contribute to a better understanding and assessment of the quality of oral anticoagulation and may be used in addition to traditional, well-established measures such as TTR.

**Key Words:** oral anticoagulation, atrial fibrillation, vitamin-K antagonists, quality of care, International Normalized Ratio, Group-based Trajectory Models, outcomes

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Vitamin K antagonists (VKAs) such as warfarin or acenocoumarol, widely used in countries such as the Netherlands and Spain, among others, have been shown in clinical trials to reduce the risk of a stroke by two thirds,[1] and, for decades, has been the gold standard for stroke prevention in patients with atrial fibrillation (AF).[2] Nowadays, although new non-VKA oral anticoagulants (NOAC) are available, VKAs remain a viable oral anticoagulant for many patients because of their availability and cost.[3] However, the effectiveness and safety of VKAs in routine clinical practice are closely associated with the quality of anticoagulation control. Use of VKAs can be challenging due to their narrow therapeutic range, the need for periodic International Normalized Ratio (INR) monitoring, high interpatient variability in treatment response, numerous drug and food interactions, and medication nonadherence.[4] Evidence worldwide shows that a large proportion of VKA-treated patients, ranging from one third to three quarters, do not achieve adequate INR control and are thus at an increased risk of stroke or bleeding.[5–9]

The therapeutic range for VKA therapy is defined in terms of the INR. In atrial fibrillation patients, a tight INR range between 2 and 3 is widely taken as providing an adequate anticoagulation control. The Time in Therapeutic Range (TTR) is the gold standard metric used in the literature to measure the quality of INR control. TTR estimates the percentage of time a patient's INR is within the desired treatment range or goal and is widely used as an indicator of anticoagulation control. TTR is commonly used to evaluate the quality of VKA therapy and is an important tool for the

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risk-benefit assessment of the therapy.[10] However, while TTR is a static measure, INR control is a dynamic process, wherein obtaining consistent INR levels in range over time maximizes the desired benefits and safety of VKA.[11] In this way, 2 patients with a similar TTR in a given period of time could, in fact, behave very differently throughout that period.

Group-based Trajectory Models (GBTM),[12] a type of latent class analysis, can be used as an alternative or complementary method to traditional measures for summarizing INR control. GBTM can address the dynamic nature of the process of maintaining an adequate control of anticoagulation by providing a classification of patients into different trajectories of INR control over time, described through graphics with high face validity. GBTM has now become widely used in health care research such as in the study of medication adherence[13] or control of cardiovascular risk factors,[14] but, to the best of our knowledge, this approach has never been used to characterize the quality of oral anticoagulation over time.

We aimed to assess the quality of INR control in a population-based cohort of new users of VKA with a diagnosis of atrial fibrillation, by using GBTM to classify the patients into different trajectories according to their propensity for being adequately anticoagulated over their first year of treatment. We further examined the association between the trajectories of INR control identified and the occurrence of relevant clinical outcomes over the following year.

# METHODS

## Design and Setting

This real-world, population-based cohort study was conducted in the Valencia Health System (VHS), the public health system for the region of Valencia in Spain, covering about 97% of the region's population of 5 million inhabitants. We selected all patients diagnosed as suffering from AF or atrial flutter [diagnosis code of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9CM) 427.31 and 427.32] initiating treatment with acenocoumarol in the period 2010–2015 and remaining under treatment for the whole year following the initiation of treatment (in fact, we required 13 months of follow-up, as we censored the first month after the initiation of therapy, as this is considered a period of dose adjustment[14] for calculations). We did not include a small fraction of patients, mainly foreigners, treated with other VKAs such as warfarin, phenprocoumon, or fluindione due to limitations of follow-up for nonresidents.

We defined new users of acenocoumarol as those patients with no prescription of any oral anticoagulant the year before the first prescription (index date) in the period of inclusion. We defined patients under treatment for the whole of the first year by selecting the following patients: (1) those who remained alive throughout the year, (2) with at least 4 determinations of INR between months 2 and 13 after the index date (with fewer than 90 days between the index date and the first INR determination available), and (3) with gaps between determinations of <90 days between months 2 and 13 (or between the last INR determination available and the end of the assessment period).

