



Perceived advantages and disadvantages of oral anticoagulants, and the trade-offs patients make in choosing anticoagulant therapy and adhering to their drug regimen



Melissa C.W. Vaanholt^a, Marieke G.M. Weernink^a, Clemens von Birgelen^{a,b}, Catharina G.M. Groothuis-Oudshoorn^a, Maarten J. IJzerman^a, Janine A. van Til^{a,*}

^a Department of Health Technology and Services Research, Faculty of Behavioural, Management and Social Sciences, Technical Medical Centre, University of Twente, Enschede, The Netherlands

^b Thoraxcentrum Twente, Department of Cardiology, Medisch Spectrum Twente, Enschede, The Netherlands

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ABSTRACT

Objective: The objective of this study was to explore the perceived advantages and disadvantages of oral anticoagulant therapies (OAT), and the trade-offs patients make in choosing therapy and adhering to their drug regimen.

Methods: Five focus group sessions were conducted across Europe among patients with atrial fibrillation to identify the most important factors impacting OAT's value and adherence.

Results: The most frequently identified barriers to OAT were lack of knowledge; poor patient-physician relationships; distraction due to employment or social environment; prior bleeding event(s) or the fear of bleeding; and changes in routine. Factors identified as promoting adherence included patients' personality, motivation, attitudes, and medication-taking habits and routines, as well as good quality health services. Inconvenient aspects of vitamin-K antagonists, such as regular blood monitoring and diet restrictions, were not reported to influence adherence, but may trigger patients to switch to direct oral anticoagulants.

Conclusion: Most patients reported that a mixture of modifiable and non-modifiable factors helps them to take their drugs as prescribed. Individual patients' particular needs and preferences regarding OAT vary. **Practice implications:** OAT adherence can be promoted if therapies are tailored to patients' needs and preferences. Patients should be supported to share their preferences with their clinician.

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1. Introduction

Oral anticoagulant therapy (OAT) is proven to be highly effective for stroke prevention in patients suffering from atrial fibrillation (AF) [1,2]. Vitamin K antagonists (VKAs), particularly warfarin, which is the most commonly used VKA, have long been the standard of care to prevent AF-related stroke [3]. However, in recent years the European Medicines Agency has approved a number of direct oral anticoagulants (DOACs) as (possible) alternatives to VKAs. The perceived benefits of DOACs include their high efficacy and low risk of bleeding, the rapid onset/offset of

action, fewer drug-food interactions, and predictable pharmacokinetics that eliminate the need for monthly coagulation monitoring and frequent dose adjustment [4,5].

The proportion of patients to whom DOACs are prescribed is rising. However, as with the VKAs, the safety and effectiveness of these drugs is highly dependent on patients' ability to adhere to their therapy regimens [6–10]. According to the World Health Organization (WHO), adherence is “the extent to which a person's behavior – taking drugs, following a diet, and/or executing lifestyle changes – corresponds with consensus recommendations from a health care provider” [10]. It is known that in chronic conditions such as AF – where patients take drugs to prevent AF-related stroke, and symptoms are frequently intermittent or not present at all [11] – rates of nonadherence can be as high as 50% [12–14]. In recent years, several studies have focused on identifying the determinants and level of non-adherence to OAT, and on the perceived benefit of DOACs over VKAs. Contradictory statements were made in previous studies. For example, in the study of Abdou

* Corresponding author at: P.O. Box 217, 7500 AE, Enschede, The Netherlands.

E-mail addresses: m.c.w.vaanholt@utwente.nl (M.C.W. Vaanholt), m.g.m.weernink@utwente.nl (M.G.M. Weernink), c.vonbirgelen@mst.nl (C. von Birgelen), c.g.m.oudshoorn@utwente.nl (C.G.M. Groothuis-Oudshoorn), m.j.ijzerman@utwente.nl (M.J. IJzerman), j.a.vantil@utwente.nl (J.A. van Til).

et al., frequent INR monitoring was identified as a barrier to medication adherence [15], but in the study of Rodriguez et al. it was suggested that regular monitoring may improve adherence as it offers opportunities to contact health care providers (HCPs) and it serves as a feedback loop in medication-taking behavior [16]. However, empirical studies identifying pros and cons of VKAs and DOACs, and the trade-offs patients make in choosing therapy and being adherent to their drugs, remain scarce. Therefore, this study aims to explore patients' experiences and perspectives regarding OAT, and the factors underlying therapy value and adherence to OAT.

