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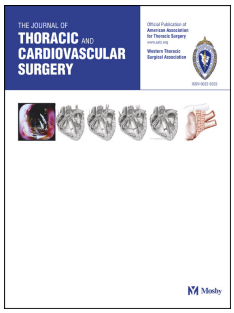
Published in:
The Journal of Thoracic and Cardiovascular Surgery

DOI (link to publication from Publisher):
10.1016/j.jtcvs.2019.02.061

Publication date:
2020

Document Version
Accepted author manuscript, peer reviewed version

Accepted Manuscript



Time in Therapeutic Range and Risk of Thromboembolism and Bleeding in Patients with Mechanical Heart Valve Prosthesis

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PII: S0022-5223(19)30506-9

DOI: https://doi.org/10.1016/j.jtcvs.2019.02.061

Reference: YMTC 14201

To appear in: *The Journal of Thoracic and Cardiovascular Surgery*

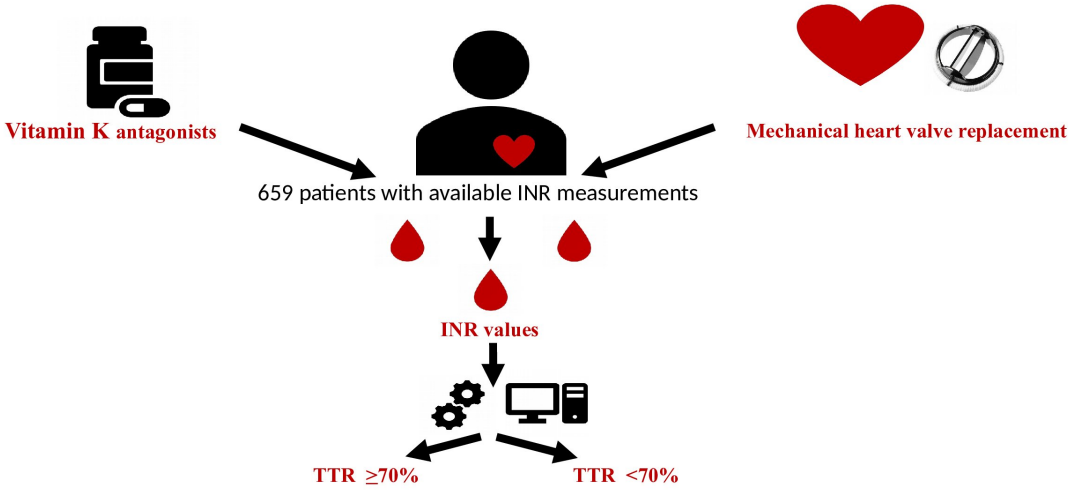
Received Date: 9 July 2018

Revised Date: 24 January 2019

Accepted Date: 12 February 2019

Please cite this article as: Havers-Borgersen E, Butt JH, Vinding NE, Torp-Pedersen C, Gislason G, Køber L, Fosbøl EL, Time in Therapeutic Range and Risk of Thromboembolism and Bleeding in Patients with Mechanical Heart Valve Prosthesis, *The Journal of Thoracic and Cardiovascular Surgery* (2019), doi: https://doi.org/10.1016/j.jtcvs.2019.02.061.

Methods:



Results: Low quality of VKA treatment defined as TTR<70% is associated with a higher risk of thromboembolism but not bleeding compared with high quality of VKA treatment defined as TTR≥70%. Further, mechanical mitral valves are associated with a lower TTR compared with mechanical aortic valves.

Implications: These results emphasize the importance of monitoring VKA therapy in mechanical heart valve patients.

Time in Therapeutic Range and Risk of Thromboembolism and Bleeding in Patients with Mechanical Heart Valve Prosthesis

Running title: *Mechanical Heart Valves and Oral Anticoagulation*

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Conflict of interest

EHB: None declared

JHB: None declared

NEV: None declared

CTP: Consultant fees and research funding from Bayer and Biotronic

GHG: Research grants from Bayer, Bristol-Myers Squibb, Pfizer, AstraZeneca, and Boehring Ingelheim

LK: None declared

ELF: Previous research funding from Janssen and Janssen and Bristol-Myers

Funding: This work was supported by the Danish Council for Independent Research.

Word count: 3416

Glossary of Abbrevations

- VKA: vitamin K antagonists
- OAC: oral anticoagulation
- INR: International Normalized Ratio
- TTR: Time in Therapeutic Range
- ICD: International Classification of Diseases
- NCSP: NOMESCO Classification of Surgical Procedures
- ATC: Anatomical Therapeutic Chemical classification
- MAV: mechanical aortic valve
- MMV: mechanical mitral valve
- MHV: mechanical heart valve

Central Message

We show that low versus high quality of vitamin K antagonist therapy, defined as time in therapeutic range <70% versus ≥70%, is associated with a higher risk of thromboembolism but not bleeding.

Perspective Statement

Oral anticoagulation with vitamin K antagonists (VKA) is recommended after mechanical heart valve replacement. However, data regarding the association between the quality of VKA treatment and the risk of complications are sparse. This manuscript contributes with important research findings emphasizing the importance of monitoring the VKA therapy in mechanical heart valve patients.

ABSTRACT

Objective: Oral anticoagulation with vitamin K antagonists (VKA) is recommended after mechanical heart valve replacement. However, data regarding the association between the quality of VKA treatment and the risk of complications are sparse.

Methods: Patients undergoing mechanical heart valve replacement (1997-2012) with available data on International Normalized Ratio (INR) values were identified in Danish registries. The quality of VKA treatment between discharge after valve replacement and 6 months post-discharge (index) was assessed as time in therapeutic range (TTR) ≥70% or <70% reflecting the percentage of time in therapeutic INR interval. Patients were followed from index until occurrence of an outcome of interest (i.e. thromboembolism and bleeding), death, or end of study (December 31, 2012), whichever came first. The risk of outcomes according to quality of VKA treatment was estimated with multivariable Cox regression.

Results: In total, 659 patients undergoing mechanical heart valve replacement were included in the study. Median number of INR measurements in the 6-month period after surgery was 13 (IQR 8-19). Median TTR was 54.9% (IQR 39.0-72.9) and 29.1% of patients had a TTR≥70%. Median follow-up was 6.1 years. The risk of thromboembolism was significantly lower in the group with TTR≥70% compared with TTR<70% (Hazard ratio (HR) 0.44, 95% CI 0.22-0.85), while no significant difference concerning risk of bleeding among groups was found (HR 0.63, 95% CI 0.36-1.08).

Conclusion: In patients undergoing mechanical heart valve replacement, TTR<70% in the 6-month period after surgery was associated with an increased risk of thromboembolic events but not bleedings compared with TTR≥70%.

Word count for the abstract: 250

INTRODUCTION

More than 100 million people worldwide suffer from valve diseases and the prevalence is expected to increase concurrently with increasing life expectancy.[1] Worldwide, approximately 300,000 valve replacements are carried out annually[1] and oral anticoagulation (OAC) therapy in patients with mechanical prosthesis is crucial in order to reduce the risk of thromboembolic complications and mortality. This comes at a natural price of an increased bleeding risk; hence, tight control of OAC therapy is clinically important in finding the optimal balance between effectiveness and safety.

Mechanical prostheses are recommended for patients younger than 65 years because of a long durability compared with bioprosthetic valves, yet they are associated with a higher risk of thromboembolic events and life-long OAC therapy with vitamin K antagonists (VKA) is recommended.[2] VKA have a slow on- and offset, a narrow therapeutic window, and a variable dose-response relationship and exhibit several drug-drug and drug-food interactions.[1] Further, guidelines recommend a continuous patient control in order to closely monitor the quality of the VKA treatment as variability of International Normalized Ratio (INR) or by Time in Therapeutic Range (TTR).[2,3]

Although the importance of a well-regulated VKA treatment in patients with atrial fibrillation is well established[4,5,6,7], little work has been done to clarify the impact of TTR on the risk of complications in mechanical heart valve patients. Among AF patients, studies have shown an association between low quality of VKA treatment and the risk of outcomes, while studies on patients with mechanical heart valve patients have shown contradictory results.[8,9,10,11] This nationwide carefully designed study sets out to examine the association between TTR and the risk of thromboembolic events and bleeding in patients with mechanical valve prostheses.

