

# A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial

Dragos Vinereanu, Renato D Lopes, M Cecilia Bahit, Denis Xavier, Jie Jiang, Hussein R Al-Khalidi, Wensheng He, Ying Xian, Andrea O Ciobanu, Deepak Y Kamath, Kathleen A Fox, Meena P Rao, Sean D Pokorney, Otavio Berwanger, Carlos Tajer, Pedro G M de Barros e Silva, Mayme L Roettig, Yong Huo, Christopher B Granger, on behalf of the IMPACT-AF investigators

## Summary:

**Background** Oral anticoagulation is underused in patients with atrial fibrillation. We assessed the impact of a multifaceted educational intervention, versus usual care, on oral anticoagulant use in patients with atrial fibrillation.

**Methods** This study was a two-arm, prospective, international, cluster-randomised, controlled trial. Patients were included who had atrial fibrillation and an indication for oral anticoagulation. Clusters were randomised (1:1) to receive a quality improvement educational intervention (intervention group) or usual care (control group). Randomisation was carried out centrally, using the eClinicalOS electronic data capture system. The intervention involved education of providers and patients, with regular monitoring and feedback. The primary outcome was the change in the proportion of patients treated with oral anticoagulants from baseline assessment to evaluation at 1 year. The trial is registered at ClinicalTrials.gov, number NCT02082548.

**Findings** 2281 patients from five countries (Argentina, n=343; Brazil, n=360; China, n=586; India, n=493; and Romania, n=499) were enrolled from 48 clusters between June 11, 2014, and Nov 13, 2016. Follow-up was at a median of 12·0 months (IQR 11·8–12·2). Oral anticoagulant use increased in the intervention group from 68% (804 of 1184 patients) at baseline to 80% (943 of 1184 patients) at 1 year (difference 12%), whereas in the control group it increased from 64% (703 of 1092 patients) at baseline to 67% (732 of 1092 patients) at 1 year (difference 3%). Absolute difference in the change between groups was 9·1% (95% CI 3·8–14·4); odds ratio of change in the use of oral anticoagulation between groups was 3·28 (95% CI 1·67–6·44; adjusted p value=0·0002). Kaplan-Meier estimates showed a reduction in the secondary outcome of stroke in the intervention versus control groups (HR 0·48, 95% CI 0·23–0·99; log-rank p value=0·0434).

**Interpretation** A multifaceted and multilevel educational intervention, aimed to improve use of oral anticoagulation in patients with atrial fibrillation and at risk for stroke, resulted in a significant increase in the proportion of patients treated with oral anticoagulants. Such an intervention has the potential to improve stroke prevention around the world for patients with atrial fibrillation.

**Funding** Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer.

## Introduction

Atrial fibrillation represents the most common sustained arrhythmia worldwide, affecting an estimated 33.5 million people.<sup>1</sup> Atrial fibrillation is also an important cause of stroke, accounting for one in five ischaemic strokes.<sup>2</sup> These strokes are more severe than those in patients without atrial fibrillation, leading to permanent disability in 60% and death in 20% of patients.<sup>3</sup> At least two-thirds of these atrial fibrillation-related strokes can be prevented by oral anticoagulation.<sup>4</sup> Nevertheless, only about half of patients for whom current guidelines recommend oral anticoagulation are treated, resulting in a substantial number of preventable ischaemic strokes.<sup>5</sup> Moreover, among patients with atrial fibrillation who experience ischaemic strokes, over 80% had inadequate therapeutic anticoagulation preceding the strokes.<sup>6</sup> Underuse of oral anticoagulation becomes even more pronounced in middle-income countries, where the use of oral anticoagulation has been reported to be less than 40% in Eastern Europe, South America, and India, and only 11% in China<sup>7</sup> in unselected populations. These regional differences have been associated with different levels of physician and patient education.<sup>7</sup> Additionally, after oral anticoagulation was started appropriately in one study, more than 30% of patients stopped therapy by the end of the first year.<sup>8</sup> Recent studies have suggested that an educational intervention might improve patient knowledge about oral anticoagulation, leading to a substantial impact on time in therapeutic range in patients with atrial fibrillation on warfarin.<sup>9,10</sup> However, these studies were relatively small, single-centre, limited to single countries, or focused only on patient education.<sup>9,10</sup> A 2017 systematic review<sup>11</sup> showed that there is insufficient evidence to draw definitive conclusions regarding the impact of educational interventions on time in therapeutic range in patients with atrial fibrillation receiving oral anti-coagulation. Thus, more trials are needed to examine the impact of interventions on anticoagulation control in patients with atrial fibrillation and the mechanisms by which they are successful. The cluster-randomised trial to IMProve treatment with AntiCoagulanTs in patients with Atrial Fibrillation (IMPACT-AF) is a prospective, international, cluster-randomised, controlled trial that assessed the impact of a customised, multifaceted, and multilevel educational intervention on the use of oral anticoagulation in patients with atrial fibrillation at 1 year, compared with usual care. Secondary objectives were to evaluate the effect of this intervention on the persistence of oral anticoagulation in patients with atrial fibrillation, as well as its impact on clinical outcomes.

## **Research in context**

### **Evidence before this study**

We did a systematic review of studies assessing educational interventions in patients with atrial fibrillation. We searched PubMed (from Jan 1, 1980, to June 1, 2017) using the terms [atrial fibrillation] AND [education] AND [anticoagulation] without language restrictions. We identified 224 papers, of which 19 were clinical trials. Seven studies addressed educational interventions in atrial fibrillation. Two studies assessed the effects of a nurse-led care initiative, providing patient education and monitoring, whereas one study reported the results of an education and support programme implemented at the level of Belgian general practitioners to improve the quality of management of oral anticoagulation. One study examined patients' knowledge and perception of atrial fibrillation and their anticoagulant treatment. One study investigated the effectiveness of a dedicated software tool to identify patients at risk of stroke not receiving oral anticoagulation. Only two studies focused on the impact of a dedicated educational intervention on patients with atrial fibrillation to improve quality of oral anticoagulation (time in therapeutic range). However, each of these seven studies was relatively small (less than 750 patients), single-centre, limited to single countries, and focused only on patient education. Meanwhile, a Cochrane systematic review showed that there is insufficient evidence to draw definitive conclusions regarding the impact of educational interventions on quality of anticoagulation care (measure to time in therapeutic range) for patients with atrial fibrillation. The coauthors concluded that more trials are needed to examine the impact of interventions on anticoagulation control in patients with atrial fibrillation and the mechanisms by which they are successful. We also searched ClinicalTrials.gov (through June 1, 2017). Our search terms were [atrial fibrillation] AND [education].

