

Mechanical heart valve patients can manage oral anticoagulant therapy themselves[☆]

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Abstract

Objectives: Thromboembolism and anticoagulant related bleeding are still the most common complications in mechanical heart valve patients. Management of the oral anticoagulant therapy is therefore a key determinant for these clinical complications. We hypothesize that patients selected to self-managed oral anticoagulant therapy have a better treatment quality than patients in conventional oral anticoagulant therapy. The aim of this study was to assess the time within the therapeutic International Normalized Ratio (INR) target range and the incidence of clinical complications in our group of patients, and compare these data with published data on conventional management. **Methods:** Mechanical heart valve patients ($N = 94$) with a mean age of 47.6 years (range 4.2–76.6 years) were trained in home blood analysis of INR using a CoaguChek[®] home coagulometer and coumarin dosage adjustment. After training, the patients were followed by weekly INR measurements. The therapeutic range was a target INR ± 0.5 . The indications for initiating oral anticoagulant therapy were: aortic valve ($N = 62$), mitral valve ($N = 29$), tricuspid valve ($N = 1$) and multiple valves ($N = 2$). **Results:** The mean observation time was 2.1 years (range 0.04–6.2 years), and the total number of patient-years was 197. The patients were within the therapeutic INR target range for a median of 76.0% (range 32.1–100.0%) of the time. There were two major thromboembolic events and five major bleedings events, comprised of two deep vein thromboses (both in the same patient), four episodes of epistaxis and one case of gastrointestinal bleeding. All the events required short hospitalization, and after treatment all the patients were discharged from the hospital without any sequelae or other complications. Using published work as references the expected number of major thromboembolic and bleeding complications in conventional management was four and 12, respectively. **Conclusions:** Self-management of oral anticoagulant therapy provides a good treatment quality for mechanical heart valve patients. We therefore consider self-management of oral anticoagulant therapy as an equally as good or potentially better treatment option for selected patients compared to conventional management.

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1. Introduction

Today, replacement of a diseased heart valve with a mechanical prosthesis is a routine procedure with a low perioperative morbidity and mortality. However, the potential risk of thromboembolism postoperatively is still a major concern for mechanical heart valve patients [1]. In order to

minimize this risk, patients receive lifelong oral anticoagulant therapy (OAT) with vitamin-K antagonist (VKA). As this treatment constitutes a delicate balance between two serious complications – thromboembolism due to underdosing and bleeding due to overdosing – tight control of the intensity of anticoagulation is mandatory. This is conventionally accomplished by laboratory analysis of the International Normalized Ratio (INR) on plasma obtained by venipuncture, and the patient's family doctor or the hospital doctor decides the dosage of VKA based on the INR. In spite of this controlled therapy thromboembolism and bleeding complications account for approximately 75% of all the postoperative complications observed in mechanical heart valve patients [2]. Therefore, even a small

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Table 1
Published studies regarding SM of OAT^a