We excluded from the cohort the following individuals: (1) non-naive users (patients with a prescription of VKA in the year before the index date); (2) patients who did not refill their first prescription (primary nonadherent); (3) patients treated for other conditions other than stroke prevention in AF; (4) patients younger than 40 years' old; (5) patients with valvular heart disease; (6) patients without INR or with incorrect INR information; and (7) patients with <395 days of follow-up. Because of these limitations on follow-up, we further excluded the following individuals: (8) people without health coverage by the VHS, mainly some government employees whose prescriptions are reimbursed by civil service insurers and are thus not included in the pharmacy databases of the VHS; and (9) patients not registered in the census (nonresidents or temporary residents), and (10) those who left the region or were disenrolled from VHS coverage for other causes (Fig. 1). Justification for inclusion and exclusion criteria is reported in Supplementary Material Table S1 (Supplemental Digital Content 1, http://links.lww.com/MLR/B910).

## Data Sources

Information was obtained from the VHS electronic information systems. The Population Information System provides information on the population under VHS coverage and registers certain demographic characteristics, including the geographical location and contextual situation of each person and the dates and causes of VHS discharge, including death. The Minimum Basic Dataset at hospital discharge is a synopsis of clinical and administrative information on all hospital discharges, including diagnoses and procedures. The electronic medical record for ambulatory care, available in all primary health care and specialty centers, has information about diagnoses, personal and family medical history, laboratory results and lifestyle, and information about both physician prescriptions and dispensations from pharmacy claims. All the information in these systems is linked at an individual level through a unique identifier.

## Outcome Measures

We used 2 measures of quality of INR control: (a) the trajectories grouping patients according to their probability of being adequately anticoagulated (ie, presenting biweekly INR values of between 2 and 3) over the first year of VKA treatment, using GBTM, and (b) TTR (mean value and percentage of patients with TTR $\geq$ 65%) for each trajectory. We calculated TTR using Rosendaal's linear interpolation method.[15]

The prespecified clinical outcomes were as follows: mortality and hospitalization for ischemic stroke, for transient ischemic attack (TIA), for gastrointestinal (GI) bleeding, for major GI bleeding (defined as a GI bleeding hospitalization needing a blood or blood components transfusion), and for intracranial hemorrhage. Only principal discharge diagnoses based on ICD9CM (Supplementary Material Table S2, Supplemental Digital Content 1, http://links.lww.com/MLR/B910) were used to define endpoints. In addition, composite outcomes of effectiveness (ischemic stroke or TIA) and safety (major bleeding-major GI bleeding or intracranial hemorrhage) were also analyzed. All outcomes were analyzed

