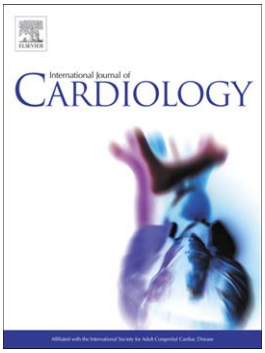

Direct oral anticoagulants in patients with hypertrophic cardiomyopathy and atrial fibrillation

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Direct oral anticoagulants in patients with hypertrophic cardiomyopathy and atrial fibrillation

Short title: Direct oral anticoagulants in HCM and AF

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Conflict of interest

Dr Garcia Pinilla has received speaking fees from Bristol-Myers Squibb (BMS) and Pfizer Inc. and payments for consultancy from Bayer. Dr Garcia-Pavia has received speaking fees and payments for consultancy from Bayer, BMS and Pfizer Inc. BMS and Pfizer Inc. have also provided research support to Dr Dominguez and Garcia-Pavia's institution.

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Abstract:

Background:

Chronic anticoagulation with vitamin K antagonists (VKAs) is recommended in patients with hypertrophic cardiomyopathy (HCM) and atrial fibrillation (AF). Direct oral anticoagulants (NOACs) are an alternative to VKAs but there are limited data to support their use in HCM. We sought to describe the pattern of use, thromboembolic events, bleeding and quality of life in patients with HCM and AF treated with NOACs.

Methods:

Data from patients treated with NOACs (*n*=99) and VKA (*n*=433) at 9 inherited cardiac diseases units were retrospectively collected. Annual rates of embolic events, serious bleeding and death were analysed and compared. Quality of life and treatment satisfaction were evaluated with SF-36 and SAFUCA questionnaires in 80 NOAC-treated and 57 VKA-treated patients.

Results:

After median follow-up of 63 months (IQR:26–109), thromboembolic events (TIA/stroke and peripheral embolism) occurred in 10% of patients on oral anticoagulation. Major/clinically relevant bleeding occurred in 3.8% and the global mortality rate was 23.3%. Thromboembolic event rate was 0.62 per 100 patient-years in the NOAC group vs. 1.59 in the VKA group [subhazard ratio (SHR) 0.32;95%CI:0.04–2.45;p=0.27]. Major/clinically relevant bleeding occurred in 0.62 per 100 person-years in the NOAC group vs. 0.60 in the VKA group (SHR 1.28;95%CI 0.18–9.30;p=0.85).

Quality of life scores were similar in both groups; however, NOAC-treated patients achieved higher scores in the SAFUCA.

Conclusions:

HCM patients with AF on NOACs showed similar embolic and bleeding rates to those on VKA. Although quality of life was similar in both groups, the NOAC group reported higher treatment satisfaction.

Word count: 250

Key words: Hypertrophic cardiomyopathy; atrial fibrillation; anticoagulation.

Abbreviation list:

AF: atrial fibrillation

CVA: cerebrovascular accident

HCM: hypertrophic cardiomyopathy

LA: Left atrium

LVEF: Left ventricular ejection fraction

LVOTO: Left ventricular outflow tract obstruction

MWT: Maximal wall thickness

NOACs: direct oral anticoagulants

NYHA: New York Heart Association

SAFUCA: satisfaction with Medical Care in Patients with Atrial Fibrillation

SAM: Systolic anterior movement

SHR: subhazard ratio

TIA: transient ischaemic attack

VKA: vitamin K antagonists

VT: Ventricular tachycardia.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most common hereditary heart disease, and is the most frequent cause of sudden death among the young[1].

Atrial fibrillation (AF) is the most common arrhythmia of patients with HCM. HCM patients who develop AF have a very high risk of thromboembolic complications and approximately 27% of them will have an embolic event during their lifetime[2]. Given the high incidence of stroke in patients with HCM and AF, clinical practice guidelines recommend that they should be anticoagulated with vitamin K antagonists (VKAs) in the absence of contraindications, irrespective of the risk score of scales used in patients with non-valvular AF ($CHADS_2$ and CHA_2DS_2VASc)[3,4].

Direct oral anticoagulants (NOACs) are recommended for patients with non-valvular AF and at least one additional risk factor for stroke based on non-inferiority or superiority to adjusted-dose warfarin in preventing stroke or systemic embolism, and reduced rates of haemorrhage achieved in clinical trials[5]. While HCM was not a formal contraindication to participate in NOACs trials, HCM patients tend to be younger and do not usually present with classical embolic risk factors. As a consequence, they were not adequately represented in these studies (mean age of participants in NOACs trials was ≥70 years, and mean $CHADS_2$ score >2)[6-8].

