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

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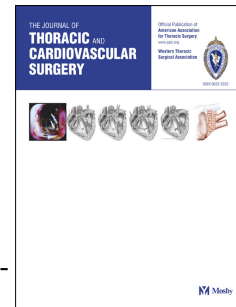
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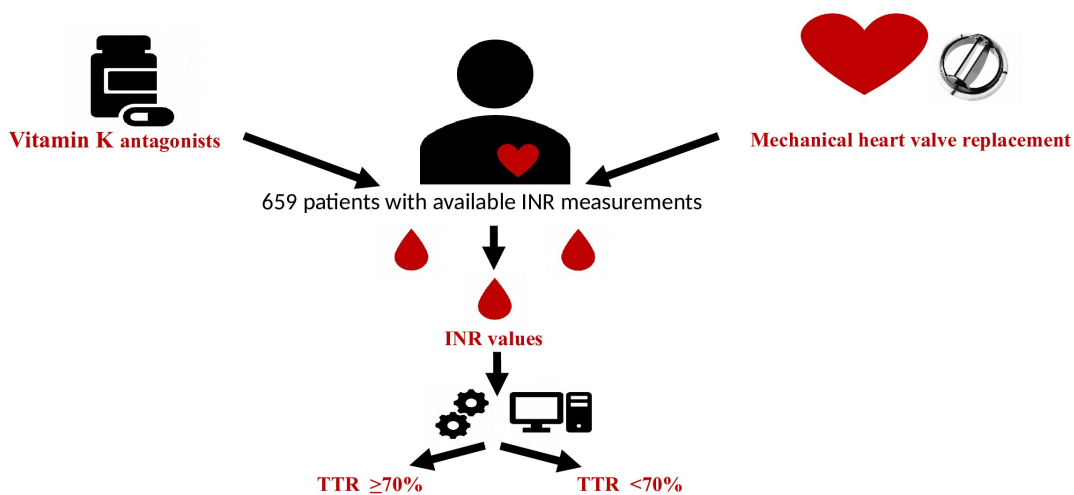
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Methods:

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 $\geq 70\%$. 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.

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

3 *Running title: Mechanical Heart Valves and Oral Anticoagulation*

4
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20
21 Conflict of interest

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32

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34

ACCEPTED MANUSCRIPT

35 **Glossary of Abbreviations**

- 36 - VKA: vitamin K antagonists
- 37 - OAC: oral anticoagulation
- 38 - INR: International Normalized Ratio
- 39 - TTR: Time in Therapeutic Range
- 40 - ICD: International Classification of Diseases
- 41 - NCSP: NOMESCO Classification of Surgical Procedures
- 42 - ATC: Anatomical Therapeutic Chemical classification
- 43 - MAV: mechanical aortic valve
- 44 - MMV: mechanical mitral valve
- 45 - MHV: mechanical heart valve

46

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47 **Central Message**

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

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52 Perspective Statement

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

58

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59 **ABSTRACT**

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

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

71 **Results:** In total, 659 patients undergoing mechanical heart valve replacement were included in the
72 study. Median number of INR measurements in the 6-month period after surgery was 13 (IQR 8-
73 19). Median TTR was 54.9% (IQR 39.0-72.9) and 29.1% of patients had a $TTR \geq 70\%$. Median
74 follow-up was 6.1 years. The risk of thromboembolism was significantly lower in the group with
75 $TTR \geq 70\%$ compared with $TTR < 70\%$ (Hazard ratio (HR) 0.44, 95% CI 0.22-0.85), while no
76 significant difference concerning risk of bleeding among groups was found (HR 0.63, 95% CI 0.36-
77 1.08).

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

81

82 Word count for the abstract: 250

83

84 **INTRODUCTION**

85 More than 100 million people worldwide suffer from valve diseases and the prevalence is expected
86 to increase concurrently with increasing life expectancy.¹ Worldwide, approximately 300,000 valve
87 replacements are carried out annually¹ and oral anticoagulation (OAC) therapy in patients with
88 mechanical prosthesis is crucial in order to reduce the risk of thromboembolic complications and
89 mortality. This comes at a natural price of an increased bleeding risk; hence, tight control of OAC
90 therapy is clinically important in finding the optimal balance between effectiveness and safety.