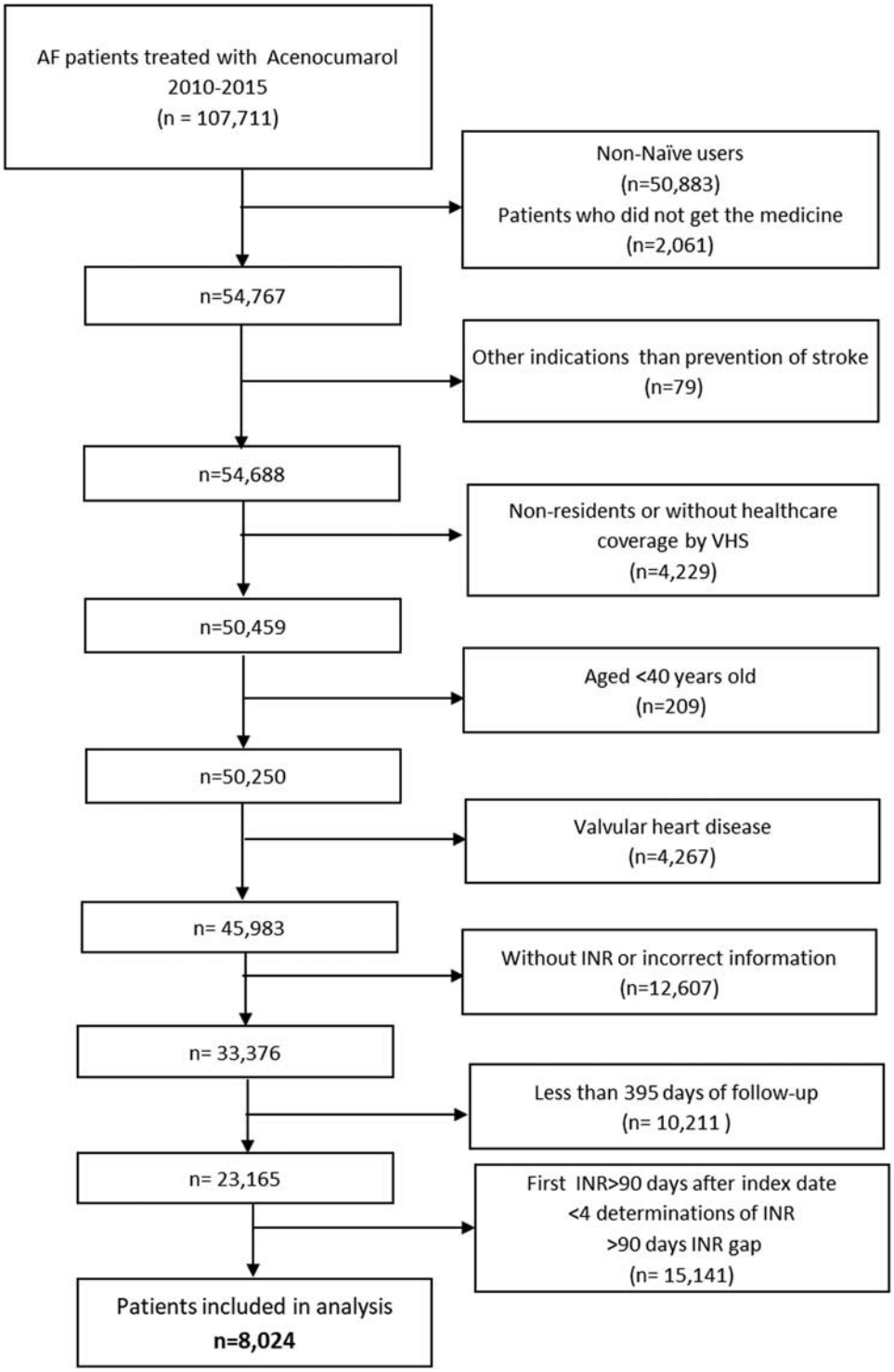


**FIGURE 1.** Flowchart. AF indicates atrial fibrillation; INR, International Normalized Ratio; VHS, Valencia Health System.

separately, and only the first event was considered for analysis. Patients were followed-up from month 14 after their first prescription and up to the relevant event, health system disenrollment, death, or end of follow-up (month 25), whichever came first.

## Covariates

Variables potentially related to the risk of stroke and bleeding were considered. These included sociodemographic characteristics, comorbidities, and health care resource utilization in the preceding 12 months.

**TABLE 1.** Patient Characteristics for the Total Cohort and for Each Trajectory of International Normalized Ratio Control