Despite the view that NOACs profile could be highly favourable for HCM patients (usually a young and very active population), data on NOACs use and effectiveness in this selected population are limited.

The purpose of this study was 2-fold: first, to describe the pattern of use, clinical profile, thromboembolic events and haemorrhages in patients with HCM and AF treated with NOACs (dabigatran, rivaroxaban and apixaban) compared with a historical

cohort of patients treated with a VKA. Second, we sought to evaluate quality of life and satisfaction with treatment of HCM patients on NOACs compared with those receiving a VKA.

2. Methods

2.1 Study design and overview

Data from a retrospective, multicentre longitudinal cohort were used. The study conformed to the principles of the Helsinki Declaration and was approved by the ethics committee of the Hospital Universitario Puerta de Hierro. The sponsors of the study had no role in study design, data collection, analysis or interpretation. F.D. and P.G-P. had access to all data and final responsibility to submit the article. The authors from each participating centre guarantee the integrity of data from their institution. All investigators have agreed to the article as written.

2.2 Study population and participating centres

The study cohort consisted of all consecutive patients with HCM and non-valvular AF treated with NOACs from the date they became commercially available in Spain (January 2011) until February 2016, followed at 9 Spanish Inherited Cardiac Disease Units (Appendix).

HCM was defined as a maximum LV wall thickness ≥15 mm unexplained solely by loading conditions or ≥13 mm in first-degree relatives[3]. Non-valvular AF was defined as AF in the absence of rheumatic valvular disease or mechanical heart valves[5].

A historical VKA-treated cohort was constructed and comprised all patients with HCM and AF treated with VKAs during the period April 1980 to October 2014 at three of the

participating centres: (i) Hospital Universitario Puerta de Hierro, Madrid, (ii) A Coruña University Hospital, A Coruña, and (iii) University Hospital Virgen de la Arrixaca, Murcia. These centres participated in recently published studies including analyses of AF appearance and stroke risk in HCM[9,10]. To avoid selection bias in the prescribed drug, the subgroup of patients who had initiated VKA therapy before NOACs were commercially available was also identified. Furthermore, to compare the quality of life and satisfaction with treatment with the NOAC group, a contemporary cohort of VKA-treated patients who started VKA therapy in the same time period was identified.

Only adult patients (≥18 years of age) were studied. Patients on treatment with NOACs or VKAs were identified from existing databases at each participating unit. Patients' clinical data, treatments and events were obtained from their clinical records at participating centres.

2.3 Clinical outcomes

Cerebrovascular accident (CVA) was defined as a sudden onset focal neurological deficit lasting >24 h and caused by ischaemia. A focal neurological deficit lasting <24 h was considered transient ischaemic attack (TIA). An acute vascular occlusion of an extremity or organ, documented by means of imaging, surgery, or autopsy was considered peripheral embolism. The composite of CVA, TIA and peripheral embolism was defined as thromboembolic event, Major or clinically relevant bleeding was defined as a decrease in the haemoglobin level of at least 2 g/dL and/or an haemorrhage leading to an unscheduled visit to a healthcare centre or a temporary interruption of the anticoagulation therapy[6-8].

2.4 Quality of life and satisfaction with anticoagulation therapy

Quality of life was evaluated with the SF-36 v2 questionnaire on health and welfare, and satisfaction with anticoagulation therapy with the SAFUCA (Satisfaction with Medical Care in Patients with Atrial Fibrillation) questionnaire.

Each of the ten SF-36 health concepts was scored on a 0–100 scale. The maximum score of 100 is achieved when no disability is reported. Regarding the SAFUCA questionnaire, a maximum score of 100 implies full satisfaction in each of the addressed items. These questionnaires are widely used in clinical research and are valid and reliable in specific disease groups[11,12].

All patients with HCM and AF on treatment with NOACs were asked to complete the questionnaires and those who were available and agreed (n=80, 80%) were included in the study once informed written consent was obtained. In the same manner, a contemporary group of HCM patients who had initiated VKA therapy from 2008 onwards was included at the 9 participating institutions. Each centre was requested to include a VKA patient per each NOAC-treated HCM patient who agreed to participate in the study. Because of this time-frame and centre restriction, the VKA group included 57 individuals. Time of enrolment was 12 months to ensure that all potential patients fulfilling inclusion criteria were invited to participate in the study during their annual follow-up visit. No additional visits were scheduled and no modifications in their usual clinical follow-up were performed because of this study.

