Telemedicine-guided, very low-dose international normalized ratio self-control in patients with mechanical heart valve implants

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Aim
To study in patients performing international normalized ratio (INR) self-control the efficacy and safety of an INR target range of 1.6–2.1 for aortic valve replacement (AVR) and 2.0–2.5 for mitral valve replacement (MVR) or double valve replacement (DVR).

Methods and results
In total, 1304 patients undergoing AVR, 189 undergoing MVR and 78 undergoing DVR were randomly assigned to low-dose INR self-control (LOW group) (INR target range, AVR: 1.8–2.8; MVR/DVR: 2.5–3.5) or very low-dose INR self-control once a week (VLO group) and twice a week (VLT group) (INR target range, AVR: 1.6–2.1; MVR/DVR: 2.0–2.5), with electronically guided transfer of INR values. We compared grade III complications (major bleeding and thrombotic events; primary end-points) and overall mortality (secondary end-point) across the three treatment groups.

Findings
Two-year freedom from bleedings in the LOW, VLO, and VLT groups was 96.3, 98.6, and 99.1%, respectively (P = 0.008). The corresponding values for thrombotic events were 99.0, 99.8, and 98.9%, respectively (P = 0.258). The risk-adjusted composite of grade III complications was in the per-protocol population (reference: LOW-dose group) as follows: hazard ratio = 0.307 (95% CI: 0.102–0.926; P = 0.036) for the VLO group and = 0.241 (95% CI: 0.070–0.836; P = 0.025) for the VLT group. The corresponding values of 2-year mortality were = 1.685 (95% CI: 0.473–5.996; P = 0.421) for the VLO group and = 4.70 (95% CI: 1.62–13.60; P = 0.004) for the VLT group.

Conclusion
Telemedicine-guided very low-dose INR self-control is comparable with low-dose INR in thrombotic risk, and is superior in bleeding risk. Weekly testing is sufficient. Given the small number of MVR and DVR patients, results are only valid for AVR patients.

Keywords
Mechanical heart valve replacement • Oral anticoagulation • Vitamin K antagonists • International normalized ratio

Introduction
Mechanical heart valves bear an inherent risk of thrombo-embolism. Therefore, patients with mechanical heart valve implants need life-long oral anticoagulation with oral anticoagulants. Vitamin K antagonists (VKA) are still the gold standard for preventing thrombo-embolism in patients undergoing mechanical heart valve replacement.1 Under VKA, the incidence of thrombotic events is 0.9–3.6% per patient-year.2 However, VKA also bear the risk of bleeding complications. In patients with mechanical heart valve implants, the
minimum risk of death is attained at an international normalized ratio (INR) of 2.3. The risk of bleedings already begins to increase at INR values of 2.5 and then sharply increases at INR values $> 6.0$. Usually, the incidence of bleeding complications is 3.0% per patient-year if the INR target range is 2.5–4.5. The incidence is twice as high compared with the incidence of thrombotic events. Therefore, the benefits of VKA have to be weighed against the risks.

New generations of mechanical heart valves bear a much lower risk of thrombotic events and therefore permit the INR target range to be reduced from formerly 2.5–4.5 to now 2.5–3.5 in patients deemed to be at intermediate or high risk (those who have a mechanical aortic valve with additional risk factors or a mechanical mitral valve). The INR target range can be reduced to 2.0–3.0 in those deemed to be at low thrombo-embolic risk (patients who have a mechanical aortic valve with no additional risk factors). Self-management of INR values permits a further reduction of the INR target range to 1.8–2.8 in patients with aortic valve replacement (AVR) without increasing the risk of thrombotic events. Nevertheless, even in patients with low-dose INR self-management the risk of clinically relevant bleeding complications remains considerably higher than the risk of severe thrombotic events.

Hemostatic markers, such as prothrombin fragment and fibrin D-dimers, are already suppressed at INR values $> 1.5$. The Early Self-Controlled Anticoagulation Trial (ESCAT II) was therefore initiated to study—in patients performing INR self-control—the efficacy and safety of a further reduction of the INR target range to 1.6–2.1 for AVR and 2.0–2.5 for mitral valve replacement (MVR) or double valve replacement (DVR). Here, we present the final data of this study and a detailed analysis of clinically relevant complications.