Reference	Design	Follow-up (months)	Indication for OAT	OAT medication	Patients (SM/control)	INR interval	Managing OAT in control group	INR measured (SM/control)	TTI (%) (SM/control)	Complications ^b (SM/control)
Cromheecke et al. [3]	PR, CO	6	All indications	Aceno, Phenpro	25/25	Target ± 0.5	HSAC	Lab/Lab	55.0/49.0 ^c	0/0 (number)
Horstkotte et al. [4]	PR	18	MV	NA	75/75	3.0–4.5	GP	Coag/Lab	92.4/58.8	5.4/14.5 (%)
Körtke and Körfer [2]	PR	24	MV	NA	305/295	2.5–4.5	GP	Coag/Lab	79.0/62.0	2.9/4.7 (%)
Sawicki [5]	PR	6	All indications	Phenpro	83/82	2.0–3.0, 3.0–4.0, 3.0–4.5 and 2.5–3.5	GP, HOC	Coag/Lab	53.0/43.2	1/3 (number)
Watzke et al. [6]	PR	12	All indications	Phenpro	49/53	2.0–3.0, 2.5–4.5	HSAC	Coag/Lab	82.2/68.9; 86.2/80.1	2/0 (number)
White et al. [7]	PR	2 ^d	All indications	Warf	23/23	NA ^e	HSAC	Coag/Lab	93.0/75.0 ^c	None
Ansell et al. [8]	Pro	11 ^d	All indications	Warf	16/none	NA	–	Coag/–	NA	NA
Ansell et al. [9]	CC	42.5 ^d	All indications	Warf	20/20	1.6–2.8, 2.25–4.0	HOC	Coag/Lab	88.6/68.0	3/1
Christensen et al. [11]	CC	39 ^d	MV	Phenpro, Warf	24/24	2.0–3.0	HOC	Coag/Lab	78.0/61.0	0/1
Christensen et al. [10]	Pro	18 ^d	Only children	Phenpro, Warf	14/none	2.0–3.0, 2.5–3.5	–	Coag/–	65.5/–	None
Cosmi et al. [12]	CC	6 ^d	All indications	Aceno, Warf	78/78	2.0–3.5, 2.5–4.5	HSAC	Coag/Lab	80.0/80.5	None
Hasenkam et al. [13]	CC	24 ^d	MV	Phenpro, Warf	20/20	2.0–3.0	HOC	Coag/Lab	77.0/53.0	0/1
Heidinger et al. [14]	Pro	> 3	AF, DVT	NA	1375/none	2.0–3.0	–	Coag/–	69.3/–	2.7/– (%)
Stigendal and Andre [15]	Pro	3 ^d	All indications	NA	9/none	NA	–	Coag/–	71.0/–	None
Sunderji et al. [16]	Pro	3 ^d	MV, AF	Warf	8/none	2.0–3.0, 2.5–3.5	–	Coag/–	76.5/–	None

^a The blank row in the table separates the prospective, randomized studies from the other conducted studies. TTI, time within the therapeutic INR target range; PR, prospective, randomized study; CO, cross-over study; Pro, prospective, descriptive study, no controls included; CC, case-control, retrospective controls; MV, mechanical heart valve patients; AF, atrial fibrillation; DVT, deep vein thrombosis; Aceno, acenocoumarol; Phenpro, phenprocoumon; Warf, warfarin; NA, not available; GP, general practitioner; HOC, hospital outpatient clinics; HSAC, highly specialized anticoagulation clinics; Coag, coagulometer; Lab, laboratory.

^b Major thromboembolic and bleedings events added.

^c Within a range of ± 0.5 from the therapeutic target INR.

^d Follow-up time is expressed as the mean.

^e Measured in prothrombin time (PT); target range defined as PT ± 0.3 .

improvement concerning OAT would have a major impact on the clinical performance of these patients, and the morbidity and mortality would therefore be significantly lowered. Several approaches can be applied to accomplish this, and optimized management of OAT is one way of improving the quality of OAT.

Today, there are different methods of managing/performing OAT: routine care, hospital outpatient clinics, specialized anticoagulation clinics, computer generated dosaging, patient self-testing (ST) and self-management (SM). SM implies self-analysis of a drop of blood obtained by finger stick using a portable coagulometer and based on the displayed INR value, the patient decides the dosage adjustment of the VKA himself or herself. ST merely implies that the patient performs blood sampling and analysis while a health care provider decides on dosage adjustment. An overview of the conducted and published studies regarding SM is shown in Table 1. Until now, there have been six prospective, randomized studies [2–7] and nine other studies (case-control and prospective, descriptive studies) [8–16]. In these studies it has been shown that SM for selected patients provides at least as good and most likely better quality of OAT than conventional/standard management (including routine care and hospital outpatient clinics) and management by highly specialized anticoagulation clinics. Furthermore, the patient satisfaction and quality of life have been reported to be significantly better by SM than conventional management (e.g. Ref. [3]). Thirteen of these 15 studies have included mechanical heart valve patients, and four were exclusively focused on this subset of patients. Except for one study [2], the number of included patients has been relatively limited. Therefore, it has been difficult to draw any conclusions regarding the clinical endpoints (bleeding and thromboembolic complications). Surrogate endpoints, namely time within the therapeutic INR target range, have therefore primarily been used to assess the quality of the OAT treatment. In order to improve the clinical outcome for mechanical heart valve patients, we postulate that improved OAT management is a key factor. Therefore, we hypothesize that patients selected to self-managed OAT have a better treatment quality than patients in conventional OAT. The aim of this study was to assess the time within the therapeutic INR target range and the incidence of clinical complications in our group of patients, and compare these data with published data on conventional management.