METHODS

Data sources

All residents in Denmark are assigned a unique and permanent civil registration number allowing accurate linkage of nationwide administrative registries at an individual level. *The Danish National Patient Registry* contains information on all hospital admissions, diagnoses (coded according to the International Classification of Diseases (ICD) eighth and tenth revision), and surgical procedures (coded according to the NOMESCO Classification of Surgical Procedures (NCSP)) since 1978. *The Danish National Prescription Registry* holds information on all claimed prescriptions since 1995 (coded according to the Anatomical Therapeutic Chemical (ATC) classification) including date of drug dispensation, strength, and quantity. All pharmacies in Denmark are by legislation obliged to register all dispensed prescriptions in order to ensure complete and accurate registration.[12] The *Danish National Population Registry* holds information on vital status and contains information on all deaths.

Information on INR values was obtained through registries of laboratory databases from general practitioners and from hospitals in the bigger part of Denmark including Northern Jutland and Zealand from 1st of January 1997 to 31th of December 2012.

Study population and TTR calculation

The study population comprised patients who underwent isolated mechanical aortic valve (MAV) or mechanical mitral valve (MMV) replacement (NCSP codes: KFMD00 and KFKD, respectively) in the period 1st of January 1997 to 31th of December 2012. Patients were followed from index (6 months post-surgery) until occurrence of an outcome (i.e. thromboembolism or bleeding), death, a maximum ten years of follow-up, or end of follow-up (December 31, 2012), whichever came first. Patients were excluded if they had undergone previous heart surgery, died before index, or experienced an outcome before index. Due to the low number of patients who underwent both

MAVR and MMVR (n=21), these patients were excluded from the study. The quality of VKA treatment can be described by means of TTR reflecting the percentage of time the patient has been in therapeutic INR interval. Current guidelines recommend an INR of 2.0-3.0 or 2.5-3.5 for patients with MAV and MMV, respectively.[2] TTR was calculated in the period from baseline (date of discharge) to index. TTR was assessed by the Rosendaal method, calculated as the total time in therapeutic interval divided by total time of observation. This method assumes a linear correlation between INR measurements and requires at least three INR values[6,13,14]; hence, patients with less than three INR values before index were excluded (Figure 1). The patients excluded due to lack of/insufficient INR values were comparable to the included patients. In order to calculate an accurate TTR in the period from baseline to index, the TTR calculation was not started until the patient was above the lower limit of their target therapeutic INR range i.e. 2.0 and 2.5 for patients with MAV and MMV, respectively, thus the individual period of TTR calculation could be less than 6 months. TTR calculation was stopped if more than 60 days passed between two successive measurements to ensure a precise analysis of the anticoagulation; hence, patients with more than 60 days between their two first INR measurements were excluded from the study (Figure 1). Thus, it is critical to have available and sufficient INR values in order to calculate TTR. In order to accurately access a reliable TTR, follow-up was initiated 6 months following discharge. According to current European guidelines[2] TTR ≥70% is considered high quality and consequently TTR <70% is considered low quality; thus, the study population was stratified into two groups according to their TTR value.

Covariates

Comorbidities were defined as at least one hospitalization any time prior to baseline (ICD-codes in Supplementary Table 1). Patients with diabetes and hypertension were identified using claimed

drug prescriptions as done previously.[15] Concomitant pharmacotherapy was defined by at least one filled prescription within six months prior to baseline.

Outcomes

Outcomes included thromboembolism, bleeding events, and all-cause mortality. Thromboembolism was defined as a composite of valve thrombosis, stroke, AMI, or arterial embolism (ICD-codes in Supplementary Table 1). Bleeding was defined as a major bleeding event requiring hospital admission (ICD-codes in Supplementary Table 1). Thromboembolism have previously been validated with high positive predictive values.[16–18]

Statistical analysis

Differences in baseline characteristics according to TTR were tested using the chi-square test for categorical variables and the Mann-Whitney test for continuous variables. Multivariable logistic regression was applied to identify baseline characteristics associated with TTR $\geq$70%. The cumulative incidences of thromboembolism and bleeding were estimated using the Aalen-Johansen estimator incorporating competing risk of death, whereas the cumulative incidence of all-cause mortality was estimated using the Kaplan-Meier estimator. Differences between groups were assessed using Gray's test and the log-rank test, respectively. In order to calculate hazard ratios (HR) for thromboembolism, bleeding, and all-cause mortality, we used multivariable cause-specific Cox regression models adjusted for sex, age, valve type, comorbidities listed in Table 1, and concomitant pharmacotherapy listed in Table 1. The proportional hazards assumption was tested and found valid. Relevant interactions were tested and found insignificant, unless otherwise stated. All statistical analyses were performed with SAS statistical software (SAS 9.4, SAS Institute, Cary, NC, USA). A two-sided p-value <0.05 was considered statistically significant.

Sensitivity analyses

To test the robustness of our findings, we assessed quality of VKA treatment by INR variability. INR variability was assessed as variance growth rate described and defined by Finn et al.[19] The variance growth rate reflects the degree to which a patient's INR deviates from his or her previous INR not taking the intensity of anticoagulation into account. Thus, the variability refers to the standard deviation of a linear curve of interpolated INR measurements. A mean of INR variability of 0.75 was chosen since the median (Supplementary Table 4) was shown to be 0.75. Thus, INR variability $\geq$0.75 was considered as high deviation, whereas INR variability <0.75 was considered as low deviation. Furthermore, a multivariable Cox regression with TTR as a time-dependent variable was performed adjusted for the aforementioned covariates. TTR was calculated continuously from three sequential INR values in the period from baseline to occurrence of an outcome (i.e. thromboembolism or bleeding), death, a maximum ten years of follow-up, or end of follow-up (December 31, 2012), whichever came first. The study population in the time dependent analysis consisted of 670 patients, since no patients with outcomes in the follow-up period were excluded. Moreover, propensity score stratification analyses were performed as a balancing method. Hazard ratios were generated using Cox proportional hazards regression stratified in three groups according to the propensity to achieve a TTR>70%. Propensity scores were calculated using a multi-variable logistic regression with the dependent outcome as achieving a TTR>70%. The propensity scores were generated from the covariates presented in Figure 2. The C index of the propensity model was 0.6 indicating relatively good discrimination. Stratification on propensity scores ensured comparison only within strata of propensity scores.

Ethics

The study was approved by the Danish Data protection Agency (reference no: 2007-58-0015/GEH-2014-012, I-suite no: 02720). Ethical approval is not required for retrospective register-based studies in Denmark.

RESULTS

Population

A total of 659 patients undergoing mechanical heart valve (MHV) replacement were included in the study; of these, the majority (80.0%) underwent mechanical aortic valve replacement (Figure 1). The median age of the study population was 58.0 years (interquartile range (IQR) 50-64) and 70.1% were men. The median amount of INR measurements in the 6-month period after surgery was 13 (IQR 8-19). Baseline characteristics for the overall study population and according to TTR are shown in Table 1.

Time in therapeutic range

Overall, 29.1% of the study population had a TTR ≥70%. Median TTR was 54.9 (IQR 39.0-73.1) and was higher among patients with MAV than patients with MMV (58.9% and 37.0%, respectively) (Table 2). The median of the average INR value was 2.6 among patients with MMV (therapeutic range 2.5-3.5) and 2.4 among patients with MAV (therapeutic range 2.0-3.0). Results from the multivariable logistic regression on factors associated with a TTR ≥70% are shown in Figure 2. In general, baseline characteristics in the two groups were similar, though TTR <70% was associated with mechanical mitral valve replacement (Odds Ratio 0.17, 95% confidence interval (95% CI) 0.17-0.53, P<0.001). Among the excluded 21 patients who underwent both MAVR and MMVR, the median TTR was 51.4% (IQR 29.4-57.8%) and 19.1% of patients had a TTR>70%.

