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Full Length Article

Quality of life after switching from well-controlled vitamin K antagonist to direct oral anticoagulant: Little to GAInN

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ABSTRACT

Background: Direct oral anticoagulants (DOAC) and vitamin K antagonists (VKA) prevent thromboembolism in atrial fibrillation (AF). DOAC have a fixed dosing regimen and obviate INR monitoring. Therefore, DOAC presumably affect quality of life (QoL) less than VKA. However, some VKA users appreciate the monitoring. A high time in the therapeutic range (TTR) leads to a lower impact on QoL. We assessed the influence of switching from well-controlled VKA to a DOAC on QoL.

Methods: In the GAInN study, 241 patients with AF, a TTR ≥ 70%, and neither bleeding nor thrombosis while on VKA were randomised to switching to DOAC (n = 121) or continuing VKA (n = 120). Health-related (SF-36) and anticoagulation-related QoL (PACT-Q) was assessed at baseline and after six and twelve months of follow-up.

Results and Conclusion.

SF-36 development did not differ between groups. After one year, average PACT-Q Convenience improvement was 2.5 (0.3–4.7) higher on DOAC. DOAC users were 6percentage points (95%CI -4–16) more likely to improve > 5 points on Convenience; 22 pp. (95%CI 1–43) in patients who scored < 95/100 at baseline. The probability to meaningfully improve on PACT-Q Satisfaction was 12 pp. (95%CI 0–25) higher on DOAC. However, 5 (4.1%) and 4 (3.3%) DOAC users resumed VKA because of side-effects and patient preference. Switching from well-controlled VKA to DOAC for AF leads to a higher probability of improved PACT-Q convenience and satisfaction, but also to a higher risk of side-effects. Arguably only patients who are not satisfied with VKA should switch, because they have more to gain by switching.

1. Introduction

Atrial fibrillation (AF) is a cardiac arrhythmia that will affect one in five persons during their lifetime [1]. A feared complication of atrial fibrillation is stroke, with a debilitating impact on quality of life [2]. Although anticoagulation reduces the risk of stroke, its impact on quality of life is not just positive: anticoagulation aggravates bleedings that, in turn, impair quality of life [3,4].

Two types of anticoagulants are commonly prescribed in AF: vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs). VKAs have been prescribed for decades, and are used by hundreds of thousands of patients in the Netherlands alone. Because of its small therapeutic window, VKA therapy needs to be regularly monitored, and the dose titrated, to maintain an anticoagulation intensity (international normalised ratio, INR) within the therapeutic range. This can be cumbersome and could affect the quality of life of its users. DOACs have been introduced as a more convenient alternative for VKAs. They are non-inferior to VKAs for stroke prevention in AF [5], have a fixed dosing regimen, and do not require INR monitoring. Therefore, DOAC could have a favourable effect on quality of life.

However, vitamin K antagonists only have a limited effect on quality of life. After the first three months of therapy, quality of life is restored to that of the general population [4]. Furthermore, patients who use VKA with a high time within the therapeutic range have lower bleeding and thrombotic risks [6] and require less frequent INR monitoring than patients with poor VKA control. At the same time, VKA

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may also come with an advantage over DOAC with respect to quality of life, as many patients find the INR monitoring reassuring.

All other things being equal, impact on quality of life could be decisive in the choice for a particular anticoagulant. We aimed to establish whether switching to a DOAC would improve quality of life in the subgroup of patients who were previously well-controlled on VKA.

2. Methods

2.1. Trial aims and design

The Good Anticoagulation In the north of the Netherlands (GAInN) study explored bleeding and thrombotic risks of continuing VKA or switching to a DOAC in patients with atrial fibrillation who were currently well-controlled on VKA. As part of this study, we assessed quality of life.

This study was registered in the Netherlands Trial Registry (NTR4770) and the EU Clinical Trials Register (2013-004805-14), and was approved by the local research ethics committee at the University Medical Center Groningen (METc UMCG 2014/002).