We identified 52 completed and ongoing clinical trials, but only six of them reported results. Only one (unpublished) enrolled more than 1000 patients with atrial fibrillation, in which patients were started on apixaban, and randomly assigned to either standard-of-care patient information or an educational programme. The primary outcome was adherence to apixaban assessed at 24 and 48 weeks, which was high in both groups, with no additional value of educational programme over usual care. This study focused on a single anticoagulant (apixaban) and not on the broad spectrum of oral anticoagulation therapy for patients with atrial fibrillation.

### **Added value of this study**

This trial adds important evidence as a large, international, randomised controlled trial showing that a multifaceted and customised educational intervention can improve use of oral anticoagulation in patients with atrial fibrillation. We have shown that an educational intervention can substantially increase the use of oral anticoagulants in patients with atrial fibrillation and at risk of stroke. Of patients with atrial fibrillation at risk of stroke who were not on oral anticoagulants, about half were successfully started and maintained on oral anticoagulants for 1 year with the intervention, an effect that could have very important public health implications. The effect was robust and consistent across countries and key subgroups of patients.

### **Implication of all available evidence**

The successful intervention in the current trial, which was customised by each country, included education of patients and their families and of health-care providers, as well as measurement and feedback of performance. Whereas the trial was not powered to show a difference in clinical outcomes, the potential clinical impact of the intervention was highlighted by the occurrence of significantly fewer strokes in the intervention group. Therefore, the aggregate evidence shows that increased education, better communication between all stakeholders (patients, caregivers, and health-care providers), and feedback are needed to improve the use of anticoagulants to reduce the occurrence of stroke in atrial fibrillation. Importantly, the interventions used in our study were simple and can be implemented in standard clinical practice, which has the potential to lead to better care of patients with atrial fibrillation around the world.

## Methods

### Study design and participants

The design and rationale of the IMPACT-AF trial has been described previously.<sup>12</sup> Briefly, IMPACT-AF was a two-arm, prospective, international, cluster-randomised, controlled- trial that enrolled patients with atrial fibrillation. IMPACT-AF was designed as a cluster-randomised study to provide a randomised control group, while minimising the presence of contamination that might occur with individual randomisation, given that the implementation of the educational intervention was applied at both the cluster and individual level. The national coordinating centres from five participating middle-income countries (Argentine Clinical Research Group [ACRG], Rosario, Argentina; Brazilian Clinical Research Institute, São Paulo, Brazil; Peking University First Hospital, Beijing, China; St John's Medical College and Research Institute, Bangalore, India; and University of Medicine and Pharmacy Carol Davila, Bucharest, Romania) were responsible for the conduct of the trial in each respective country. Clusters (sites) were identified by each coordinating centre based on feasibility and patient volume. All clusters demonstrated access to adequate numbers of eligible patients by providing pre-screening lists of 40–90 eligible patients.

IMPACT-AF included patients aged 18 years or older with atrial fibrillation not due to reversible causes and who had an indication for oral anticoagulation (CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  or rheumatic valvular heart disease). Diagnosis of atrial fibrillation was confirmed by a 12-lead electrocardiograph (ECG) or rhythm strip at enrolment, or two ECGs or rhythm strips or both at least 2 weeks apart, showing atrial fibrillation if patients were not in atrial fibrillation at the time of enrolment. Patients were excluded if they met any of the following criteria: mechanical prosthetic valve; clinically unstable at the time of enrolment (eg, with ongoing shock); life expectancy less than 6 months; unable to provide consent (eg, severe cognitive impairment);- unable to have 1 year of follow-up; or absolute contraindication to oral anticoagulation (eg, active bleeding or recent life-threatening bleeding or multiple attempts on oral anticoagulation with bleeding each time).

The study was approved by the Duke University Institutional Review Board and by ethics committees in each country. All patients gave written informed consent before enrolment into the study. An independent data monitoring committee reviewed the protocol, data progress, and accumulating data, with no formal stopping rules.

### Randomisation and masking

Clusters in each of the five participating countries were randomised (1:1) to receive a quality-improvement educational intervention (intervention group) or usual care (control group). Randomisation was done by the central coordinating centre (Duke Clinical Research Institute, Durham, NC, USA) using the eClinicalOS electronic data capture system. Eligible intervention and control sites were matched into pairs and randomised<sup>13</sup> within each country (five in the intervention group and five in the control group) based on practice type, practice size, and proportion of patients eligible for anticoagulation-. Each cluster enrolled eligible and consenting patients in a sequential manner. Investigators and site personnel were not masked to the intervention.

### Procedures

The intervention included two main components: education, and regular monitoring and feedback. The educational component had two target audiences. The first was patients and their families and involved the use of educational brochures, use of web-based and video educational materials, and encouragement of patients and family interactions with physicians, nurses, health workers, or other staff members at each site regarding the benefits and risks of oral anticoagulation in atrial fibrillation. The second audience was health-care providers and involved systematic review of the current guideline recommendations for oral anticoagulation; regular emails containing articles of interest; use of webinars, podcasts, dedicated monographs, social media, and instant messaging; and telephone calls with the coordinating centre. The focus

