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ORIGINAL ARTICLE

Dynamics of vitamin K antagonist and new oral anticoagulants use in atrial fibrillation: a Danish drug utilization study

A. POTTEGÅRD,*† B. K. POULSEN,‡ M. D. LARSEN§ and J. HALLAS*†

Clinical Pharmacology, Institute of Public Health, University of Southern Denmark; †Department of Clinical Chemistry & Pharmacology, Odense University Hospital, Odense; ‡Department of Clinical Pharmacology, University Hospital of Aarhus, Aarhus; and §Clinical Epidemiology, Odense University Hospital, Odense, Denmark

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Summary. *Background:* Detailed data on real-life utilization of vitamin K antagonists (VKAs) and new oral anticoagulants (NOACs) in atrial fibrillation are sparse. *Objectives:* To describe the dynamics of VKA and NOAC use: that is, (i) how patients moved in and out of, as well as between, use of VKAs and NOACs; (ii) how patients adhered to treatment; and (iii) which type of prescriber initiated, maintained, and changed treatment with VKAs and NOACs. *Methods:* We conducted a drug utilization study in the region of southern Denmark (population 1.2 million) using prescription data. We included all subjects using VKAs or NOACs during the period of August 22, 2011, through June 30, 2013, restricted to subjects with a diagnosis of atrial fibrillation. *Results:* We identified 20 911 subjects, of whom 20 769 and 1639 used VKAs and NOACs, respectively. The number of VKA users was stable at ~ 14 000 subjects during the study period, whereas the number of NOAC users increased to 903. The majority of NOAC users had previously used VKAs (n = 974), whereas 389 anticoagulant-naïve users initiated NOAC therapy. Among the latter, 51.2% had changed to VKAs within 6 months. 57.3% of VKA users were initiated by a hospital physician, whereas maintenance treatment was predominantly handled by the patient's general practitioner (97.6%). Switches from NOAC to VKA were initiated by a general practitioner in 69.2% of the cases. For users of NOACs, these numbers were 73.5%, 94.0%, and 63.3%. *Conclusions:* A large proportion of NOAC users switch to a VKA within a short time frame. The reasons for this are not clear.

Correspondence: Anton Pottegård, Clinical Pharmacology, University of Southern Denmark, JB Winsløwsvej 19, 2, 5000 Odense C, Denmark.
Tel.: +45 2891 3340.
E-mail: apottegaard@health.sdu.dk

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Introduction

Vitamin K antagonists (VKAs) have traditionally been the drug of choice for the prevention of cerebral embolisms in patients with atrial fibrillation [1]. However, new oral anticoagulants (NOACs) have recently been introduced, led by the direct thrombin inhibitor dabigatran etexilate, which in the RE-LY study showed comparable efficacy and safety with warfarin [2]. Dabigatran etexilate was the first NOAC to be approved for stroke prophylaxis in atrial fibrillation (October 2010 in the United States and August 2011 in the European Union), quickly followed by the two factor Xa inhibitors rivaroxaban (2012) and apixaban (2012) [3,4]. NOACs are now recommended as first-line anticoagulant treatment in atrial fibrillation by the American College of Chest Physicians [5] and the European Society of Cardiology [6]. However, some national guidelines (e.g. in Denmark and Sweden) regard high-standard treatment with VKAs (time in therapeutic interval ≥ 70%) to be both as effective and as safe as treatment with NOACs. While the uptake of NOACs is monitored closely (e.g. by the Danish Health and Medicines Authority) [7], there remain several unanswered questions with regard to the use of these new drugs. For example, knowledge is lacking on which physicians choose NOACs over VKAs in patients with atrial fibrillation and when, and by whom, users of VKAs are changed to NOACs or from NOACs to VKAs. Knowledge of these utilization parameters is necessary to identify potential problems and to promote the optimal and rational use of this new therapeutic option.