Outcomes

During a median follow-up of 6.1 years, 79 patients experienced a thromboembolic event (AMI n=20, stroke n=57, arterial embolism n=3, valve thrombosis n=2). In total, 66 of the patients with a TTR <70% and 13 of the patients with a TTR ≥70% had a thromboembolic event. A significant difference was found when looking at the unadjusted cumulative incidence curve (P=0.011) (Figure 3). Also, in the multivariable model (Table 3) the risk of thromboembolism was significantly lower in the group with TTR ≥70% compared with TTR <70% (Hazard ratio (HR) 0.44, 95% CI 0.22-0.85, P=0.015).

During the follow-up period, 94 patients experienced a bleeding event. When stratified according to TTR, 69 of the patients with a TTR <70% and 25 of the patients with a TTR ≥70% experienced a bleeding event. In the cumulative incidence curve (Figure 4) and in the multivariable analysis (Table 3), no significant difference was found concerning risk of bleedings among groups (TTR≥70% vs. TTR<70%) (P=0.60 and HR 0.63, 95% CI 0.36-1.08, P=0.094, respectively).

Patients with a history of stroke, ischemic heart disease, atrial fibrillation, or hypertension were at risk of for thromboembolic events, whereas patients with prior bleeding event, a history of hypertension, or abnormal liver function were at risk of a new bleeding event. Supplementary Table 2 and 3 summarize factors associated with thromboembolic events and bleedings, respectively. Among patients experiencing a first-time outcome (i.e. thromboembolic event or bleeding), 3 and 9 patients experienced a recurrent thromboembolic event or bleeding, respectively.

During the follow-up period, 95 patients died and the incidence of mortality was shown to be lower in the group with TTR ≥70% compared with the group with TTR <70% (n=21 and n=74, respectively). TTR ≥70% was shown to be associated with a similar risk of mortality compared with TTR <70% in the cumulative incidence curve (P=0.15) (Figure 5) and in the multivariable analysis (Table 3) (HR 0.84, 95% CI 0.50-1.42, P=0.52).

Sensitivity analyses

A sensitivity analysis was performed using INR variability as an alternative way of describing the quality of anticoagulation treatment. Median INR variability was 0.75 (IQR 0.49-1.16). Overall, 67.7% of the population group had INR variability <0.75; however, it concerned 55.2% of the MAV patients and 29.6% of the MMV patients (Supplementary Table 4). In unadjusted analyses, INR variability ≥0.75 was associated with higher risk of bleedings and death (P=0.0001 and P=0.0012, respectively) when compared with INR variability <0.75, while no significant difference was found with respect to risk of thromboembolism (P=0.15). In adjusted analyses, no significant difference between the two groups (INR variability ≥0.75 vs. <0.75) was found concerning the risk of thromboembolism (HR 0.63, 95% CI 0.37-1.07, P=0.087), bleedings (HR 0.72, 95% CI 0.44-1.18, P=0.20), and mortality (HR 0.68, 95% CI 0.43-1.07, P=0.096) (Supplementary Table 5).

Additionally, a multivariable Cox regression analysis with TTR as a time-dependent covariate was performed. The median amount of INR measurements per patient was 44 (IQR 19-90). No differences were found in terms of risk of thromboembolism (HR 0.87, 95% CI 0.30-2.52, P=0.80), bleeding (HR 1.23, 95% CI 0.51-2.97, P=0.65), or all-cause mortality (HR 1.57, 95% CI 0.64-3.89, P=0.33) between patients with TTR <70% and patients with TTR ≥70%.

Further, propensity score stratification analyses were performed yielding similar findings as the main results (Hazard ratio (HR) 0.51, 95% CI 0.27-0.95 and HR 0.59, 95% CI 0.33-1.06 for thromboembolism and bleeding, respectively).

DISCUSSION

In this study, we examined the association between the quality of VKA treatment, as measured by TTR, and the risk of adverse outcomes in patients undergoing MHV replacement. Our study yielded three principal findings. First, baseline characteristics were found similar between the two groups (TTR <70% vs. TTR ≥70%) with the exception that MMV patients more often had TTR <70%. Second, TTR was found lower in MMV patients compared with MAV patients. Third, TTR <70%

was associated with an increased risk of thromboembolism but not bleeding and all-cause mortality, compared with TTR ≥70% in patients with MHV.

Few studies have examined the association between baseline characteristics and quality of VKA treatment, though their findings have not been consistent. A Korean study showed no significant associations between variables and quality of VKA treatment in an adjusted model.[6] Also, Wypasek et al. found in a multiple regression analysis that MAV patients with TTR ≥60% did not differ from patients with TTR <60% with respect to demographic or cardiovascular risk factors, yet, coronary artery disease and previous stroke were associated with higher TTR, while CYP2C9*2 allele variant was associated with lower TTR.[14] In studies on AF patients, variables associated with TTR have been summarized in the SAMe-TT2R2 score (female sex, age <60 years, medical history [more than two comorbidities], treatment [interacting drugs, eg. Amiodarone], tobacco use [doubled], race [doubled]); a higher score was associated with an increased risk of labile INR (reflected as low TTR) and outcomes.[20,21] Hence, the current research gives an ambiguous picture of the association between baseline characteristics and the quality of TTR; thus, our study emphasizes the fact that it is difficult to predict which patients are susceptible of a low quality of VKA treatment.

MMV have been shown to be more thrombogenic than MAV.[22] The relative risk of prosthetic valve thrombosis have shown to be twice as high for MMV compared with MAV[23], and also, the risk of mortality has been shown to be highest for patients with a MMV prosthesis.[10] Overall, studies have shown that the risk of outcomes is higher in MMV patients compared with MAV patients.[11,22,24] We found that MMV patients had lower quality of VKA treatment compared with MAV patients, and since lower TTR is associated with higher risk of outcomes, MMV patients are, prima facie, at higher risk of outcomes compared with MAV patients.

Several studies have shown an association between increased risk of bleeding with increasing INR and increased risk of thromboembolic events with decreasing INR.[3,13] Also, studies have shown that lack of anticoagulation treatment results in a thromboembolic rate of up to 12% per year for MAV patients and 22% per year for MMV patients, and that VKA treatment reduces these risks to 1-4 % per year.[25]

In our study, patients with TTR <70% had a significant higher risk of thromboembolism compared with patients with TTR ≥70%, and trends towards differences were observed regarding the risk of bleeding and all-cause mortality among groups. In the sensitivity analysis on INR variability, trends towards differences concerning the risk thromboembolism, bleeding, and all-cause mortality were found, although no differences in outcomes were found in the time-dependent analysis among groups. The quality of VKA treatment is usually defined over a longer period of time as in our six months follow-up, but since the INR value can change rapidly, the time-dependent analysis could give a more precise picture of the risk of outcomes at any given time. However, the amount of INR measurements showed great variance in our study population and as a result of the limited amount of INR measurements in some patients, the time-dependent analysis has limited power because of its time specific nature.