### Methods

#### Study design

ESCAT III is an investigator-initiated, multicentre, prospective, randomized, open-labelled trial which was performed at seven heart centres in two European countries. The Institute for Applied Telemedicine (IFAT) at the Heart and Diabetes Center North Rhine-Westphalia, Germany, coordinated the study, managed the database and performed the data analysis. The investigation was performed according to the Consolidated Standards of Reporting Trials (CONSORT) Statement for randomized controlled trials (www.consort-statement.org). The study protocol was approved by all participating centres and the study was registered at clinicaltrials.gov as NCT00528671. Initially, the plan was to include 1800 patients with mechanical heart valve replacement. However, patient enrolment was stopped prematurely in April 2012 due to the increasing number of biological heart valve implants instead of mechanical valves (even in patients aged 60–70 years) and the increasing number of mitral valve reconstructions instead of MVR.

#### Patients

Patients 18 years of age or older were eligible if they were scheduled for mechanical heart valve replacement. Patients were excluded if they had a contraindication to phenprocoumon (i.e. allergy), known ulcerous disease with bleeding tendency, hypocogulability or hypercoagulability (medical history) or an age $< 18$ years. All study participants gave written informed consent to the study procedures before study randomization.

### Randomization and study treatment

All the patients received heart valves provided by St Jude Medical GmbH (Nuremberg, Germany), with the exception of eight patients who received heart valves provided by Medtronic (Meerbusch, Germany; $n = 3$), Sorin Group GmbH (Munich, Germany; $n = 1$), and ATS Medical, Inc. (Minneapolis, MN, USA; $n = 4$). Patients had to stop aspirin use before surgery and the study protocol did not include aspirin use. All surgical procedures were performed via median sternotomy. Minimally invasive procedures were not performed. Similar to the study design of ESCAT II, patients were randomized immediately post-operatively into one of three study groups (see below). Allocation concealment was achieved by sequentially numbered, opaque, sealed envelopes. Patients were trained in INR self-control (and management) before discharge as previously described. Briefly, it is explained that several factors such as the vitamin K content of the diet, concomitant medications, alcohol consumption, climate, stress, and physical activity can influence the result of the anticoagulation therapy. Procedures are described which have to be performed if the measured INR value lies outside the target range. It is explained how to adjust the daily dose of anticoagulants to optimize the INR value. During the first 6 postoperative months, all patients performed low-dose INR self-management and checked their INR values once a week. The INR target value was 2.3 (range: 1.8–2.8) for AVR recipients and 3.0 (range: 2.5–3.5) for MVR and DVR recipients. One-third of the patients ($n = 526$) continued to achieve the aforementioned INR target range for the next 18 months (low-dose control, one measurement/week, designated LOW group), whereas the INR target value was set at 2.0 (range: 1.6–2.1) for the remaining patients with AVR and 2.3 (range: 2.0–2.5) for the remaining patients with MVR or DVR. One half of this latter group ($n = 521$) had to check their INR values once a week (very low dose: one measurement/week, designated VLO group) the other half ($n = 524$) twice a week (very low dose: two measurements/week, designated VLT group). The INR measurements were performed with a coagulation monitor (CoaguChek XS, Roche Diagnostics, Mannheim, Germany). Validity and accuracy of the coagulation monitor has previously been demonstrated.

Patients were followed up for 24 months. Every 6 months, the study participants visited the study centre as outpatients. The self-control was assisted by telephone care and the possibility of consultation around the clock. The patients had the opportunity to adjust their anticoagulation therapy with the help of specialized cardiologists. During the entire study period, INR control was active and passive in the VLO and VLT group, and only active in the LOW group. The measured INR values in the VL groups were automatically transferred from the coagulation monitor to the IFAT via infrared interface and a specifically developed transmitter which generated an SMS (passive INR control). Data were then checked by a specialized cardiologist. The patient was immediately contacted by the cardiologist if the INR value was beyond the target range. In addition, once a month patients in the VL groups also had to send their INR values to the IFAT using a standardized protocol (active INR control). Patients in the LOW group only had to send their INR values to the IFAT once a month (active INR control). However, in case of uncertainties, questions or inconsistencies they had the opportunity to contact the specialized cardiologist immediately. In contrast to the active and passive INR control in the VL groups, we consider the active INR control in the LOW group as true self-management.