We aimed at describing the use of VKAs and NOACs by using data from Danish drug and patient registries. Specifically, we investigated (i) how patients moved in and out of, as well as between, use of VKAs and NOACs, respectively; (ii) how long patients adhered to treatment (i.e. continued to fill prescriptions); and (iii) what type of prescriber initiated, maintained, and changed treatment with VKAs and NOACs.

Method

The study was a descriptive drug utilization study. In the period where both drug classes were available against atrial fibrillation (August 2011–June 2013), we identified the cohorts of VKA and NOAC users who had a diagnosis of atrial fibrillation.

Data sources

Data were extracted from the Odense University Pharmacoepidemiological Database (OPED) and the Danish National Patient Registry. OPED [8] is a research prescription database that contains information on redeemed, reimbursed prescriptions. OPED has covered the Region of Southern Denmark (population 1.2 million) since 2007. Among the data included are identification of the individual patient, a full account of the dispensed product, and the date of dispensing. The indication and dose instruction are not recorded. The product is classified according to the hierarchical anatomical-therapeutic-chemical (ATC) code developed by the World Health Organization for drug utilization studies [9]. The OPED also contains a demographic module with information on residency, migration, births, and deaths.

The Danish National Patient Registry contains data on all non-psychiatric hospital admissions in Denmark since 1977 and outpatient contacts since 1995. Discharge/contact diagnoses have been coded according to the *International Classification of Diseases, 10th Edition* since 1994 [10].

Data sources were linked by use of the personal identification number, a unique identifier assigned to all Danish citizens since 1968 that encodes sex and date of birth [11].

Data material

We included all subjects having redeemed a prescription for either a VKA or an NOAC according to OPED during the study period of August 22, 2011, through June 30, 2013. For these subjects, we collected all available information in OPED and the Patient Registry. The VKAs that were included were warfarin (ATC, B01AA03) and phenprocoumon (B01AA04), and the NOACs that were included were dabigatran etexilate (B01AE07), rivaroxaban (B01AX06, B01AF01), and apixaban (B01AF02).

We restricted the material to patients who were taking to treat atrial fibrillation. This was achieved by excluding everyone with a history of venous thromboembolic disease (ICD10: I80–I82) or artificial heart valve replacement (ICD10: Z95.2) according to the Patient Registry and requiring each subject to either have a diagnosis of atrial fibrillation (ICD10: I48.9) in the Patient Registry or have redeemed a prescription for either digoxin (ATC: C01AA05) or verapamil (ATC: C08DA01) in OPED. These criteria should be met by the time of each subject's first VKA or NOAC prescription within the study period. Furthermore, users of NOAC were excluded if they had undergone alloplastic hip or knee replacement < 1 month before the first dispensing of an NOAC according to the Patient Registry. Last, we excluded subjects who were not continuously enrolled in OPED (due to migrations) from August 22, 2009 (i.e. 2 years before the start of the study period and up to the date of that subjects' first VKA or NOAC prescription within the study period).

Cohorts and analysis

We identified two cohorts consisting of users of VKAs and NOACs, respectively. Subjects were considered users at the start of the study if they had redeemed a prescription for either a VKA or an NOAC within 180 days before the start of the study period. Users were allowed to switch cohort, contributing follow-up to one cohort until the date of redeeming a prescription that included them in the other cohort. Users were censored on treatment discontinuation, defined as the date on which 180 days had passed without having redeemed a new prescription. Furthermore, users were censored on death or migration. The flow of subjects to, from, and between the cohort of VKA users and NOAC users was described. This included individuals changing from non-use to use of either drug class, subjects ceasing treatment, those changing from VKA to NOAC or vice versa, and those changing both back and forth within the study period. Event rates (e.g. of switches from one cohort to the other), were expressed as an incidence rate (i.e. 'percent per person-year'). For a graphic representation of the cohorts and flow of subjects, see Fig. 1.

