SUPPLEMENTAL APPENDIX

Telemedicine-based specialized care improves the outcome of anticoagulated individuals with venous thromboembolism – Results from the thrombEVAL study

Running title: Telemedicine-based specialized care in VTE

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Supplemental Methods

In the RMC cohort, patients' OAC-treatment-management was continued by the physicians in charge (i.e. general practitioner, but also specialists) after study enrolment. Regarding the observational character of the thrombEVAL study, decisions were left to the discretion of the treating physicians in charge and were not influenced by the study protocol or the investigators.[1] In the RMC in Germany, the physicians take the blood samples ambulatory during standard visits at the doctor's office. Blood samples were analysed in the laboratory cooperating with the respective physician. Afterwards, depending the laboratory results, the dosing was performed by the physician contacting the patient.

In contrast, the coagulation service was operated by the Center of Thrombosis and Hemostasis, University Medical Center Mainz (Germany) (**Figure S1 in the supplementary appendix**). In the CS, specialized staff consisting of physicians and nurses, who were trained in hemostasis, shouldered the responsibility for patients' OAC-treatment adjustments. Standardized visits for anticoagulation control at 16 urban and rural service points at fixed consultation hours were carried out. Additionally, the CS staff performed home visits for frail and disabled patients, depending on their physical status and the individual need.[1,2] The OAC treatment-relevant information, which included standardized assessment of clinical status at each visit, identification of complications and the level of international normalized ratio (INR) was assessed and recorded digitally in a web-based electronic patient file (Portavita B.V., Amsterdam, the Netherlands).[1] The blood samples were analyzed in a central reference laboratory at the university medical center Mainz (Germany), which facilitated comparability of INR values. The staff performed individual VKA dosing by incorporation of all relevant information in the electronic file, with support of computer-assisted dosing algorithms and subsequent professional optimization, if necessary.[1] Additionally, the electronic file provided the interface for patient management in collaboration with general practitioners, specialists and health care institutions.[1,2] Additionally, patients with deviated INR-values from the INR target range were contacted by telephone and precise management recommendations were given by the CS. Telemedicine CS was based on

the experiences of other INR-clinics. The RMC as well as the telemedicine-based CS are described in detail in the design paper of the thrombEVAL study programme [2].

In the future, demographic changes will increase the proportion of older patients. Risk of VTE increases exponentially with aging[3-7] and an incline of individuals with VTE events with the need for OAC treatment has to be expected. Additionally, with an aging population numbers of multi-morbid patients is growing.[3-9] Future concepts have to take these changes into account, particularly changes in OAC treatment regarding aging process, therapy adherence, mental and physical capabilities and influence of co-morbidities on treatment.[10,11] Therefore, VKA-treatment will maintain its position in OAC treatment.

Supplemental Results

Supplemental Table S1: Inclusion and exclusion criteria of the thrombEVAL study.

Inclusion criteria		**Exclusion crieria**
Regular medical care	**Coagulation service**	
Age ≥18 years		Age <18 years
Written informed consent		Withdrawal of priorly given consent
Performance of VKA therapy ≥4 months		Contraindications to VKA treatment (e.g. pregnancy or known hypersensitivity)
	Indication for at least 3 months duration of VKA treatment	Participation in other clinical trials

Abbreviations: VKA indicates vitamin K antagonist treatment

Supplemental Table S2. Baseline characteristics of VTE patients in regular medical care (RMC) and coagulation service (CS) groups after propensity score weighting.