Previous studies have focused on Cox regression analyses on TTR or INR variability, and the risk of outcomes in MHV patients has been associated with lower quality of TTR. Grzymala-Lubanski et al. found that the risk of thromboembolic events, bleeding, and death was significantly higher at lower TTR levels in MHV patients[10,11], while other studies found that high INR variability was associated with significant higher risk of thromboembolic events, bleeding, and mortality in MHV patients.[19,26] The majority of these studies included rather small study populations. More work has been done regarding the quality of VKA treatment and the risk of outcomes in AF patients. Björck et al found that the risk of bleeding, thromboembolism, and mortality was higher at TTR <70% and INR variability above mean when compared with TTR ≥70% and INR variability

329 below mean[5]. Likewise, Gallagher et al. found that AF patients with TTR >70% had lower risk of
330 stroke and mortality when compared with patients with TTR <70%.[13] The studies on AF patients
331 included large study populations compared with the studies on MHV patients, hence, our study is
332 important because of a relatively large and representative study population of MHV patients. Thus,
333 our study has the advantage of a more complete analysis that supports the current evidence on the
334 association between low TTR (<70%) and high INR variability (≥0.75) and a higher risk of adverse
335 outcomes.
336
337 Strengths and limitations
338 The main strength of our study is the combination of complete administrative registries including
339 data on hospital admissions, deaths, and filled prescriptions in Denmark in combination with data
340 on INR values. This retrospective study was carried out on every patient with accessible data;
341 however, the main limitation was the number of patients with accessible blood samples. In addition,
342 patients can have their INR values analysed at general practitioners or by self-monitoring at home
343 without reporting the result; thus the laboratory databases might not be fully representative,
344 although we tried to overcome this challenge with the restriction of 60 days between measurements.
345 Due to exclusion criteria, the study population is smaller than the total population undergoing
346 mechanical heart valve replacement. Further, TTR was calculated in a 6-month period, and so it
347 cannot be excluded that TTR could change later on. Moreover, additional events may have occurred
348 in the first six months post-discharge but these events are not included due to the nature of this
349 study. We tried to overcome this challenge in the time-dependent analysis, however, due to a great
350 variance of the amount of INR measurements per patient this analysis has limited power. Thus,
351 more INR measurements will be needed in order to strengthen this sensitivity analysis.
352 Additionally, patients may require anticoagulation interruption during surgical procedures etc.
353 possibly affecting the risk of outcomes which we do not have available data on to take into account.

In the propensity score stratification analyses, similar results were found compared with the main analysis; the difference in risk of bleeding was non-significant between groups, however, a tendency towards a difference was found. The Cox analyses were adjusted for relevant demographics, comorbidities, and use of medication, yet the influence of potential confounders and thereby residual confounding cannot be omitted.

Conclusions

Our study supports the existing knowledge that low quality of VKA treatment, defined as TTR <70%, is associated with a higher risk of thromboembolic events compared with high quality of VKA treatment (TTR ≥70%), and also that MMV was associated with lower TTR compared with MAV. Therefore, it is essential to emphasize the awareness of the monitoring of anticoagulant therapy in every patient on OAC VKA treatment. For graphical overview of methods, results, and implications of the study, see also graphical abstract.

368 Acknowledgements

369 None

370

LEGENDS

Central picture Cumulative incidence of thromboembolism in patients with mechanical heart valves according to quality of VKA treatment (TTR ≥70% vs. TTR<70 %). TTR, Time in Therapeutic Range.

Figure 1 Selection of the study population. INR: International Normalized Ratio

Figure 2 Baseline characteristics associated with TTR <70% and TTR >70%.
TTR: Time in therapeutic range. CI: Confidence intervals. COPD: Chronic obstructive lung disease.

Figure 3 Cumulative incidence of thromboembolism in patients with mechanical heart valves according to quality of VKA treatment (TTR ≥70% vs. TTR <70%). TTR: Time in therapeutic range. VKA: vitamin K antagonists.

Figure 4 Cumulative incidence of bleeding in patients with mechanical heart valves according to quality to quality of VKA treatment (TTR ≥70% vs. TTR <70%). TTR: Time in therapeutic range. VKA: vitamin K antagonists.

Figure 5 Cumulative incidence of mortality in patients with mechanical heart valves according to quality of VKA treatment (TTR ≥70% vs. TTR <70%). TTR: Time in therapeutic range. VKA: vitamin K antagonists.

Graphical abstract Association between quality of VKA treatment (TTR ≥70% vs. TTR <70%) and risk of outcomes in patients with mechanical heart valves and implications of the findings. VKA: vitamin K antagonists. TTR: Time in therapeutic range.

Video The importance of monitoring the VKA therapy in patients with mechanical heart valves. VKA: vitamin K antagonists.

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480 **Table 1** Baseline characteristics divided by TTR at time of discharge

Variable	***TTR* <70***	***TTR ≥70***	***Standardized mean differences***
Number (%)	466 (70.7 %)	193 (29.3 %)	
Median age (IQR)	58.0 (50-64)	58.0 (49-64)	-0.04
Male sex (%)	319 (68.5 %)	149 (77.2 %)	0.20
Comorbidities			
Ischemic heart disease	139 (29.7 %)	48 (25.0 %)	-0.09
Acute myocardial infarction	33 (7.1 %)	7 (3.7 %)	-0.15
Chronic heart failure	145 (31.1 %)	46 (24.0 %)	-0.15
Atrial fibrillation	140 (30.0 %)	52 (27.1 %)	-0.05
Stroke	56 (12.0 %)	14 (7.8 %)	-0.14
Transient ischemic attack	36 (7.7 %)	14 (7.29 %)	0.01
Arterial embolism	4 (0.9 %)	3 (1.6 %)	0.06
Pulmonic embolism	11 (2.4 %)	2 (1.0 %)	-0.10
Deep vein thrombosis	10 (2.1 %)	1 (0.5 %)	-0.14
Diabetes mellitus	19 (4.1 %)	14 (7.3 %)	0.05
Peripheral vascular disease	20 (4.3%)	5 (2.6%)	-0.09
Coagulopathy	25 (5.4 %)	10 (5.2 %)	-0.01
Prior bleeding	110 (23.6 %)	46 (24.0 %)	0.02
Chronic obstructive lung disease	40 (8.6 %)	18 (9.4 %)	0.05
Malignancy	73 (15.6 %)	32 (16.7 %)	0.02
Abnormal liver function	17 (3.6 %)	6 (3.13 %)	-0.03
Chronic renal failure	29 (6.2 %)	11 (5.7 %)	-0.02
Aortic regurgitation	152 (32.6 %)	59 (30.7 %)	-0.03
Aortic stenosis	240 (51.4 %)	119 (62.0 %)	0.22

Mitral regurgitation	107 (22.9 %)	22 (11.4 %)	-0.31
Mitral stenosis	34 (7.3 %)	12 (6.3 %)	-0.31
Endocarditis	95 (20.3 %)	32 (16.7 %)	-0.10
Alcohol abuse	32 (6.9 %)	14 (7.3 %)	0.02
Hypertension	172 (36.9 %)	77 (39.9 %)	0.06
Concomitant therapy			
Statins	95 (20.4 %)	48 (24.9 %)	0.11
Beta-blockers	113 (24.3 %)	57 (29.5 %)	0.12
Calcium channel blockers	78 (16.7 %)	40 (20.7 %)	0.10
Renin-angiotensin system inhibitors	130 (27.9 %)	56 (29.0 %)	0.02
Amiadarone	21 (4.5 %)	8 (4.15 %)	-0.02
Digoxin	53 (11.4 %)	22 (11.4 %)	0.00
Acetylsalicylic acid	121 (26.0 %)	48 (25.0 %)	-0.03
ADPi†	4 (0.9 %)	2 (1.0 %)	0.02
Dipyridamol	9 (1.9 %)	5 (2.6 %)	0.044
Vitamin K antagonists	105 (22.5 %)	52 (26.9 %)	0.10
Thiazid	71 (15.2 %)	35 (18.1 %)	0.08
NSAID‡	99 (21.2 %)	41 (21.4 %)	0.04

*TTR: time in therapeutic range. †ADPi: adenosin diphosphate receptor inhibitors. ‡NSAID: non-steroidal anti-inflammatory drugs.