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

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

106

107 **METHODS**

108 **Data sources**

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

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

123

124 **Study population and TTR calculation**

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

132 MAVR and MMVR (n=21), these patients were excluded from the study. The quality of VKA
133 treatment can be described by means of TTR reflecting the percentage of time the patient has been
134 in therapeutic INR interval. Current guidelines recommend an INR of 2.0-3.0 or 2.5-3.5 for patients
135 with MAV and MMV, respectively.² TTR was calculated in the period from baseline (date of
136 discharge) to index. TTR was assessed by the Rosendaal method, calculated as the total time in
137 therapeutic interval divided by total time of observation. This method assumes a linear correlation
138 between INR measurements and requires at least three INR values^{6,13,14}; hence, patients with less
139 than three INR values before index were excluded (Figure 1). The patients excluded due to lack
140 of/insufficient INR values were comparable to the included patients. In order to calculate an
141 accurate TTR in the period from baseline to index, the TTR calculation was not started until the
142 patient was above the lower limit of their target therapeutic INR range i.e. 2.0 and 2.5 for patients
143 with MAV and MMV, respectively, thus the individual period of TTR calculation could be less than
144 6 months. TTR calculation was stopped if more than 60 days passed between two successive
145 measurements to ensure a precise analysis of the anticoagulation; hence, patients with more than 60
146 days between their two first INR measurements were excluded from the study (Figure 1). Thus, it is
147 critical to have available and sufficient INR values in order to calculate TTR. In order to accurately
148 access a reliable TTR, follow-up was initiated 6 months following discharge. According to current
149 European guidelines² TTR $\geq 70\%$ is considered high quality and consequently TTR $< 70\%$ is
150 considered low quality; thus, the study population was stratified into two groups according to their
151 TTR value.

152

153 **Covariates**

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

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

158

159 **Outcomes**

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

165

166 **Statistical analysis**

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

180

181 **Sensitivity analyses**

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

202

203 **Ethics**

204 The study was approved by the Danish Data protection Agency (reference no: 2007-58-0015/GEH-
205 2014-012, I-suite no: 02720). Ethical approval is not required for retrospective register-based
206 studies in Denmark.

207

208 **RESULTS**

209 **Population**

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

216

217 **Time in therapeutic range**

218 Overall, 29.1% of the study population had a TTR $\geq 70\%$. Median TTR was 54.9 (IQR 39.0-73.1)
219 and was higher among patients with MAV than patients with MMV (58.9% and 37.0%,
220 respectively) (Table 2). The median of the average INR value was 2.6 among patients with MMV
221 (therapeutic range 2.5-3.5) and 2.4 among patients with MAV (therapeutic range 2.0-3.0). Results
222 from the multivariable logistic regression on factors associated with a TTR $\geq 70\%$ are shown in
223 Figure 2. In general, baseline characteristics in the two groups were similar, though TTR $< 70\%$ was
224 associated with mechanical mitral valve replacement (Odds Ratio 0.17, 95% confidence interval
225 (95% CI) 0.17-0.53, $P < 0.001$). Among the excluded 21 patients who underwent both MAVR and
226 MMVR, the median TTR was 51.4% (IQR 29.4-57.8%) and 19.1% of patients had a TTR $> 70\%$.

227

228 **Outcomes**

229 During a median follow-up of 6.1 years, 79 patients experienced a thromboembolic event (AMI
230 n=20, stroke n=57, arterial embolism n=3, valve thrombosis n=2). In total, 66 of the patients with a
231 TTR <70% and 13 of the patients with a TTR \geq 70% had a thromboembolic event. A significant
232 difference was found when looking at the unadjusted cumulative incidence curve (P=0.011) (Figure
233 3). Also, in the multivariable model (Table 3) the risk of thromboembolism was significantly lower
234 in the group with TTR \geq 70% compared with TTR <70% (Hazard ratio (HR) 0.44, 95% CI 0.22-
235 0.85, P=0.015).