#### Study end-points

Primary end-points were the rates of grade III thrombotic events (heart valve thrombosis or severe thrombo-embolism) or bleeding events (severe bleeding requiring transfusion or other interventions). Data collection was both ‘active’ and ‘passive’, which means that study participants...
had to report any complication to the study centre immediately. In addition, the patients were asked during their follow-up visits whether a complication had occurred within the last 6 months. All reports of grade III complications had to be sent from the emergency hospital to the study centre and were double-checked by a cardiologist from the centre.

Secondary end-point was overall mortality. Mortality data were assessed from hospital databases (until discharge) or reported on a standardized form completed by the patients, their relatives, or their general practitioner. Missing data were added by conducting phone interviews. Quality of INR control was assessed from the protocols which the patients sent to the study centre and was expressed as the time in therapeutic range (TTR).

**Statistics**

We report categorical variables as number and percentages of observations and continuous variables as means with standard deviations. The $\chi^2$ test, ANOVA, and Kruskal–Wallis test, respectively, was used to assess group-specific differences in categorical variables and continuous variables when appropriate. We generated Kaplan–Meier estimates to investigate the association of study group with the probability of freedom from grade III complications or the probability of surviving during the follow-up. The log-rank test was used to test for differences in survival or complication rates between groups. We also performed Cox regression analysis to adjust for those baseline variables, which differed significantly between study groups (see Results section). Because of potential non-linear associations between age and grade III complications, we performed sensitivity analyses where we added age as a categorical variable (classified as: ≤60 and >60 years) to the model. Results are presented as hazard ratio (HR) and 95% confidence interval (CI). Data were evaluated following the intention-to-treat principle (ITT), which means that all patients assigned to one of the three study groups were analysed as randomized. Dropouts were censored at their last visit. In addition, data were analysed according to the per-protocol (PP) principle, which means that dropouts and patients who crossed over to another treatment group were excluded from data analysis. The incidence rate per patient-year was determined by dividing the number of events by the total number of person-years accumulated. The 95% CI around the estimates was calculated based on the Poisson distribution. The $P$-values <0.05 were considered statistically significant. The study was originally powered ($\alpha = 0.05$; $\beta = 0.20$) to detect a reduction in the incidence of bleeding events from 2.0% per annum to 0.5% per annum, thereby assuming a dropout rate of 17%. We applied the statistical software package SPSS, version 20 (IBM Corp, Armonk, NY, USA) to perform the analyses.

**Results**

**Patients and baseline characteristics**

From January 2006 to April 2012, a total of 1571 patients were enrolled (Figure 1). One thousand three hundred and four patients underwent AVR, 189 patients MVR and 78 patients DVR.
Heart and Diabetes Center North Rhine-Westphalia, Germany, contributed the vast majority of patients (n = 1354), followed by the Clinic for Thoracic and Cardiovascular Surgery, Magdeburg, Germany (n = 59), Hospital Santa Anna, Catanzaro, Italy (n = 54), Academic City Hospital Ludwigshafen, Germany (n = 44), Mediclin Heart Institute Lahr, Germany (n = 39), Clinic for Cardiac and Vascular Surgery, Kiel, Germany (n = 15) and Azienda Ospedaliera S. Camillo Forlanini, Roma, Italy (n = 10). The baseline characteristics of the study groups are given in Table 1. The mean age of the study participants was 58–60 years (range: 18–81 years). The majority of patients were males and were classified as having NYHA functional class II or higher. There were significant differences in age, gender distribution, prevalence of atrial fibrillation, previous myocardial infarction, and AVR across the study groups.