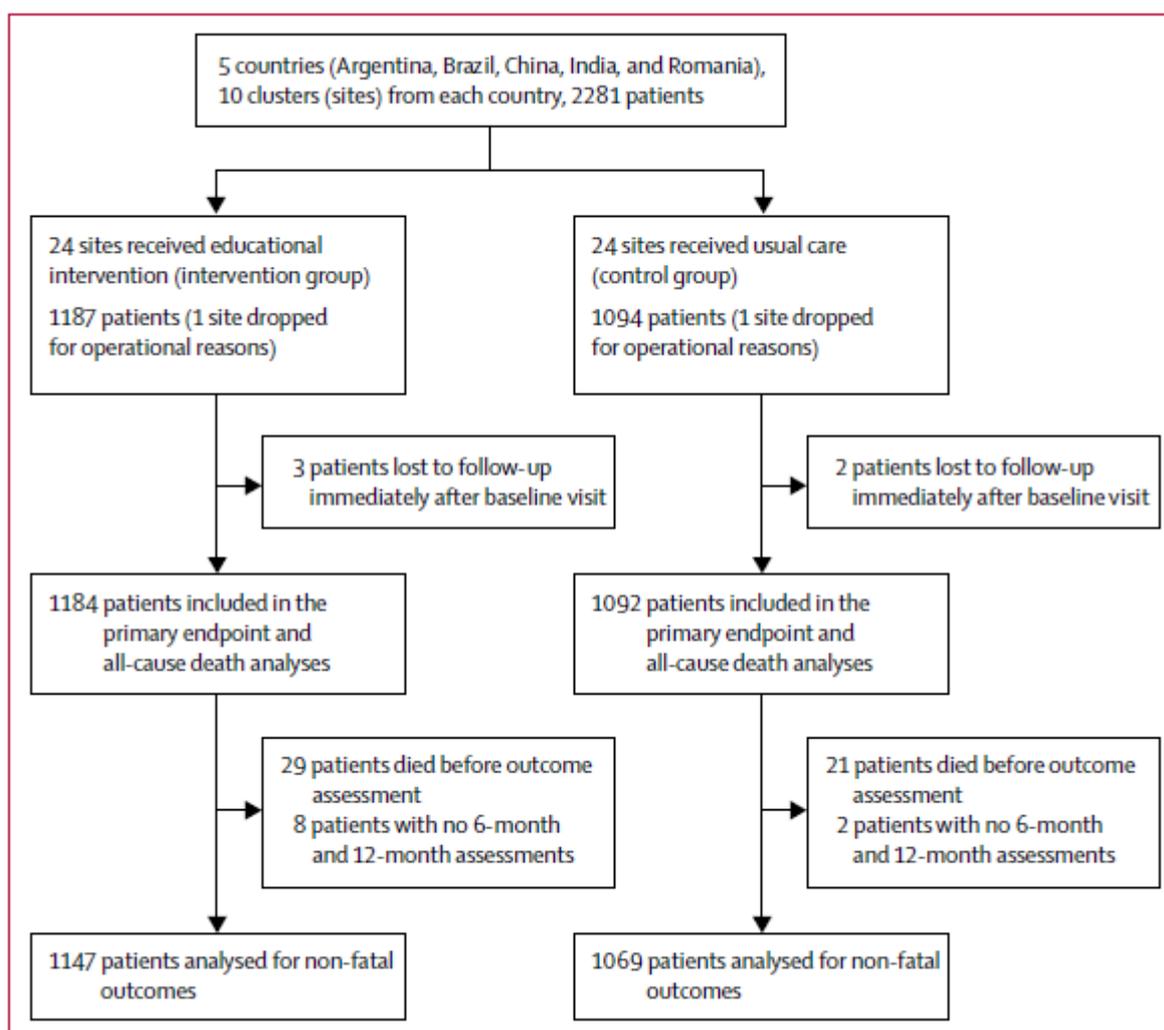
was encouraging initiation and persistence of oral anticoagulation. Educational materials were available only to clusters randomised to intervention, via a dedicated study website. The website included patient and provider educational materials, including a monograph, three webinars, a podcast, a trifold for patient education, and links to helpful websites and additional references. The monograph (appendix) was provided to and discussed with all interventional sites, with a question-and-answer session between the coordinating centre and the sites. The use of the online webinars (appendix), accessed from the Duke Learning Management System, varied among the five country intervention site leaders, ranging from 100% in Romania to only one site in China, where internet access was limited and the materials were shared as electronic files. Each country's national coordinating centre modified these resources to be more country-specific and to meet language needs. For example, in China, WeChat, a social media and instant messaging tool, was used for sharing best practices across intervention sites, under the coordination of a physician from the coordinating centre; in India, the materials were translated into the five common languages, and non-physician health workers educated patients and their families.

The monitoring and feedback component was developed to provide relevant information to coordinating centres and investigators in each country in order to: identify patients enrolled in the study who were not being treated with oral anticoagulants and to review opportunities for each patient not on treatment to start or restart medications; and identify patients at risk for not staying on medications, and to intervene to prevent discontinuation of oral anticoagulation and improve adherence. Finally, newsletters were distributed and monthly teleconferences between the physician national coordinators were done to share best practices between the intervention centres.

Data were collected at baseline, 6 months, and 12 months at all sites, whereas for the intervention sites there were additional telephone calls or patient visits at 1 month, 3 months, and 9 months. Otherwise, data collection was the same at all sites. Each country had a system for quality assurance that included site visits and data review verification of about 5% of the enrolled patients.

## Outcomes

The primary outcome was the change in the proportion of patients treated with oral anticoagulants, from baseline assessment to evaluation at 1 year. This included starting oral anticoagulation for patients who were not treated at baseline and continuing treatment for those who were treated at baseline. Key secondary outcomes were: proportion of patients who were on oral anticoagulation at baseline and were on oral anticoagulation at 6-month and 12-month visits (rate of persistence); and the proportion of patients who were not on oral anticoagulation at baseline but were on oral anticoagulation at 6-month and 12-month visits (rate of initiation). Other secondary clinical outcomes were: all-cause death; stroke (haemorrhagic and non-haemorrhagic); transient ischaemic attack; systemic embolism; major bleeding; clinically relevant non-major bleeding; myocardial infarction; atrial fibrillation ablation; and electrical cardioversion. Clinical events were reported by investigators according to the prespecified definitions<sup>12</sup> and were not adjudicated. Stroke was defined as a non-traumatic abrupt onset of a focal neurological deficit lasting at least 24 h. Transient ischaemic attack was defined as a non-traumatic abrupt onset of a focal neurological deficit lasting less than 24 h. Systemic embolism diagnosis required a history consistent with an acute loss of blood flow to a peripheral artery supported by evidence of embolism. Major bleeding was defined according to the International Society on Thrombosis and Hemostasis (ISTH) criteria. Clinically relevant non-major bleeding was defined as bleeding not meeting the ISTH definition for major bleeding but requiring change in therapy or extended hospitalisation.



**Figure 1: Trial profile**

## Statistical analysis

Sample size and power for the primary outcome was calculated by the Farrington and Manning score test<sup>14</sup> method using PASS13 (NCSS, LLC, Kaysville, UT, USA). Assuming oral anticoagulant use of 60% at baseline in the control group, an intra-cluster correlation of 0.02, 20–25 clusters per group with an average cluster size of 40–70 patients, and a two-sided type 1 error of 0.05, the study was powered at 88–98% to detect 10% absolute improvement in oral anticoagulant use at 1 year, and powered at 71–89% to detect 8% of such an improvement. With an expected average cluster size of 40 patients and 25 clusters in each group, we projected a total of 2000 patients needed to be enrolled in this study.

All analyses followed the intention-to-treat principle. Baseline characteristics for continuous variables were summarised as means (SDs) and medians (IQRs), with comparisons between groups made using the Wilcoxon rank-sum test; categorical variables were summarised as counts (percentages), with comparisons made using Pearson's  $\chi^2$  test. The primary outcome was analysed using a logistic regression model with generalised estimating equation (GEE)<sup>15</sup> to account for clustering effect and adjusted for baseline use of oral anticoagulants, country, and baseline risk factors. The odds ratio (OR; odds of change to use of oral anticoagulation in the intervention group to odds of change to use of oral anticoagulation in the control group at 12 months of follow-up) and 95% CIs were derived from the logistic model. Time-to-event methodology of Kaplan-Meier estimates (log-rank test) and Cox proportional hazards models, with shared frailties to account for the effect of clustering, adjusted for country and baseline risk factors, were used to analyse all-cause death, stroke, major bleeding, and systemic embolism. Hazard ratios (HRs; hazard of intervention to control) and 95% CIs were estimated using the Cox model. Additionally, for some clinical outcomes (clinically relevant non-major bleeding, myocardial infarction, transient ischaemic attack, atrial fibrillation ablation, and electrical cardio- version) for which date of the event was not collected, a logistic regression model was used to estimate the ORs and 95% CIs for intervention versus control. Adjusted models included country, oral anticoagulant use at baseline, and other potential baseline risk factors (appendix). All statistical tests were done at the nominal 0.05 (two-sided) significance level. All statistical analyses were done by the Duke Clinical Research Institute (Durham, NC, USA) using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