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

241 Patients with a history of stroke, ischemic heart disease, atrial fibrillation, or hypertension were
242 at risk of for thromboembolic events, whereas patients with prior bleeding event, a history of
243 hypertension, or abnormal liver function were at risk of a new bleeding event. Supplementary Table
244 2 and 3 summarize factors associated with thromboembolic events and bleedings, respectively.
245 Among patients experiencing a first-time outcome (i.e. thromboembolic event or bleeding), 3 and 9
246 patients experienced a recurrent thromboembolic event or bleeding, respectively.

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

252

253 **Sensitivity analyses**

254 A sensitivity analysis was performed using INR variability as an alternative way of describing the
255 quality of anticoagulation treatment. Median INR variability was 0.75 (IQR 0.49-1.16). Overall,
256 67.7% of the population group had INR variability <0.75 ; however, it concerned 55.2% of the
257 MAV patients and 29.6% of the MMV patients (Supplementary Table 4). In unadjusted analyses,
258 INR variability ≥ 0.75 was associated with higher risk of bleedings and death ($P=0.0001$ and
259 $P=0.0012$, respectively) when compared with INR variability <0.75 , while no significant difference
260 was found with respect to risk of thromboembolism ($P=0.15$). In adjusted analyses, no significant
261 difference between the two groups (INR variability ≥ 0.75 vs. <0.75) was found concerning the risk
262 of thromboembolism (HR 0.63, 95% CI 0.37-1.07, $P=0.087$), bleedings (HR 0.72, 95% CI 0.44-
263 1.18, $P=0.20$), and mortality (HR 0.68, 95% CI 0.43-1.07, $P=0.096$) (Supplementary Table 5).

264 Additionally, a multivariable Cox regression analysis with TTR as a time-dependent covariate
265 was performed. The median amount of INR measurements per patient was 44 (IQR 19-90). No
266 differences were found in terms of risk of thromboembolism (HR 0.87, 95% CI 0.30-2.52, $P=0.80$),
267 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,
268 $P=0.33$) between patients with TTR $<70\%$ and patients with TTR $\geq 70\%$.

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

272

273 DISCUSSION

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

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

281

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

295

296 MMV have been shown to be more thrombogenic than MAV.²² The relative risk of prosthetic valve
297 thrombosis have shown to be twice as high for MMV compared with MAV²³, and also, the risk of
298 mortality has been shown to be highest for patients with a MMV prosthesis.¹⁰ Overall, studies have
299 shown that the risk of outcomes is higher in MMV patients compared with MAV patients.^{11,22,24} We
300 found that MMV patients had lower quality of VKA treatment compared with MAV patients, and
301 since lower TTR is associated with higher risk of outcomes, MMV patients are, *prima facie*, at
302 higher risk of outcomes compared with MAV patients.

303

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

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

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

329 below mean⁵. 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.

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

359

360 Conclusions

361 Our study supports the existing knowledge that low quality of VKA treatment, defined as TTR
362 $<70\%$, is associated with a higher risk of thromboembolic events compared with high quality of
363 VKA treatment (TTR $\geq 70\%$), and also that MMV was associated with lower TTR compared with
364 MAV. Therefore, it is essential to emphasize the awareness of the monitoring of anticoagulant
365 therapy in every patient on OAC VKA treatment. For graphical overview of methods, results, and
366 implications of the study, see also graphical abstract.

367

368 Acknowledgements

369 None

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371 **LEGENDS**

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

375

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

377

378 **Figure 2** Baseline characteristics associated with TTR <70% and TTR >70%.

379 TTR: Time in therapeutic range. CI: Confidence intervals. COPD: Chronic obstructive lung disease.

380

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

384

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

388

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

392

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

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397 **Video** The importance of monitoring the VKA therapy in patients with mechanical heart valves.
398 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
<i>Concomitant therapy</i>			
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
Amiodarone	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
ADP \dagger	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 \ddagger	99 (21.2 %)	41 (21.4 %)	0.04
*TTR: time in therapeutic range. \dagger ADP \dagger : adenosin diphosphate receptor inhibitors. \ddagger NSAID: non-steroidal anti-inflammatory drugs.			