The 1571 patients accrued 2551 patient-years of observation, 730 within the first 6 months and 1821 from month 7 to month 24. Study duration in the LOW, VLO, and VLT groups was 17.8 ± 9.1 months, 20.5 ± 6.6 months, and 20.2 ± 6.9 months, respectively. Between 18.0% (VLT group) and 24.6% (LOW group) did not complete the overall study. In total, 162 490 INR values were submitted to the study centre (LOW group: 48 351; VLO group: 47 562; VLT group: 66 577). Mean INR values are presented in Figure 2A and B, broken down by study month, study group, and type of valve replacement. Beyond study month 6, INR values were in the LOW, VLO, and VLT groups with AVR 2.29 ± 0.38, 2.07 ± 0.33, and 2.06 ± 0.31, respectively (P < 0.001). The corresponding values for the subgroups with MVR/DVR were 2.98 ± 0.50, 2.56 ± 0.50, and 2.59 ± 0.49, respectively (P = 0.001). Compared with the LOW group, TTR was lower and time below or above the group-specific target range was higher in the groups with very low dose INR self-control (Table 2).

### Primary end-points

Freedom from major bleeding complications in the LOW, VLO, and VLT group was 96.3, 98.6, and 99.1%, respectively (P = 0.008). Events occurred in 15 patients with AVR (1.2%), 7 patients with MVR (3.7%), and 3 patients with DVR (3.9%). The incidence of bleedings per patient-year in the LOW, VLO, and VLT groups was 1.93% (95% CI: 1.17–2.88%), 0.67% (95% CI: 0.27–1.27%), and 0.51% (95% CI: 0.18–1.04%), respectively. The risk-adjusted HR with low-dose INR self-management as a reference was 0.379 (95% CI: 0.146–0.985; P = 0.046) for the VLO group and = 0.273 (95% CI: 0.089–0.835; P = 0.023) for the VLT group. Risk-adjusted results of bleeding events remained unchanged when age entered the statistical model as categorical variable (< 60 years and ≥ 60 years; data not shown). Two weeks and 1 week before the bleeding event occurred, INR values of the patients were 2.60 ± 0.68 and 2.38 ± 0.55, respectively. The corresponding percentages of values ≥ INR 2.5 were 56.0 and 40.0%, respectively. Only in two out of the 25 patients with bleeding events, the values were lying outside their INR target range. Three patients switched over from the VL groups to the LOW group already before the event occurred.

In the LOW, VLO, and VLT groups, freedom from major thrombotic events was 99.0, 99.8, and 98.9%, respectively (P = 0.258). The incidence of thrombotic events per patient-year was 0.51% (95% CI: 0.18–1.04%), 0.11% (0.07–0.40%), and 0.57% (95% CI: 0.21–1.13%), respectively (risk-adjusted HR and 95% CI with low-dose INR self-

### Table 1  Characteristics of the study groups (mean ± SD and percentages of observations when appropriate)

<table>
<thead>
<tr>
<th></th>
<th>Low-dose group (n = 526)</th>
<th>Very low-dose group 1 measurement/week (n = 521)</th>
<th>Very low-dose group 2 measurements/week (n = 524)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>59.2 ± 10.9</td>
<td>57.3 ± 11.9</td>
<td>56.7 ± 11.9</td>
<td>0.002</td>
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<tr>
<td>Male (%)</td>
<td>67.7</td>
<td>71.8</td>
<td>74.9</td>
<td>0.036</td>
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<tr>
<td>Body weight (kg)</td>
<td>83.5 ± 15.4</td>
<td>83.4 ± 15.7</td>
<td>83.4 ± 15.7</td>
<td>0.962</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>174 ± 9</td>
<td>174 ± 9</td>
<td>175 ± 9</td>
<td>0.462</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>12.9</td>
<td>15.1</td>
<td>16.3</td>
<td>0.407</td>
</tr>
<tr>
<td>NYHA class ≥ II (%)</td>
<td>58.6</td>
<td>54.8</td>
<td>61.4</td>
<td>0.092</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>11.8</td>
<td>5.7</td>
<td>7.7</td>
<td>0.011</td>
</tr>
<tr>
<td>Blood pressure, systolic (mmHg)</td>
<td>136 ± 22</td>
<td>135 ± 21</td>
<td>135 ± 20</td>
<td>0.992</td>
</tr>
<tr>
<td>Blood pressure, diastolic (mmHg)</td>
<td>76 ± 13</td>
<td>76 ± 13</td>
<td>77 ± 13</td>
<td>0.490</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73 ± 12</td>
<td>75 ± 14</td>
<td>76 ± 13</td>
<td>0.063</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>63.2 ± 11.5</td>
<td>63.3 ± 12.4</td>
<td>62.8 ± 11.7</td>
<td>0.825</td>
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<td>Concomitant diagnoses</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus (%)</td>
<td>14.1</td>
<td>12.8</td>
<td>9.8</td>
<td>0.095</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>47.0</td>
<td>49.4</td>
<td>46.4</td>
<td>0.587</td>
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<tr>
<td>Previous myocardial infarction (%)</td>
<td>5.1</td>
<td>2.7</td>
<td>2.7</td>
<td>0.044</td>
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<tr>
<td>Peripheral arterial occlusive disease (%)</td>
<td>2.9</td>
<td>1.9</td>
<td>2.7</td>
<td>0.577</td>
</tr>
<tr>
<td>Type of cardiac surgery (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Isolated aortic valve replacement</td>
<td>78.7</td>
<td>85.8</td>
<td>84.5</td>
<td>0.005</td>
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<tr>
<td>Isolated mitral valve replacement</td>
<td>14.8</td>
<td>10.4</td>
<td>10.9</td>
<td>0.052</td>
</tr>
<tr>
<td>Double valve replacement</td>
<td>6.5</td>
<td>3.8</td>
<td>4.6</td>
<td>0.131</td>
</tr>
</tbody>
</table>