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483 **Table 2** Time in therapeutic range (TTR) according to valve type

	Combined	**MAV†**	**MMV**
TTR <70%*	467 (70.9 %)	351 (66.6 %)	115 (87.1 %)
TTR ≥70%	192 (29.1 %)	176 (33.4 %)	17 (12.9 %)
Median TTR, (IQR)	54.9 (39.0-73.1)	58.9 (44.5-75.0)	37.0 (23.8-54.0)
Mean TTR, (SD)	55.5 (24.0)	59.1 (22.9)	41.1 (22.9)

*TTR: time in therapeutic range. Combined includes all patients with a mechanical aortic or mitral valve. †MAV: mechanical aortic valve. ‡ MMV: mechanical mitral valve.

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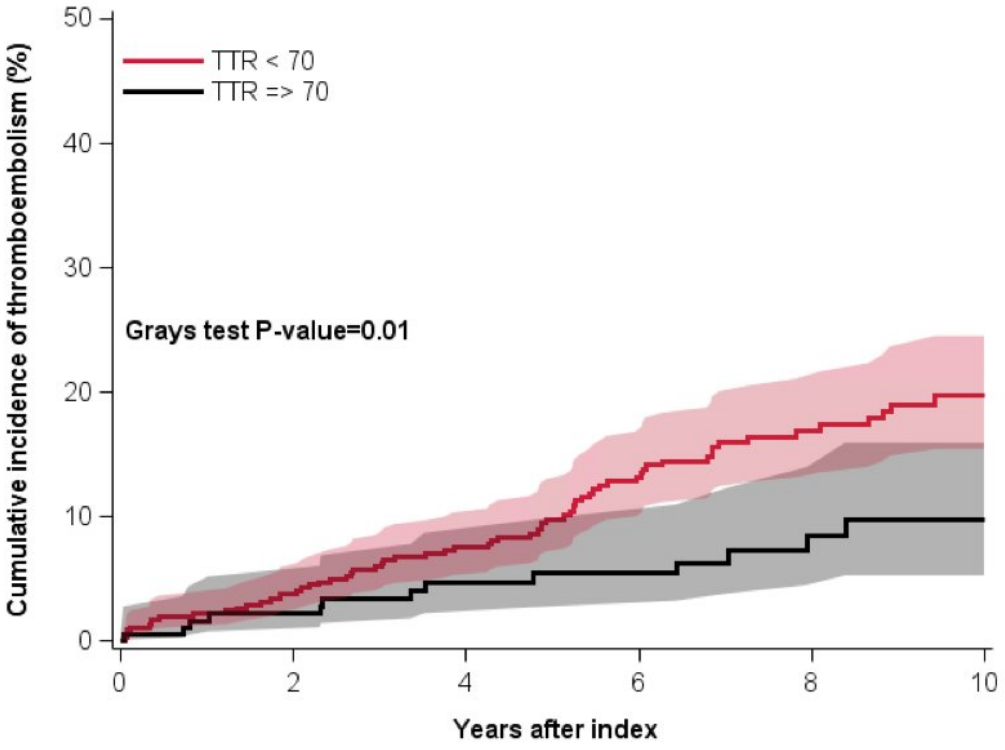
Table 3 Multivariable analysis on risk of thromboembolism, bleeding and all-cause mortality depending on quality of VKA treatment measured as TTR

	Events (n)		Hazard ratio (95% CI)	P value
	TTR ≥70%	*TTR <70%*		
Thromboembolism	13	66	0.44 (0.22-0.85)	0.02
First year after index	3	10		
Remaining 9 years after index	10	56		
Bleeding	25	69	0.63 (0.36-1.08)	0.05
First year after index	5	10		
Remaining 9 years after index	20	59		
All-cause mortality	21	74	0.84 (0.50-1.42)	0.52
First year after index	2	5		
Remaining 9 years after index	19	69		

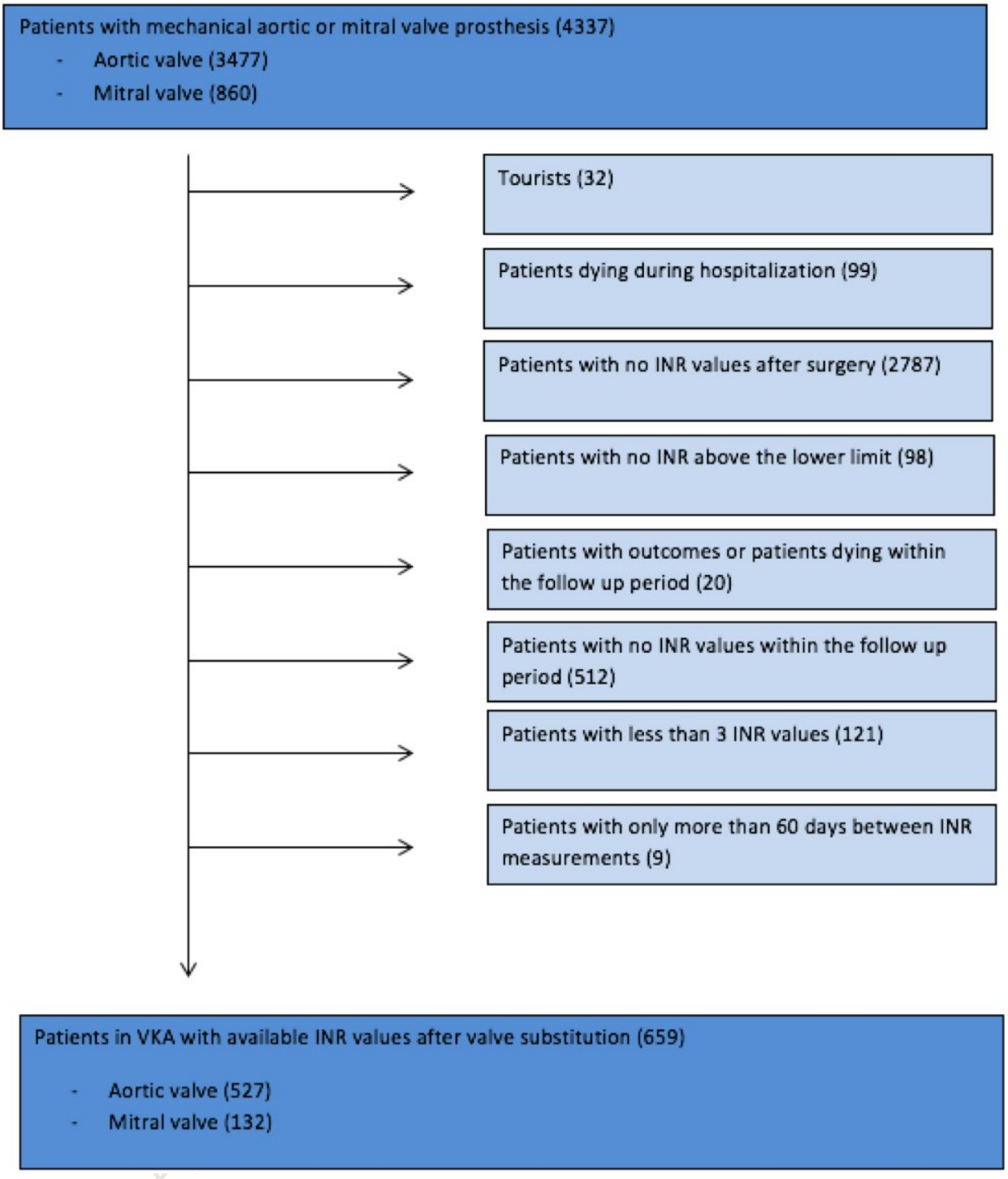
High (≥70%) vs. low (<70%) TTR is considered high vs. low TTR quality, receptively.