| | Total | Optimal | Poor | Worsening | Improving |
|---|---|---|---|---|---|
| N (%) | 8024 | 780 (9.7) | 2799 (34.9) | 2249 (28.0) | 2196 (27.4) |
| Sociodemographics, n (%) | | | | | |
| Female | 4034 (50.3) | 384 (49.2) | 1465 (52.3) | 1063 (47.3) | 1122 (51.1) |
| Age (Mean, SD%) | 74.89 (9.01) | 73.8 (9.5) | 74.9 (9.2) | 75.1 (8.9) | 75,0 (8,6) |
| <65 | 1065 (13.3) | 125 (16.0) | 395 (14.1) | 284 (12.6) | 261 (11.9) |
| 65–74 | 2271 (28.3) | 250 (32.1) | 718 (25.7) | 663 (29.5) | 640 (29.1) |
| >75 | 4688 (58.4) | 405 (51.9) | 1686 (60.2) | 1302 (57.9) | 1295 (59.0) |
| Country | | | | | |
| Spain | 7497 (93.4) | 737 (94.5) | 2565 (91.6) | 2118 (94.2) | 2077 (94.6) |
| Europe (other than Spain) | 264 (3.3) | 20 (2.4) | 116 (4.1) | 63 (2.8) | 65 (2.7) |
| Other | 263 (3.3) | 23 (2.9) | 118 (4.2) | 68 (3.0) | 54 (2.4) |
| Income | | | | | |
| 0–18,000 | 4899 (61.0) | 515 (66.0) | 1606 (57.4) | 1450 (64.5) | 1328 (60.5) |
| >18,000 | 3125 (39.0) | 265 (34.0) | 1193 (42.6) | 799 (35.5) | 868 (39.5) |
| Diagnosis, n (%) | | | | | |
| Atrial fibrillation | 7595 (94.7) | 739 (94.7) | 2659 (95.0) | 2127 (94.6) | 2070 (94.3) |
| Atrial flutter | 429 (5.3) | 41 (5.3) | 140 (5.0) | 122 (5.4) | 126 (5.7) |
| Comorbidities, n (%) | | | | | |
| Congestive heart failure | 1322 (16.5) | 85 (10.9) | 577 (20.61) | 344 (15.30) | 316 (14.39) |
| Hypertension | 6353 (79.2) | 594 (76.1) | 2250 (80.4) | 1781 (79.2) | 1728 (78.7) |
| Diabetes | 2746 (34.2) | 249 (31.9) | 1045 (37.3) | 707 (31.4) | 745 (33.9) |
| Liver disease | 499 (6.2) | 64 (8.2) | 181 (6.5) | 131 (5.8) | 123 (5.6) |
| Renal disease | 893 (11.1) | 60 (7.7) | 381 (13.6) | 229 (10.2) | 223 (10.1) |
| Previous ischemic stroke or TIA | 1115 (13.9) | 111 (14.2) | 416 (14.86) | 302 (13.4) | 286 (13.0) |
| Thromboembolism | 540 (6.7) | 49 (6.3) | 230 (8.2) | 130 (5.8) | 131 (6.0) |
| Hemorrhagic stroke | 50 (0.6) | 6 (0.8) | 15 (0.5) | 14 (0.6) | 15 (0.7) |
| GI bleeding | 281 (3.5) | 30 (3.8) | 115 (4.1) | 82 (3.6) | 54 (2.5) |
| Other bleeding | 1609 (20.1) | 118 (15.1) | 631 (22.5) | 443 (19.7) | 417 (19.0) |
| Vascular disease | 1193 (14.9) | 90 (11.5) | 473 (16.9) | 321 (14.3) | 309 (14.1) |
| Dementia | 415 (5.2) | 28 (3.6) | 167 (6.0) | 96 (4.3) | 124 (5.6) |
| Depression | 1009 (12.6) | 77 (9.9) | 392 (14.0) | 284 (12.6) | 256 (11.7) |
| Cancer | 969 (12.1) | 96 (12.3) | 348 (12.4) | 257 (11.4) | 268 (12.2) |
| Alcohol | 138 (1.7) | 10 (1.3) | 62 (2.2) | 34 (1.5) | 32 (1.4) |
| Events during the first year of treatment (13 mo), n (%) | | | | | |
| Ischemic stroke | 72 (0.9) | 4 (0.5) | 25 (0.9) | 19 (0.8) | 24 (1.1) |
| TIA | 17 (0.2) | 3 (0.4) | 5 (0.2) | 4 (0.2) | 5 (0.2) |
| GI bleeding | 55 (0.7) | 2 (0.3) | 28 (1.0) | 11 (0.5) | 1 (0.6) |
| Hemorrhagic stroke | 9 (0.1) | 0 (0.0) | 3 (0.1) | 4 (0.2) | 2 (0.1) |
| Health care utilization (Mean, SD%) | | | | | |
| Hospitalizations | 0.7 (1.2) | 0.58 (1.0) | 0.89 (1.3) | 0.68 (1.1) | 0.69 (1.1) |
| ED visits | 1.4 (1.8) | 1.32 (1.7) | 1.56 (2.1) | 1.28 (1.7) | 1.26 (1.7) |
| Outpatient visits | 11.4 (7.2) | 11.02 (7.5) | 11.70 (7.6) | 11.31 (7.0) | 11.16 (6.8) |
| Specialist visits | 0.5 (2.0) | 0.34 (1.3) | 0.66 (2.3) | 0.49 (2.0) | 0.47 (1.7) |
| Cardiology visits | 0.2 (0.8) | 0.13 (0.7) | 0.22 (0.9) | 0.18 (0.8) | 0.17 (0.7) |
| Neurologic visits | 0.1 (0.5) | 0.09 (0.4) | 0.14 (0.5) | 0.99 (0.4) | 0.11 (0.5) |
| Mental health visits | 0.01 (0.2) | 0.00 (0.0) | 0.01 (0.2) | 0.01 (0.2) | 0.01 (0.2) |
| Social care visits | 0.1 (0.8) | 0.08 (0.5) | 0.12 (0.9) | 0.09 (0.5) | 0.10 (0.8) |
| Medication use, n (%) | | | | | |
| NSAID | 1681 (21.0) | 157 (20.1) | 595 (21.3) | 445 (19.8) | 484 (22.0) |
| ASA | 2901 (36.2) | 273 (35.0) | 1004 (35.9) | 835 (37.1) | 789 (35.9) |
| Clopidogrel | 378 (4.7) | 33 (4.2) | 133 (4.7) | 98 (4.4) | 114 (5.2) |
| ASS and clopidogrel | 323 (4.0) | 27 (3.5) | 141 (5.0) | 76 (3.4) | 79 (3.6) |
| Other antiagre. | 370 (4.6) | 28 (3.6) | 145 (5.2) | 91 (4.0) | 106 (4.8) |
| Coxibs | 522 (6.5) | 43 (5.5) | 212 (7.6) | 138 (6.1) | 129 (5.9) |

ASA indicates acetylsalicylic acid; ED, emergency department; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; TIA, transient ischemic attack.