Variable	Coagulation Service	Regular medical care	P-value
Age (years; median IQR)	73.0 (60.5/81.0)	72.0 (60.0/79.0)	0.32
Sex (Men)	51.6% (193/375)	53.9% (194/360)	0.57
Classical cardiovascular risk factors			
Arterial hypertension	73.1% (274/375)	71.9% (259/360)	0.76
Diabetes	25.5% (96/375)	26.7% (96/360)	0.74
Dyslipidemia	46.5% (174/375)	51.4% (185/360)	0.23
Family history of myocardial infarction	38.0% (142/375)	39.7% (143/360)	0.66
Concomitant diseases			
Arterial fibrillation	49.8% (186/375)	46.1% (166/360)	0.37
Chronic lung disease	29.5% (111/375)	28.3% (102/360)	0.75
Coronary artery disease	33.2% (124/375)	35.3% (127/360)	0.58
Heart failure	38.4% (144/375)	35.3% (127/360)	0.42
Peripheral artery disease	29.0% (109/375)	21.9% (79/360)	0.044
Renal disease	24.5% (92/375)	23.6% (85/360)	0.80
OAC therapy management			
Self measurement and management	17.4% (65/375)	15.8% (57/360)	0.60
Other Medication			

Anti-platelet agents	13.1% (49/375)	18.1% (65/360)	0.088
Proton pump inhibitor	34.2% (128/375)	35.0% (126/360)	0.84
Amiodarone	4.8% (18/375)	5.8% (21/360)	0.56

Data are expressed as relative and absolute frequencies in binary variables. Variables are shown as median with $25^{th}/75^{th}$ percentiles. Double entries were possible for those study participants in CS cohort with prior treatment duration in RMC.

Abbreviations: IQR indicates inter-quartile range.

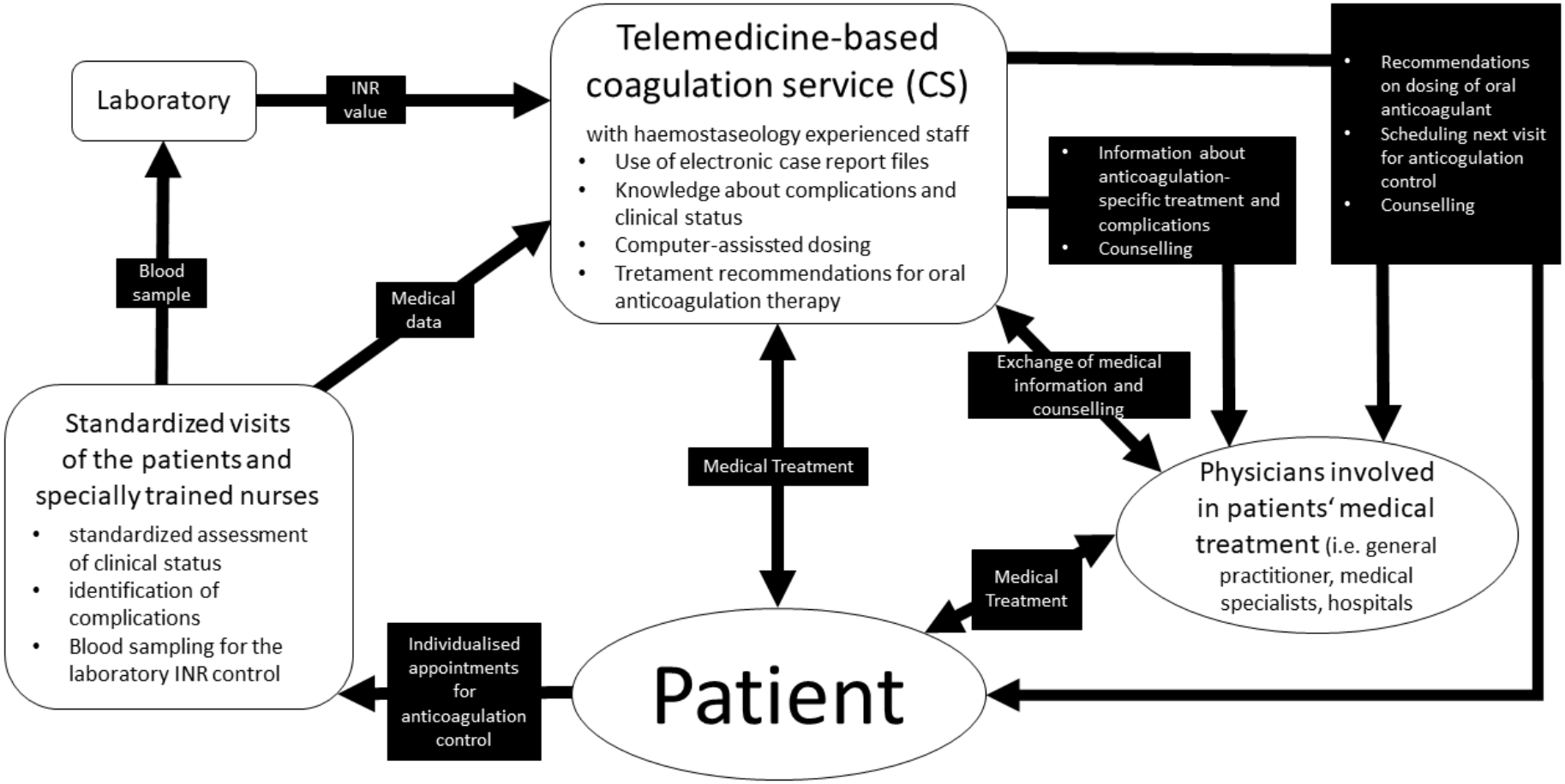
Table S3. Comparison of outcome in regular medical care and coagulation service by adjusted effect measures in a competing risks analysis.