2. Materials and methods

2.1. Study population

The study population consisted of 94 patients (61 male and 33 female), who had mechanical heart valve replacement performed and who fulfilled the criteria for SM.

2.1.1. Inclusion criteria

- Long-term indication of OAT.
- Interest in SM of OAT and an anticipated high level of compliance as judged from interviews with the patient and/or their parents.

2.1.2. Exclusion criteria

- Coagulopathies.
- Hepatic disorders.
- Addiction to drugs and alcohol.

In our database comprising all our patients conducting SM, the patients with mechanical heart valves were therefore identified and included. Patient demographics are given in Table 2.

The first 24 adults and ten children were study patients in different studies with a shorter follow-up and a different design than this study [10,11,13]. The protocol for conducting these initial studies complied with the Helsinki II Declaration and was approved by the local scientific ethical committee. The patients (and their parents for patients under the age of 18 years) were included after oral and written consent. After these initial studies, SM was a general treatment offered to all suitable referred patients. Therefore, according to Danish law, consent from the patients in order to review these data was not required.

The therapeutic range was a target INR ± 0.5 . The therapeutic INR target range was 2.0–3.0 for aortic and tricuspid valves and 2.5–3.5 for mitral and multiple valves. The oral anticoagulant drugs used were phenprocoumon (Marcoumar[®]) or warfarin (Marevan[®]).

Table 2
Patient demographics^a

Variable	
Number of patients	94
Gender	
Male	61
Female	33
Age in years (mean and range)	47.6 (4.2–76.6)
Valve position	
Aortic	62
Mitral	29
Tricuspid	1
Multiple	2
Valve type	
BS	1
CM	10
MH	1
SJM	84
Therapeutic INR target range	Target INR ± 0.5

^a There are a total number of 96 valves in 94 patients, since two had multiple valve replacement. BS, Björk–Shiley valve; CM, CarboMedics valve; MH, Medtronic Hall valve; SJM, St. Jude Medical valve.

2.2. Study design

This is a prospective, descriptive study of clinical data on mechanical heart valve patients conducting SM. All the patients were trained and monitored by the Center for Self-Managed Oral Anticoagulation, Skejby Sygehus, Aarhus University Hospital, Denmark.

2.3. INR analysis methods and INR values

Patients used the CoaguChek[®] coagulometer (Roche Diagnostics, Switzerland) and CoaguChek[®] PT-test strips. A finger puncture device (Softclix[®]) was used to release a drop (10–25 µl) of capillary whole blood, which was applied on the test strip, and inserted into the coagulometer. The INR value was displayed after 1–2 min and recorded by the patient in a dedicated data sheet. The working principle and operation of the CoaguChek[®] coagulometer have been described previously [13]. INR was measured once a week.

During the training phase (see below) hospitalized blood sampling analysis was performed at the Department of Clinical Biochemistry, Skejby Sygehus, Aarhus University Hospital or at the hospital laboratory nearest to the patient's home (same laboratory for each patient during the study period). INR was analyzed on plasma obtained by centrifugation of the blood sample obtained from a cubital venipuncture.

The hospital laboratories were all part of the Danish Quality Assurance program, which aims at a uniform level of quality in all participating laboratories.

2.4. Management of OAT

The training program for SM of OAT is shown schematically in Fig. 1. The training took place at our Center for Self-Managed Oral Anticoagulation. The patient commenced training by practicing blood sampling and analysis. The patient then gradually took over the management of the OAT, initially by having approval for suggested VKA dosage and subsequently by taking over the dosage adjustment followed by monitoring. After 27 weeks the patients had to display their skills through a

multiple choice performance test. The hospitalized INR analyses were terminated upon passing this test, and the patient was considered self-managing. Weekly home blood analysis was performed throughout the entire study and patients reported their INR values, drug doses and complications on a dedicated INR file to the training center on a 3 monthly basis. During daytime hours the patient could contact the Center for Self-Managed Oral Anticoagulation if she/he had problems or questions regarding the OAT.