2.5 Statistical analysis

Results are presented as mean (standard deviation) for continuous variables with normal distribution, as median (interquartile range) for continuous variables without normal distribution, and as number (percentage) for categorical data. For statistical

analysis, Student's t test and Mann-Whitney nonparametric test were used in two-group comparisons for continuous variables, whereas Chi-square test or Fisher's exact test were used for categorical variables. Kaplan-Meier survival analysis was used to compare the treatment groups in the length of time after start of therapy until occurrence of death. All other clinical events were studied with competing-risks regression by the method of Fine and Gray, to take into account competing risks (e.g., death). A 2-tailed p value <0.05 was considered statistically significant. A propensity score analysis was thought to be unnecessary because most patients treated with VKA (88%) started the drug when NOACs were not available (before 2011), so they could not have been allocated to NOAC treatment. The entire analysis was performed using STATA v14.0 (StataCorp, College Station, TX).

3. Results

A total of 532 HCM patients with AF on VKA (*n* = 433) or NOAC (*n* = 99) treatment were retrospectively studied (Figure 1). Within the NOAC group, 47 patients were receiving rivaroxaban (47.5%), 29 dabigatran (29.3%) and 23 apixaban (23.2%). All patients in the VKA group were receiving acenocoumarol.

More than 65% of patients in the NOAC group were male and almost 58% in the VKA group (p=0.16). Mean age at start of treatment was similar in both groups (61±14 vs. 61±12; p=0.64) and most clinical and echocardiographic characteristics were comparable in both groups (Table 1). Clinical and echocardiographic characteristics of NOAC-treated patients and VKA-treated patients started on a VKA before NOACs became available (January 2011) were also comparable (Table 1). Regarding comorbidities, only renal disease was more prevalent in patients on NOACs than in those on a VKA (Table 1). Baseline treatment was also different between the two groups, with a higher use of concomitant antithrombotic therapy (clopidogrel and aspirin) in the VKA group (Table 1).

The median follow-up time from the start of anticoagulation therapy to the last follow-up was 63 months (17 months in the NOAC group and 78 months in the VKA group).

In total, 57 of the NOAC-treated patients (57.6%) had been switched from a VKA while 42 (42.4%) had been started directly on NOACs. Reported reasons for initiation of NOAC therapy were physician's choice in 69 patients (69%), history of labile INR in 27 (27.2%) and previous bleeding under VKA treatment in 12 (12.1%).

3.1 Clinical events

Considering the NOAC and VKA groups together, thromboembolic events (TIA, CVA and peripheral embolism) occurred in 10% of HCM patients with AF on oral anticoagulation (10% of patients with paroxysmal AF, 9.4% of those with persistent AF and 10.4% with permanent AF; p=0.952) after a median follow-up of 63 months (interquartile range 26–109). During this period, major or clinically relevant bleeding occurred in 3.8% of cases (70% gastrointestinal, 15% genitourinary and 15% other sites; no intracranial bleedings occurred). The global mortality rate during follow-up was 23.3%.

Patients who presented TIA, CVA or peripheral embolism had a higher prevalence of prior stroke or peripheral vascular disease than those without thromboembolic events after initiation of oral anticoagulation (31.8% vs. 6.6%; p<0.001 and 21.8% vs. 7.5%; p<0.001, respectively). Moreover, the left atrium (LA) diameter was greater in patients who presented TIA, CVA or peripheral embolism (51.73±7.55 mm vs. 48.82±7.97 mm; p=0.013). History of hypertension and diabetes was similar among patients with and without thromboembolic events (Table 1S).

Annual all-cause mortality was 1.26 per 100 patients in the NOAC group and 3.81 in the VKA group [hazard ratio 0.55, 95% confidence interval (CI):0.13–2.30;p=0.41]. TIA and stroke rate in the NOAC group was 0 and 0.62 per 100 patient-years, while in the VKA group it was 0.25 and 1.06, respectively. The difference was not statistically significant [subhazard ratio (SHR) 0.46, 95%CI:0.06–3.62;p=0.46]. PE did not occur in any patient on NOAC treatment and it was present at an annual rate of 0.35 per 100 patients in the VKA group. The combined event of stroke, TIA and PE occurred in 0.62

per 100 patient-years in the NOAC group and in 1.59 per 100 patient-years in the VKA group (SHR 0.32, 95%CI:0.04–2.45;p=0.27).

Regarding bleeding, 0.62 per 100 patients treated with NOAC presented this complication per year, compared with 0.60 yearly per 100 patients on a VKA (SHR 1.28, 95%CI:0.18–9.30;p=0.85)(Table 2).