2.2. Participants and study procedures

Records of patients who satisfied the inclusion criteria were extracted by Certe Trombosedienst, a large, first-line, thrombosis service for the northern provinces of the Netherlands. Inclusion criteria were: patients aged 18 and above who were treated with VKA for non-valvular atrial fibrillation and managed by Certe Trombosedienst; a minimum duration of treatment of six months at the time of selection; a time within the therapeutic range (INR 2.0–3.5) of at least 70% over the previous four months. From all consecutive patients, we randomly selected eligible subjects who were sent patient information and contact information to plan an information visit if they were interested.

After the patient had provided written informed consent, eligibility was re-checked. Exclusion criteria were: a thrombo-embolic event or major bleeding ever while on VKA; indication for anticoagulation other than atrial fibrillation; contra-indication to receive any kind of DOAC; a life expectancy < 1 year. We aimed to include 240 patients to obtain a reliable estimate of the effect on clinical outcomes; sample size calculation was based on the primary objective of the trial and not on a difference in quality of life.

Participants had four study visits: the first one to provide informed consent and be checked for eligibility, a second one a few weeks later for randomisation, followed by visits six and twelve months later (end of study).

2.3. Randomisation, masking, and study drugs

We randomised all eligible and willing patients in a 1:1 ratio to either continuing treatment with vitamin K antagonists, or switching to a direct oral anticoagulant. Randomisation was performed using an interactive computer system provided by the hospital's trial coordination centre, without stratification. Blocks of 4 and 6 were used in random order. Patients were unblinded for their allocated treatment to allow proper assessment of quality of life.

Treatment with VKA was continued as usual. The time between INR monitoring visits was based on the INR and was 6 weeks at most. Treatment with DOAC was started following local guidelines. Most patients received twice-daily apixaban; one patient received rivaroxaban because of concurrent use of diltiazem.

2.4. Study outcomes

The primary outcomes of the GAInN study were clinical events and have been described elsewhere [7]. The secondary outcome was quality of life. We assessed general health-related and anticoagulation-related quality of life, using the Medical Outcomes Study Short-Form 36 (SF-36) [8] and Perception of Anticoagulant Treatment Questionnaire (PACT-Q) [9]. Patients filled in the questionnaires before randomisation and during the research visits six and twelve months later.

The PACT-Q consists of two parts. The first part assesses treatment expectations for new patients. Because all our patients were, by definition, experienced users, we did not administer this part of the questionnaire. The second part consists of eleven questions about convenience, two about burden of disease and treatment, and seven about satisfaction. All questions were scored on a five-point Likert scale. The answers to the questions about satisfaction were summed and rescaled from 0 to 100 to produce the satisfaction scale. The responses to the questions about convenience and burden of disease and treatment were combined to produce the convenience scale [9]: first, the answers were inverted, then summed, and then rescaled from 0 to 100. A higher score indicates higher satisfaction or higher convenience.

The SF-36 is scored to obtain eight scales, and two summary component scores: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health, and the physical and mental component scores. The physical and mental components scores were determined by norming on a Dutch population [10], using weights from the United States of America [11] because data from the Netherlands are not available. A priori we considered it unlikely that anticoagulants would have an effect on the scales for bodily pain, physical functioning, role emotional and role physical. However, the SF-36 needs to be administered in full. We chose not to postulate hypotheses for these subscales, and will not analyse differences from baseline for these subscales.

We assessed overall treatment satisfaction highlighting one item in the PACT-Q questionnaire: “Overall, how satisfied are you with your anticoagulant treatment?” The answer to this question is on a five-point (Likert) scale. For the baseline value, the answer to this question at the time before randomisation was used. For development during the study, we also looked at whether a patient decided to switch from their allocated treatment to the other treatment (e.g. because of side-effects). If that was the case, the answer to the treatment satisfaction question could no longer be unambiguously interpreted. We then interpreted the switch as a sign that the patient was less satisfied with the allocated treatment. If the patient was still on the allocated treatment when (s)he filled in the questionnaire, we used the answer to the question.

2.5. Statistical analysis

We calculated differences from baseline for every subject for all quality of life outcomes. We assessed between-group differences using an independent *t*-test or Mann-Whitney *U* test, as appropriate.