Statistical tests: ANOVA for continuous data and χ² test for percentages of observations.
Figure 2. Time course of international normalized ratio values in patients with aortic valve replacement (A) and mitral or double valve replacement (B), broken down by study group. Data are expressed as mean values and 95% confidence intervals; filled circle, LOW group; filled diamond, very low-dose one/week group; filled triangle, very low dose, twice/week group.
control as a reference = 0.242 (0.027–2.176; \( P = 0.205 \)) for the VLO group and = 1.217 (0.322–4.606; \( P = 0.772 \)) for the VLT group. Risk-adjusted results of thrombotic events remained unchanged when age entered the statistical model as a categorical variable (<60 years and >60 years; data not shown). There were no cases of valve thrombosis. A detailed description of the other thrombotic events is given in Table 3. Two patients switched over from the VLO group to the LOW group before the event occurred.

The composite of grade III thrombotic and bleeding events was highest in the LOW group (Figure 3). In the ITT-population, risk-adjusted HR and 95% CI with low-dose INR self-control as a reference = 0.364 (0.143–0.029; \( P = 0.035 \)) for the VLO group and = 0.457 (0.188–1.110; \( P = 0.084 \)) for the VLT group. In the PP-population (low group: \( n = 379 \); VLO group: \( n = 371 \); VLT group: \( n = 382 \)), the corresponding values with the LOW group as a reference were = 0.307 (0.102–0.926; \( P = 0.036 \)) for the VLO group and = 0.241 (0.070–0.836; \( P = 0.023 \)) for the VLT group.

**Secondary end-point**

In the LOW, VLO, and VLT groups, overall survival was 98.9, 98.7, and 97.1%, respectively (\( P = 0.087 \)). Causes of death were myocardial infarction (\( n = 1 \)), sepsis (\( n = 1 \)), tumour (\( n = 1 \)), and unknown (\( n = 2 \)) in the LOW group, myocardial infarction (\( n = 1 \)), tumour (\( n = 2 \)), sudden cardiac death (\( n = 2 \)), aortic aneurysm (\( n = 1 \)), and surgery-related bleeding (\( n = 1 \)) in the VLO group, tumour (\( n = 3 \)), cardiac failure (\( n = 3 \)), kidney failure (\( n = 1 \)), sepsis (\( n = 5 \)), accident (\( n = 1 \)), multiple organ failure (\( n = 1 \)), and myocardial infarction (\( n = 1 \)) in the VLT group. In the ITT-population, the risk-adjusted HR and 95% CI of overall mortality with the LOW group as a reference was for the VLO group = 1.36 (0.46–4.12; \( P = 0.577 \)) and for the VLT group = 3.15 (1.20–8.29; \( P = 0.020 \)). In the PP-population, differences were even more pronounced: compared with the LOW group as a reference, risk-adjusted HR and 95% CI of overall mortality was for the VLO group = 1.685 (0.473–5.996; \( P = 0.421 \)) and for the VLT group = 4.70 (1.62–13.60; \( P = 0.004 \)).
Discussion

The present study in patients with mechanical heart valve replacement demonstrates that telemedicine-guided very low-dose INR self-control is comparable with low-dose INR in thrombotic risk, and is superior in bleeding risk. Data also demonstrate that weekly testing is sufficient, whereas more frequent testing is unnecessary.

