*Original Research*

# Reduced Time in Therapeutic Range and Higher Mortality in Atrial Fibrillation Patients Taking Acenocoumarol

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## ABSTRACT

**Purpose:** The efficacy and tolerability of vitamin K antagonists (VKAs) depends on the quality of anticoagulant control, reflected by the mean time in therapeutic range (TTR) of international normalized ratio 2.0 to 3.0. In the present study, we aimed to investigate the association between TTR and change in TTR (ΔTTR) with the risk of mortality and clinically significant events in a consecutive cohort of atrial fibrillation (AF) patients.

**Methods:** We included 1361 AF patients stable on VKAs (international normalized ratio 2.0–3.0) during at least the previous 6 months. After 6 months of follow-up we recalculated TTR, calculated ΔTTR (ie, the difference between baseline and 6-month TTRs) and investigated the association of both with the risk of mortality and "clinically significant events" (defined as the composite of stroke or systemic embolism, major bleeding, acute coronary syndrome, acute heart failure, and all-cause deaths).

**Findings:** The median ΔTTR at 6 months of entry was 20% (interquartile range 0–34%), 796 (58.5%) patients had a TTR reduction of at least 20%, while 330 (24.2%) had a TTR <65%. During follow-up, 34 (2.5% [4.16% per year]) patients died and 61 (4.5% [7.47% per year]) had a clinically significant event. Median ΔTTR was significantly higher in patients who died (35.5% vs 20%; $P = 0.002$) or sustained clinically significant events (28% vs 20%; $P = 0.022$). Based on Cox regression analyses, the overall risk of mortality at 6 months for each decrease point in TTR was 1.02 (95% CI, 1.01–1.04; $P = 0.003$), and the risk of clinically significant events was 1.01 (95% CI, 1.00–1.03; $P = 0.028$). Patients with TTR <65% at 6 months had higher risk of mortality (hazard ratio = 2.96; 95% CI, 1.51–5.81; $P = 0.002$) and clinically significant events (hazard ratio = 1.71; 95% CI, 1.01–2.88; $P = 0.046$).

**Implications:** Our findings suggest that in AF patients anticoagulated with VKAs, a change in TTR over 6 months (ie, ΔTTR) is an independent risk factor for mortality and clinically significant events. Even in a cohort with good anticoagulation control, the risk for mortality and clinically significant events increases with every point deterioration of TTR. (*Clin Ther*. 2017;▮:▮▮▮–▮▮▮) 

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**Key words:** atrial fibrillation, vitamin K antagonists, time in therapeutic range, mortality.

## INTRODUCTION

Risk of mortality is reduced in atrial fibrillation (AF) patients after oral anticoagulation.[1] Despite the increasing use of non-vitamin K antagonists oral anticoagulants, vitamin K antagonists (VKAs, mainly warfarin and acenocoumarol) are still the most commonly used anticoagulant for stroke prevention in AF. However, the efficacy and tolerability of VKAs depend on the quality of anticoagulant control, as reflected by the mean time in therapeutic range (TTR) of international normalized ratio (INR) 2.0 to 3.0. Therefore, the therapeutic window is narrow, and monitoring and dose adjustments are necessary to achieve an optimal TTR for AF patients.[2] Indeed, a high TTR translates into a lower risk of adverse events.[3,4] Given that mortality rates are significantly higher in patients with poor TTR (often defined as TTR $<65\%$),[3] more efforts should be directed to achieve and maintain a high TTR when VKAs are chosen as the anticoagulation option.[5] Nevertheless, the difficulties in achieving a high TTR, the inconvenience of regular anticoagulation monitoring, and various food or drug restrictions associated with VKA use might also lead patients to stop oral anticoagulation treatment, leading to worse clinical outcomes.[6]

In the context of clinical trials, AF patients are often carefully selected and followed up regularly. This results in a higher TTR. However, AF patients from daily clinical practice tend to be older, with associated comorbidities and polypharmacy.

In the present study, we investigated the association of TTR and the change in TTR over 6 months (ie, ΔTTR) with the risk of mortality and "clinically significant events" (defined as the composite of stroke or systemic embolism, major bleeding, acute coronary syndrome, acute heart failure, and all-cause deaths) in a consecutive cohort of AF patients taking VKAs.

## PATIENTS AND METHODS

From May 1, 2007 to December 1, 2007, we recruited patients with paroxysmal, persistent, or permanent AF who were stable on VKAs (INR 2.0–3.0) for at least the previous 6 months in our single anticoagulation center in a tertiary hospital in Murcia (Southeast Spain). At entry, all patients had a TTR of 100% to ensure baseline homogeneity. We selected these patients because suboptimal TTR (ie, with a period of INRs out of range) is predictor of adverse thrombotic and bleeding events and a previous 6 months of (very) stable INRs would allow us to assess clinical outcomes, avoiding the bias produced by a low TTR or unstable INRs. We excluded patients with rheumatic mitral valves, prosthetic heart valves, and those with any acute coronary syndrome, stroke, hemodynamic instability, hospital admissions, or surgical interventions in the preceding 6 months.

At baseline, a complete medical history was recorded and stroke ($CHA_2DS_2$-VASc) and bleeding risks (HAS-BLED) calculated. The SAMe-$TT_2R_2$ score was calculated as an indirect clinical measure of the likelihood of achieving a good TTR.[7] At 6 months of inclusion, we calculated the TTR by the linear interpolation method of Rosendaal and the ΔTTR (ie, the difference between baseline and 6-month TTR).

### Study Outcomes

The primary end point was all-cause mortality. The secondary end point was a clinically significant event. The latter includes stroke or systemic embolism, major bleeding (using 2005 International Society on Thrombosis and Haemostasis criteria),[8] acute coronary syndrome, acute heart failure, and all-cause deaths. The investigators identified, confirmed, and recorded all adverse events, as well as other clinical outcomes. Follow-up was performed by personal interview at each visit to the anticoagulation clinic and through medical records. No patient was lost to follow-up.

The study protocol was approved by the Ethics Committee from University Hospital Morales Meseguer and was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki. All patients gave informed consent to participation in the study.

### Statistical Analysis

Categorical variables were expressed as frequencies and percentages. Continuous variables were presented as mean (SD) or median and interquartile range (IQR), as appropriate.

The Pearson $\chi^2$ test was used to compare proportions. Multivariate Cox proportional hazard regression