We assessed an individual's probability to obtain a relevant improvement or decline in quality of life. We considered a change of 5/100 or less irrelevant; an improvement of > 5 was considered a relevant improvement, a decline of > 5 a relevant decline. This a priori set threshold was chosen arbitrarily: there is no consensus about a cut-off for relevance. We calculated absolute risk differences (ARD) for a relevant improvement or relevant decline on all PACT-Q scores, the SF-36 component scores, and the SF-36 scales for which an effect was not a priori unlikely (see above). All changes in the 5-point scale of treatment satisfaction were considered relevant. In addition, a switch based on patient preference, side effects, or clinical events was considered a relevant decline.

If subjects scored ≥95/100 on a particular scale at baseline, they could not experience a relevant improvement. As a sensitivity analysis, we re-assessed absolute risk differences in the group of patients who did not score ≥ 95/100 at baseline.

All analyses were performed in the intention-to-treat group, using R version 3.6.1 (2019-07-05) (R Foundation for Statistical Computing, Vienna, Austria). Data are reported as mean ± standard deviation or median (interquartile range), as appropriate.

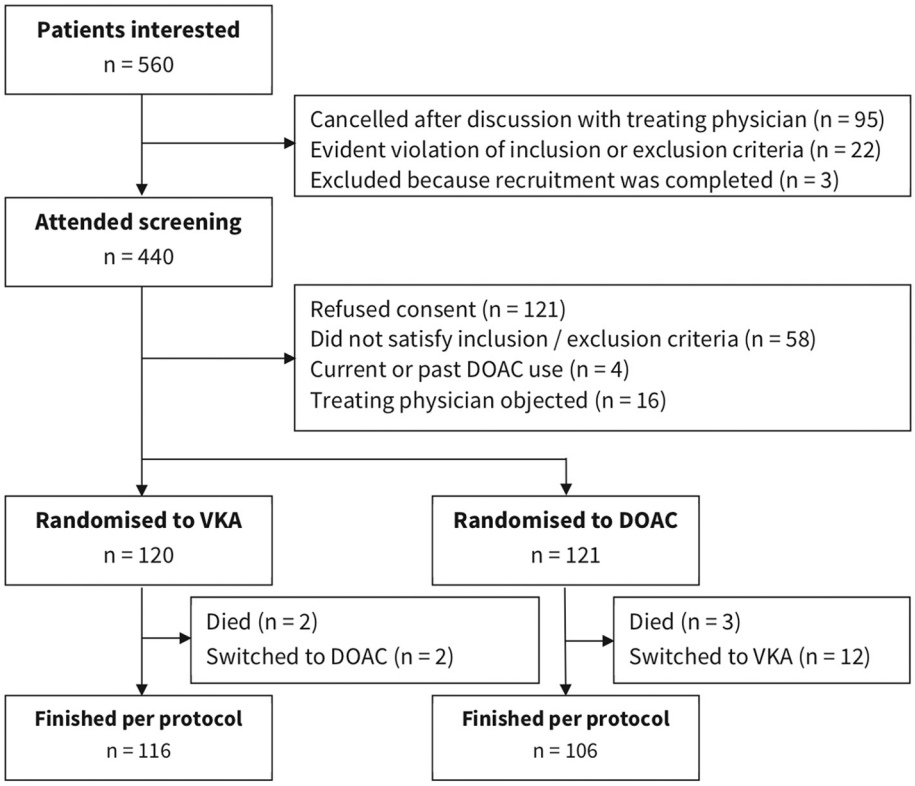

Fig. 1. Patient flow in this study.

3. Results

3.1. Patient flow and follow-up

The flow of participants is outlined in Fig. 1. 5502 patients were randomly selected and contacted by the Thrombosis Service. Between January 13, 2015, and November 1, 2016, 241 patients provided informed consent and were enrolled in the study. 121 patients were randomly assigned to DOAC treatment; 120 were assigned to VKA. All randomised patients started their allocated treatment; all of them were included in the analysis. The study was closed when the last patient completed the one-year follow-up on October 17, 2017. Median follow-up time was 364 (362–369) days, leading to 240 patient-years of follow-up.

The included patients were comparable with the selected eligible patients in age (mean 72.3 versus 72.8 years), but were more likely to be male (75.9% versus 67.3%).