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482

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

	Combined	MAV†	MMV
<i>TTR* <70%</i>	467 (70.9 %)	351 (66.6 %)	115 (87.1 %)
<i>TTR ≥70%</i>	192 (29.1 %)	176 (33.4 %)	17 (12.9 %)
<i>Median TTR, (IQR)</i>	54.9 (39.0-73.1)	58.9 (44.5-75.0)	37.0 (23.8-54.0)
<i>Mean TTR, (SD)</i>	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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486 **Table 3** Multivariable analysis on risk of thromboembolism, bleeding and all-cause mortality

	Events (n)		Hazard ratio (95% CI)	P value
	<i>TTR</i> \geq 70%	<i>TTR</i> <70%		
Thromboembolism	13	66	0.44 (0.22-0.85)	0.02
First year after index	3	10		491
Remaining 9 years after index	10	56		492
Bleeding	25	69	0.63 (0.36-1.08)	0.05
First year after index	5	10		494
Remaining 9 years after index	20	59		495
All-cause mortality	21	74	0.84 (0.50-1.42)	0.52
First year after index	2	5		498
Remaining 9 years after index	19	69		499
500				
<p>High (\geq70%) vs. low (<70%) TTR is considered high vs. low TTR quality, receptively.</p> <p>TTR \geq70% is set as reference for the analysis.</p> <p>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).</p>				

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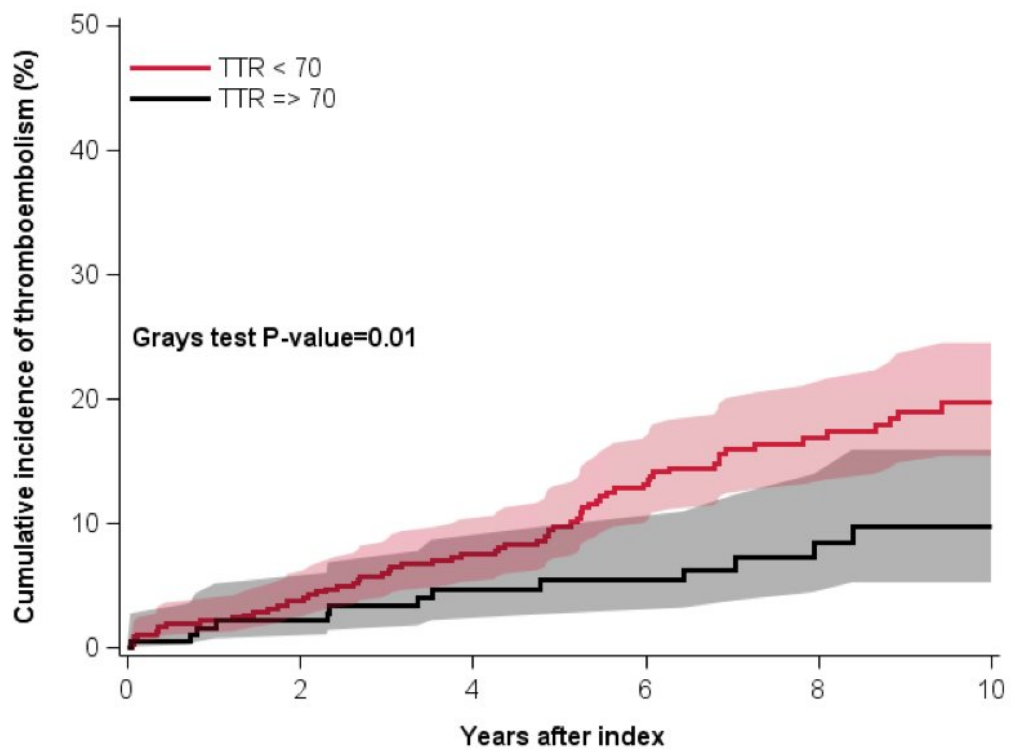
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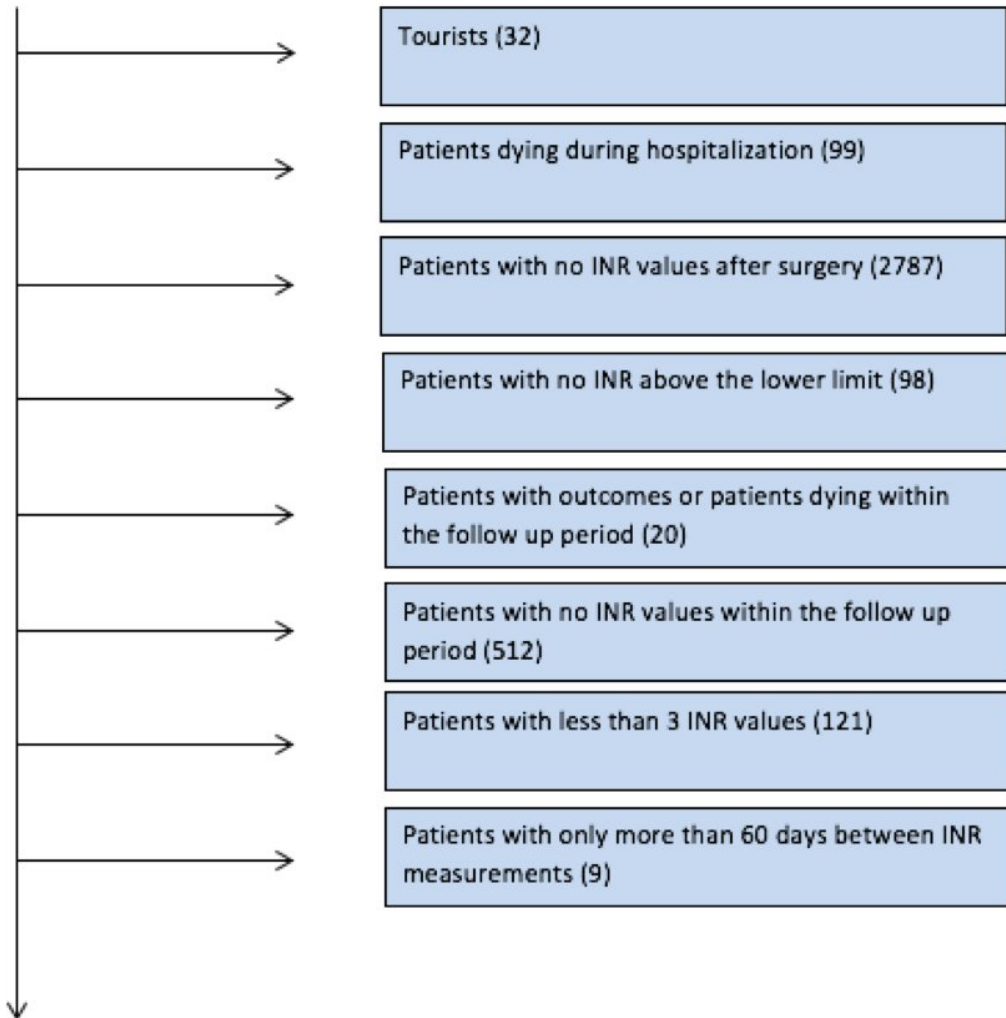
Patients at risk