For each cohort, we produced a Kaplan–Meier plot for 'drug survival' (i.e. the proportion of patients still being treated after a given number of days). In this analysis, we only included patients having initiated treatment after the study start. Discontinuation was defined as given earlier or when the subject filled a prescription for the other drug class. Subjects were censored on death, migration, and the end of the study period (June 30, 2013).

We further described which type of physician initiated, maintained, and changed treatment within each of the two cohorts. Prescriptions were divided into three categories: 'new use' (prescriptions that marked the entry of a new user into the cohort); 'maintenance treatment'

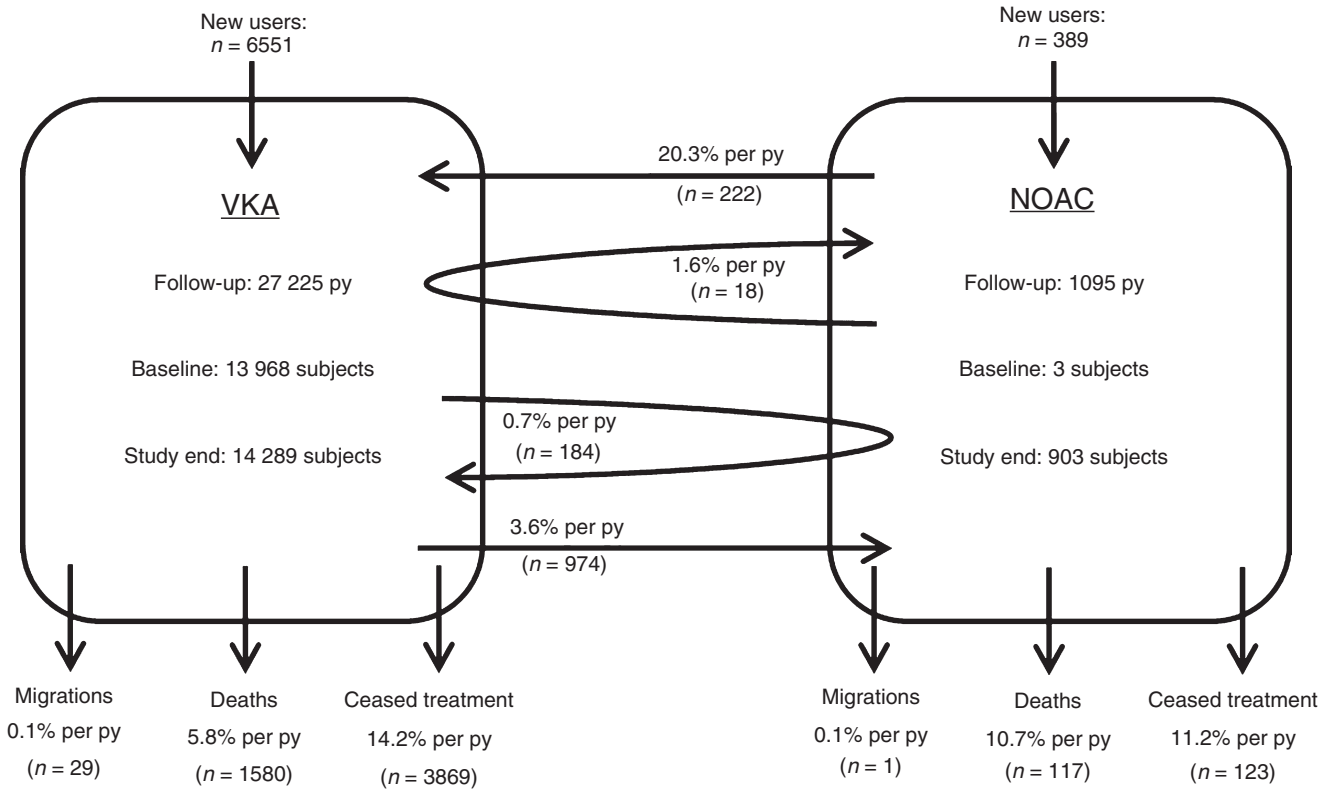

Fig. 1. The flow of subjects to, from, and between the cohorts of VKA users and NOAC users. Baseline was August 22, 2011, and study end was June 30, 2013. VKA, vitamin K antagonist; NOAC, newer oral anticoagulant; py, person-years.