2. Methods

2.1. Development of the focus group guide

The aims of the study were to explore: (1) the perceived pros and cons of OAT, and (2) the trade-offs patients make in choosing therapy and being adherent to their drug regimes. Given that this study was exploratory in nature, it was decided to use focus groups because they provide an interactive way to identify how patients think and feel about adherence to OAT. Furthermore, they provide an opportunity for discussion between patients with opposing views [17]. Each focus group began with an introductory round in

which the moderator and patients introduced themselves, followed by a brief description of the main topic. An initial discussion took place on patient's medication-taking behavior, after which attention was given to specific domains that can affect adherence. The domains were derived from the WHO model, which sorted these factors into five categories: (1) social and economic factors; (2) condition-related factors; (3) health care team and system-related factors; (4) patient factors; and (5) therapy-related factors [10]. Additionally, literature review and expert consultations were used to generate more specific questions and probes for the five domains (Table 1). The moderator was specifically instructed to use probes and follow-up questions when patients reported full adherence or said that they had no problems in specific domains.

2.2. Study design

Five focus group sessions were conducted across Europe (United Kingdom, Germany, Spain, Italy and France) between the 31st of January 2017 and the 15th of February 2017 among patients suffering from AF who take OACs to prevent AF-related stroke. A specialist recruitment agency (Lightspeed Research) contacted healthcare providers to recruit eligible patients for this study. Patients were eligible if they were at least 18 years old; had a

Table 1
Focus group questions.

Interview Domains	Sample questions and probes
Overall medication taking behaviour	<ul style="list-style-type: none"> Do you experience any problems taking your drugs? Do you take your anticoagulation drug as prescribed? <p>Probe: Why do you take it? Why don't you take it? What motivates you to take it regularly as prescribed? What hinders you from taking it as prescribed?</p>
Socio-economic-related determinants	<p>Out-of-pocket costs</p> <ul style="list-style-type: none"> Do you have to pay "out-of-pocket" for your drugs? If so, how much? Are high costs a reason for you/ or would high costs be a reason for you to: <ul style="list-style-type: none"> -Not always taking your drugs as prescribed? -Not taking the drugs at all? <p>Probe: are you cutting back due to high out-of-pocket costs (splitting tablets, skipping doses etc.)?</p> <p>Social environment</p> <ul style="list-style-type: none"> Now think about other people or groups with whom you relate, such as your family, friends, the physician who takes care of you, co-workers (if you work); in other words the people who interact with you. In what way, if any, have the actions, reactions, comments or attitudes of some of these people prevented you from taking your medication as prescribed?
Therapy-related determinants	<p>Drug regimen</p> <ul style="list-style-type: none"> Are there factors that hinder you taking your medication (e.g. number of tablets you have to take, tablet size, difficulty with swallowing, combining drugs with food, avoiding certain foods, regular blood monitoring etc.)? <p>Drug packaging</p> <ul style="list-style-type: none"> Do you think that the way in which your drugs are wrapped make it less convenient and or easy to use? (e.g. bottle or blister-packaging, the number of tablets per package etc.) <p>Probe: Does this influence your decision whether or not to take the drugs as prescribed?</p> <ul style="list-style-type: none"> What things about the drug itself do you feel need to change that would help you to take the drugs as prescribed?
Patient-related determinants	<p>Personality traits</p> <ul style="list-style-type: none"> Do you think that some of your personality traits (e.g. careless, chaotic vs. secure, organized) prevent you from or help you to take the drugs as prescribed?
Condition-related determinants	<p>Severity of symptoms/illness</p> <ul style="list-style-type: none"> What difficulties or symptoms do you have? In what way(s), if any, does your illness impact your daily life?
Health system/health care team-related determinants	<p>Understanding of the disease/effectiveness</p> <ul style="list-style-type: none"> What is the problem when you have AF and why do you take the drugs? <p>Probe: Do you know what your prescribed drug does and why you take it?</p> <p>Patient-doctor relationship</p> <ul style="list-style-type: none"> How is the relationship with your doctor? Does he or she involve you in treatment process? Would you prefer to be more involved in the treatment process? Do you think that the nature of the relationship(s) with your doctor influences the adherence to your drug regime, and to what extent?

formal diagnosis of AF; were currently using OACs; and were able to give informed consent. Due to the involvement of patients in the focus group part of this project, ethical approval was obtained from the institutional review board of the University of Twente. All patients gave written informed consent and all data were anonymized before analysis. All participants were paid €90,- for participation in the study. Before the focus group sessions, patients provided background information, including demographic data and data about their health status.