	Intervention group (n=1187)	Control group (n=1094)
<b>Country</b>		
Argentina	213 (18%)	130 (12%)
Brazil	212 (18%)	148 (14%)
China	305 (26%)	281 (26%)
India	208 (18%)	285 (26%)
Romania	249 (21%)	250 (23%)
<b>Demographics</b>		
<b>Age (years)</b>		
Mean (SD)	70 (11)	69 (12)
Median (IQR)	70 (63-77)	70 (62-78)
<b>Sex</b>		
Male	616 (52%)	586 (54%)
Female	571 (48%)	508 (46%)
<b>Years of education</b>		
<5	325 (27%)	329 (30%)
5-10	440 (37%)	413 (38%)
>10	422 (36%)	352 (32%)
<b>Residence area type</b>		
Urban or city	882 (74%)	809 (74%)
Rural or village	305 (26%)	285 (26%)
<b>Who lives with the patient?</b>		
Lives alone	127 (11%)	115 (11%)
Family	713 (60%)	663 (61%)
Spouse	325 (28%)	260 (27%)
Roommate	4 (<1%)	3 (<1%)
Other	11 (1%)	16 (2%)
<b>Medical history</b>		
New or recent atrial fibrillation (<3 months)	352 (30%)	351 (32%)
<b>Type of atrial fibrillation (for not new or recent atrial fibrillation)</b>		
Paroxysmal	156 (19%)	142 (19%)
Permanent	549 (67%)	437 (59%)
Persistent	112 (14%)	157 (21%)
<b>History of rheumatic valvular heart disease</b>	89 (8%)	131 (12%)
<b>Previous electrical cardioversion</b>	93 (8%)	92 (8%)
<b>Previous ablation for atrial fibrillation</b>	24 (2%)	14 (1%)
<b>History of major bleeding</b>	71 (6%)	28 (3%)
<b>History of peptic ulcer</b>	44 (4%)	49 (5%)
<b>History of anaemia requiring transfusion</b>	35 (3%)	22 (2%)
<b>History of deep vein thrombosis or pulmonary embolism</b>	34 (3%)	22 (2%)
<b>Creatinine clearance (ml/min)</b>		
Mean (SD)	71.4 (33.2)	72.8 (56.5)
Median (IQR)	68.0 (50.4-87.6)	65.1 (48.9-84.4)
<b>Renal dialysis</b>	8 (1%)	4 (<1%)
<b>Liver disease</b>	19 (2%)	18 (2%)
<b>Alcohol abuse (previous or ongoing)</b>	35 (3%)	39 (4%)

(Table 1 continues in next column)

	Intervention group (n=1187)	Control group (n=1094)
(Continued from previous column)		
<b>HAS-BLED score</b>		
Mean (SD)	1.6 (1.1)	1.5 (1.0)
Median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)
<b>Risk factors for stroke</b>		
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc score</b>		
Mean (SD)	3.6 (1.5)	3.7 (1.6)
Median (IQR)	3.0 (2.0-4.0)	4.0 (3.0-5.0)
<b>Age ≥75 years</b>	419 (35%)	413 (38%)
<b>Previous stroke</b>	216 (18%)	177 (16%)
<b>History of stroke</b>		
Recent (<1 year)	55 (5%)	52 (5%)
Remote (>1 year)	160 (14%)	125 (12%)
Unknown	1 (<1%)	0
<b>Type of stroke</b>		
Ischaemic	129 (60%)	99 (56%)
Embolic	46 (21%)	46 (26%)
Haemorrhagic	8 (4%)	12 (7%)
Unknown	33 (15%)	20 (11%)
<b>History of transient ischaemic attack</b>	73 (6%)	49 (5%)
<b>History of systemic embolism</b>	37 (3%)	15 (1%)
<b>Hypertension requiring treatment</b>	917 (77%)	854 (78%)
<b>Uncontrolled hypertension (&gt;160 mm Hg)</b>	164 (14%)	118 (11%)
<b>Diabetes</b>	298 (25%)	316 (29%)
<b>Heart failure or ejection fraction &lt;40%</b>	343 (29%)	378 (35%)
<b>Vascular disease</b>	76 (6%)	103 (9%)
<b>History of myocardial infarction</b>	231 (20%)	325 (30%)
<b>History of coronary revascularisation</b>	96 (8%)	97 (9%)
<b>Type of revascularisation</b>		
Coronary artery bypass grafting	18 (19%)	26 (27%)
Coronary stent placement	73 (76%)	67 (69%)
Both	5 (5%)	4 (4%)
<b>Antithrombotic treatment</b>		
<b>Type of anticoagulant at baseline</b>		
Vitamin K antagonist	697 (87%)	548 (78%)
Dabigatran	47 (6%)	71 (10%)
Rivaroxaban	31 (4%)	31 (4%)
Apixaban	13 (2%)	38 (5%)
Others	17 (2%)	16 (2%)
<b>Currently on aspirin</b>	330 (28%)	350 (32%)
<b>Currently on clopidogrel, prasugrel, or ticagrelor</b>	132 (11%)	103 (9%)

Data are n (%), unless indicated otherwise.

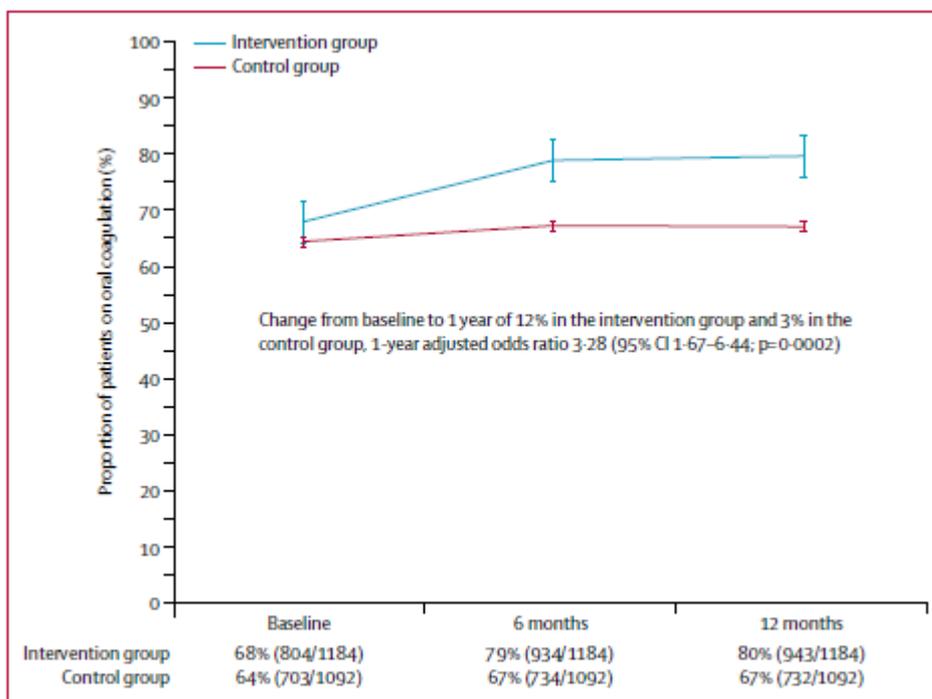
**Table 1: Baseline characteristics of the intervention and control groups**