3.2. Baseline characteristics

Baseline characteristics are summarised in Table 1. The mean age was 72 ± 6.9 (range 46–91). 76% was male. The majority of participants had comorbidities, with hypertension (75%) being the most common. Fewer subjects reported a stroke before starting VKA (10%) or vascular disease (22%). Beta-blockers were prescribed in 65% of participants; 13% used digoxin. Almost all patients were treated with acenocoumarol, reflecting local preference. In both groups, there was 1 patient who used phenprocoumon at randomisation.

3.3. Quality of life

Quality of Life scores are summarised in Table 2. Before randomisation, patients were very content with their treatment. Patients rated their overall treatment satisfaction on average 4.2 ± 0.8 out of 5. 79 (65.3%) patients gave the maximum rating of 5. The PACT-Q treatment satisfaction score was lower: median [IQR] 64 [57–71] out of 100. Patients found their treatment very convenient (PACT-Q convenience scale 98 [92–100], with 156 (64.7%) patients scoring ≥95/100). The relevant SF-36 scales were well-balanced between the two groups. Scores on a priori irrelevant SF-36 scales are reported in Supplementary Table 1.

In general, the relevant health-related quality of life scores remained constant during follow-up (Table 2) and changes during follow-up were the same in both groups. Social functioning was an exception: its score decreased over time in both groups. When excluding the 115 patients with a score of ≥95/100 at baseline, scores on social functioning remained constant. After one year of follow-up, more patients on DOAC than on VKA said their health was “somewhat” or “much better” than at the start of the study: 24 versus 12 (absolute risk difference 10% (95% CI 1 to 19)). A similar number of patients reported “somewhat” or “much” worse health compared with one year earlier: 17 versus 19 (ARD -2% (95% CI -11 to 7)).

Table 1
Patient characteristics.

	DOAC (n = 121)	VKA (n = 120)
Age (years) - mean (SD)	73.1 ± 7.5	71.5 ± 6.1
Sex female - n (%)	29 (24%)	29 (24%)
Body mass index (kg/m2) - mean (SD)	28.3 ± 4.6	28.4 ± 4.7
CHA2DS2-VASc - median [IQR]	3.0 [2.0–4.0]	3.0 [2.0–4.0]
Prior stroke - n (%)	12 (10%)	11 (9%)
Heart failure - n (%)	34 (28%)	25 (21%)
Hypertension - n (%)	92 (76%)	89 (74%)
Diabetes mellitus - n (%)	25 (21%)	29 (24%)
Vascular disease - n (%)	28 (23%)	25 (21%)
Betablocker use - n (%)	79 (65%)	77 (64%)
Digoxin use - n (%)	20 (17%)	11 (9%)
Platelet aggregation inhibitor - n (%)	3 (2%)	9 (8%)
Non-steroidal anti-inflammatory agent - n (%)	5 (4%)	3 (2%)

Table 2
General health-related, and anticoagulation related quality of life.

Scale	Baseline		Change after six months			Change after one year		
	DOAC	VKA	DOAC	VKA	p	DOAC	VKA	p
Full study population								
PACT-Q convenience	98 [92–100]	96 [92–99]	2.6 ± 6.9	0.8 ± 4.2	0.02	2.4 ± 7.4	−0.1 ± 9.7	0.03
PACT-Q satisfaction	64 [57–71]	64 [57–71]	4.7 ± 19.2	1.4 ± 16.9	0.17	3.9 ± 18.7	2.3 ± 18.9	0.51
General Health	67 [52–77]	62 [52–77]	−0.9 ± 13.3	1.3 ± 13.4	0.22	−1.0 ± 13.2	0.5 ± 14.0	0.41
Vitality	70 [55–80]	75 [65–85]	−0.4 ± 14.3	−2.3 ± 11.9	0.29	−0.6 ± 12.3	−1.8 ± 13.1	0.49
Social Functioning	88 [75–100]	88 [75–100]	−2.4 ± 18.0	−2.8 ± 15.8	0.85	−4.1 ± 15.9	−3.2 ± 17.5	0.68
Mental Health	82 [72–92]	84 [76–92]	−0.3 ± 13.3	−1.7 ± 12.4	0.42	0.1 ± 10.9	0.1 ± 10.1	0.96
SF-36 Physical component	47 [40–52]	51 [44–54]	−0.7 ± 7.0	−0.6 ± 6.9	0.87	−0.6 ± 6.7	−1.6 ± 7.1	0.28
SF-36 Mental component	55 [49–58]	55 [49–58]	0.0 ± 8.2	−0.8 ± 6.9	0.45	0.0 ± 6.7	0.1 ± 7.2	0.94
Subgroup with baseline score < 95								
PACT-Q convenience	88 [80–92]	90 [88–92]	7.9 ± 9.3	2.9 ± 5.2	0.004	8.4 ± 9.4	3.1 ± 6.1	0.004
Social Functioning	75 [62–88]	88 [62–88]	3.6 ± 18.3	0.9 ± 16.8	0.40	−0.6 ± 18.2	−0.8 ± 21.9	0.95