To avoid a drug indication bias, we performed a sub-analysis including those VKA patients who started VKA therapy before NOACs were available for thromboembolism prevention in patients with AF. The total number of patients who started VKA before 2011 was 381. Annual all-cause mortality was 3.72 per 100 patient-years and TIA annual rate per 100 patients was 0.26. CVA and PE occurred at a rate of 1.11 and 0.36 per 100 patients yearly, respectively. Globally, annual thromboembolic events were present in 1.65 per 100 patients on VKA, whereas bleeding presented an annual rate of 0.56 per 100 patients-year. Again, no statistical differences were found between VKA and NOAC groups for all the variables (Table 2).

The different NOAC subgroups (dabigatran, rivaroxaban and apixaban) did not present statistically significant differences regarding clinical events. No patients presented TIA or peripheral embolism; only one patient treated with rivaroxaban presented CVA (1/47: 2.1%) and another treated with apixaban experienced a clinically relevant bleeding event (gastrointestinal) (1/23: 4.3%). Two patients in the rivaroxaban group died (2/47: 4.2%; 1 due to heart failure and the other noncardiac). No deaths were reported in the other two groups, but the differences were again not significant.

3.2 Quality of life and satisfaction with treatment

Eighty patients from the 99 who had been started on NOACs accepted to answer the SF-36 and SAFUCA questionnaires. Additionally, a contemporary group of 57 VKA-treated patients who had started a VKA from November 2008 onwards were studied. Both groups presented similar clinical characteristics including age, gender, comorbidities, echocardiographic characteristics and baseline treatments. Only LA diameter was slightly greater in the NOAC group (Table 2S).

The SF-36 questionnaire results were similar in both groups regarding all the included items (physical component, mental component, physical functioning, role-physical, bodily pain, global health, vitality, social functioning, role-emotional and mental health). Specific scores are shown in Table 3.

Nonetheless, the NOAC group achieved a higher score in most of the SAFUCA questionnaire items, which were graded according to the degree of satisfaction (%). These included convenience of the medication (83.86±17.80% vs. 76.3±23.02%; p=0.03), interference with daily life (92.34±11.16% vs. 79.21±19.07%; p<0.001), adverse effects (88.24±18.75% vs. 75.87±25.14%; p=0.001) and general opinion of the drug (84.58±16.46% vs. 73.69±22.44%; p=0.001). SAFUCA scores on medical follow-up and the efficacy of the anticoagulant therapy were similar in both groups (Table 3).

4. Discussion

This study describes the clinical characteristics as well as the thromboembolic and bleeding events in HCM patients with AF on NOAC therapy and compares them with a historical cohort of patients treated with a VKA. Additionally, it provides data about quality of life and satisfaction with treatment of HCM patients on NOACs compared with those receiving a VKA. The results of the study show that HCM patients receiving NOACs have similar embolic and bleeding rates to those receiving a VKA and, at the same time, have higher satisfaction with treatment despite reporting similar quality of life.

AF is the most common arrhythmia in patients with HCM. Prospective data show that after 10 years of follow-up, 22% to 30% of HCM patients develop AF[2,13,14]. AF has a strong impact on HCM clinical course and on patients' quality of life. Due to very high embolic risk, chronic oral anticoagulation is recommended in all HCM patients with AF. This recommendation is based on observational studies showing that warfarin-treated HCM patients with AF presented about one half of embolic events (18% vs 31%) and stroke (10% vs 39%) to those not receiving anticoagulation treatment[13]. Currently, ESC HCM clinical guidelines recommend VKAs as the anticoagulant agents of choice in HCM and restricts NOACs use to patients who cannot maintain INR in the therapeutic range or have had VKA-related side effects[3]. However, the latest ESC AF guidelines state that NOACs are broadly preferable to VKAs in the vast majority of patients with non-valvular AF[5], based on clinical trials that have shown non-inferiority compared with VKAs, as well as better safety and less intracranial haemorrhage[6-8]. Furthermore, recent studies have observed that NOACs are more cost effective than adjusted dose

VKAs[15], and that non-valvular AF patients are more satisfied with medical care when treated with NOACs[12].

While HCM patients were not formally excluded from NOACs trials, the number of HCM patients included in these studies is unknown and presumably was low because they tend to be younger (mean age of patients included in NOACs trials was >70) and do not exhibit the traditional $CHADS_2$ factors required to participate in NOAC studies. Therefore, little data currently supports the use of NOACs in HCM despite the notion that NOACs could represent a valid alternative to VKA in this younger, active population.