Variables of adjustment	Crude model		Adjustment for age and sex		Adjustment for age, sex and Charlson-Index		Adjustment for age, sex, diabetes, arterial hypertension, dyslipidemia, smoking, family history of myocardial infarction, heart failure, peripheral artery disease, history of stroke/TIA, atrial fibrillation, chronic lung disease, renal disease, home visits for treatment, anticoagulant treatment self-management, HAS-BLED-Score, CHA_2DS_2-VASc-Score	
	Hazard Ratio (95% CI)	**P Value**	**Hazard Ratio (95% CI)**	**P Value**	**Hazard Ratio (95% CI)**	**P Value**	**Hazard Ratio (95% CI)**	**P Value**
Primary outcome	5.85 (2.33-14.71)	<0.001	5.44 (2.16-13.74)	<0.001	5.96 (2.28-15.62)	0.00028	4.96 (1.50-16.34)	0.0086
Clinically relevant bleeding	5.43 (1.92-15.34)	0.0014	5.09 (1.79-14.46)	0.0022	6.13 (2.06-18.20)	0.0011	5.13 (1.30-20.26)	0.020
Thromboembolic events	6.51 (1.54-27.50)	0.011	6.12 (1.42-26.42)	0.015	6.16 (1.38-27.46)	0.017	4.27 (0.73-24.97)	0.11
Hospitalization	1.84 (1.34-2.53)	<0.001	1.76 (1.28-2.44)	<0.001	1.83 (1.28-2.61)	0.00090	1.82 (1.18-2.82)	0.0066