Our study has several strengths, starting with the fact that its results are based on a large number of patients and INR values. Also, for safety reasons it was important that patients had the possibility of 24-h telephone care and control of their INR values by a specialized cardiologist, if necessary. This approach allows rapid adjustment of the VKA dose and is thus an important prerequisite for reducing the lower INR target range to 1.6. It is also noteworthy that our training concept before discharge consists not only in INR self-testing but also in the possibility of INR self-correction. Thus, if necessary, patients were able to adjust their VKA dose by themselves.

Our data on thrombotic and bleeding complications are in general agreement with data from the LOWERING-IT trial. Compared with a conventional INR group (mean and SD values: 2.61 ± 0.25) low INR values (mean and SD: 1.94 ± 0.21) resulted in lower haemorrhagic events without increasing the risk of thrombo-embolic events in that earlier study. However, in contrast to ESCAT III only low-risk patients (age < 60 years, no atrial fibrillation) were included. Moreover, that study was restricted to patients with isolated AVR. Importantly, mortality was not enhanced in patients of the low INR target range.

A recent meta-analysis has already demonstrated that INR self-monitoring and testing is able to reduce thrombotic events compared with testing by a general practitioner, especially in patients with mechanical valve replacement. Thus, self-control is a promising treatment strategy. Our risk-adjusted statistical analysis demonstrates that even if patients are beyond the age of 60 years and/or have atrial fibrillation/pacemaker implantation, a very low-dose INR target range is feasible without reducing efficacy to prevent thrombotic events.

It is well known that the quality of oral anticoagulation determines VKA-related complications. Although in our study, the mean TTR was highest in the LOW group, it is noteworthy that the target range was restricted to 0.5 INR in the VLO and VLT group and was thus much smaller than the 1.0 INR in the LOW group. This can reliably explain the differences across study groups. Since the risk of bleeding events begins to increase above INR 2.5, strict anticoagulation monitoring is of importance. In our patients with bleeding events, mean INR values were 2.6 and 2.4 2 weeks and 1 week before the event occurred, and thus in a range where bleeding risk begins to increase. The incidence of thrombotic events was very low across the study groups and, all in all, the INR values which were measured before the event occurred do not indicate insufficient anticoagulation, at least in patients with AVR. Notably, some thrombotic events may occur independently of valve replacement. Embolic events are a well-known serious complication that is often observed in elderly people. The aetiology is of multiple origins and is at least in part due to an increased risk of dehydration caused by age-related

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\text{Figure 3} \quad \text{Kaplan–Meier freedom from grade III complications. Kaplan–Meier curves are shown for the first occurrence of the primary endpoint—a composite of grade III thrombo-embolic events and grade III bleeding complications in the overall study period. There were significant differences between study groups (log-rank test: } P = 0.013). \text{Low, low-dose INR self-management once weekly; very low dose one/week, very low-dose INR self-management once weekly; VLT, very low-dose INR self-management twice weekly.}
\]
changes in kidney function, thirst perception, body water content, and homeostatic capacity.\textsuperscript{17} Whereas in earlier analyses bleeding complications were twice as high as thrombo-embolic complications,\textsuperscript{6,9} in the present study the incidence per patient-year was low and very similar for bleedings and thrombotic events in the two VL groups. It is also of importance that our data demonstrate sufficiency of one INR testing per week, whereas a twice-weekly testing does not improve efficacy and safety. In total, data suggest that it is hardly possible to further reduce VKA-related complications by additional improvements in INR control, at least in AVR patients.

It was an important finding that overall mortality was higher in the VLT group compared with the LOW group. Given the small numbers of deaths in each group and the fact that some causes of death were obviously unrelated to anticoagulation control, it may well be that this is a chance finding. This assumption is supported by the fact that the incidence of bleedings and thrombotic events was not related to mortality risk. Nevertheless, results should be interpreted with caution, and a causal relation to anticoagulation control should not be neglected. It may be that frequent INR testing and frequent advice by cardiologists has increased mortality risk in the VLT group. Altogether, results substantiate our conclusion that weekly testing is sufficient and more frequent testing should not be recommended.