4.1 NOAC versus VKA for the prevention of clinical events in patients with HCM and AF

The annual rate of thromboembolic events (TIA, CVA, peripheral embolism) was 1.59 per 100 patient years in the VKA group and 0.62 in the NOAC group, although this difference did not reach statistical significance. While meta-analyses with pooled results from NOAC trials have shown a significant reduction of stroke and systemic embolism for the general population with non-valvular AF[16], the sample of patients in those studies was considerably larger.

NOAC trials have also demonstrated a significant reduction in haemorrhagic stroke with NOACs and in meta-analyses there was a trend towards reduced major bleeding[16]. In our study, major or clinically relevant bleeding per 100 patient-years was similar in both groups, but the bleeding rates were substantially lower as compared with those found in the NOACs trials[6-8]. However, HCM patients in our study were younger (mean age 61) and bleeding rates were similar to those reported in patients aged <65 with dabigatran[17] and warfarin[18]. No intracranial bleedings were reported in

our study, which may have also been influenced by age and the fact that hypertension was present in 54% of patients in our cohort, as compared to 80–90% of patients included in the NOAC trials [6-8].

A recent study that used a large American commercial insurance database evaluated stroke and bleeding risks in patients with HCM and AF treated with NOACs and VKAs[19]. In line with our findings, the data from this study suggested that this patient group could be safely treated with NOACs. In contrast to our study, the aforementioned study did not provide patients' clinical characteristics, and its design (information was extracted from billing codes) made it impossible to know whether factors that may predispose to cardioembolism, such as mitral valve dysfunction, left atrial enlargement and left ventricular dysfunction, or factors that confer an increased risk of bleeding including concomitant antiplatelet therapy, were balanced between groups. In the present study, we found that clinical characteristics were well balanced between VKA and NOAC groups except for kidney disease (higher in the NOAC group) and concomitant antiplatelet therapy (higher in the VKA group). Both the American study and ours are probably underpowered in terms of number of individuals to demonstrate superiority of NOACs over VKAs in HCM patients with AF. However, the results of the American study taken together with ours would favour the upgrading of NOACs to a similar level of recommendation to VKAs in guidelines because a clinical trial with both agents is unlikely to be carried out and current VKA recommendation in HCM also arises from observational findings.

The fact that impaired renal function was more prevalent in the NOAC group was surprising, although this includes patients with mild renal disease in whom NOACs can be used. Nevertheless, the limited number of patients in the NOAC group may have

also played a role in this finding. Moreover, the use of concomitant antithrombotic therapy was higher in the VKA group. Regrettably, information about indications for antiplatelet therapy and history of coronary artery disease was not available. However, patients treated with a VKA had a 56.6% prevalence of hypertension, and 20.8% of diabetes mellitus versus 47.5% and 16.2% in the NOAC group, respectively. Although these differences did not reach statistical significance, when assessing both cardiovascular risk factors together (hypertension and/or diabetes mellitus), the VKA group presented a prevalence of 60.3% versus 49.5% in the NOAC group (p=0.05). As the burden of cardiovascular disease risk factors seems to be higher in the first group, this might explain why antiplatelet therapy was more frequently used. Furthermore, an indication bias could be present as the NOAC cohort belongs to a more recent time period in which antiplatelet therapy is not generally advocated for primary prevention in patients receiving anticoagulants. Nevertheless, the bleeding risk of the VKA group was not higher than that in patients on NOAC therapy.

4.2 Quality of life and treatment satisfaction

Current guidelines only consider NOACs in HCM when INR optimal range is not achieved with VKAs, or when side effects occur. In our study, only 28% of the patients treated with NOACs had previous history of labile INR and just 12% experienced bleeding or intolerance to VKA; the remaining 69% initiated NOAC therapy due to physician or patient's choice.

Mean age of patients included in our study was approximately 61 years in both groups, so many were presumably still in employment. In contrast to NOACs, VKA treatment requires frequent analytical work-ups and visits to monitor the INR, which has an

important impact on lifestyle and is also time consuming. Therefore, it is not surprising that HCM patients would prefer NOACs to VKAs on the assumption that they are equally effective and safe.

Similar scores were obtained by patients in the two groups who completed the SF-36 questionnaire. SF-36 addresses different health concepts that are relevant to HCM patients, including physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. HCM patients have been assessed with the SF-36 questionnaire in previous studies[20,21], and it has been observed that quality of life is substantially impaired when compared with that of the general population. We did not observe that quality of life as assessed by the SF-36 was better in NOAC-treated patients, suggesting that quality of life in HCM patients mainly depends on the condition itself rather than on the medication that patients receive.