## Role of the funding source

This study was an investigator-initiated project, with limited funding by independent research and educational grants from four pharmaceutical companies, who had no Nov 13, 2016 (figure 1). Five patients (<1%) were lost to follow-up after the baseline visit (three in the intervention group and two in the control group). None of the clusters were further excluded from the trial. The median follow-up was 12.0 months (IQR 11.8–12.2).

Site characteristics and baseline clinical and treatment-related patient characteristics according to country have been published previously.<sup>16</sup> In that analysis of the IMPACT-AF baseline dataset, we have demonstrated existing regional differences in patient characteristics and antithrombotic treatment among patients enrolled from the

five middle-income countries.<sup>16</sup> Baseline characteristics according to the randomised groups are presented in table 1. Age and sex were well balanced between the two groups. Similarly, educational level and socioeconomic factors were not different between the two groups. The intervention group had a higher proportion of patients with permanent atrial fibrillation, history of major bleeding, systemic embolism, and uncontrolled hypertension, and a lower proportion of patients with rheumatic valvular heart disease, heart failure, or left ventricular role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.



**Figure 2: Primary outcome**

Changes in the proportion of patients on oral anticoagulation treatment from baseline to 1 year in the intervention and control groups, adjusted for cluster effect, country, oral anticoagulation usage at baseline, and 27 baseline covariates (appendix).

	Intervention group (n=1184)	Control group (n=1092)	Adjusted odds ratio* (95% CI)	p value
Patients who were on oral anticoagulation at baseline, and were on oral anticoagulation at 1 year	761/804 (95%)	661/703 (94%)	1.68 (0.90-3.12)	0.10
Patients who were on oral anticoagulation at baseline, and were on oral anticoagulation at 6 months	775/804 (96%)	665/703 (95%)	1.81 (0.79-4.12)	0.16
Patients who were not on oral anticoagulation at baseline, but were on oral anticoagulation at 1 year	182/380 (48%)	71/389 (18%)	4.60 (2.20-9.63)	<0.0001
Patients who were not on oral anticoagulation at baseline, but were on oral anticoagulation at 6 months	159/380 (42%)	69/389 (18%)	3.94 (2.11-7.37)	<0.0001

Data are n/N (%), unless indicated otherwise. \*Representing the proportion increase in the intervention versus control groups, adjusted for cluster effect, country, oral anticoagulation usage at baseline, and 27 baseline covariates (see appendix).

**Table 2: Key secondary anticoagulation treatment outcomes in the intervention and control groups**

## Results

A total of 50 clusters (ten in each of the five countries) were initially recruited into the trial. Two clusters (both from Brazil), one from each group, were removed before enrolling any patient due to unexpected inability to engage in the trial. In the remaining 48 clusters, a total of 2281 patients were enrolled from June 11, 2014, to dysfunction, vascular disease, and previous myocardial infarction than the control group. Patients from the intervention group had a slightly lower mean CHA<sub>2</sub>DS<sub>2</sub>-VAsC score than patients from the control group (3·6 [SD 1·5] vs 3·7 [1·6]). There was an imbalance of type of antithrombotic treatment, with higher usage of the vitamin K antagonist in the intervention group and higher usage of the non-vitamin K-dependent oral anticoagulants and aspirin in the control group.

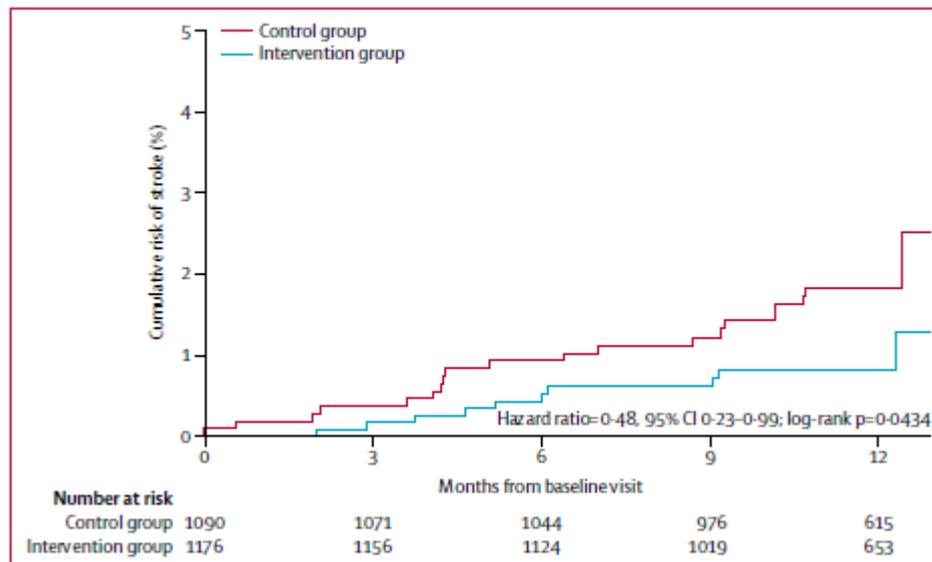
The proportion of patients on oral anticoagulation increased from 68% (804 of 1184 patients) at baseline to 80% (943 of 1184 patients) at 1 year in the intervention group (difference 12%) and from 64% (703 of 1092 patients) to 67% (732 of 1092 patients) in the control group (difference 3%), with an absolute difference in the change of oral anticoagulation use of 9·1% (95% CI 3·8–14·4; figure 2). This corresponds to an odds ratio of 3·28 (95% CI 1·67–6·44; adjusted p value=0·0002), representing the proportional increase in anticoagulation use from baseline to 1 year in the intervention group compared with the control group. The effect size in favour of the intervention was consistent across prespecified subgroups, with a significant interaction in the aspirin subgroup (appendix). The effect size in favour of the intervention was also preserved in the small subgroup of patients (n=220) with a history of rheumatic valvular heart disease (interaction p value=0·18). Although the study was not powered to show the intervention's effectiveness within each country, the primary outcome was consistent (interaction p value=0·41) across all five countries. Key secondary anticoagulation treatment outcomes by intervention versus control are presented in table 2. 761 (95%) of 804 patients who were on oral anticoagulants at baseline in the intervention group and 661 (94%) of 703 patients in the control group continued taking oral anticoagulants at 1 year, with no significant difference between groups. In the intervention group, the proportion of patients on vitamin K antagonists decreased slightly (from 87% [697 of 805 of patients] at baseline to 78% [700 of 893 of patients] at 1 year), in favour of the non-vitamin K-dependent oral anticoagulants; whereas in the control group, the proportion of patients on vitamin K antagonists remained the same (from 78% [548 of 704 patients] at baseline to 78% [551 of 707 patients] at 1 year). For patients who were not on oral anticoagulants at baseline, 48% (182 of 380 patients) in the intervention group and 18% (71 of 389 patients) in the control group were on oral anticoagulants at 1 year. This corresponds to an odds ratio of 4·60 (95% CI 2·20–9·63; adjusted p value <0·0001), representing the proportional increase in anticoagulation use from baseline to 1 year in the intervention group compared with the control group.