2.3. Data analysis

Focus group sessions were audiotaped, subsequently transcribed verbatim and ATLAS.ti 7.0 (Scientific Software Development GmbH, Berlin) was used for qualitative data management [18,19]. Two coders (MV and MW) independently examined each transcript and coded patient statements. First, the five dimensions of the WHO model (described above) were used in the coding scheme [10]. Next, subcategories were generated from the focus group data. Coder 1 (MV) analyzed the transcripts, which resulted in a set of 33 codes. The second coder (MW) coded the transcripts using the coding scheme provided by the first coder. Furthermore, both coders labelled each text fragment as positive, negative, or neutral. The neutral label was assigned to fragments for which no positive or negative statements could be identified; for example, because the fragment was too general. Occasionally (n = 23),

fragments were double-coded (both positive and negative) if they contained both positive and negative statements. Cohen's kappa was calculated to provide a measure of inter-coder agreement [20]. Differences in classifications were discussed between the two coders until consensus was reached [21].

3. Results

3.1. Coding

The focus group data resulted in 33 subcategories for the five WHO-dimensions. The percentage of agreement between the two coders was 92% and the Cohen's kappa value was 0.92; indicating almost perfect agreement [21]. Text fragments were also labeled as positive, negative or neutral. The percentage of agreement between the two coders was 87%, and Cohen's kappa was 0.83 indicating almost perfect agreement [21].

3.2. Patient characteristics

The patients' sociodemographic and treatment-related characteristics are presented in Table 2. Of the 48 patients included in this study, 24 (50%) were men; their mean age was 62 years; the majority of the patients (n = 26, 58%) had a high level of education; and self-reported high levels of adherence (n = 28; 58%); and almost two-thirds of patients (n = 28, 58%) were taking VKAs.

Table 2
Socio-demographic and clinical characteristics of the patients included in this study (n = 48).