TTR < 70	460	405	314	238	148	71
TTR ≥ 70	189	159	132	99	70	43

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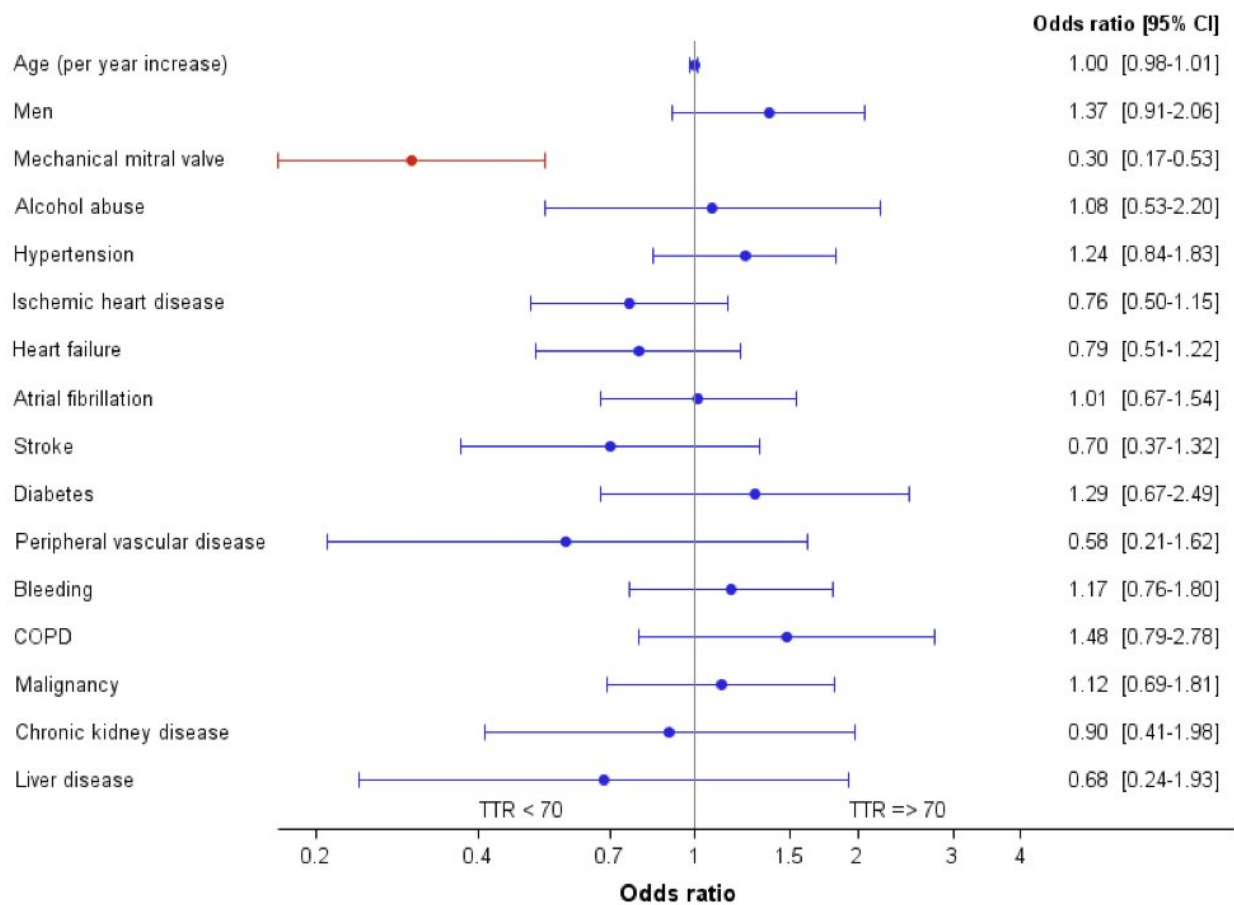
Patients with mechanical aortic or mitral valve prosthesis (4337)

- Aortic valve (3477)
- Mitral valve (860)