Clinical outcomes by intervention versus control are presented in table 3. There was a nominally significant reduction in stroke in the intervention group in comparison with the control group (HR 0·48, 95% CI 0·23–0·99; log-rank p=0·0434; figure 3). Adjusted Cox modelling for the stroke outcome resulted in a similar point estimate, but a wider confidence interval (HR 0·49, 95% CI 0·21–1·13; p=0·09). The number needed to treat was 100 patients exposed to intervention to prevent one stroke event over a 1-year period. All-cause death and the composite of stroke, systemic embolism, or major bleeding did not differ between the intervention and control groups. Major bleeding was also similar in the two groups (nine [1%] of 1147 patients vs seven [1%] of 1069 patients), whereas clinically relevant non-major bleeding was numerically higher in the intervention group versus the control group (40 [3%] of 1147 patients vs 31 [3%] of 1069 patients).

	Intervention group (n=1147)	Control group (n=1069)	Hazard ratio or odds ratio (95% CI)	p value
All cause death	62/1184 (5%)	56/1092 (5%)	1.03 (0.72-1.48)	0.88
Stroke	11 (1%)	21 (2%)	0.48 (0.23-0.99)	0.0434
Haemorrhagic	2 (<1%)	5 (<1%)	-	-
Ischaemic	9 (1%)	16 (2%)	-	-
Transient ischaemic attack	15 (1%)	14 (1%)	1.00 (0.48-2.08)*	0.99
Systemic embolism	2 (<1%)	1 (<1%)	1.87 (0.17-20.6)	0.61
Major bleeding	9 (1%)	7 (1%)	1.22 (0.45-3.27)	0.69
Clinically relevant non-major bleeding	40 (3%)	31 (3%)	1.21 (0.75-1.95)*	0.43
Myocardial infarction	19 (2%)	17 (2%)	1.04 (0.54-2.02)*	0.90
Atrial fibrillation ablation	8 (1%)	18 (2%)	0.41 (0.18-0.95)*	0.0369
Electrical cardioversion	8 (1%)	12 (1%)	0.62 (0.25-1.52)*	0.29
Composite outcome of stroke, systemic embolism, or major bleeding	22 (2%)	29 (3%)	0.70 (0.40-1.22)	0.21

Data are n/N (%) or n (%), unless indicated otherwise. \*Logistic regression models with odds ratio and 95% CIs were used for the comparison between the treatment groups.

**Table 3: Secondary clinical outcomes in the intervention and control groups**



**Figure 3: Kaplan-Meier curves for the cumulative risk of stroke**

## Discussion

We found that a multifaceted and multilevel educational intervention, which aimed to improve the use of oral anticoagulation in patients with atrial fibrillation and at risk for stroke, resulted in a significant increase in the proportion of patients treated with oral anticoagulants in five middle-income countries. The intervention, which was customised in each country, included education of patients and their families and of health-care providers, measurement, and feedback of performance. Although the trial was not powered to show a difference in clinical outcomes, the potential clinical impact of the intervention was highlighted by the observation of significantly fewer strokes in the intervention group, counterbalanced by modest and non-significant higher rates of clinically relevant non-major bleeding.

Whereas oral anticoagulation is highly effective in preventing atrial fibrillation-related strokes, worldwide it is used only in 58% of patients with risk factors for stroke, as shown by the RE-LY registry, including 164 sites from 46 countries.<sup>7</sup> Published registries have reported higher rates of treatment with oral anticoagulants in patients with atrial fibrillation.

The GARFIELD-AF registry found that the proportion of patients with atrial fibrillation on oral anticoagulation increased by almost 15% (from 57% in 2010–2011 to 71% in 2014–2015).<sup>17</sup> Similarly, in the GLORIA-AF registry, prescription of oral anticoagulants in patients with atrial fibrillation increased by 16% (from 64% in phase 1, when non-vitamin K-dependent oral anticoagulants were not available, to 80% in phase 2, enrolling patients between 2011 and 2014).<sup>18</sup>

However, these registries are typically initiated in centres that are focused on anticoagulation care and among patients who provide consent, and thus, the use of oral anticoagulants is likely overestimated compared with unselected populations.

Use of oral anticoagulation is even more limited in patients with atrial fibrillation from low-income and middle-income countries. Oral anticoagulant use is less than 40% in Eastern Europe and South America and less than 38% in Asia.<sup>7,19</sup> The reason might be related to the regional differences in health-care systems and resource availability, but also insufficient education of patients and physicians. This generates misperceptions around bleeding risk and a protective effect of antiplatelet therapy, and a lack of systematic approaches to review appropriateness of anticoagulation status at the patient level.<sup>7,19,20</sup> Therefore, increased education and better communication between all stakeholders (patients, caregivers, and health-care providers) are needed to improve anticoagulation treatment and reduce the occurrence of stroke in atrial fibrillation.<sup>20</sup>

A recent survey of 1147 patients with atrial fibrillation from eight high-income European countries suggested that the patients' education level and knowledge are directly related to the use of antithrombotic treatment.<sup>21</sup> Overall, 54% of patients reported knowing that oral anticoagulation was associated with risk of bleeding.<sup>21</sup> The awareness of oral anticoagulation-related risk of bleeding was lowest in patients without schooling (38%) and highest in those with a college or university education (57%).<sup>21</sup> This survey highlighted the potential opportunity to improve anticoagulation treatment in atrial fibrillation with education. Consequently, a European Heart Rhythm Association consensus document emphasised the need for patient education.<sup>21,22</sup> Additionally, physician decisions not to initiate oral anticoagulation therapy in eligible patients is one of the main barriers for the effective use of antithrombotic therapy in atrial fibrillation.<sup>23</sup> The need for frequent monitoring, medication costs, and lack of knowledge regarding the appropriate use of non-vitamin K antagonist oral anticoagulants were all shown to be related to unwillingness to initiate and maintain oral anticoagulation treatment in individual patients.<sup>23</sup> Health-care providers require the tools necessary not only to identify high-risk patients who would benefit from anticoagulation therapy, but also to provide appropriate therapy given the increasing choices in anticoagulants. We designed a multifaceted and multilevel educational intervention to address these well known barriers.