Regarding the patients under the age of 18 years, the level of involvement required by the parents was strongly dependent on the age of the patient. The younger the patient, the greater was the involvement required from the parents in conducting SM. It should be emphasized, nonetheless, that independent of the age of the patient, the parents would always be involved to some extent. When we refer to the patient, therefore, this implicitly includes the parental involvement.

2.5. Statistical analysis

All data obtained from the patient's home INR analyses and the hospital counterparts were typed into a database (Microsoft[®] Access). The statistical analyses were performed in a spread sheet (Microsoft[®] Excel) and in SAS[®] statistical software package version 6.12.

The rate of clinical complications per patient-year was calculated using the number of major complications divided by the total number of patient-years obtained in this study. The definition of major clinical complications (thromboembolic and bleeding events) as suggested by Cannegieter et al. [17] was applied. Clinical complications were registered from the day the patients commenced the training in SM. The therapeutic INR target range was assessed using linear interpolation, and it was also used as a parameter for assessment of treatment quality.

The time within the therapeutic INR target range was assessed after the 18th study week; that is, when the patients made dosage adjustment themselves.

Week number	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	
Hospital INR	Weekly		Every 3rd week			Every 4th week			None										
CoaguChek [®] INR	Daily		Weekly																
Anticipated skills	Training		Approval first			Check after			Self-management and report										
Interview	?	?				?					?								
Examination											+								
Self control	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Laboratory control	✓								✓									✓	

Fig. 1. SM of the OAT training program. The patient starts with 3 weeks of daily INR measurements on the CoaguChek[®] coagulometer and with weekly hospital INR measurements. After these 3 weeks of daily training, INR measurements are made weekly and hospital INR measurements are obtained every 3rd or 4th week for another 24 weeks. In this 24 week period co-responsibility for dosage adjustment is gradually transferred from doctor to patient. During the entire period self control analyses and laboratory control of the CoaguChek[®] coagulometer are made every 4th week and 6th month, respectively.

Table 3
Time within therapeutic INR target range and clinical complications

Variable	
Observation time in years (mean and range)	2.1 (0.04–6.2)
Total number of patient-years	197
Within therapeutic INR target range in % (median and range)	
All patients	76.0 (32.1–100.0)
Aortic valve (<i>N</i> = 62)	76.3 (32.4–97.1)
Mitral valve (<i>N</i> = 29)	73.6 (32.4–100.0)
Tricuspid valve (<i>N</i> = 1)	80.6
Multiple valves (<i>N</i> = 2)	58.7 (53.4–64.0)
Number of clinical complications	
Thromboembolism	2
Bleeding	5
Clinical complications rate per patient-year in % and <i>n</i> in parentheses	
Total	3.5 (7)
Tromboembolism	1.0 (2)
Bleeding	2.5 (5)
Type of clinical complications	
Tromboembolism	
Deep vein thrombosis	2
Bleeding	
Epistaxis	4
Gastrointestinal	1

3. Results

The results are shown in Tables 3 and 4. The mean observation time was 2.1 years (range 0.04–6.2 years), and the total number of patient-years was 197. The patients were within the therapeutic INR target range for a median of 76.0% (range 32.1–100.0%) of the time, and the results of the time within the therapeutic INR target range separating the different positions of the mechanical heart valve are also shown in Table 3.

In total, there were seven major clinical complications; two thromboembolic events and five bleedings events. They were comprised of two deep vein thromboses (both in the same patient), four episodes of epistaxis and one case of gastrointestinal bleeding. All the events necessitated short hospitalization, and after treatment all the patients were discharged from the hospital without any sequelae or other complications.

Table 4
Distribution of the number of patients in various therapeutic INR target range intervals (in percent)

Time within therapeutic INR target range (%)	Number of patients
30–40	6
40–50	4
50–60	8
60–70	14
70–80	30
80–90	24
90–100	8

The distribution of the number of patients in various therapeutic INR target range intervals (in percent) is shown in Table 4.