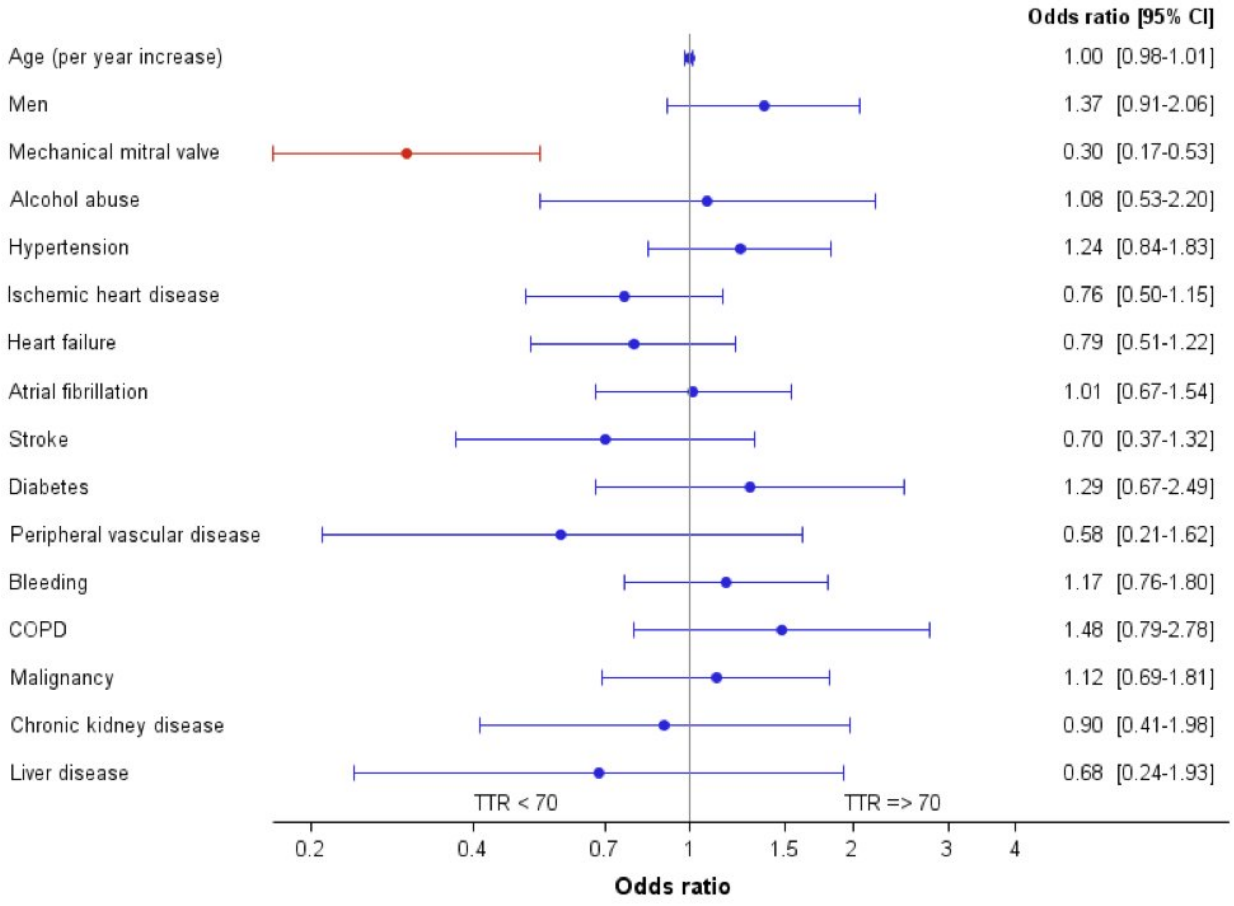
TTR ≥70% is set as reference for the analysis.

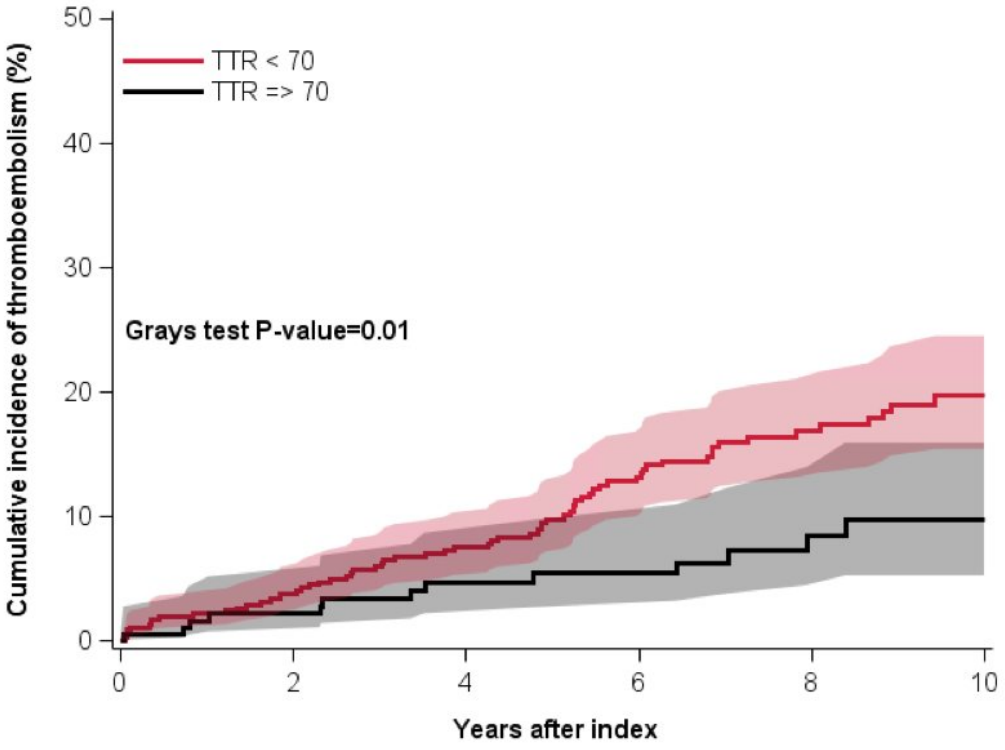
HR is adjusted for sex, age, valve type, comorbidities (ischemic heart disease, chronic heart failure, atrial fibrillation, prior stroke, transient ischemic attack, peripheral vascular disease, coagulopathy, bleeding, chronic obstructive lung disease, malignancy, chronic renal failure, abnormal liver function, alcohol abuse, endocarditis, hypertension, and diabetes mellitus), and concomitant pharmacotherapy (statins, beta-blockers, calcium channel blockers, RAS inhibitors, acetylsalicylic acid, and ADP inhibitors).



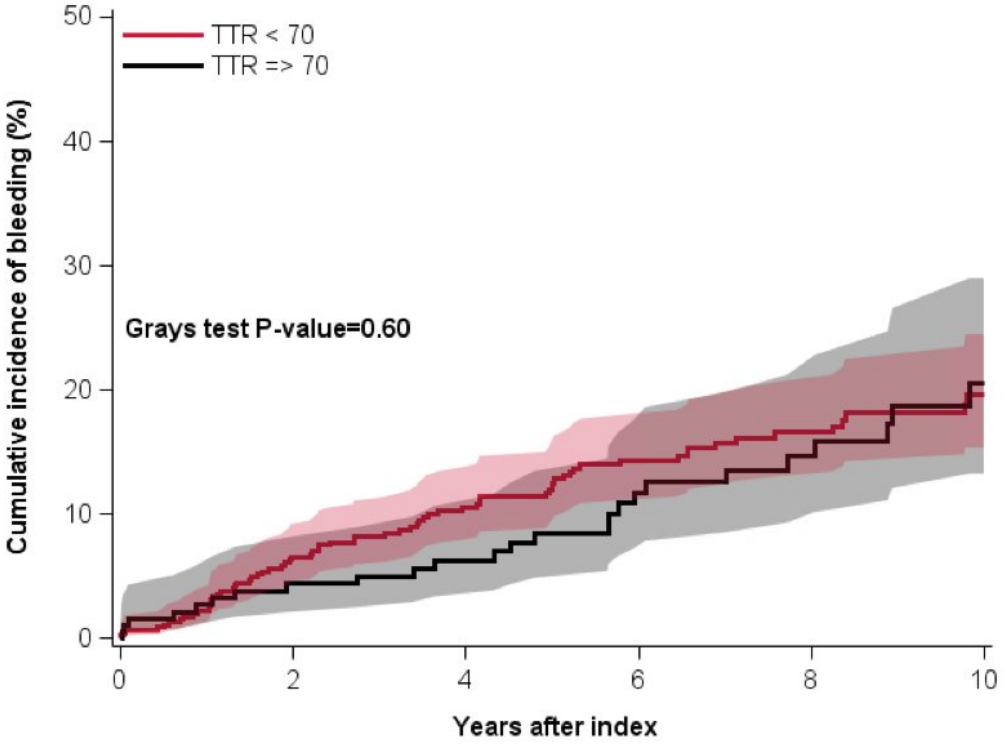
Patients at risk						
TTR < 70	460	405	314	238	148	71
TTR => 70	189	159	132	99	70	43