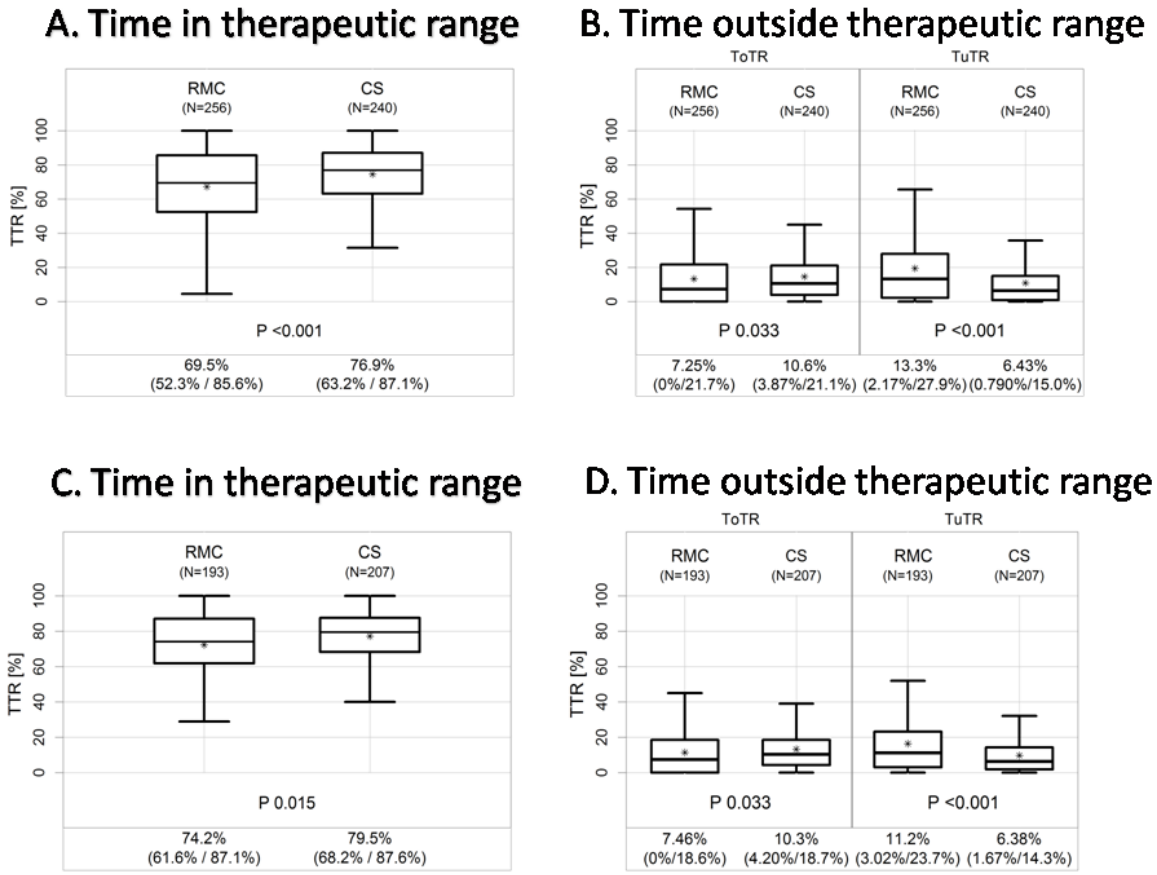
Hazard ratios for the endpoints were presented with different adjustments. Hazard ratios of RMC are provided as multiples in comparison to the reference group of CS. Bleeding events were categorized regarding to RELY criteria. Significant differences were seen if p was <0.05.

Abbreviations: CI indicates confidence interval

Supplemental Figure S1: Work flow of the telemedicine-based coagulation service.



Supplemental Figure S2.



A: Overall patients' quality of oral anticoagulation therapy in regular medical care (RMC) and coagulation service (CS): Time in therapeutic range (TTR). TTR was calculated according to linear interpolation method and presented as median (first quartile/third quartile); *P* value for z-test. Mean TTR values are depicted graphically as asterisks within box-plots. *TTR variability is expressed by median absolute deviation (MAD), *P* value for Ansari-Bradley-test.