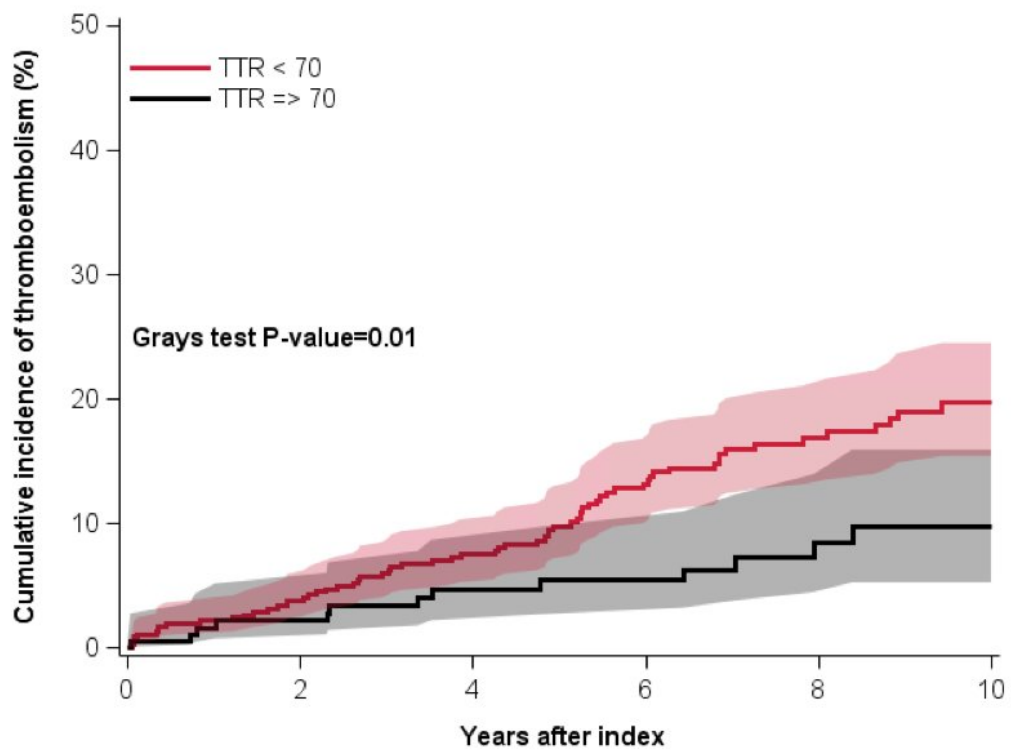


Patients in VKA with available INR values after valve substitution (659)

- Aortic valve (527)