Conversely, the SAFUCA questionnaire generated higher scores in the NOAC group. NOAC-treated patients thought that NOACs were more convenient, had less interference with daily life activities and had lower rate of adverse events, compared with patients treated with a VKA. Nonetheless, no differences were found regarding perceived efficacy and medical follow-up. These results suggest that NOAC-treated patients are more satisfied with treatment than VKA-treated patients, but both groups perceive that the two drugs are equally useful and medical attention is the same irrespective of the baseline treatment.

Interestingly, the SAFUCA questionnaire was recently used in a Spanish study with more than 1,200 anticoagulated patients with non-valvular AF[12], and in that study the NOAC-treated group generated higher scores in all the items of the questionnaire.

4.3 Clinical predictors of thromboembolism in anticoagulated HCM patients with AF

In our study, 10% of anticoagulated HCM patients with AF presented thromboembolic events during follow-up, similar to thromboembolic rates described in other warfarin-treated HCM series.

LA diameter was greater in subjects who had thromboembolic events, which is also consistent with previous studies[9,22]. The present study also supports recent ESC guidelines that advise against CHA_2DS_2-VASc score use in HCM with AF, as the group of patients who suffered thromboembolic events did not present a higher prevalence of vascular risk factors such as hypertension or diabetes[3]. Nonetheless, it should be noted that peripheral vascular disease and stroke before initiating anticoagulant therapy were more prevalent among patients with thromboembolic events during follow-up.

5. Limitations

We acknowledge that the number of patients included in this study is limited and therefore our study is underpowered to statistically demonstrate equivalency or superiority of NOACs over VKAs in HCM individuals with AF. Patients on NOACs belong to a more contemporary cohort than those treated with VKA, which also have a longer follow-up period. In this latter group, time in therapeutic range was not available. Furthermore, the retrospective nature of our study should also be taken into consideration.

6. Conclusions

Our results suggest that NOACs are safe and effective for the prevention of cardioembolism in patients with HCM and AF. Moreover, compared with those treated with a VKA, HCM patients treated with NOACs report higher satisfaction with treatment despite having similar quality of life.

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Tables

Table 1. Clinical and echocardiographic characteristics in 532 HCM patients with AF according to anticoagulation therapy.

Table 2. Clinical events in NOAC-treated and VKA-treated HCM patients with AF.

Table 3. SF-36 and SAFUCA questionnaires scores in 137 HCM patients with AF treated with NOACs (*n* = 80) or VKA (*n* = 57).

Table 1. Clinical and echocardiographic characteristics in 532 HCM patients with AF according to anticoagulation therapy

	NOACs (*n* = 99)	VKA (*n* = 433)	VKA <2011 (*n* = 381)	p-value (NOAC vs. VKA)	p-value (NOAC vs. VKA <2011)
Age at start of treatment	61.14 ± 13.25	61.79 ± 12.49	61.62 ± 12.62	0.64	0.74
Male sex	65.7%	58.0%	56.7%	0.16	0.11
Hypertension	47.5 %	56.6 %	57.2%	0.14	0.11
Diabetes	16.2%	20.8%	20.5%	0.30	0.34
Peripheral vascular disease	6.1%	9.7%	10.5%	0.25	0.18
Liver disease	2%	5.8%	5.5%	0.13	0.15
Renal disease	13.3%	6.7%	6.3%	**0.03**	**0.02**
NYHA I	42.1%	38.9%	37.1%	0.56	0.37
NYHA II-IV	57.9%	61.1%	62.9%	0.56	0.37
Non sustained VT	31.9%	31.0%	31.0%	0.88	0.88
MWT (mm)	20.62 ± 4.53	20.15 ± 4.63	20.05 ± 4.64	0.64	0.30
LVOTO max at rest (mmHg)	24.65 ±32.55	27.48 ± 37.76	26.34 ± 36.17	0.64	0.71
Obstructive HCM, %*	26.7%	29.5%	27.4%	0.62	0.90
LVEF (%)	63.09 ±10.39	61.45 ± 15.62	58.64 ± 16.18	0.64	0.11
SAM of the mitral valve	40.9%	41.4%	40.0%	0.93	0.88
LA diameter (mm)	48.66 ±7.85	49.21 ± 7.92	49.20 ±7.95	0.54	0.44
Aspirin	13.7%	24.5%	24.0%	**0.02**	**0.03**
Clopidogrel	0%	5.1%	5.8%	**0.03**	**0.02**
Beta-blockers	82.6%	77.4%	75.6%	0.27	0.15
Calcium channel blockers	15.2%	31.2%	31.8%	**0.002**	**0.002**
Amiodarone	43%	37.2%	37.5%	0.29	0.33
Sotalol	2.2%	8.3%	10.6%	0.07	0.03
Disopyramide	13.8%	7.4%	6.6%	**0.04**	**0.02**