(continued treatment within the same cohort); and prescriptions that marked switch to the other cohort. For each of the three groups, we estimated the total number of prescriptions and the proportion of the prescriptions that had been issued by the different type of physicians (general practitioner [GP], hospital, or unknown).

Other

All calculations were performed using STATA Release 13.0 (StataCorp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency. According to Danish law, ethical approval is not required for purely registry-based studies [12].

Results

We identified 28 603 unique subjects using either VKAs (25 366 subjects) or NOACs (4863 subjects) during the study period. We excluded 3079 users of NOACs who had undergone recent knee or hip surgery, 3591 subjects who did not qualify as having atrial fibrillation, and 1019 subjects with recent migrations. Last, we excluded three subjects filling both VKA and NOAC prescriptions on the date of their first prescription. The proportion of individuals who were classified as having atrial fibrillation based on prescription data only was 5.6%. The final cohorts consisted of 20 911 unique subjects; 20 769 and 1639 filled one or more prescription for VKAs and NOACs, respectively. During the study period, these subjects filled a total of 153 551 prescriptions for VKAs (150 250 for warfarin and 3301 for phenprocoumon) and 10 523 prescriptions for NOACs (9765 for dabigatran, 699 for rivaroxaban, and 59 for apixaban). Two of the 699 prescriptions for rivaroxaban were filled before the drug was registered for use in atrial fibrillation, while this was not the case for any of the prescriptions for apixaban.

Figure 1 describes the flow to, from, and between the cohorts of VKA users and NOAC users. While the size of the cohort of VKA users was stable at ~ 14 000 subjects during the study period, the cohort of NOAC users increased from 3 to 903 subjects. Also, 20.3% of patients in the NOAC cohort changed to a VKA per person-year.

Among incident users of VKAs during the study period, the median age was 73 years (interquartile range 64–80) and 56.4% were male. For incident users of NOACs, these values were 71 (65–80) and 57.8%. Last, the values for users switching from VKAs to NOACs were 75 (68–82) and 54.2%.

The duration of treatment among those initiating anticoagulant treatment for the first time within the study period is shown in Fig. 2. We observed a markedly higher proportion of users of NOACs with early discontinuation of treatment. After 6 months, 377 of the new users of NOACs were still eligible for follow-up, of whom 51.2% (n = 193) had changed to VKAs. The corresponding