Values are given as median [IQR] or mean ± SD as appropriate.
Ps from unpaired t-tests. No Ps are given for baseline, because the subjects were randomised. No hypothesis testing was performed for scales that are unlikely to be affected by anticoagulants.
Abbreviations: DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

Patients on DOAC reported an average increase in convenience, compared with VKA: a difference of 1.8 (0.3–3.3) after six months. This effect persisted after one year: 2.5 (0.3–4.7). In 156 patients who did not score ≥ 95/100 at baseline the difference between DOAC and VKA was more pronounced: 5.1 (1.7–8.4) after six months and 5.3 (1.8–8.9) after one year, versus 0.3 (−0.6 to 1.2) and 1.4 (−1.3 to 4.0) in patients with a baseline convenience score ≥ 95/100. The average PACT-Q Satisfaction score initially improved as well, but this effect was not significant (3.3 (−1.4 to 8.1)) and the difference shrank after one year (1.6 (−3.3 to 6.5)).

Patients on DOAC were more likely than patients on VKA to improve > 5 points on PACT-Q convenience, during six months of follow-up: their probability was 11% (95% CI 2 to 21) higher than for patients on VKA (Fig. 2). After one year of follow-up, this difference had diminished: patients on DOAC then only had a 6% (95% CI -4 to 16) higher probability to improve (Fig. 3), which was no longer significant. The likelihood to experience a decline was the same in both groups, with a difference in probabilities of −2% (95% CI -8 to 4) after six months and 0% (95% CI -7 to 8) after one year. Likewise, patients on DOAC were more likely to improve on PACT-Q satisfaction at six months, but no longer after one year, as illustrated in Figs. 2 and 3. The probability to decline was similar on VKA and DOAC.

We found no differences in probabilities to improve or decline on the SF-36 scales after either six months or one year.

Patients on DOAC were more likely to experience an improvement in general treatment satisfaction (the probability was 10% (95% CI -1 to 20) higher than on VKA after six months), yet also more likely to experience a decline or reason to switch (difference in probabilities 8%