## Analysis

First, we used GBTM to identify trajectories of the likelihood of being correctly anticoagulated (ie, presenting an INR of between 2 and 3) over time. We created a biweekly series of INR values for each patient. We assigned to each fortnightly INR value the value of the closer INR determination available. GBTM was modeled with linear polynomial functions of time. Model selection was based on higher Bayesian information criterion, moderated by a preference for a useful parsimonious model that fitted the data well, the correspondence between each group's estimated probability and the proportion of study members classified to that group according to the maximum posterior probability rule, an average posterior probability value of <0.7 for each group, the odds of correct classification based on the posterior probabilities of group membership >5 for each group, and a

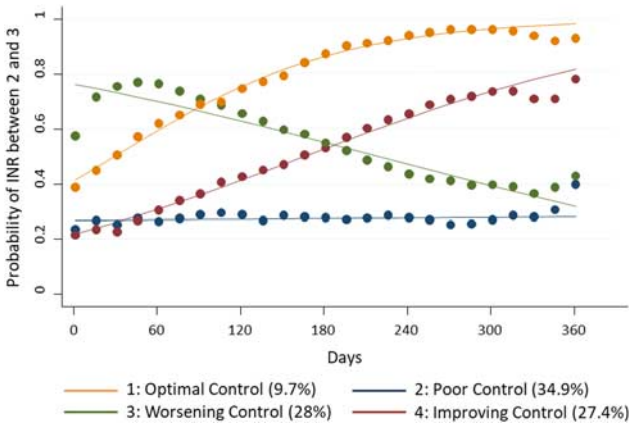


**FIGURE 2.** Trajectories of INR control in the first year of treatment (n = 8024) and the percentage of patients included in each trajectory (Central illustration). INR indicates International Normalized Ratio.

minimum group size in the range of 10% of the study population to facilitate the analysis of association of group membership with outcomes. Second, we described patient characteristics. Third, we jointly estimated with the trajectories themselves the relationship of individual-level characteristics with trajectory group membership.[16] Fourth, we calculated the TTR using Rosendaal's method, and calculated mean TTR and the percentage of patients with TTR ≥ 65% for each trajectory. In addition, we constructed TTR density plots for each trajectory, highlighting the TTR: 65% reference, which is commonly used as a threshold for adequate INR control.[17] Fifth, we used Cox proportional hazard models (crude and adjusted for sociodemographic, clinical, and health care utilization information) to evaluate the occurrence of effectiveness and safety outcomes associated with each trajectory. All analyses were performed using Stata version 14.

## RESULTS

### Characteristics of the Cohort and Trajectories of INR Control

We included 8024 patients in the cohort who fulfilled the inclusion criteria. The mean age was 75 years, and 50.3% were women. The most frequent comorbidities were hypertension (79.2%) and diabetes (34.2%), and 36.2% of patients used acetylsalicylic acid concomitantly (Table 1). The mean number of INR determinations over the first year of treatment was 13.9.

A 4-group model with linear specifications for all groups was chosen on the basis of specified selection criteria (Supplementary Material Table S3, Supplemental Digital Content 1, http://links.lww.com/MLR/B910). The diagnostics of accuracy for the 4-group model are reported in Supplementary Material Table S4 (Supplemental Digital Content 1, http://links.lww.com/MLR/B910). The characteristics of the groups are shown in Table 1. Figure 2 illustrates the estimated biweekly probability of presenting an INR of between 2 and 3 for patients in each trajectory. An overall 9.7% of the patients in the cohort were classified into trajectory 1, designated as "Optimal Control," and were likely to be in the range most of the time throughout the year, with a mean TTR of 83.8% (Fig. 3). In all, 34.9% of the patients were classified into trajectory 2, designated as "Poor Control," wherein patients were most of the time out of range throughout the year (mean TTR: 41.5%). Trajectory 4 showed a positive trend of improving INR control (designated as "Improving Control") and comprised 27.4% of the patients, while trajectory 3 showed the opposite trend (designated as "Worsening Control") and comprised 28% of the patients. The mean TTR for patients classified into the group of Improving Control was 61.2% and 69.1% in the case of patients in the Worsening Control group (Fig. 3).