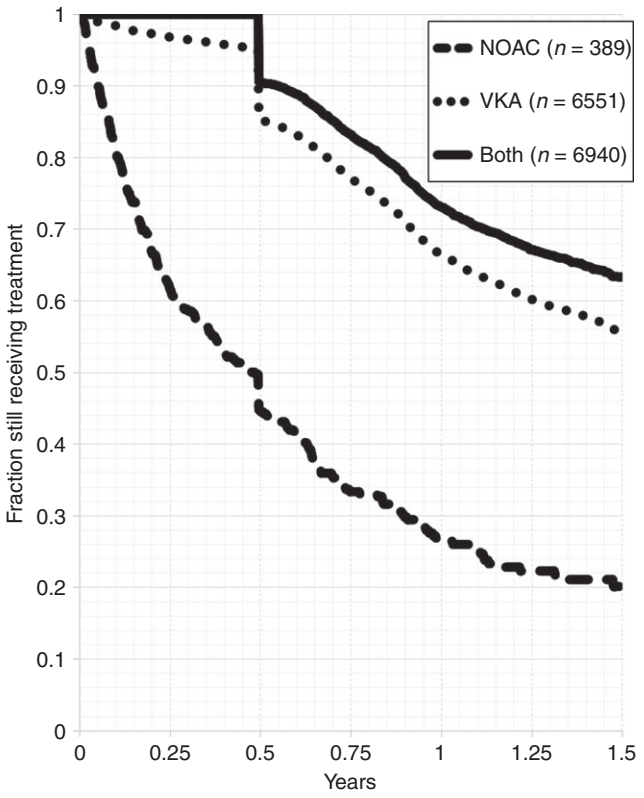

Fig. 2. Kaplan–Meier plot of drug survival among incident users of VKAs or NOACs within the study period (August 22, 2011, through June 30, 2013). Treatment was considered stopped when a subject filled a prescription for the opposite drug group or when 180 days had passed without filling a prescription. VKA, vitamin K antagonist; NOAC, newer oral anticoagulant.

proportion of VKA users that had changed to NOACs within 6 months was 4.5% (279 of 6227).

Table 1 shows the type of prescriber issuing the prescription that marked new use, prevalent use (maintenance treatment), or switching from VKA to NOAC or vice versa. While hospital prescribers were responsible for the initiation of 57.3% and 73.5% of all new VKA users and NOAC users, respectively, GPs were almost exclusively responsible for maintenance treatment (97.6% and 94.0%). Change from one drug class to the other was most often initiated by the GP (63.3% from VKAs to NOACs and 69.2% from NOACs to VKAs).

We performed supplementary analyses of the group of 'early switchers' who switched from NOAC to VKA within 6 months of their first prescription ($n = 193$). Compared to all incident NOAC-users ($n = 389$), the early switchers were similar with regard to age (median age 70 vs. 71) and sex (males 61% vs. 58%). In 32.6% of cases, the switch was carried out by a prescriber other than the one who had initiated the therapy. When only considering the type of prescriber (e.g. GP and hospital) and not the individual prescriber, this figure dropped to 22.5%. The distribution of types of prescribers for the first prescription and the prescription marking the switch to VKA were comparable to the overall distribution seen in Table 1. Further, to assess whether potential drug–drug interactions contributed to early switching, we estimated the proportion of subjects filling a drug known to interact with NOACs [13] within 6 months before and up to 1 month after treatment cessation. This was the case in 2% ($n = 3$) filling prescriptions for clarithromycin ($n = 2$) and carbamazepine ($n = 1$). Last, a supplementary analysis comparing treatment persistence among anticoagulant-naïve NOAC users ($n = 389$) to that of NOAC users who previously used VKAs ($n = 1158$) showed that previous use of VKA predicted markedly better drug persistence (70.1% vs. 26.8% after 1 year, data not shown in full).

Discussion

This study is among the first to provide detailed information from clinical practice on the dynamics of VKA and

Table 1 Distribution between type of prescriber for filled prescriptions marking new use, prevalent use (maintenance treatment), or switching from the other group

			Prescriber		
Drug	Type of prescription*	Prescriptions	GP	Hospital	Unknown
VKA	New use	6551	41.5% ($n = 2720$)	57.3% ($n = 3752$)	1.2% ($n = 79$)
	Switch from NOAC	497	69.2% ($n = 344$)	29.8% ($n = 148$)	1.0% ($n = 5$)
	Prevalent use	146 503	97.6% ($n = 143\ 025$)	2.0% ($n = 2973$)	0.3% ($n = 505$)
NOAC	New use	389	24.2% ($n = 94$)	73.5% ($n = 286$)	2.3% ($n = 9$)
	Switch from VKA	1309	63.3% ($n = 829$)	35.8% ($n = 468$)	0.9% ($n = 12$)
	Prevalent use	8825	94.0% ($n = 8293$)	5.5% ($n = 486$)	0.5% ($n = 46$)

VKA, vitamin K antagonist; NOAC, newer oral anticoagulant; GP, general practitioner. *Definitions are provided in the Methods section. Prescriptions were classified as registered in the OPED prescription database.

NOAC use in atrial fibrillation. We observed a slight increase in the number of patients receiving anticoagulant treatment, that hospital physicians most often initiated patients, and, surprisingly, that half of all patients initiating therapy with NOACs had changed to VKAs within 6 months.