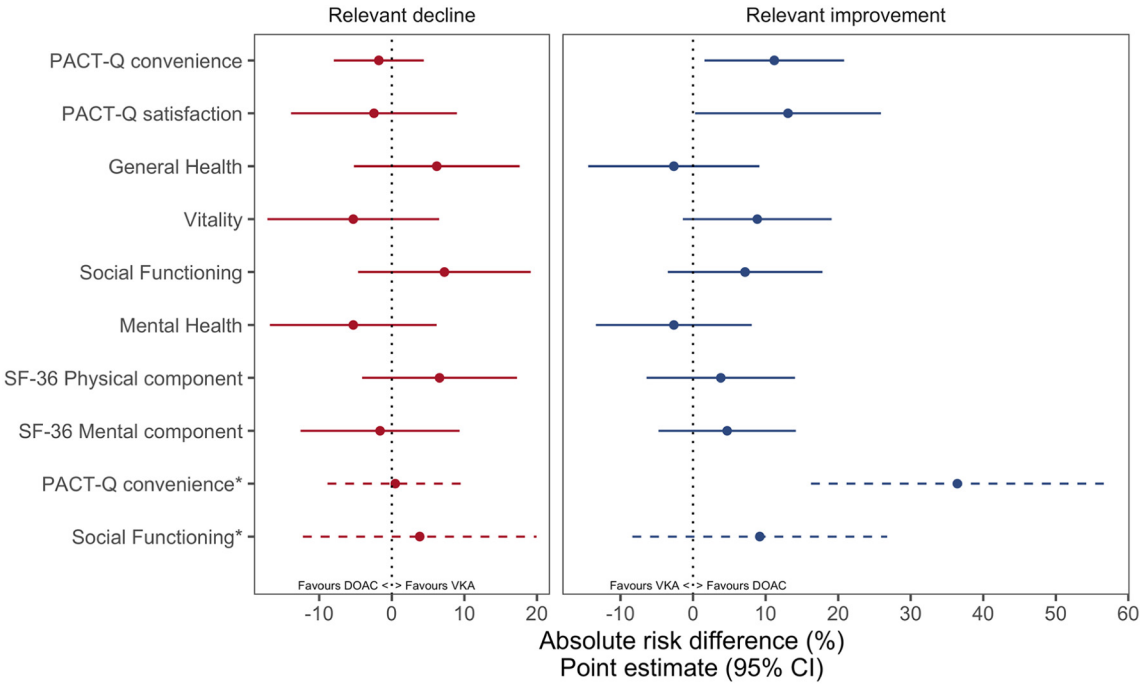

Fig. 2. Quality of life after six months.
Difference in proportions of patients experiencing a relevant decline resp. improvement on a direct oral anticoagulant, compared with a vitamin K antagonist, after six months of follow-up.
Items marked with * exclude subjects with a score of ≥95/100 or 5/5 at baseline.

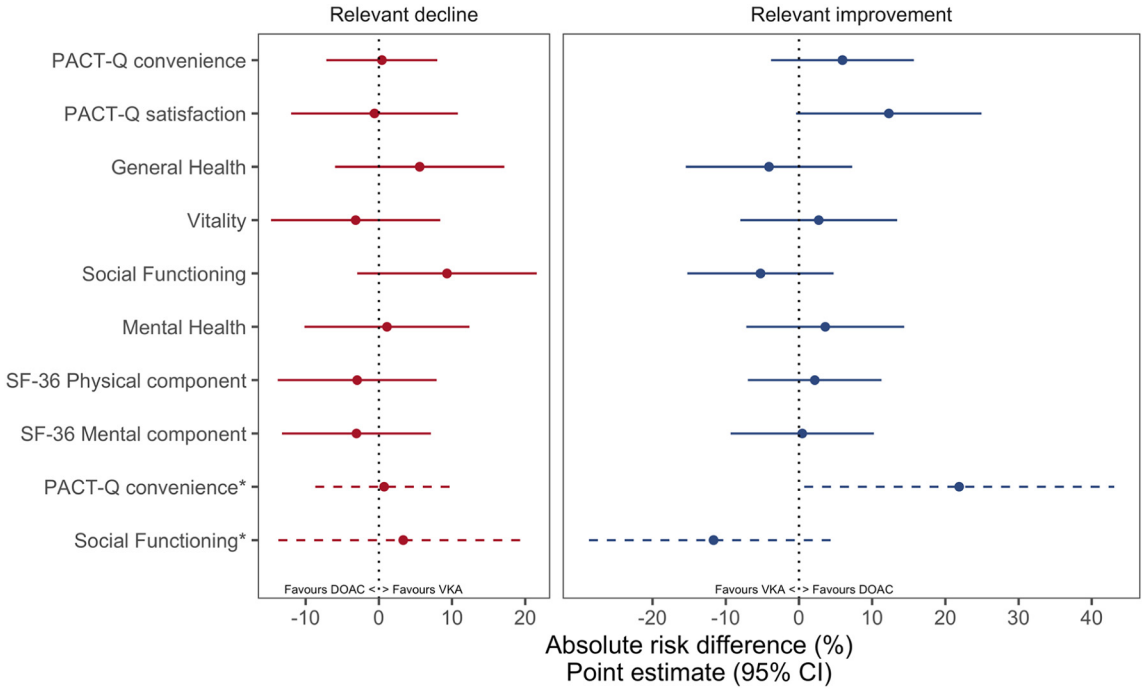

Fig. 3. Quality of life after one year.
Difference in proportions of patients experiencing a relevant decline resp. improvement on a direct oral anticoagulant, compared with a vitamin K antagonist, after 1 year of follow-up.
Items marked with * exclude subjects with a score of ≥95/100 or 5/5 at baseline.