4. Discussion

The number of patients with mechanical heart valves is steadily increasing. After the operation OAT is often their main concern and limitation for conducting a normal life, and the quality of OAT is a major determinant for morbidity and mortality in this group of patients. Several means for improving the quality of OAT have been evaluated: e.g. using INR instead of prothrombin time (PT), using sensitive thromboplastin in the laboratory analysis process, individualized and low therapeutic INR target range, ST and SM. Optimized management of OAT will reduce the number of thromboembolic and bleeding complications significantly [18], and SM is perhaps one of the methods of achieving this in selected patients. The studies listed in Table 1 have concurrently shown that SM entails at least as good and most likely better treatment quality than conventional management. The patient's satisfaction is improved, time within the therapeutic INR target range is higher and the number of clinical complications seems to be lowered.

The optimum way of assessing the treatment quality is to register the number of clinical complications. However, such studies require a large number of patients in order to provide a clear outcome. Several studies have clearly demonstrated that the number of complications is paralleled with the time patients spend outside the therapeutic INR target range [19], and it is considered reasonable to use time within the therapeutic INR target range as a surrogate measure for assessing the quality of treatment.

SM is a relatively new treatment, and additional studies (including prospective, descriptive studies) are obviously needed in order to thoroughly investigate and document the results of this new treatment, especially regarding different indications (e.g. coagulopathies, atrial fibrillation and mechanical heart valve patients) for undertaking SM, preferably including a large number of patients.

The coagulometer used for assessing the INR value must be easy to operate for the patient, be handy, and estimate a precise INR compared to the standard laboratory test (see below). Today, many different coagulometers are on the market. The American Food and Drug Administration (FDA) have approved three of these, and one of these is the CoaguChek[®] coagulometer (Roche Diagnostics, Switzerland) used in the present study. It has been used in many of the conducted studies (e.g. Refs. [2,3,13]), both for ST and SM. The coagulometer has to have a satisfactory precision and accuracy compared with an INR measured in a laboratory using a standardized method. The CoaguChek[®] coagulometer fulfills these requirements with an imprecision for analyses, stated in a coefficient of variation in % (CV%) of approximately

5% [20,21], and on accuracy below ± 0.2 INR [21,22]. It can therefore be concluded that the coagulometer can be reliably used for monitoring INR.

Our study was merely descriptive and prospective and as such has several limitations: most importantly, only a randomized study with a control group will clarify sufficiently whether SM provides a better treatment quality than conventional management. However, we consider our data powerful enough to provide a valid message. Our finding of patients being within the therapeutic INR target range for a median of 76% of the time is in agreement with findings in other studies (Table 1). With patients on standard care, with highly specialized anticoagulation clinics and using computer dosaging, the therapeutic INR target range is approximately 60%, 68% and 63%, respectively [2,4,6,18,23]. Therefore, it seems that SM in selected patients provides a better treatment quality in terms of the therapeutic INR target range than other methods of management. However, it is important to emphasize that it is a treatment which can only be offered to selected and suitable patients (see below).

None of the clinical complications in our study impaired the patient's life after discharge from the hospital. The expected rate of major thromboembolic and bleeding complications is difficult to assess, and thereby it is difficult to give a valid and useful figure, since the incidence of complications depends on various variables, e.g. indication for OAT, definition of major complications, patient age, concomitant diseases and drug use, and history of previous complications [18]. It also seems that patients included in different sets of trials have a lower incidence of complications compared with population-based studies [24]. It is therefore difficult to assess the expected number of complications. However, published data show that the incidence of major thromboembolic and bleeding complications is approximately 2% and 6% per patient-year, respectively, giving a total of 8% of major complications per patient-year [17,18,24,25]. Applying these findings to our group of patients, we should have experienced four major thromboembolic and 12 major bleeding complications. However, this comparison should of course be made with caution, since our SM patients are a selected group, and the study is a prospective, descriptive study. Our data show, however, that in selected patients the incidence of clinical complications seems to be lower than standard management and management by highly specialized anticoagulation clinics. These findings are in agreement with the other conducted studies regarding SM (see Table 1). Furthermore, the low incidence of complications seems to be in agreement with our findings of a relatively long time within the therapeutic INR target range (76%).

The fraction of patients eligible for this treatment is difficult to assess. In the ESCAT study [2] approximately 80% of their heart valve operated patients were considered eligible, while others have estimated the figure to be closer to 20% in a mixed group of patients [15]. Obviously the frac-

tion of eligible patients depends on age, and underlying and concomitant diseases. Our experience is that a large percentage (approximately 70%) of all mechanical heart valve patients are able to perform SM due to the relatively young age and few concomitant diseases in this patient group. Large-scale multi-center studies and/or experience are needed to estimate a more reliable figure.