The study findings are based on the early phase of patient care with NOACs in atrial fibrillation. For the same reason, dabigatran is the dominant NOAC in this analysis. Therefore, the results should be interpreted with caution and might not be generalizable to current everyday practice. However, the analyses identified areas that potentially should receive greater attention.

The main strength of our study is that it is based on a data source with full coverage of the VKA and NOAC prescriptions for a geographically defined, stable population. We were able to account for their patients' individual secondary care diagnoses, for their comedications, and for their individual migration and mortality. In addition, the population covered by our data source is representative of the entire Danish population with respect to socioeconomic and health-related parameters [8].

The study also has potential limitations. First, we do not have data on the indication for use. The algorithm applied to identify individuals with atrial fibrillation was not validated. However, it was based on input from cardiologists used to treating patients with atrial fibrillation. A restrictive algorithm was preferred to ensure that those included were likely to have atrial fibrillation. The algorithm does not include those who do not have a registered diagnosis or receive rate-controlling treatment, which we believe is a minor group of patients. Second, we do not have data on renal function, which for some subjects might be the reason for cessation of treatment with NOACs. Last, the validity of data on prescriber type in OPED is currently unknown. This variable is central to the analysis of the types of behavior of different prescribers. For electronic prescriptions, which constitute an increasing proportion of all prescriptions (currently > 50%), the prescriber identifier is expected to be almost perfectly accurate. For nonelectronic prescriptions, the variable is registered manually by the pharmacy staff. As the patient's GP is often registered as the 'preferred prescriber' in the pharmacy dispensing system, there might be some misclassification of prescriptions from other physicians being erroneously registered as being issued by the GP. Furthermore, when the prescriber ID is illegible on the prescriptions, the pharmacy staff might choose to register it as 'unknown prescriber.' This is most often a problem for prescriptions from hospitals and specialists. This might bias the result in that the proportion of prescriptions being attributed to the GP will be overestimated.

The number of patients treated with oral anticoagulants increased from 13 971 to 15 192 during the 2-year study period (Fig. 1). This might be explained by an increased focus on anticoagulant treatment in atrial fibrillation, possibly mediated through the focus that has accompanied the introduction of NOACs, and the possibility of initiating anticoagulant treatment with NOACs among patients who were not considered candidates for VKA treatment.

The large proportion of switchers from NOACs to VKAs within the first 6 months of treatment is surprising, especially considering the practical implications of changing treatment, potentially leaving the patient without sufficient anticoagulant treatment during the switch [14]. We observed that the physician who was responsible for switching from NOACs to VKAs was most often the same physician who initiated NOACs. This suggests that switching is not mainly explained by different physicians' preferences toward NOAC versus VKAs but rather that something new has developed in the patients' profiles, such as an intolerance to NOAC or a change in renal function [13]. We observed that new NOAC users who had previously used VKAs had a markedly better persistence to treatment than did entirely treatment-naïve NOAC users. This should be interpreted cautiously (as we are comparing a first treatment episode to a second) but might infer that the strength of the indication also affects the persistence of NOAC use, thereby assuming that patients who used VKAs before NOACs had a more severe treatment indication. That previous use of VKAs predicts better drug survival among users of NOACs also indicates that side effects are not the only important driving force for the treatment changes among anticoagulant-naïve NOAC users; the presence of side effects is not likely to be affected by prior use of VKA. In the RE-LY study [2], ~ 19% stopped treatment during the trial due to adverse effects [15]. Our data indicate that this might be an even higher proportion in real life. After 1 year, only 26.8% of the patients, who started treatment with an NOAC, were still using this kind of medication. In comparison, this proportion was 66.6% among VKA users. No immediate reason is apparent and because we do not have data on, for example, side effects or renal function, the explanations offered are purely speculative. The patient population underlying these findings consists of the first 389 patients in the region of southern Denmark who were given NOACs as first-line treatment for atrial fibrillation. As such, one explanation for the high proportion of early switching might be lack of experience with these new drugs among the physicians handling the follow-up treatment and the lack of control that usually follows with the frequent visits related to international normalized ratio measurements. Also, some might switch treatment if subsequent measurements of kidney function reveals that treatment with NOACs is contraindicated, as the Danish health authority has repeatedly focused on in warning letters to all Danish physicians [16].