	Overall (N = 48)	UK, n = 10 (21%)	Germany, n = 10 (21%)	France, n = 8 (17%)	Spain, n = 10 (21%)	Italy, n = 10 (21%)
Gender – Male	24 (50%)	7 (70%)	5 (50%)	1 (13%)	5 (50%)	6 (60%)
Age [†] – yr. (mean, SD) ^a	N = 42 62 (13)	N = 10 69 (8)	N = 10 59 (11)	N = 8 48 (11)	N = 10 70 (12)	N = 10 62 (13)
Education	N = 45	N = 10	N = 10	N = 8	N = 10	N = 10
Low	11 (23%)	4 (40%)	0 (0%)	0 (0%)	5 (50%)	2 (20%)
Medium	11 (23%)	2 (20%)	3 (30%)	1 (13%)	1 (10%)	4 (40%)
High	26 (54%)	4 (40%)	7 (70%)	7 (88%)	4 (40%)	4 (40%)
Married or cohabiting – yes.	N = 45 36 (75%)	N = 10 9 (90%)	N = 10 6 (60%)	N = 8 5 (63%)	N = 10 6 (60%)	N = 10 10 (100%)
Employment Status ^a	N = 47	N = 10	N = 10	N = 8	N = 9	N = 10
Retired	23 (49%)	7 (70%)	4 (40%)	0 (0%)	6 (67%)	6 (60%)
Working	22 (47%)	3 (10%)	5 (50%)	7 (88%)	3 (33%)	4 (40%)
Unemployed	2 (4%)	0 (0%)	1 (10%)	1 (13%)	0 (0%)	0 (0%)
Median annual household income –€	N = 48	N = 10	N = 10	N = 8	N = 8	N = 10
0-15000	7 (15%)	1 (10%)	1 (10%)	1 (17%)	2 (20%)	2 (20%)
15001-25000	9 (19%)	0 (0%)	2 (20%)	1 (17%)	2 (20%)	4 (40%)
25001-50000	13 (27%)	5 (50%)	3 (30%)	2 (25%)	2 (20%)	1 (10%)
50,001+	7 (15%)	1 (10%)	1 (10%)	2 (25%)	2 (20%)	1 (10%)
Unknown [#]	12 (25%)	3 (30%)	3 (30%)	2 (25%)	2 (20%)	2 (20%)
Current OAT	N = 48	N = 10	N = 10	N = 8	N = 10	N = 10
VKA Warfarin	12 (25%)	6 (60%)	0 (0%)	0 (0%)	0 (0%)	6 (60%)
VKA Acenocoumarol	6 (13%)	0 (0%)	0 (0%)	0 (0%)	5 (50%)	1 (10%)
VKA Phenprocoumon	6 (13%)	0 (0%)	6 (60%)	0 (0%)	0 (0%)	0 (0%)
VKA Fluindione [‡]	4 (8%)	0 (0%)	0 (0%)	4 (50%)	0 (0%)	0 (0%)
DOAC Dabigatran	7 (15%)	1 (10%)	3 (30%)	1 (13%)	1 (10%)	1 (10%)
DOAC Rivaroxaban	7 (15%)	1 (10%)	1 (10%)	2 (25%)	3 (30%)	0 (0%)
DOAC Apixaban	6 (13%)	2 (20%)	0 (0%)	1 (13%)	1 (10%)	2 (20%)
Time period on OAT	N = 46	N = 9	N = 10	N = 8	N = 9	N = 10
<3 months	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3 months - 1 year	7 (15%)	0 (0%)	1 (10%)	3 (38%)	1 (11%)	2 (20%)
1 year- 5 years	22 (48%)	5 (56%)	6 (60%)	3 (38%)	2 (22%)	6 (60%)
5 years+	17 (37%)	4 (44%)	3 (30%)	2 (25%)	6 (67%)	2 (20%)

Notes: Values are means (percentages) unless indicated otherwise. Abbreviations: NOAC= New oral anticoagulant; OAT= oral anticoagulant therapy; SD=standard deviation; VKA= vitamin K antagonists. a=Numbers do not count to the total due to missing data. #This number represents all respondents who did not wish to address this question. ‡Not a VKA, but same mode of action.

3.3. Overall medication-taking behavior

Initially, all patients reported taking their medication as directed, mentioning perceived health risks and especially fear of AF-related stroke as the greatest motivators. However, as the focus group

discussion continued, some patients admitted that they occasionally skipped or missed a dose. Although specific responses varied among patients, the identified advantages and disadvantages of VKAs and DOACs, and the motivators for being adherent (or not) are addressed in the following paragraphs and presented in Table 3.

Table 3

Summary of factors impacting OAT value that emerged from the focus group data.