(95% CI -2 to 18)). After one year, the probability to improve was 5% (95% CI -6 to 16) higher on DOAC, and the probability to decline or switch was 8% (95% CI -2 to 18) higher than on VKA.

In another analysis, we only included patients who could actually improve, because they scored < 95/100 or < 5/5 at baseline. They were even more likely to increase in PACT-Q convenience under DOAC (as indicated by the asterisk in Figs. 2 and 3). Although the effect attenuated after one year in this group as well, it remained significant. The subgroup of patients who were not fully satisfied with their treatment at baseline was far more likely to increase in overall satisfaction after the switch to a DOAC: the probability was 18% (95% CI 4 to 33) higher than that on VKA after six months. In contrast to the overall group, the probability to decline was not higher on DOAC: the difference was −1% (95% CI -10 to 8) after six months. After one year of follow-up, patients remained more likely to improve (difference 13% (95% CI -2 to 28)) and less likely to decline (difference 4% (95% CI -5 to 13)) than the complete population, but the differences diminished and were no longer statistically significant.

At the end of the study, DOAC patients could choose whether to continue DOAC or switch back to VKA. Out of the 121 patients randomised to DOAC, 105 (86.8%) chose to continue their DOAC. 12 (9.9%) had switched back to VKA during the study (mainly over perceived side-effects: one developed another indication for VKA; two had an event under DOAC). 2 (1.7%) patients had died. 2 (1.7%) patients preferred to switch back to VKA at the end of the study (mainly because of the higher out-of-pocket expense of DOAC).

4. Discussion

In patients who were well-controlled on VKA, we found that switching to a DOAC only marginally improved average treatment convenience and did not affect other parameters of quality of life. On the individual level, a minority of patients experienced a “relevant improvement” of > 5 points on anticoagulation-related, but not general, quality of life. However, the effect of a switch to a DOAC was not just positive: the number of patients who were more satisfied overall was the same as the number of patients who were less satisfied or decided to switch back to a VKA. Only in the subgroup of patients who were not fully satisfied at baseline did the DOAC cause more patients to improve than to decline or switch.

Our study is the first to focus exclusively on patients who were well-controlled on VKA at baseline. Our findings are in line with results from the RE-LY trial [12], where no differences were found in quality of life between patients randomised to dabigatran or warfarin. Other studies assessed quality of life outside a randomised controlled setting. This makes results more difficult to interpret, as patients with lower thrombotic and bleedings risks are switched more often [13]. Differences in clinical characteristics can confound the relationship between prescribed anticoagulant and quality of life scores. One study accounted for this with propensity score matching and found no difference in quality of life between DOAC and VKA [14]. Another study used regression analysis to correct for confounders and found that patients on DOAC experienced less burden and more benefit from treatment [15]. Other studies that report a higher quality of life on DOAC should be interpreted with caution, because they did not address baseline differences [16,17].

Our study benefits from randomisation while maintaining a design that closely resembles “real-life”. Patients randomised to DOAC had no appointments at the anticoagulation clinic, except for a study visit at six months and one year. This allowed them to experience the absence of INR monitoring visits (which was impossible in the registration trials) and associated reassurance. A potential limitation of the randomised setting is the generalisability: patients with a strong preference to continue VKA have not been included in the study. However, these patients would not be switched with current shared decision making either. Enrolled subjects were representative of the identified patients in age but slightly more often male. Because this study was a pilot study aimed at clinical events, we did not perform a sample size calculation for quality of life outcomes. In our study, we adopted an arbitrary cutoff of more than five points. Most analyses have been performed according

to the intention-to-treat principle: patients who discontinued their allocated treatment were analysed in their allocated group. Theoretically, the switch away from the allocated treatment could lead to an improvement in quality of life (e.g. when a patient no longer suffered side-effects); if this were attributed to the allocated treatment this could distort the results. This effect would be strongest on the single question about general treatment satisfaction. We therefore took switching into account for this question; for the other questions we maintained the intention-to-treat principle. However, results in the per-protocol analyses were not meaningfully different, making this distortion unlikely. Symptoms of AF, such as palpitations and dyspnoea, also affect quality of life [18]. We have not assessed symptom severity but an effect of anticoagulation on AF symptoms is pathophysiologically implausible. Furthermore, we have excluded SF-36 scales most sensitive to AF symptoms.