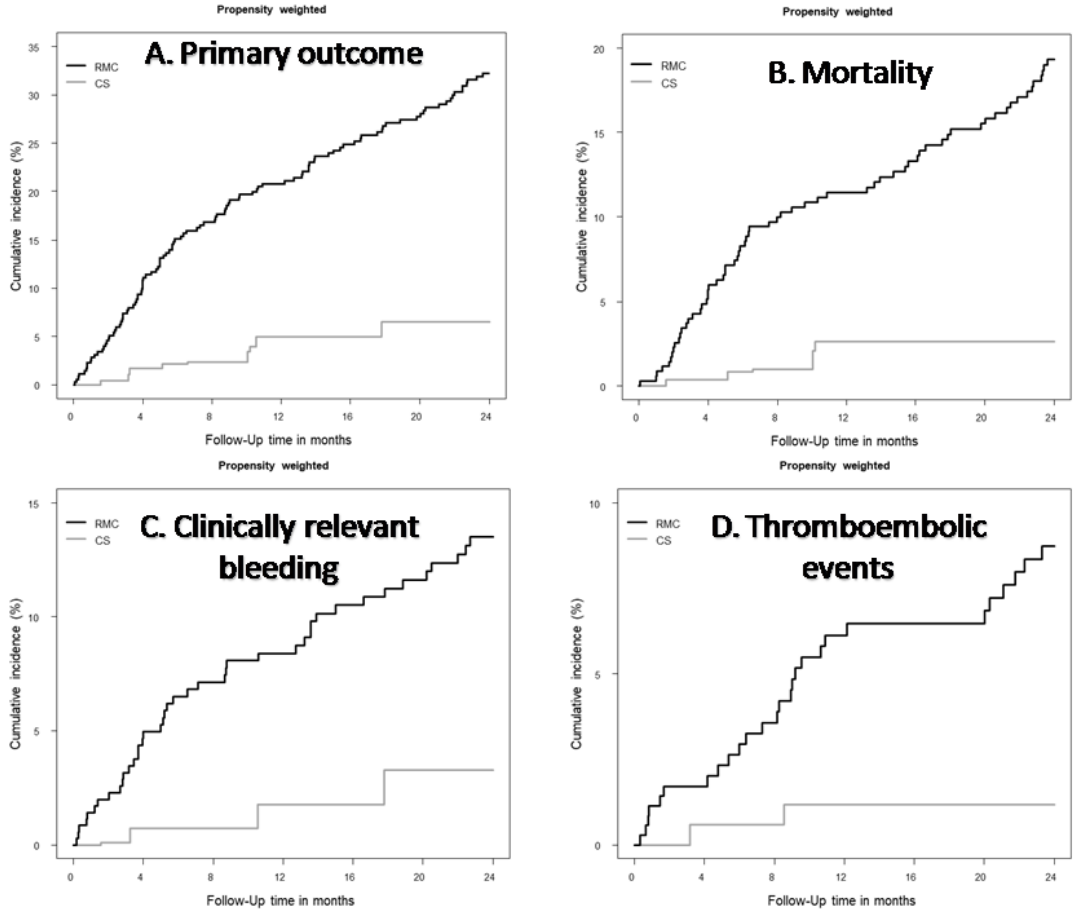
B: Overall patients' quality of oral anticoagulation therapy in regular medical care (RMC) and coagulation service (CS): Time outside therapeutic range. Percentage of Time outside therapeutic range is calculated according to linear interpolation method and presented as median (first quartile/third quartile); *P* value for z-test. ToTR means Time over therapeutic range,TuTR has the meaning Time under therapeutic range.

C: Stable adjusted patients' quality of oral anticoagulation therapy in regular medical care (RMC) and coagulation service (CS): Time in therapeutic range (TTR). TTR was calculated

according to linear interpolation method and presented as median (first quartile/third quartile); *P* value for z-test. Mean TTR values are depicted graphically as asterisks within box-plots. *TTR variability is expressed by median absolute deviation (MAD), *P* value for Ansari-Bradley-test.