In addition to the patients switching between treatments, there are patients who discontinue NOACs without

switching to VKAs. This can be harmful, as treatment persistence is crucial to achieving the same effects as in the clinical studies. Unfortunately, nonpersistence might even be unnoticed by the treating physician, as patients using NOACs do not require regular international normalized ratio controls. This needs to be taken into account, both when planning clinical controls for these patients and when planning educational efforts toward physicians. The overall rate of treatment cessation (i.e. 14.2% and 11.2% per year for VKAs and NOACs, respectively; Fig. 1) is in accordance with rates observed in trials such as the RE-LY study, where 10% of individuals assigned to VKAs and 15–16% of individuals assigned to dabigatran had ceased treatment within 1 year [17].

This high proportion of incident patients switching treatment from NOACs to VKAs warrants further investigations. The introduction of NOACs as first-line treatment in some guidelines [5,6] will probably affect the organization of thrombosis clinics and GPs' handling of patients in anticoagulant therapy. If our findings can be confirmed in other studies, the high proportion of early switchers needs to considered as a factor in this reorganization.

Addendum

A. Pottegård has carried out all analyses. All authors have contributed to the concept and design of the study. All authors have participated in the interpretation of data and the writing of the manuscript. All authors have approved the final version of the manuscript.

Disclosure of Conflicts of Interests

J. Hallas has received fees for consulting and teaching from Nycomed, the manufacturer of warfarin. J. Hallas has also participated in research projects funded by Nycomed. The remaining authors state that they have no conflicts of interest.

References

1 Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**: 160S–98S.

2 Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener H-C, Joyner CD, Wallentin L, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139–51.

3 ROCKET AF Study Investigators. Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. *Am Heart J* 2010; **159**:340.e1–47.e1.

4 Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, *et al*. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365**: 981–92.

5 You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, Hylek EM, Schulman S, Go AS, Hughes M, Spencer FA, Manning WJ, Halperin JL, Lip GYH. American College of Chest Physicians. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**: e531S–75S.

6 Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; **33**: 2719–47.

7 Danish Health and Medicines Authority. *News about Pradaxa (dabigatran etexilate) and Xarelto (rivaroxaban)*. Danish Health and Medicines Authority (in Danish) https://sundhedsstyrelsen.dk/da/nyheder/2013/~/media/7AEFE599582A4F268E4F757B86D4799E.ashx. Accessed 19 June 2014.

8 Gaist D, Sørensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997; **44**: 445–8.

9 WHO Collaborating Centre for Drug Statistics methodology. *Guidelines for ATC Classification and DDD Assignment 2013*. WHO Collaborating Centre for Drug Statistics methodology, 2012.

10 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; **39**: 30–3.

11 Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; **39**: 22–5.

12 Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011; **39**: 12–6.

13 Poulsen BK, Grove EL, Husted SE. New oral anticoagulants: a review of the literature with particular emphasis on patients with impaired renal function. *Drugs* 2012; **72**: 1739–53.

14 Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P, European Heart Rhythm Association. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013; **15**: 625–51.

15 Department of Health and Human Services, FDA. Questions: Dabigatran [Internet]. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM247244.pdf. Accessed 19 June 2014.

16 Danish Health and Medicines Authority. Pradaxa – consider age and follow dose recommendations [Internet]. http://sundhedsstyrelsen.dk/en/news/2012/pradaxa-consider-age-and-follow-dose-recommendations. Accessed 19 June 2014.

17 U.S. Food and Drug Administration. NDA 22-512 Dabigatran Efficacy Review [Internet]. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm226704.pdf. Accessed 19 June 2014.