Overall, patients in our study already scored high on treatment convenience at baseline. These patients were selected because they had a high TTR, which allows for more time between INR monitoring. This lowers treatment burden [19] and increases convenience [4]. Furthermore, they are less likely to suffer from bleeding and thrombotic events than patients with a poor TTR [6]. Another explanation for the high convenience would be that these patients are managed by a well-organised, dedicated, anticoagulation clinic with wide opening hours. Patients from this clinic expressed high convenience before [4].

With treatment convenience already so high, switching to a DOAC could not make much of a difference. Indeed, an increase in convenience was confined to patients who scored < 95 on convenience at baseline (the difference was 5.3 (1.8–8.9) points relative to VKA, versus 1.4 (-1.3 to 4.0) in patients who scored ≥ 95 at baseline). Of these patients, 1 additional patient out of every 4.6 (95% CI 2.3–140.5) who switched experienced a relevant increase in convenience. A possible explanation is that patients prefer taking a fixed dose of 1 tablet of apixaban twice daily, compared with multiple and a variable number of tablets for acenocoumarol once daily.

Furthermore, switching to a DOAC did not result in a meaningful difference on other measures of quality of life. Nevertheless, the majority of patients on DOAC preferred to continue their DOAC at the end of the study, instead of switching back to VKA. This could indicate that patients favour DOAC over VKA, despite the only small difference in anticoagulation-related quality of life.

Another explanation, however, for their preference to continue DOAC could be that patients dread drug changes when they do not expect much benefit. This could also explain the low participation rate in our study. 5 (4.1%) patients on DOAC experienced side-effects; an additional 4 (3.3%) patients had another reason why they wanted to resume VKA therapy. This effect negated the positive effects on general treatment satisfaction that other patients experienced.

However, even if switching to a DOAC would have no positive effect on quality of life, switching could still be justified if it would lead to better clinical outcomes. In this study, we hypothesised that well-controlled patients on VKA would actually be harmed by switching to a DOAC. However, we found no evidence to support this hypothesis: clinical endpoints were distributed evenly between the two groups [7]. In a more general study population, DOACs lead to a reduced risk of intracranial haemorrhage and ischaemic stroke, although the absolute risk reductions are modest [5]. Although well-controlled patients who find VKA therapy inconvenient have more to gain by switching to a DOAC, we believe all patients should be counselled about the different options available for stroke prevention in AF. This study can be helpful in shared decision making and weighing a possible improvement in treatment convenience against the risk of side-effects.

5. Conclusion

In a population with good VKA control, a switch to a DOAC has no effect on general health-related quality of life, but leads to a small increase in anticoagulation-related quality of life. However, the switch introduced side-effects and other reasons patients decided to resume VKA therapy. These should be considered before switching from well-controlled VKA to a DOAC. Patients who are not satisfied with treatment with VKA have more to gain by switching to a DOAC. Physicians and their patients should together weigh the advantages and disadvantages.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2020.04.007.

Data sharing statement

Individual participant data will not be made available, as this was not covered in the informed consent given by participants.

Author contributions

- Conception: H.A.M. Kooistra, N.J.G.M. Veeger, K. Meijer
- Data collection: J.H.A. van Miert, H.A.M. Kooistra, A. Westerterp, M. Piersma-Wichers
- Data analysis and interpretation: J.H.A. van Miert, H.A.M. Kooistra, N.J.G.M. Veeger, K. Meijer
- Drafting the article: J.H.A. van Miert
- Critical revision of the article: H.A.M. Kooistra, N.J.G.M. Veeger, A. Westerterp, M. Piersma-Wichers, K. Meijer
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Declaration of competing interest

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