Factors negatively impacting OAT value	
Forgetting	Especially in the weekends, on holidays, or other occasions when their schedule is different than usual. <ul style="list-style-type: none"> • “Over the weekends if the schedule is different. If the morning starts differently than for example going to work, then it can happen that I really forget it.” [changes in routine] • “Yes, I’ll be quick. It happened to me, when I’m on holiday or eating out, or you fall asleep and forget about it.” [holiday]
Complex regimen	<ul style="list-style-type: none"> • “I take [de-identified pill]. It is a very small pill. [. . .] I take half a pill twice per day. I have a pill cutter and they are so slippery. [..] Sometimes I can’t see them. They just vanish.” Some patients were confused about adjusted doses due to fluctuating INR. <ul style="list-style-type: none"> • “Yes, I’ve encountered some difficulties, mostly with remembering my schedule. Because the dosing varies.”
Lack of knowledge and motivation	Some patients are unaware of the seriousness of not taking their medication as directed. The absence of symptoms and side effects due to the often asymptomatic nature of NVAF can also negatively impact adherence. <ul style="list-style-type: none"> • “Then I just leave the pill. I was also told that if I forget it, then it is not such a big problem.” [unaware of the seriousness of nonadherence] • “When I go to my doctor he tells me, ‘You shouldn’t look at the patient information leaflet! Because if you look at it, you won’t take your drug.’ [inadequate information provided by health care providers] • “I don’t know how long you have been taking medication. After years and years, you start to rationalise. If you don’t take it once, you are not going to die, anticoagulation is still working and there is no clot yet.” [decreased motivation]
Poor patient-doctor relationship	<ul style="list-style-type: none"> • “He doesn’t explain anything. This is when I lost all my trust in my doctor. I also didn’t go to see him anymore. I am now looking for a new cardiologist.”
Dietary restrictions or food-drug interactions	<ul style="list-style-type: none"> • “It was a problem because I felt so weak. I’m used to eating lots of vegetables.”
Regular INR monitoring	<ul style="list-style-type: none"> • “I was really annoyed by all the tests and I wanted to find something else because [..] I was annoyed by the tests, and I stopped taking it.”
Experiences with and fear of nonadherence consequences.	<ul style="list-style-type: none"> • “One of the major problems we have is anxiety because it’s the fear of the unknown.” • “The people I have seen, who already have consequences and this is why I regularly take them.”
Side effects	Experience of side effects prompted some patients to change therapies <ul style="list-style-type: none"> • “I even got a mild depression. That’s why they changed my treatment.”
Labour market participation	<ul style="list-style-type: none"> • “I do night shifts from 7PM-7AM. And at the beginning it was difficult because my work shifts did not correspond to the treatment times.”
Social context	<ul style="list-style-type: none"> • “Well, usually when I’m with my colleagues, after we get our coffees, nobody takes a pill, someone goes to the toilet etc. one tends to hide.” [social stigma] • “I don’t want to talk about it either. When you start to talk about your health issues, people leave you.” • “The only problem is distractions. If someone distracts you, you may take it 15-20 minutes late.”
Factors positively impacting OAT value	
Knowledge of perceived importance of being adherent	<ul style="list-style-type: none"> • “I think many of us take other drugs for different conditions, and I think anticoagulants are among the most important ones. I wouldn’t mind cutting my hypertension pill in half, but I wouldn’t do it with anticoagulants. I’m afraid of the consequences when I miss my anticoagulant pill one day; while I’m not so worried about forgetting to take my hypertension drug for even a week.”
Personality traits (being secure, organised)	<ul style="list-style-type: none"> • “Well, efficient and organised and I need to have a system that is reliable and ensures that I meet the requirement.”
Social support	<ul style="list-style-type: none"> • “My family ask me if I’m taking my pills.”
Established, individualised habits and routines.	Most patients use external reminders and have developed routines to help them form a habit and consistently remember to take their medication as directed. <ul style="list-style-type: none"> • “You just need to remember to take it. You need to get organised. Personally, I set the breakfast table in the evening and place the tablet on the spoon.” [integrating regimens into daily routine]
Self-education	Many patients felt the need to actively search for more information regarding their condition and treatment. <ul style="list-style-type: none"> • “In my experience, my doctor didn’t explain it to me particularly well and if I hadn’t been involved in a support group I don’t think I would have been as aware as clearly I am now. “
Good patient-doctor relationship	<ul style="list-style-type: none"> • “In the past I forgot it a lot, but when the doctor told me that stopping is dangerous, either your life or your pills. Then I thought that I have to make sure I take them.” • “The doctor has a very big influence.”

^aAll factors met the same criteria for frequency of report. They were spontaneously mentioned by at least 3 patients in each of the five focus groups. OAT = oral anticoagulant therapy; INR = international normalized ratio.

3.4. Drug efficacy, health status and occurrence of negative side effects

Not many statements were made regarding patients' current health status. One patient mentioned that his dependence on multiple medications made it harder for him to take his drugs as prescribed: *"I already take 8 pills each day, for my heart and so on, so it could happen that I forget."* The importance of taking OACs as directed seemed to be clear to the patients included in this study, citing the seriousness of the condition as a major motivator: *"I think many of us take other drugs for different conditions, and I think anticoagulants are among the most important ones. I wouldn't mind cutting my hypertension pill in half, but I wouldn't do it with anticoagulants. I'm afraid of the consequence."* The side effects of OAT mentioned most often were decreased general strength, trouble sleeping, nose bleeding, and hair loss. Although none of the patients cited side effects as a reason for non-adherence, these side effects interfere with patients' daily life and were therefore a reason for two patients to switch between OATs. Previous personal experiences or experiences of close friends/relatives and the emotions caused by these appeared to be strong motivational drivers to take medication as prescribed. A patient: *"I'm so afraid because I have some friends who had clotting in their heads. But my doctor told me that I wouldn't have any problems if I took my medication properly."*