### Factors Associated With Suboptimal Control

Poor Control patients were more likely to be other European [ref: Spain, odds ratio (OR): 1.76], to have heart failure (OR: 1.72), vascular disease (OR: 1.40), diabetes (OR: 1.25), renal disease (OR: 1.41), depression (OR: 1.43), and a higher income (OR: 1.50) than Optimal Control patients. Worsening Control patients were more likely to be older and have depression than optimally treated patients. Improving Control patients were more prone to have a higher income than Optimal Control patients (Supplementary Material Table S5, Supplemental Digital Content 1, http://links.lww.com/MLR/B910).

### Association of Trajectories and Outcomes

In adjusted analyses, Poor Control patients had a significantly higher risk of death than Optimal Control patients [hazard ratio (HR): 1.79; IC 95%, 1.36–2.36], as did patients in a trajectory of Worsening Control (HR:1.36; IC 95%, 1.02–1.81). The difference was nonsignificant for Improving Control patients (HR: 1.34; IC 95%, 1.00–1.78). Improving control patients showed a reduced risk of TIA (OR: 0.27, IC 95%, 0.08–0.90). No additional significant differences were found with respect to stroke, any bleeding, or TIA. A trend toward a higher risk of hemorrhagic stroke and major bleeding could be observed in all groups with respect to the Optimal Control group (Fig. 4).

## DISCUSSION

In the population of patients initiating treatment with acenocoumarol, we identified 4 distinct trajectories of anticoagulation control over the first year of treatment. Patients who maintained optimal INR control throughout their first year of VKA therapy had a lower risk of mortality with respect to patients with inadequate or unsustained INR control over time. The mortality risk was higher for patients in the trajectory systematically out of range and the worsening trajectory than for patients classified in the trajectories of improving or optimal control. Importantly, only 10% of the patients achieved a sustained level of INR determinations in range, while more than a third were systematically out of control, and the remaining had periods of good control combined with periods of inadequate INR. These findings should cause concern with regard to the overall quality of care we deliver to these patients.