The reasons why SM patients seem to perform better than conventionally managed patients, both in terms of therapeutic INR target range and regarding the incidence of clinical complications, are probably multifactorial; the patients seem to be generally younger and have fewer concomitant diseases than the bulk of the OAT patients. SM patients can perform more frequent testing than what is practically possible with conventional management, and they have a more detailed knowledge about OAT and the influence of diet, infectious diseases, alcohol, drug interactions, etc. than patients under standard management. The impact of all these factors is evaluated by each patient on a much higher level of detail than is practically feasible for the average health care provider. They are therefore very much aware of the potential complications concerning this treatment. Furthermore, the patients have a high degree of compliance because they are highly motivated, since they do not need to go to the hospital or family doctor for blood specimen and drug dosage adjustment. It therefore reduces their binding to the health care system and allows these patients to travel and manage their job without the interruption which conventional management has on their daily life.

Obviously, additional prospective, randomized studies are needed for elucidation of these questions and for further documentation of SM as a treatment option for patients on OAT.

We consider it pertinent that although patients are labeled 'self-managing', they should be followed and have their quality of OAT monitored carefully by a specialized training and monitoring center.

We conclude that SM of OAT provides a good treatment quality for mechanical heart valve patients. We therefore consider SM of OAT as an equally as good or potentially better treatment option for selected patients than conventional management.

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References

- [1] Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJ, Vandembroucke JP, Briet E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med* 1995;333(1):11–17.
- [2] Körte H, Körfer R. International normalized ratio self-management after mechanical heart valve replacement: is an early start advantageous? *Ann Thorac Surg* 2001;72(1):44–48.
- [3] Cromheecke ME, Levi M, Colly LP, de Mol BJ, Prins MH, Hutten BA, Mak R, Keyzers KC, Buller HR. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. *Lancet* 2000;356(9224):97–102.
- [4] Horstkotte D, Piper C, Schulte HD, Schultheiss HP. Improvement of prognosis by home prothrombin estimation in patients with life-long anticoagulant therapy (abstract). *Eur Heart J* 1996;17(Suppl):230.
- [5] Sawicki PT. A structured teaching and self-management program for patients receiving oral anticoagulation: a randomized controlled trial. Working Group for the Study of Patient Self-Management of Oral Anticoagulation. *J Am Med Assoc* 1999;281(2):145–150.
- [6] Watzke HH, Forberg E, Svolba G, Jimenez-Boj E, Krinninger B. A prospective controlled trial comparing weekly self-testing and self-dosing with the standard management of patients on stable oral anticoagulation. *Thromb Haemost* 2000;83(5):661–665.
- [7] White RH, McCurdy SA, von Marensdorff H, Woodruff Jr. DE, Leftgoff L. Home prothrombin time monitoring after the initiation of warfarin therapy. A randomized, prospective study. *Ann Intern Med* 1989;111(9):730–737.
- [8] Ansell J, Holden A, Knapic N. Patient self-management of oral anticoagulation guided by capillary (fingerstick) whole blood prothrombin times. *Arch Intern Med* 1989;149(11):2509–2511.
- [9] Ansell JE, Patel N, Ostrovsky D, Nozzolillo E, Peterson AM, Fish L. Long-term patient self-management of oral anticoagulation. *Arch Intern Med* 1995;155(20):2185–2189.
- [10] Christensen TD, Attermann J, Hjortdal VE, Maegaard M, Hasenkam JM. Self-management of oral anticoagulation in children with congenital heart disease. *Cardiol Young* 2001;11(3):269–276.
- [11] Christensen TD, Attermann J, Pilegaard HK, Andersen NT, Maegaard M, Hasenkam JM. Self-management of oral anticoagulant therapy for mechanical heart valve patients. *Scand Cardiovasc J* 2001;35(2):107–113.
- [12] Cosmi B, Palareti G, Carpanedo M, Pengo V, Biasiolo A, Rampazzo P, Morstabilini G, Testa S. Assessment of patient capability to self-adjust oral anticoagulant dose: a multicenter study on home use of portable prothrombin time monitor (COAGUCHECK). *Haematologica* 2000;85(8):826–831.
- [13] Hasenkam JM, Kimose HH, Knudsen L, Grønnesby H, Halborg J, Christensen TD, Attermann J. Self management of oral anticoagulant therapy after heart valve replacement. *Eur J Cardiothorac Surg* 1997;11(5):935–942.
- [14] Heidinger KS, Bernardo A, Taborski U, Müller-Berghaus G. Clinical outcome of self-management of oral anticoagulation in patients with atrial fibrillation or deep vein thrombosis. *Thromb Res* 2000;98(4):287–293.
- [15] Stigendal L, Andre U. Workshop: patient self-management: update of ongoing studies in Sweden. *J Thromb Thrombolysis* 1998;5(Suppl 1):63–64.
- [16] Sunderji R, Campbell L, Shalansky K, Fung A, Carter C, Gin K. Outpatient self-management of warfarin therapy: a pilot study. *Pharmacotherapy* 1999;19(6):787–793.
- [17] Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation* 1994;89(2):635–641.
- [18] Ansell JE, Hughes R. Evolving models of warfarin management: anticoagulation clinics, patient self-monitoring, and patient self-management. *Am Heart J* 1996;132(5):1095–1100.
- [19] Samsa GP, Matchar DB. Relationship between test frequency and outcomes of anticoagulation: a literature review and commentary with implications for the design of randomized trials of patient self-management. *J Thromb Thrombolysis* 2000;9(3):283–292.
- [20] Attermann J, Kynde K, Hasenkam JM. Precision of patients' measurements of the international normalized ratio (INR) using a patient operated whole blood home coagulometer. *Thromb Res* 1998;92(6):287–291.
- [21] Van den Besselaar AM. Accuracy, precision, and quality control for point-of-care testing of oral anticoagulation. *J Thromb Thrombolysis* 2001;12(1):35–40.
- [22] Van den Besselaar AM. A comparison of INRs determined with a whole blood prothrombin time device and two international reference preparations for thromboplastin. *Thromb Haemost* 2000;84(3):410–412.
- [23] Poller L, Shiach CR, MacCallum PK, Johansen AM, Munster AM, Magalhaes A, Jespersen J. Multicentre randomised study of computerised anticoagulant dosage. European Concerted Action on Anticoagulation. *Lancet* 1998;352(9139):1505–1509.
- [24] Steffensen FH, Kristensen K, Ejlersen E, Dahlerup JF, Sørensen HT. Major haemorrhagic complications during oral anticoagulant therapy in a Danish population-based cohort. *J Intern Med* 1997;242(6):497–503.
- [25] Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. *Am J Med* 1993;95(3):315–328.