3.5. Regime complexity

In general, patients seem to prefer drug therapies that are easier to administer. Most patients preferred once-daily dosing, and the motivation given was that a once-daily drug is less likely to be forgotten. In contrast, some patients preferred twice-daily dosing because of the shorter half-lives of the drug and their fear of a life-threatening bleed. As one patient put it: *"[de-identified NOAC] doesn't have an antidote; if I have a hemorrhage within 24 h after taking it, the doctors will be praying for me not to bleed to death. This doesn't happen with [de-identified VKA]. A 24-hour lapse is much longer than a 12-hour lapse. I would have normal coagulation after 12 h, when the effect is gone. This would be safer in case of emergency."* The above-mentioned statement emphasizes the lack of adequate knowledge of patients regarding the availability of reversal strategies. Although there are reversal strategies available to reverse the anticoagulant effects of OACs in cases of emergency (accidents, urgent surgery), it appeared that some patients were not aware of these reversal strategies, as they made negative comments about the effect of OAT on bleedings. A patient: *"If you have a car accident, that's it. I can't conceive the fact that I can't recover from coagulation immediately."*

3.6. Blood monitoring

Values and preferences related to International Normalised Ratio (INR) monitoring appeared to be heterogeneous. While nine patients spontaneously emphasize the assurance INR monitoring provides: *"I feel much safer if I have taken them every month and I get to know about my precise [INR] levels"*, an equal number of patients found regular INR monitoring burdensome since it impacts daily life, disrupts work commitments or interferes with holiday plans. A patient: *"You have to restrict a few activities so that you have time to go and see a doctor. You have to deal with opening times and working hours."* There was consensus among VKA-users that fluctuating INR levels and the dose adjustments needed for the VKAs made it more difficult to remember to take their medication. *"I've encountered some difficulties, mostly with remembering my schedule because the dosing of [de-identified VKA] varies."*

3.7. Dietary restrictions

Patients talked about receiving varying dietary instructions. While the consumption of vitamin-K-rich foods was discouraged

for some patients, others were told that it was sufficient to maintain stable dietary habits and avoid significant changes in the intake of vitamin K. The VKA-users were generally worried about the consequences of not following dietary restrictions properly and perceived dietary restrictions as burdensome. Two patients indicated they experienced mild depression and felt weaker due to decreased vegetable intake. This in turn motivated them to switch from VKAs to DOACs.

3.8. Quality of serviced provided and the patient-doctor relationship

Patients made contradictory statements on the quality of the relationship with their physician, although many patients would like to have a more effective relationship with their physician. While some patients had great faith in and respected their doctor's advice, others reported switching doctors due to poor experiences. These poor experiences included treatment failures, poor advice or conflicting advice given by other HCPs, non-approval of consent to switching from VKAs to DOACs, or restrictions in the use of self-monitoring devices. Some patients also reported having more confidence in the competence of their general practitioner compared to that of their cardiologist. Two patients expressed that a trustworthy, involved and supportive relationship is particularly important at the diagnosis stage: *"Feeling involved at a psychological level is essential at the beginning of a treatment. Afterwards, when you've understood the treatment, that's it. You must take the pills and say: very well! I'll see you in a couple of months."*

Across the countries, patients discussed the need for more in-depth, stable and non-conflicting information from their HCPs. One patient: *"Nobody tells us anything. Every one of us you'll ask the same question, we'll all give you a different answer."* There was a general consensus among patients that HCPs were too busy and consultation times were too short to adequately discuss all questions and concerns. Another patient: *"I realised that he just gives me a summary and that's it. He also doesn't explain that much [..]".* As a result of this, some patients felt the need to take responsibility and educate themselves through internet or support groups.