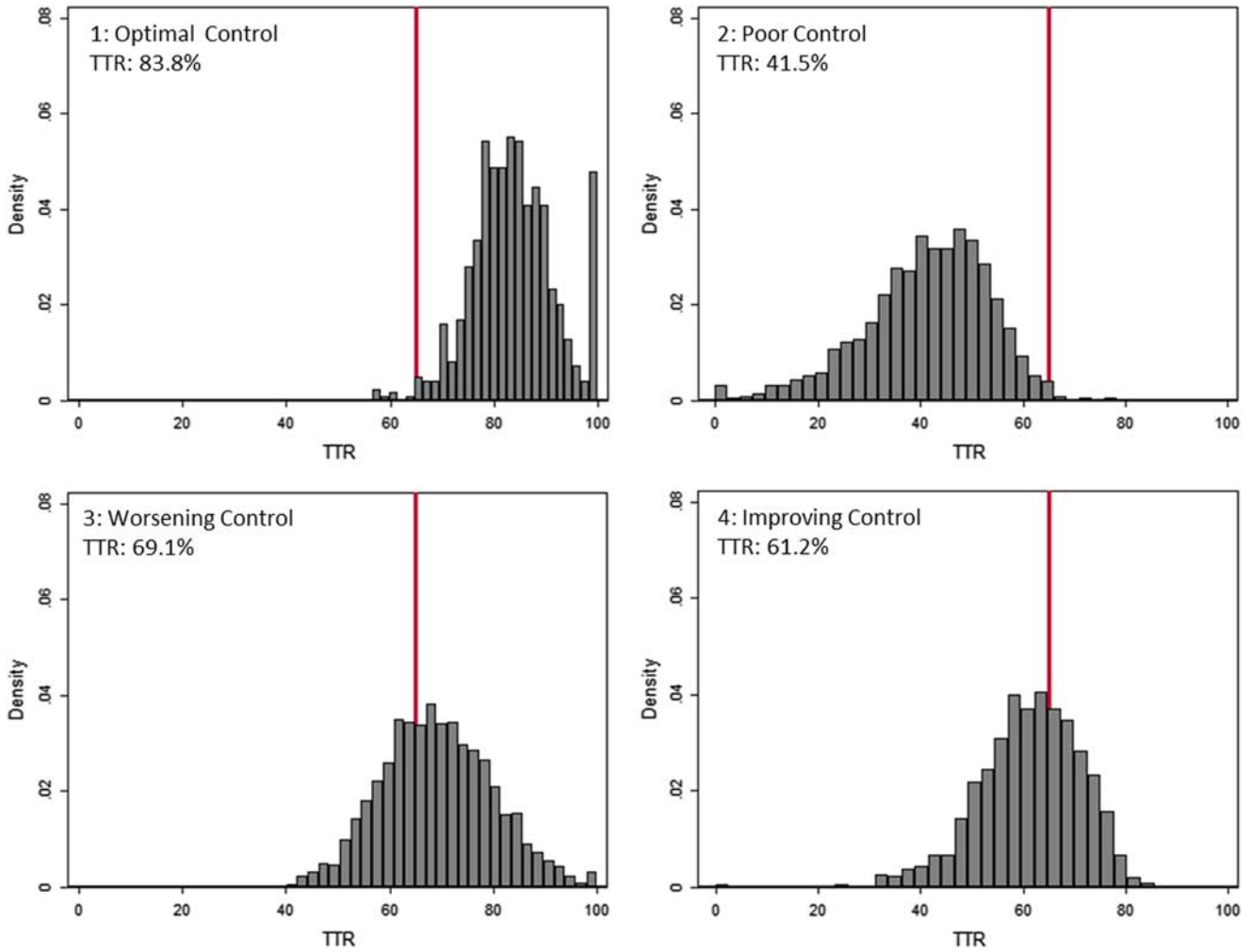


**FIGURE 3.** Density plots of the distribution of individual TTRs under each trajectory, and the mean TTR for each trajectory. TTR: 65% is marked with a line as a reference for adequate quality of International Normalized Ratio control. TTR indicates time in therapeutic range.

GBTM proved to be a useful tool for characterizing the dynamic process of INR control over time, and for identifying distinct subgroups of patients with regard to their propensity to be adequately anticoagulated. For instance, patients with improving and worsening control over the year had similar mean yearly TTR values but behaved in opposite directions. In the light of our results, improvement interventions may be tailored differently for these 2 groups of patients who could be considered as similar if the assessment was based solely in average, cross-sectional measures such as TTR.

The threshold of TTR > 65% is a commonly used indicator of optimal VKA control. Using this criterion, most patients classified in the group of improving control (mean TTR: 61.2%; TTR ≥ 65%: 38.0%) would be considered as inadequately treated, whereas the majority of patients in the group of worsening control (mean TTR = 69%; TTR ≥ 65%: 63.4%) would be considered as optimally treated. However, at the end of the year, patients in the latter group, for whom control is worsening, may be at a higher risk than patients for whom the likelihood of being in range is increasing with time (importantly, mortality in the following year was higher in the worsening control group than in the improving control group). The opposite would apply if facing the issue prospectively (at the moment of treatment initiation, patients in the Improving Control group are at a higher risk than patients in the Worsening Control group). In this sense, the longitudinal characterization of the process of INR control provides additional information to assess patient risk that can be useful for targeting priority groups for intervention at different moments of time. Moreover, with regard to our results relative to the association of suboptimal control trajectories with higher mortality risk, and consistent with other findings in the literature, consideration should be given to revising the TTR threshold for good INR control upward to values in the range of 80%.[18,19]

Characterizing anticoagulation control trajectories over time may provide a better understanding of the mechanisms, their associated factors, and their associated outcomes underlying suboptimal anticoagulation control than static, average/cross-sectional measures such as TTR. And, at the