LVEF: Left ventricular ejection fraction, LA: Left atrium, LVOTO: Left ventricular outflow tract obstruction, MWT: Maximal wall thickness, NYHA: New York Heart Association, SAM: Systolic anterior movement, NOAC: Direct oral anticoagulants; VKA: vitamin K antagonist; VKA<2011: VKA-treated patients started on VKA before 2011, VT: Ventricular tachycardia.

- Obstructive HCM: LVOT gradient >30 mmHg.

Table 2. Clinical events in NOAC-treated and VKA-treated HCM patients with AF

	NOAC (*n* = 99)	**VKA (*n* = 433)**	**VKA < 2011 (*n* = 381)**	**HR/SHR** NOAC vs. VKA	**95%CI** NOAC vs. VKA	**p-value** NOAC vs. VKA	**HR/SHR** NOAC vs. VKA<2011	**95%CI** NOAC vs. VKA<2011	**p-value** NOAC vs. VKA<2011
Transient ischaemic attack (per 100 patient-years)	0	0.25	0.26	-	-	-	-	-	-
Stroke (per 100 patient-years)	0.62	1.06	1.10	0.46*	0.06–3.62	0.46	0.41*	0.05–3.29	0.40
Peripheral embolism (per 100 patient-years)	0	0.35	0.36	-	-	-	-	-	-
Thromboembolic event (per 100 patient-years)	0.62	1.59	1.65	0.32*	0.04–2.45	0.27	0.29*	0.04–2.21	0.23
Major/clinically relevant bleeding on anticoagulation (per 100 patient-years)	0.62	0.60	0.56	1.28*	0.18–9.30	0.85	1.98*	0.32–12.49	0.47
• Gastrointestinal (%)	100	68.4	68.8						
• Intracranial (%)	0	0	0						
• Genitourinary (%)	0	15.8	18.7						
• Others (%)	0	15.8	12.5						
Death (per 100 patient-years)	1.26	3.81	3.72	0.55	0.13–2.30	0.41	0.69	0.16–2.93	0.61

* Subhazard ratio

HR: Hazard ratio, SHR: Subhazard ratio; NOAC: Direct oral anticoagulants; VKA: vitamin K antagonist ; VKA<2011: VKA-treated patients started on VKA before 2011.

Table 3. SF36 and SAFUCA questionnaires scores in 137 HCM patients with AF treated with NOACs (*n* = 80) or VKA (*n* = 57)

SF36 QUESTIONNAIRE			
	NOAC	**VKA**	**p-value**
Physical component	43.06 ± 9.74	41.07 ± 10.07	0.26
Mental component	49.18 ± 11.71	49.96± 9.91	0.69
Physical functioning	42.10± 10.87	40.40 ± 10.86	0.37
Role-Physical	43.98 ± 11.50	43.40 ± 12.24	0.78
Bodily pain	51.53 ± 11.77	48.35 ± 11.98	0.13
Global health	38.94 ± 10.20	37.03 ± 9.84	0.28
Vitality	48.42± 11.45	47.2 ± 11.04	0.54
Social functioning	47.42 ± 11.43	47.34 ± 11.99	0.97
Role-Emotional	47.05 ± 11.60	47.21 ± 11.37	0.94
Mental Health	47.61 ± 11.89	48.87 ± 9.1	0.51
SAFUCA QUESTIONNAIRE			
	NOAC (% satisfaction)	**VKA (% satisfaction)**	**p-value**
Efficacy of medication	80.70 ± 16.65	75.58 ± 20.95	0.12
Convenience of medication	83.86 ± 17.80	76.3 ± 23.02	**0.03**
Interference of medication with daily life	92.34 ± 11.16	79.21 ± 19.07	**<0.001**
Adverse effects caused by the anticoagulant medication	88.24 ± 18.75	75.87 ± 25.14	**0.001**
Medical follow-up of the disease	89.32 ± 15.43	87.57 ± 18.50	0.55
General opinion on the medication and health condition	84.58 ± 16.46	73.69 ± 22.44	**0.001**

Figure.

Figure 1. Flowchart showing the patients' selection process.