Patients with mechanical aortic or mitral valve prosthesis (4337)
- Aortic valve (3477)
- Mitral valve (860)
Tourists (32)
Patients dying during hospitalization (99)
Patients with no INR values after surgery (2787)
Patients with no INR above the lower limit (98)
Patients with outcomes or patients dying within the follow up period (20)
Patients with no INR values within the follow up period (512)
Patients with less than 3 INR values (121)
Patients with only more than 60 days between INR measurements (9)
Patients in VKA with available INR values after valve substitution (659)
- Aortic valve (527)
- Mitral valve (132)

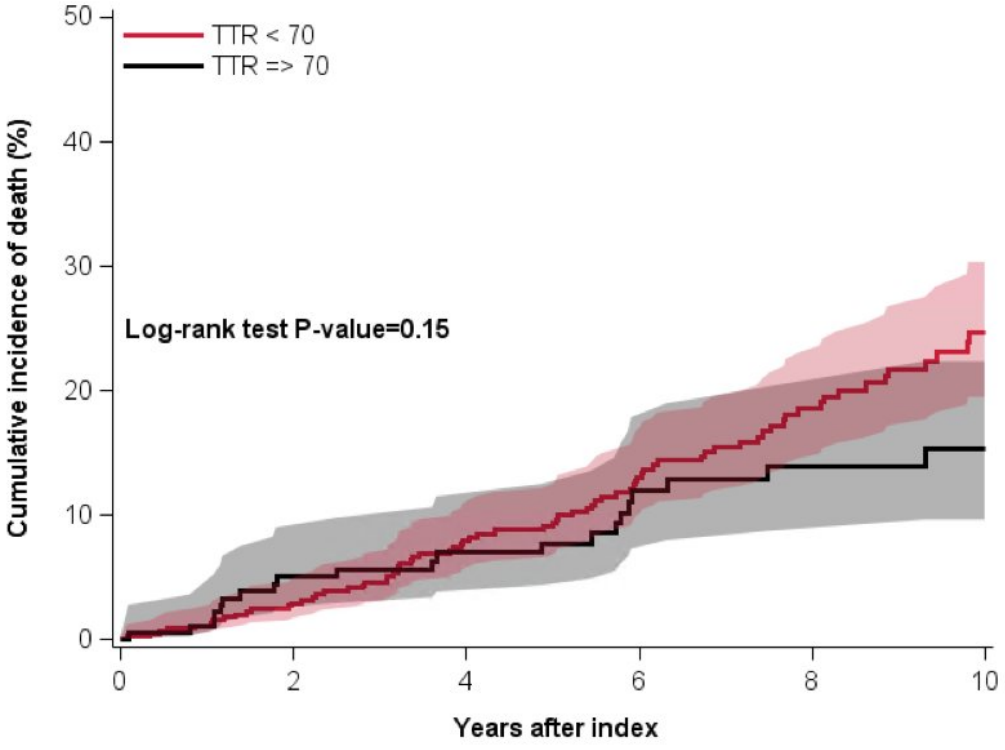

Odds ratio [95% CI]
Age (per year increase)
1.00 [0.98-1.01]
Men
1.37 [0.91-2.06]
Mechanical mitral valve
0.30 [0.17-0.53]
Alcohol abuse
1.08 [0.53-2.20]
Hypertension
1.24 [0.84-1.83]
Ischemic heart disease
0.76 [0.50-1.15]
Heart failure
0.79 [0.51-1.22]
Atrial fibrillation
1.01 [0.67-1.54]
Stroke
0.70 [0.37-1.32]
Diabetes
1.29 [0.67-2.49]
Peripheral vascular disease
0.58 [0.21-1.62]
Bleeding
1.17 [0.76-1.80]
COPD
1.48 [0.79-2.78]
Malignancy
1.12 [0.69-1.81]
Chronic kidney disease
0.90 [0.41-1.98]
Liver disease
0.68 [0.24-1.93]
TTR < 70
TTR => 70
0.2
0.4
0.7
1
1.5
2
3
4
Odds ratio



Patients at risk						
TTR < 70	460	405	314	238	148	71
TTR => 70	189	159	132	99	70	43



Patients at risk						
TTR < 70	460	392	311	242	150	75
TTR => 70	189	158	133	95	67	38



Patients at risk						
TTR < 70	460	418	339	270	170	85
TTR => 70	189	163	137	102	74	47

Supplemental Material

Time in Therapeutic Range and Risk of Thromboembolism and Bleeding in Patients with Mechanical Heart Valve Prosthesis

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Supplementary Table 1 Comorbidities, pharmacotherapy, and outcomes

Comorbidity	
	ICD-codes (ICD-8 and ICD-10)
Ischemic heart disease	ICD8: 410, 411, 412, 413, 414 ICD10: I20, I21, I22, I23, I24, I25,
AMI*	ICD8: 410 ICD10: I21, I22
Chronic heart failure	ICD8: 425, 428 ICD10: I42, I50, I110, I130, I132, J819
Atrial fibrillation	ICD8: 42794, 42793 ICD10: I48
Stroke	ICD8: 430, 431, 432, 433, 434, 436 ICD10: I63, I64
TIA†	ICD8: 435 ICD10: G45
Arterial embolism	ICD8: 444 ICD10: I74
Pulmonic embolism	ICD8: 450 ICD10: I26
Deep vein thrombosis	ICD8: 45100, 45108, 45109, 45190, 45199, 45300, 45302, 45303, 45304, 45809 ICD10: I801, I802, I803, I808, I809, I821, I822, I823, I828, I829
Diabetes mellitus	ICD8: 250 ICD10: E10-E14

Peripheral vascular disease	ICD8: 440 ICD10: I70
Coagulopathy	ICD8: 286 ICD10: D66. D67. D68, D69
Bleeding	ICD8-10: I60, I61, I62, N02, R31, R04, D62, H052A, G951A, S368D, K298A, K228F, I864A, K638B, K638C, K838F, K868G, I312, H313, H356, H431, H450, S064, S065, S066, J942, D500, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K286, K290, K625, K661, K920, K921, K922, I850
Alcohol abuse	ICD8: 57109, 57110, 57710 ICD10: F10, K70, E52, T51, K860, E244, G312, I426, O354, Z714, Z721, G621, G721, K292, L278A ATC-code: N07BB
Chronic obstructive lung disease	ICD8: 490, 491, 492 ICD10: J42, J43, J44
Malignancy	ICD8: 140-209 ICD10: C00-C97
Abnormal liver function	ICD8: 571, 572, 573, 155, 070 ICD10: B15-B19, K70-K77, C22, I982, Z944, D684C, Q618A
Chronic renal failure	ICD8: 403, 404, 581, 582, 583, 584, 25002, 50039, 59009, 59320, 75310, 75311, 75319 ICD10: N02, N03, N04, N05, N06, N07, N08, N11, N12, N14, N18, N19, N26 M321B, N158, N159, N160, N162, N164, N168,