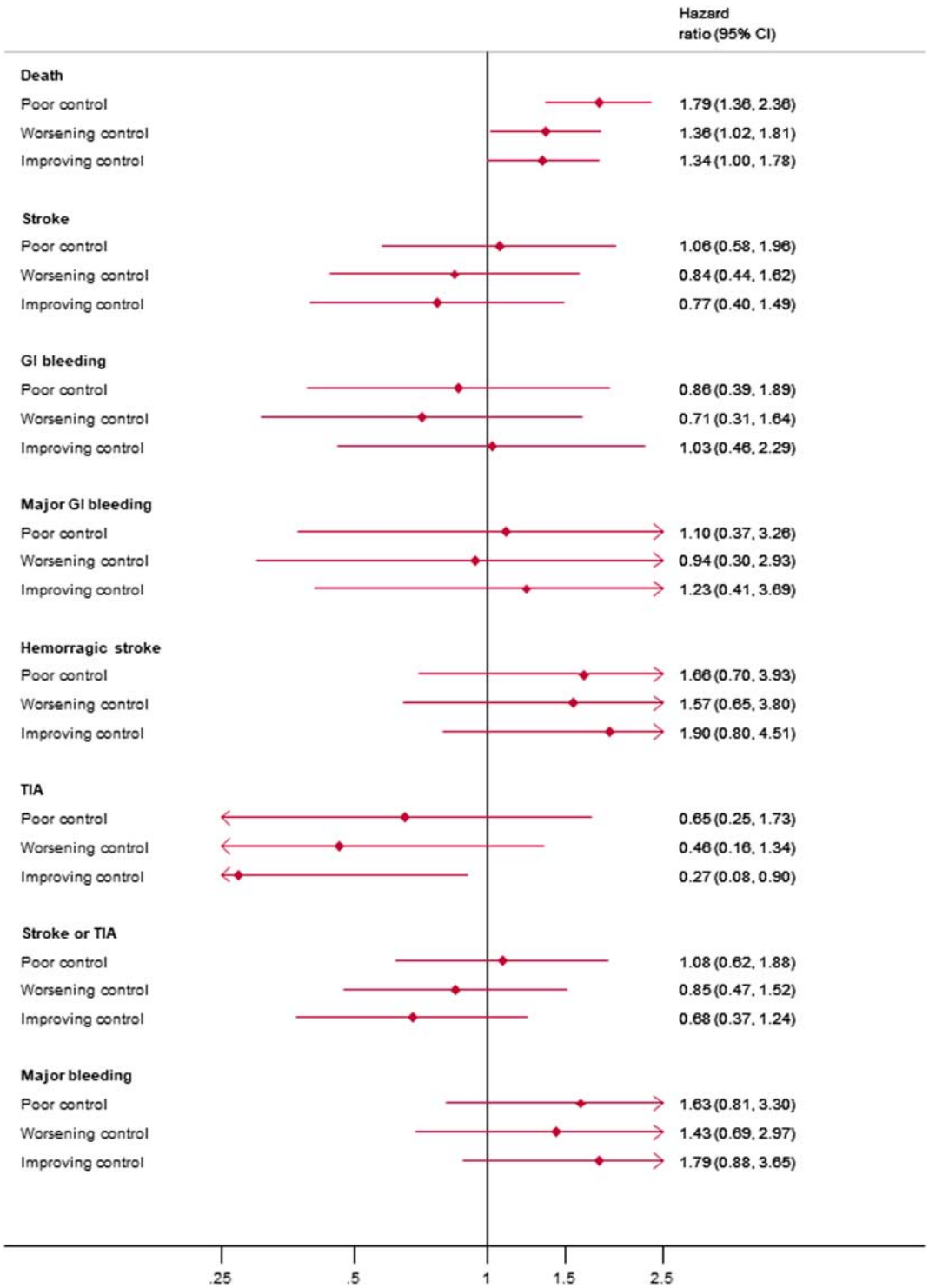


**FIGURE 4.** Association of clinical outcomes and trajectories of INR control. Hazard ratios (and 95% CI interval) are shown. CI indicates confidence interval; GI, gastrointestinal; INR, International Normalized Ratio; TIA, transient ischemic attack.

same time, they have also been shown to work in a consistent way with regard to traditional metrics of INR control. For instance, we observed that the distribution of patients' individual TTR under each trajectory and the mean TTR associated with each trajectory reflected an adequate summary measure of what could be observed over time with the trajectories. In this sense, TTR and trajectories coincide in the overall directionality of results and seem to work well

together to provide a more complete vision of the quality of INR control.

## Limitations

Our study is subject to some limitations. First of all, the construction of trajectories requires certain inclusion criteria that exclude a large proportion of patients, and probably produces a population that is different from the general one of patients with AF under OAC treatment (but with less severity, as they have not died in the first year, with greater adherence, as they have a minimum of INR controls, etc.). This restriction, largely inherent to GBTM methodology, is an important limitation for the generalizability of our results. Second, despite including many relevant individual variables in our analysis, we cannot rule out the existence of unmeasured confounding. These factors could be affecting the construction of the trajectories and the analysis of association to outcomes. Third, information biases due to absent registration or differing data-recording practices in the electronic databases might exist, although this is an inherent problem of any study using data from routine clinical practice. Moreover, misclassification (on exposure and covariates) is expected to be nondifferential across the groups of study subjects. Fourth, a healthy adherer effect may be lying behind the differences between groups with respect to outcomes.

# CONCLUSIONS

To the best of our knowledge, there are no previous studies using GBTM to represent the evolution of INR control in patients with atrial fibrillation treated with VKA. Four distinct trajectories of anticoagulation control over the first year of treatment (optimal control, improving control, worsening control, and poor control) were identified. Patients in trajectories of improving and maintained optimal INR control over their first year of VKA treatment had a lower risk of mortality than patients in trajectories of unsustained control. This highlights the interest in and relevance of analyzing the phenomenon of INR control in a longitudinal way. GBTM can contribute to a better understanding and assessment of the quality of oral anticoagulation with VKA and may be used in addition to traditional, well-established measures such as TTR.

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