3.9. The importance of social support, habit formation, and reminders

A patients' social environment was identified as having a positive impact on adherence; *"My family asks me if I'm taking my pill"* (reminder), as well as having a negative impact on adherence; *"When you are having lunch with friends or colleagues, you might feel annoyed or ashamed"* (social stigma/taboo) and *"I used to forget it because I am a father of five children. On Sundays they come home, on those days, with all these people around me, I end up forgetting about it"* (distraction).

Personality traits (e.g. careless, secure, or organized), attitudes and motivation to change behavior in order to adhere to therapy plans were often named as factors influencing OAT adherence. During the focus group sessions, two type of patients were identified: patients who reported that preventing AF-related stroke is the main motivator for taking medication as directed, and patients who have experienced side effects, and for whom drug-related side effects have become a major problem.

Many patients acknowledged the need to be efficient and organized in order to be adherent. In some cases, while describing themselves as forgetful and not organized, patients stated that the perceived benefit of therapy overrode their personality traits. For example, one patient said, *"Most people don't want a cerebral bleed because that's fatal. So they have to be disciplined, it's mainly brought about through anxiety [. . .] I wasn't particularly organized as a younger man, but I'm a bit more organized now."*

Almost all patients reported that they developed tactics, habits or use aids to make adherence to their therapy regimen easier. These range from reminders (text alerts, or mobile phone reminder apps), to specific pill locations (visible places; in the bathroom near the toothbrush or on the bedside table or in pill boxes). Patients also mentioned that it helped them to schedule medication intake around daily activities. A number of patients reported having more problems adhering to the medication regimen during the weekend, on holidays, or other times when their schedule is different than usual.

3.10. Out-of-pocket costs

Across countries, patients reported that out-of-pocket costs are not a problem. In most countries, costs are 100% reimbursed or patients only have to pay a small contribution. Patients stated that higher out-of-pocket costs would not be a reason for them to not adhere to therapy plans, but that higher out-of-pocket costs might trigger them to switch therapies. Many patients stressed the influence of income-level on this decision. A patient, *"I can afford it. Imagine a person whose pension is €500-€600 and has to pay almost €100 for this every month"*.

3.11. Medication packaging

According to our patients, medication packaging does not influence adherence, but suitable packaging can improve medication convenience. Packaging should be easy to open, preferably a bottle packaging (or a blister with quantity for a week), the tablet should be large enough to handle, and easy to swallow. Patients also reported that they would be in favor of reminder packaging (a label with the day, date and time to be taken on it) and smaller-dose tablets so that they don't have to cut their tablet anymore. Also, many patients reported that they know elderly patients who experience difficulties opening medication packaging, handling small tablets, or swallowing tablets. There was discussion about the benefit of having a tablet that melts on the tongue and does not have to be swallowed. Some patients were in favor of this melt-in-the-mouth tablet, since it would facilitate intake or they believed it would be better for their stomach. One patient: *"that would be nice because we wouldn't need gastric protectors."* Others had no specific preference, or preferred to swallow tablets whole. There was a general consensus among patients that in case of melting tablets, taste would be an important factor.

4. Discussion and conclusion

4.1. Discussion

The aim of this study was to explore the perceived advantages and disadvantages of VKAs and DOACs, and the trade-offs patients make in choosing a therapy and being adherent to their drug regimens. When patients were asked what helps or motivates them to take their drugs as directed, most patients reported a mixture of factors. Patients' own beliefs and fears; the provision of univocal and adequate information; and external reminders and routines, were most often named as factors positively impacting OAT adherence. Lack of knowledge; a poor patient-doctor relationship; distraction due to employment or social environment; prior bleeding event(s) or the fear of bleeding; and changes in routine, were most often cited as factors negatively impacting adherence. Major incentives for patients to switch from VKAs to DOACs were dietary restrictions or food-drug interactions, regular INR monitoring, fluctuating INR-values, and side effects.

Our findings are supported by the literature and show that patients suffering from AF seem to prefer easy-to-administer

therapies. Once-daily dosing is preferred over twice-daily intake, a finding previously demonstrated by Böttger et al. [22]. Furthermore, Elewa et al. found that dietary freedom was the major incentive of over half (52%) of patients to switch from VKAs to DOACs [23] and according to several studies INR monitoring is the key difficulty for patients taking VKAs [24–33]. Moreover, up to 55% of VKA users are adversely affected by INR fluctuations [26,28,29,31,34–38], and this makes it more difficult to develop habit and routines.