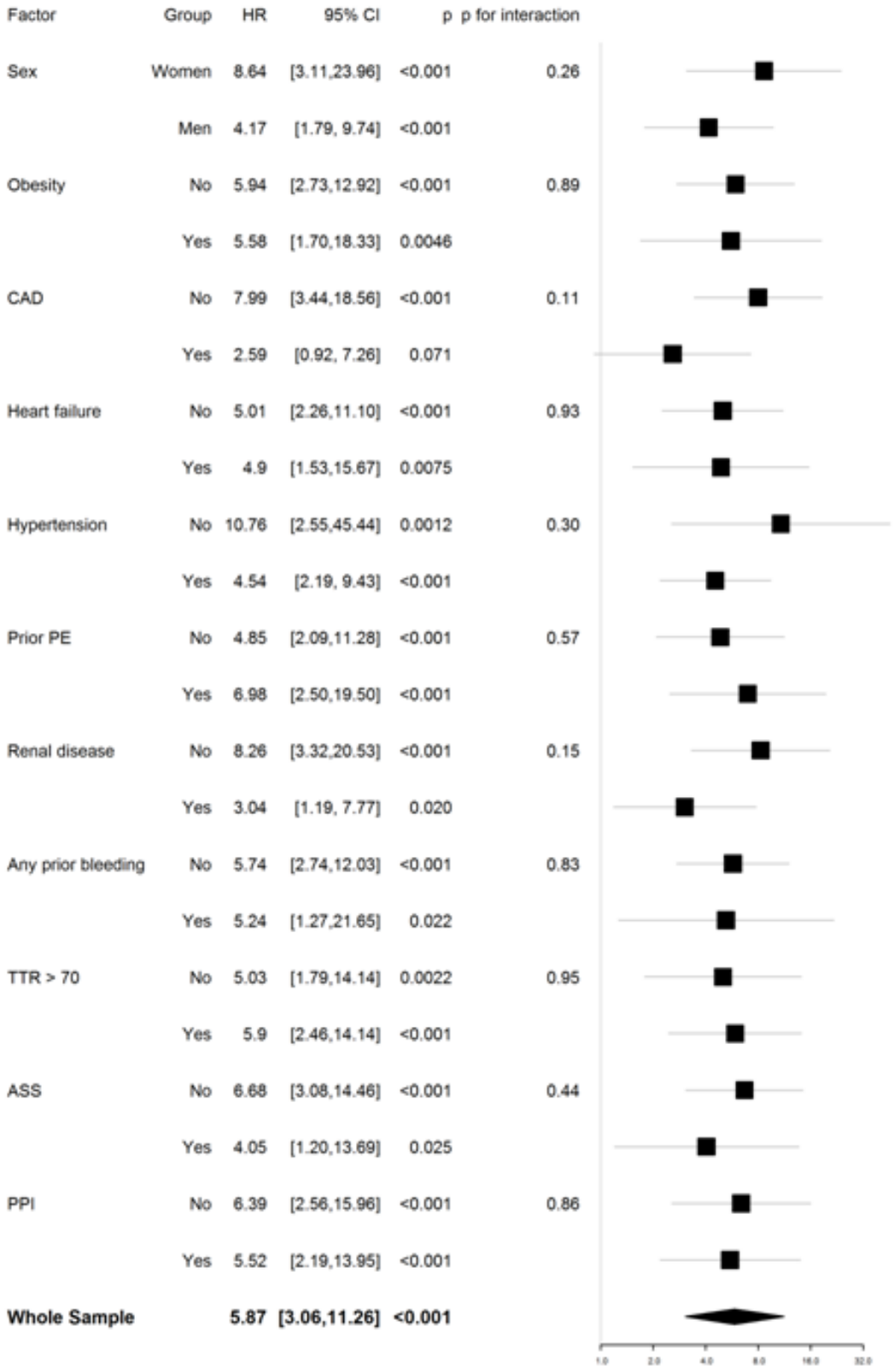
D: Stable adjusted patients' quality of oral anticoagulation therapy in regular medical care (RMC) and coagulation service (CS): Time outside therapeutic range. Percentage of Time outside therapeutic range is calculated according to linear interpolation method and presented as median (first quartile/third quartile); *P* value for z-test. ToTR means Time over therapeutic range,TuTR has the meaning Time under therapeutic range.

Supplemental Figure S3. Comparison of clinical endpoints in individuals with VTE by health care model.



Crude cumulative incidence plots of adverse events in regular medical care (RMC) and coagulation service (CS): RMC in black and CS in grey colour for the adverse events under OAC treatment during 2 years follow-up period.

Supplemental Figure S4: Primary outcome in coagulation service versus regular medical care according to subgroups.



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