Appendix:

Participating centres:

(i) Hospital Universitario Puerta de Hierro Majadahonda, Madrid

(ii) A Coruña University Hospital, A Coruña

(iii) University Hospital Virgen de la Arrixaca, Murcia

(iv) Hospltal Clinico, Malaga

(v) Hospital Son Llatzer, Mallorca

(vi) Hospital Universitario y Politécnico La Fe, Valencia

(vii) Hospital Universitari Bellvitge, Barcelona

(viii) Hospital General Universitario, Alicante

(ix) Hospital Virgen del Rocio, Seville

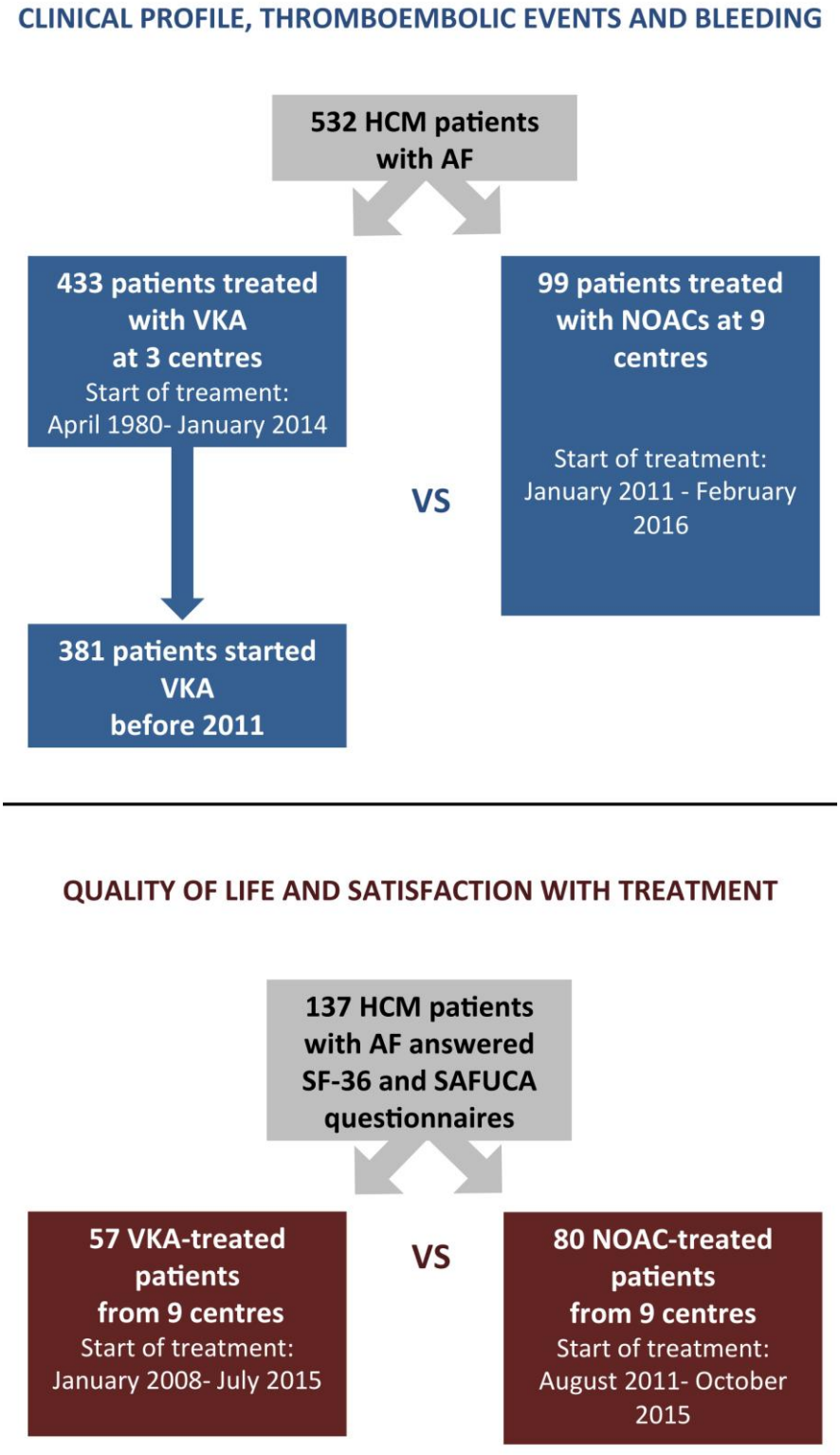

Figure 1