Appendix A. Conference discussion

Dr P. Sergeant (Leuven, Belgium): I am very well aware of the high quality of the medical care and the surrounding care in Denmark. A very similar issue is happening in the Netherlands where the environment for the patient is a nearly optimal environment. You have not expanded in your presentation on the quality of that environment of the support the patients are having on the one side. This is the first part of my question. And my second part would be, are you sure that you can repeat this same experience in countries where the environments surrounding the patients are totally different than the high quality of Denmark?

Dr Christensen: To answer the first question, I would say that self-management consists of many factors, such as the intervals of self-testing and the knowledge of the patient and the training of the patient. So, of course, there are multiple factors.

Dr Sergeant: What kind of support are the patients getting? Are they getting support from their family practice physician, have they been called up to see how much systematic they are placing in their control?

Dr Christensen: With regard to the patient and self-management?

Dr Sergeant: Yes.

Dr Christensen: We have a training center and a center which the patients are affiliated to, and they can always call in the daytime; they can always call the center.

Dr Sergeant: And does the center call the patients at random?

Dr Christensen: No. The patient has to send in a file every 3 months.

And to take the last question you asked regarding, for example, other countries where the system is not so well functioning, you can have a system where you could have a doctor having an apparatus and that patient could make self-testing, or some patients could make self-testing and then call in the doctor, who could then prescribe the dosage of the medication.

Dr Sergeant: Because Denmark is one of the few countries where the patients are registered with the family practice physician. In many countries a patient is not even linked to one particular family practice physician, and that might totally change the environment of safety that is surrounding this practice.

Dr Christensen: Agree.