Our study has some limitations: owing to premature study termination, a significant proportion of the patients in each group did not complete the study period. Moreover, the study was not powered to detect differences in study end-points between the AVR and MVR/DVR subgroups. Furthermore, the vast majority of our patients received St Jude mechanical heart valves. It cannot be excluded that haemodynamic profiles may vary between different bileaflet valves and thus influence study outcomes. However, in the LOWERING-IT study 75% of patients received Sorin Bicarbon prosthesis\textsuperscript{54} with results being comparable with our data. The PROACT trial (ClinicalTrials.gov Identifier:NCT00291525) aims to determine whether patients receiving the On-X bileaflet valve can be safely managed by aspirin and clopidogrel (low-risk AVR group), INR 1.5–2.0 plus aspirin (high-risk AVR group) and INR 2.0–2.5 plus aspirin (MVR group). Nevertheless, unless VKA-free management is proved to be safe and is accepted by regulatory authorities, patients with On-X valves should continue using standard professionally recommended anticoagulant therapy.\textsuperscript{18} Thus, there is currently no evidence that oral anticoagulation should differ according to the provider of the bileaflet valve. Another limitation of our trial is that telemedicine-guided transfer of INR values was not provided to the LOW group. Therefore, we cannot definitively decide whether very low-dose INR self-control, the telemedicine-guided approach of INR transfer or both were responsible for the low complications rates in the VLO and VLT groups. Thus, especially patients with AF and/or an age of 60 years and above should combine very low-dose INR self-control with a telemedicine-guided approach of INR transfer.

In conclusion, our data demonstrate that telemedicine-guided very low-dose INR self-control is comparable with low-dose INR in thrombotic risk, and is superior in bleeding risk. Weekly testing is sufficient, whereas more frequent testing cannot be recommended. This recommendation is supported by the finding that overall survival was comparable in the LOW and VLO groups (weekly testing) but lower in the VLT group (twice weekly testing). Given the small number of MVR and DVR patients, results are only valid for AVR patients.

**Authors’ contributions**

Study concept and design: H.K.; acquisition of data: O.W., S.S., C.H., A.S., W.S., F.U.S., J.E., J.C., F.M., and J.F.G.; analysis and interpretation of data: A.Z., O.W., and H.K.; drafting the manuscript: A.Z.; critical revision of the manuscript for important intellectual content: J.F.G. and H.K.

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**References**


**Transthoracic echocardiogram-guided agitated-saline aortography for post-TAVR peri-prosthetic leak evaluation**

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A 75-year-old man was evaluated for a new diastolic murmur 3 months post-TAVR. Cardiac examination demonstrated a 2/6 systolic ejection murmur at the right upper sternal border and a 3/6 diastolic decrescendo murmur at the left sternal border. Transthoracic echocardiogram showed progressive left ventricular enlargement compared with immediate post-TAVR imaging. The aortic bio-prosthesis’ function appeared normal on transthoracic echocardiogram (TTE). Anterior periprosthetic regurgitation (pAR) was noted by colour-Doppler in parasternal short axis (Panel A, arrow; Supplementary material online, Video S1) and apical long axis (Panel B, arrow; Supplementary material online, Video S2) comprising 0.7 cm of the 7.3 cm valve circumference, thus classified as mild—moderate by current guidelines (~10% of annulus). Given clinical concern for significant pAR, aortic root angiography seemed appropriate but serum creatinine was 3.1 mg/dl precluding radiopaque contrast administration. Therefore, agitated-saline was injected directly into the aortic root during left heart catheterization and visualized by TTE. Agitated-saline densely opacified the entire left ventricle within two cardiac cycles (Panels C and D, five-chamber view, Supplementary material online, Video S3), confirming severe pAR as the source of clinical findings. Transthoracic echocardiogram-guided agitated-saline aortography may be valuable for post-TAVR patients with indeterminate pAR severity, particularly those with contraindications to radiopaque contrast use. RV, right ventricle; AoV, aortic valve; LA, left atrium; Ao, aorta; LV, left ventricle.

Supplementary material is available at *European Heart Journal* online.