- Mitral valve (132)



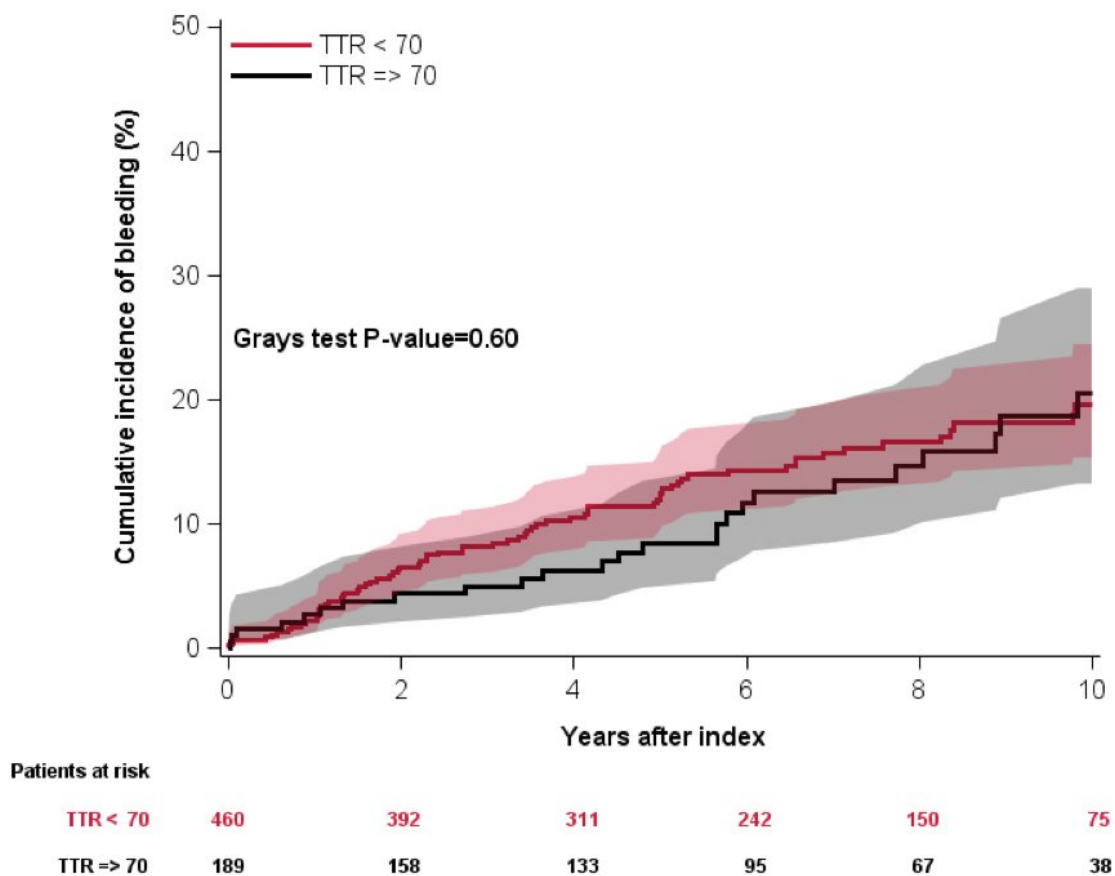
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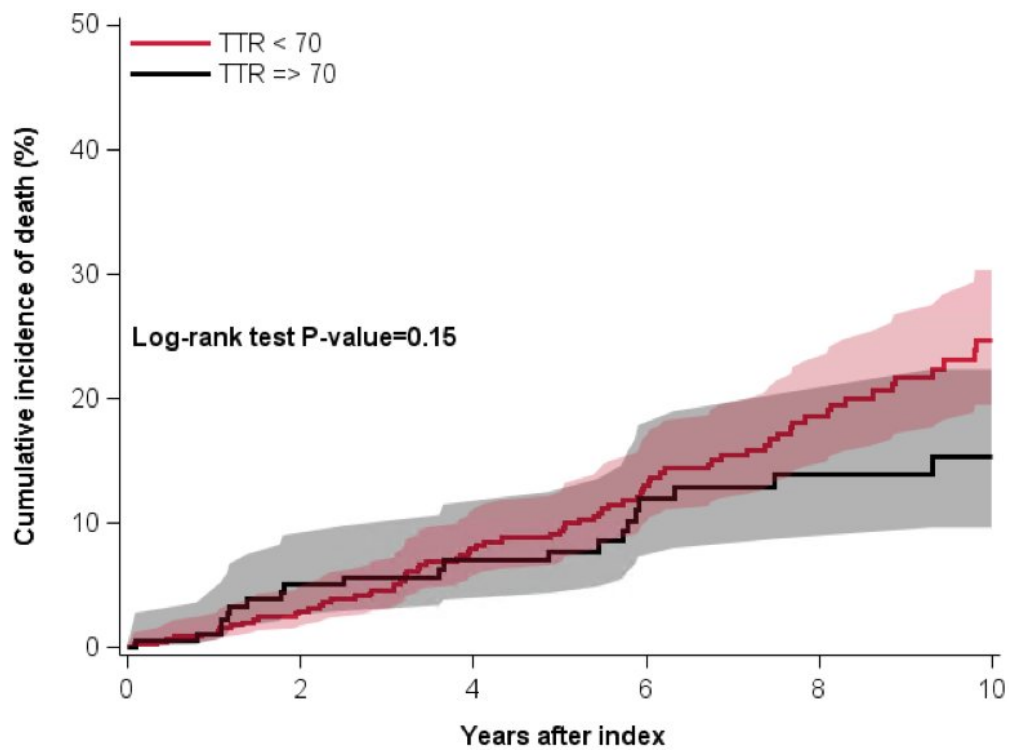