Our study supports the importance of social support and the use of reminders. Many patients stressed the importance of habits and routine to consistently remind them to take their medication. This is in line with previous research, which demonstrated that being married or living with someone else was associated with better medication adherence [39]. In addition, some patients indicated that due to their working schedule they struggled to take their medication as prescribed. This is in agreement with previous studies, which found that active employment can lead to poor adherence [40–42].

Another barrier to OAT adherence was patients' inadequate understanding of the need to take their medication in terms of risks-benefits, and conflicting instructions they receive from various HCPs. A prime example in this study was that patients were unaware of the fact that there are reversal strategies available to reverse the anticoagulant effect in emergencies (accidents, urgent surgery), for all OACs, and not only for the OACs that have a specific antidote available. One potential solution is to train doctors to explain and educate patients with information and offer them continued support, and, whenever necessary, to refer them to patient organizations and support groups [43]. Studies have shown that the odds of patients' adherence to therapy plans can be more than two times higher if a doctor communicates effectively [44]. Through effective communication, patients are informed about their illness, and the risks and benefits of their therapy [6], and encouraged and supported in their motivation to change behavior in order to follow therapy regimes [45].

This study contributes to the scant published literature on factors affecting medication adherence and specifically focuses on the patient's perspective. However, the focus group methodology has its limitations. First, although the recruitment process in this study can be criticized because we included a limited number of patients through convenience sampling (selection bias), we did rely on a process of open, semi-structured and structured interview questions. Second, topics can be dictated and dominated by the group members as well as by the moderator. Therefore we chose to describe the phenomena observed, and not report the frequency of comments, because it can be that frequency is a result of dominant focus group members or topic selection by the moderator. Finally, although focus groups best fitted the purpose of our study, the presence of other patients in the focus group might have influenced patients' answers, prompting them to answer in what they regard as a socially desirable manner [46,47].

4.2. Conclusion

This study shows that the practical aspects of managing OAT, particularly the way in which these therapies interfere with daily life, have a major impact on the perceived advantages and disadvantages of OACs and adherence to these drugs. In contrast, convenience aspects of OAT, such as regular INR-monitoring, diet restrictions, and dose adjustments, do impact the value of therapy and can motivate patients to change from VKAs to DOACs, but are not perceived as factors impacting OAT adherence. In considering these findings, it can be seen that DOACs may overcome inconveniences of VKAs, such as frequent dose adjustment, dietary considerations, and routine INR-monitoring. However, patients' needs and preferences for OAT

vary: one patient may prefer a once-daily pill-intake and the feeling of assurance that INR monitoring provides, while others prefer twice-daily pill-intake and no INR monitoring.

4.3. Practice implications

In conclusion, the results of this study indicate that there is no “one-size-fits-all” therapy and that optimal medication-taking behavior can only be achieved if therapies are tailored to patients’ needs and preferences. Patients suffering from AF benefit from a shared-decision making (SDM) approach, given the number of available OACs, the availability of risk calculators and tools, and the importance of patient values and preferences [48,49]. SDM implies that clinicians actively engage with patients as partners in making complex treatment decisions and this strengthens a good patient-clinician relationship [50]. Decision aids may help the clinician to educate patients on the benefits and risks of OAT, and assist the process of integrating patients’ preferences into this decision [51,52].

Author contributions

All authors contributed substantially to the design of the work; the acquisition, interpretation of data, and were involved with drafting or revising the manuscript for important intellectual content. Melissa C.W. Vaanholt and Marieke G.M. Weernink searched the literature and were involved in the data collection, entry, and analysis. Melissa C.W. Vaanholt wrote the first draft of the manuscript. All authors approved the final version. As principal investigator, Melissa C.W. Vaanholt has full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. She is the guarantor.

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Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. I confirm all patient/personal identifiers have been removed or disguised so the patient/person(s) described are not identifiable and cannot be identified through details of the story.

Conflict of interest

All authors have indicated they have no conflicts of interest to disclose.

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