In addition to education of patients and physicians, the intervention included engagement of health-care providers in reviewing each patient's eligibility for oral anticoagulation. Because changing practice might be more successful by leveraging regional opportunities to enhance implementation, each country was encouraged to

customise their intervention based on local practice and resources. Patient education was part of the intervention in all countries, which was enhanced in India, for example, by the use of non-physician (or community) health workers, who have been part of a successful intervention in improving adherence following acute coronary syndromes.<sup>24</sup> Communication and sharing best practices among physicians was part of the intervention in all countries, and this was also enhanced with messaging tools in China (WeChat) and Argentina (WhatsApp), used for physician education, information sharing, and case discussions.

The PICANT study, done in Germany in 736 patients with an indication for long-term oral anticoagulation treatment (81% with atrial fibrillation), suggested that an educational intervention focused on patients might improve their knowledge about oral anticoagulation.<sup>10</sup> The TREAT study, which included 97 patients with atrial fibrillation on warfarin randomised to educational intervention or usual care, showed that theory-driven patient education had a significant impact on time in therapeutic range.<sup>9</sup> However, these studies were small and focused only on patient education. A larger and not yet published study (AEGEAN trial) randomised 1162 patients with atrial fibrillation who were initiating apixaban to receive either standard-of-care patient information or an educational programme. At 24 and 48 weeks, adherence to apixaban was high in both groups, with no additional value of educational programme over usual care.<sup>25</sup> However, this study had a more than 90% adherence rate to apixaban in both groups, highlighting the challenge of enrolling patients representative of general practice and the importance of a rigorous control group to determine whether anticoagulation-care is truly changed by a given intervention.

Our trial differs from earlier studies in being a large, international, randomised controlled trial, and the results establish that a customised, multifaceted, and multilevel educational intervention can improve the use of oral anticoagulation in patients with atrial fibrillation at risk for stroke. We used a cluster-randomised trial design in five countries representing five different world regions, according to the Global Burden of Disease classification.<sup>26</sup> This cluster-randomised design has previously been successful in showing improvement in the use of evidence-based therapies for patients with acute coronary syndromes in Brazil<sup>27</sup> and improvement in walking distance in newly detected heart failure treated by general practitioners.<sup>28</sup> In our study, the significant 9.1% absolute increase in the change of oral anticoagulant use from baseline to 1 year, observed in the intervention versus the control group, is clinically relevant. Based on registry data of relatively unselected patients,<sup>7,17–19,29</sup> we believe that the proportion of untreated patients in general practice in the countries included in our study is even higher than what we observed.

The relatively high use of oral anticoagulants at baseline in our study might relate in part to the inclusion of experienced centres and to the need for patients to provide informed consent, which likely resulted in a selected population. The fact that 94% of patients on oral anticoagulation at baseline remained on oral anticoagulation at 1 year in the control group underscores the high quality of care at these centres. When we examined the patients without oral anti-coagulation treatment at baseline, we demonstrated that about half of these untreated patients were able to be successfully treated with oral anticoagulants with the intervention that was tested in our trial. This study is one of the first to provide information about a crucially important question: of all patients with atrial fibrillation and risk of stroke who are not treated with oral anti-coagulants, what proportion could be treated as the result of a comprehensive intervention? Finally, in the intervention-group, improvement in oral anticoagulation use reduced the total number of strokes (ischaemic and haemorrhagic) by about 50%. Our findings of improved clinical outcomes are aligned with the results from another study where a nurse-led atrial fibrillation care initiative, providing patient education and monitoring, decreased the combined outcome of cardiovascular hospitalisation and cardiovascular death by 35%.<sup>30</sup>

Due to the cluster-randomised nature of our study design, in which recruited centres were assigned to the control group and to the need for consenting patients before entering the study, the baseline use of oral anticoagulation likely overestimates what is seen in general practice in the participating countries. Meanwhile, most of the sites were tertiary, academic, or private centres and, therefore, highly experienced centres. However, even in these well treated patients at baseline, an educational intervention improved the use of oral

anticoagulation. There were some imbalances between the intervention and control site populations, including a difference of about 10% between the number of patients enrolled, related to the modest total number of sites and potentially to the open-label nature of the trial. However, the enrolment procedures were similar at intervention and control sites. The open-label nature of the trial could be a limitation, although the small number of patients lost to follow-up is reassuring that this did not have an impact on follow-up or outcome ascertainment. The trial was an investigator-initiated project with limited funding, which did not allow the development of sophisticated tools for education and adherence measurement or intense intervention at the individual patient level. However, this might also be considered a strength, since the interventions used in this trial were simple, and therefore could be implemented in standard clinical practice, at least in middle-income countries. Another limitation is that the study was not powered to assess differences in the clinical outcomes between study groups. However, even though a much larger study would be needed to be adequately powered for clinical outcomes, the reduction in stroke observed in the intervention group was nominally significant and thus consistent with an important clinical benefit.

In conclusion, a customised, multifaceted, and multi-level educational intervention, aimed to improve oral anticoagulation use in patients with atrial fibrillation and at risk for stroke, resulted in a significant increase in the proportion of patients treated with anticoagulation. Such an intervention has the potential to improve stroke prevention around the world for patients with atrial fibrillation.

### **Contributors**

DV, RDL, MCB, DX, JJ, HRA, MPR, and CBG contributed to the study conception and design. DV, RDL, MCB, DX, JJ, HRA, and WH contributed to the acquisition of data. DV, RDL, MCB, DX, JJ, HRA, WH, YX, AOC, DYK, SDP, PGMBS, MLR, and CBG contributed to the analysis and interpretation of data. DV and CBG drafted the first version of the manuscript. All authors critically revised the manuscript and approved the final text.