Patients at risk

TTR < 70	460	405	314	238	148	71
TTR ≥ 70	189	159	132	99	70	43

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Patients at risk

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

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Supplemental Material

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

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MD, DMSc; Gunnar Gislason, MD, PhD; Lars Køber, MD, DMSc; Emil L. Fosbøl, MD, PhD

Supplementary Table 1 Comorbidities, pharmacotherapy, and outcomes

Comorbidity	
	<i>ICD-codes (ICD-8 and ICD-10)</i>
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	
	<i>ATC code</i>
Statins	C10AA
Beta-blockers	C07, C09BX
Calcium channel blockers	C08, C07F, C09BB, C09DB
Renin-angiotensin system inhibitors	C09
Diabetes mellitus drugs	A10
Amiodarone	C01BD01
Digoxin	C01AA05
Acetylsalicylic acid	B01AC06
ADP \ddagger	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	
	<i>ICD-code</i>
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 \geq 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 \geq 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†
<i>INR variability <0.75</i>	446 (67.7 %)	291 (55.2 %)	39 (29.6 %)
<i>INR variability >0.75</i>	213 (32.3 %)	236 (44.8 %)	93 (70.1 %)
<i>INR variability median, (IQR)</i>	0.75 (0.49-1.16)	0.70 (0.46-1.06)	1.01 (0.61-1.34)
<i>INR variability mean, (SD)</i>	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
	<i>INR variability</i> ≥ 0.75	<i>INR variability</i> < 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, respectively.

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

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

Year	Patients with TTR \geq70% (%)	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%