	Q612, Q613, Q615, Q619, E102, E112, E132, E142, I120, M300, M313, M319, T858, T859, Z992
Aortic insufficiency	ICD10: I351, I352
Aortic stenosis	ICD8: 395, 396 ICD10: I350, Q253, I352
Mitral insufficiency	ICD8: 394, 396 ICD10: I340, I051, I052, I348A
Mitral stenosis	ICD10: I050, I052, I342
Endocarditis	ICD8: 42100-42199, 42499 ICD10: I33, I38, I398
Pharmacotherapy	
	ATC code
Statins	C10AA
Beta-blockers	C07, C09BX
Calcium channel blockers	C08, C07F, C09BB, C09DB
Renin-angiotensin system inhibitors	C09
Diabetes mellitus drugs	A10
Amiadarone	C01BD01
Digoxin	C01AA05
Acetylsalicylic acid	B01AC06
ADPi‡	B01AC04, B01AC22, B01AC24, B01AC25

Dipyridamol	B01AC07
Vitamin K antagonists	B01AA03, B01AA04
Antiadrenergic drugs	C02A, C02B, C02C
Thiazid	C03A, C07B, C07D
Loop diuretics	C03C, C03EB01, C03EB02
Spironolacton	C03DA01
Diuretics combined	C07C, C08G, C03B, C09Ba, C09DA
NSAID§	M01A
Hypertension	2 or more of BB, CBB, RASi, antiadrenergics, thiazid, loop diuretics, spironolacton, diuretics combined
Outcomes	
	ICD-code
Thromboembolism (valve thrombosis, AMI, ischemic stroke, systemic embolism and thrombosis, TCI‖)	ICD8: 410 ICD10: T828, I21, I22, I63, I64, G458, G459, I74
Bleeding	I60, I61, I62, N02, R31, R04, D62, H052A, G951A, S368D, K298A, K228F, I864A, K638B, K638C, K838F, K868G, I312, H313, H356, H431, H450, S064, S065, S066, J942, D500, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K286, K290, K625, K661, K920, K921, K922, I850

*AMI: acute myocardial infarction. † TIA: Transient ischemic attack. ‡ADPi: adenosin diphosphate receptor inhibitors. §NSAID: non-steroidal anti-inflammatory drugs. ||TCI: Transient Ischemic infarction

Supplementary Table 2 Factors associated with thromboembolic events

	Hazard ratio (95% Confidence interval)	**P value**
Age	0.99 (0.64-2.40)	0.55
Sex (men)	1.23 (0.70-2.15)	0.21
TTR ≥70%	0.44 (0.22-0.85)	0.01
Mechanical aortic valve	1.24 (0.64-2.40)	0.53
Ischemic heart disease	2.92 (1.70-5.00)	0.0001
Heart failure	0.78 (0.44-1.38)	0.39
Atrial fibrillation	0.46 (0.24-0.86)	0.01
Stroke	12.26 (7.10-21.17)	<0.0001
Hypertension	2.28 (1.01-5.13)	0.05
Diabetes mellitus	2.12 (0.66-6.80)	0.21
Peripheral vascular disease	1.52 (0.65-3.55)	0.34
Bleeding	1.05 (0.60-1.81)	0.88
Alcohol abuse	1.41 (0.45-4.39)	0.55
Chronic obstructive lung disease	1.02 (0.46-2.24)	0.97
Malignancy	0.74 (0.37-1.51)	0.41
Abnormal liver function	1.82 (0.58-5.76)	0.31
Chronic renal failure	1.95 (0.77-4.97)	0.16

Supplementary Table 3 Factors associated with bleeding

	Hazard ratio (95% Confidence interval)	**P value**
Age	1.01 (0.99-1.04)	0.40
Sex (men)	1.49 (0.83-2.66)	0.18
TTR ≥70%	0.63 (0.36-1.08)	0.09
Mechanical aortic valve	0.71 (0.41-1.24)	0.23
Ischemic heart disease	1.01 (0.60-1.70)	0.98
Heart failure	0.99 (0.59-1.67)	0.97
Atrial fibrillation	0.94 (0.57-1.57)	0.82
Stroke	1.61 (0.81-3.22)	0.18
Hypertension	2.61 (1.34-5.11)	0.005
Diabetes mellitus	0.77 (0.26-2.27)	0.63
Peripheral vascular disease	0.72 (0.30-1.70)	0.45
Bleeding	15.93 (8.99-28.24)	<0.0001
Alcohol abuse	1.85 (0.95-3.61)	0.073
Chronic obstructive lung disease	0.82 (0.39-1.71)	0.59
Malignancy	1.58 (0.95-2.63)	0.08
Abnormal liver function	2.62 (1.16-5.95)	0.02
Chronic renal failure	1.81 (0.88-3.73)	0.11

Supplementary Table 4 INR variability according to valve type

	Combined	**MAV***	**MMV†**
INR variability <0.75	446 (67.7 %)	291 (55.2 %)	39 (29.6 %)
INR variability >0.75	213 (32.3 %)	236 (44.8 %)	93 (70.1 %)
INR variability median, (IQR)	0.75 (0.49-1.16)	0.70 (0.46-1.06)	1.01 (0.61-1.34)
INR variability mean, (SD)	0.94 (0.81)	0.86 (0.62)	1.25 (1.28)

Combined includes all patients with a mechanical aortic or mitral valve.
*MAV: mechanical aortic valve. † MMV: mechanical mitral valve.

Supplementary Table 5 Multivariable analysis on risk of thromboembolism, bleeding and all-cause mortality depending on quality of VKA treatment using mean INR variability of 0.75 as cut-off

	Events (% of group)		**Hazard ratio (95% Confidence interval)**	**P value**
	INR variability ≥0.75	*INR variability <0.75*		
Thromboembolism	13.4%	10.6%	0.63 (0.37-1.07)	0.087
Bleeding	19.2%	9.4%	0.72 (0.44-1.18)	0.20
All-cause mortality	18.2%	10.6%	0.68 (0.43-1.07)	0.096

High (>0.75) vs. low (<0.75) INR variability is considered low vs. high TTR quality, receptively.
INR variability <0.75 is set as reference for the analysis
HR is adjusted for sex, age, valve type, comorbidities (ischemic heart disease, chronic heart failure, atrial fibrillation, prior stroke, transient ischemic attack, peripheral vascular disease, coagulopathy, bleeding, chronic obstructive lung disease, malignancy, chronic renal failure, abnormal liver function, alcohol abuse, endocarditis, hypertension, and diabetes mellitus), and concomitant pharmacotherapy (statins, beta-blockers, calcium channel blockers, RAS inhibitors, acetylsalicylic acid, and ADP inhibitors).

Supplementary Table 6 Time-dependent multivariable Cox regression

	Hazard ratio (95% Confidence interval)	**P value**
Thromboembolism	0.87 (0.30-2.52)	0.80
Bleeding	1.23 (0.51-2.97)	0.65
All-cause mortality	1.57 (0.64-3.89)	0.33

Supplementary Table 7 Patients with TTR ≥70% versus TTR <70% over time (1996-2012)

Year	Patients with TTR ≥70% (%)	Patients with TTR <70%
1996	22.2%	77.8%
1997	44.4%	55.6%
1998	20.0%	80.0%
1999	27.8%	72.2%
2000	30.0%	70.0%
2001	23.8%	76.2%
2002	30.6%	69.4%
2003	17.0%	83.0%
2004	32.8%	67.2%
2005	26.5%	73.5%
2006	24.6%	75.4%
2007	30.0%	70.0%
2008	31.1%	68.9%
2009	29.4%	70.6%
2010	34.8%	65.2%
2011	48.0%	52.0%
2012	30.4%	69.6%