### **Declaration of interests**

DV reports grants and speaker fees from Novartis Pharma Services, Pfizer, Servier Pharma, Johnson and Johnson, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Berlin Chemie Menarini, and Abbott/ Mylan; and consulting fees from AstraZeneca, Gedeon Richter, and Terapia, outside the submitted work. RDL reports consulting fees from Bayer Corporation US (Bayer AG/Bayer Japan), Boehringer Ingelheim, Daiichi Sankyo, Merck & Co, and Portola Pharmaceutical; grants and consulting fees from Bristol-Myers Squibb, GlaxoSmithKline, Medtronic PLC, and Pfizer, outside the submitted work. MCB reports research grants from Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer, and consulting fees and honoraria from Boehringer Ingelheim. DX reports grants from Cadila Pharmaceuticals, Boehringer Ingelheim, AstraZeneca India, Sanofi Aventis, Pfizer, National Institutes of Health (NIH), National Heart Lung and Blood Institute, outside the submitted work. YX reports grants from Daiichi Sankyo, Genentech, Janssen Pharmaceutica Products, and the American Heart Association, outside the submitted work.

DYK reports personal fees from AstraZeneca India, outside the submitted work. MPR reports grants from Medtronic Foundation, outside the submitted work. SDP reports grants and personal fees from Boston Scientific, Janssen Pharmaceutical, Bristol-Myers Squibb, Pfizer, grants from Daiichi Sankyo, Boehringer Ingelheim, US Food and Drug Administration (FDA), Gilead, and personal fees from Medtronic, outside the submitted work. OB reports grants from AstraZeneca, Amgen, Bayer, Roche Diagnosis, Boehringer Ingelheim, Ethicon (Johnson & Johnson), and Sanofi, outside the submitted work. CT is the national coordinator of the TREAT trial that compares ticagrelor versus clopidogrel (this is an independent study, with economic support from AstraZeneca). CT also reports grants from AstraZeneca, and personal fees from Pfizer, outside the submitted work. PGMBS reports grants from AstraZeneca, Sanofi, Pfizer, Bayer, and fees and honoraria from Boehringer Ingelheim and Daiichi Sankyo, outside the submitted work. CBG reports grants and personal fees from Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo; and grants from Bayer and Janssen, during the conduct of the study; personal fees from AbbVie, Boston Scientific,

Eli Lilly, Gilead, Hoffmann-La Roche, NIH, Sirtex, and Verseon; grants and personal fees from Armetheon, AstraZeneca, GlaxoSmithKline, The Medicine's Co, Medtronic, and Novartis; and grants from FDA, outside the submitted work. JJ, HRA, WH, AOC, KAF, MLR, and YH declare no competing interests.

### Acknowledgments

The authors thank Morgan deBlecourt, who provided editorial assistance for this manuscript as part of her regular duties as a medical editor employed by the Duke Clinical Research Institute, Durham, NC, USA. This study was supported by independent grants from Bayer Pharmaceuticals, Boehringer Ingelheim, and Daiichi Sankyo, and educational grants from Bristol-Myers Squibb, Pfizer Inc, and, in Argentina, Boehringer Ingelheim SA Argentina.

### References

- 1 Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014; 129: 837–47.
- 2 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; 22: 983–88.
- 3 Gladstone DJ, Bui E, Fang J, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke* 2009; 40: 235–40.
- 4 Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; 146: 857–67.
- 5 Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med* 2010; 123: 638–45.
- 6 Xian Y, O'Brien EC, Liang L, et al. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. *JAMA* 2017; 317: 1057–67.
- 7 Oldgren J, Healey JS, Ezekowitz M, et al. Variations in cause and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation Registry. *Circulation* 2014; 129: 1568–76.
- 8 Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation* 2007; 115: 2689–96.
- 8: Clarkesmith DE, Pattison HM, Lip GY, Lane DA. Atrial fibrillation patients: the TREAT randomised trial. *PLoS One* 2013; e74037.
- 9 Maikranz V, Siebenhofer A, Ulrich LR, et al. Does a complex intervention increase patient knowledge about oral anticoagulation?—a cluster-randomised controlled trial. *BMC Fam Pract* 2017; 18: 15.
- 10 Clarkesmith DE, Pattison HM, Khaing PH, Lane DA. Educational and behavioural interventions for anticoagulant therapy in patients with atrial fibrillation. *Cochrane Database Syst Rev* 2017; CD008600.
- 12 Rao MP, Ciobanu AO, Lopes RD, et al. A clustered randomized trial to IMProve treatment with AntiCoagulanTs in patients with Atrial Fibrillation (IMPACT-AF): design and rationale. *Am Heart J* 2016; 176: 107–13.
- 13 Donner A, Klar N. Design and analysis of cluster randomization trials in health research. London: Arnold, 2000.
- 14 Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Stat Med* 1990; 9: 1447–54.

- 15 Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986; 73: 13–22.
- 16 Vinereanu D, Al-Khalidi HR, Rao MP, et al. Regional differences in presentation and antithrombotic treatment of patients with atrial fibrillation: baseline characteristics from a clustered randomized trial to IMProve treatment with AntiCoagulanTs in patients with atrial fibrillation (IMPACT-AF). *Am Heart J* 2017; 192: 38–47.
- 17 Camm AJ, Accetta G, Ambrosio G, et al. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. *Heart* 2017; 103: 307–14.
- 18 O'Brien AD, et al. 2016 ESC Guidelines on Atrial Fibrillation. *European Heart Journal* 2016; 37: 286–366.
- 19 O'Brien AD, et al. 2016 ESC Guidelines on Atrial Fibrillation. *European Heart Journal* 2016; 37: 286–366.
- 20 Frankel DS, Parker SE, Rosenfeld LE, Gorelick PB. HRS/NSA 2014 Survey of atrial fibrillation and stroke: gaps in knowledge and perspective, opportunities for improvement. *J Stroke Cerebrovasc Dis* 2015; 24: 1691–700.
- 21 Hernández Madrid A, Potpara TS, Dagres N, et al. Differences in attitude, education, and knowledge about oral anticoagulation therapy among patients with atrial fibrillation in Europe: result of a self-assessment patient survey conducted by the European Heart Rhythm Association. *Europace* 2016; 18: 463–67.
- 22 Amara W, Larsen TB, Sciaraffia E, et al. Patients' attitude and knowledge about oral anticoagulation therapy: results of a self-assessment survey in patients with atrial fibrillation conducted by the European Heart Rhythm Association. *Europace* 2016; 18: 151–55.
- 23 Glauser TA, Barnes J, Nevins H, Cerenzia W. The educational needs of clinicians regarding anticoagulation therapy for prevention of thromboembolism and stroke in patients with atrial fibrillation. *Am J Med Qual* 2016; 31: 38–46.
- 24 Xavier D, Gupta R, Kamath D, et al. Community health worker-based intervention for adherence to drugs and lifestyle change after acute coronary syndrome: a multicentre, open, randomised controlled trial. *Lancet Diabetes Endocrinol* 2016; 4: 244–53.
- 25 Montalescot G. Adherence and persistence to Apixaban treatment in patients with non valvular atrial fibrillation is high and similar with standard of care patient education or with an additional educational program: the randomized AEGEAN study. *Circulation* 2016; A18842.
- 26 GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 385: 117–71.
- 27 Berwanger O, Guimarães HP, Laranjeira LN, et al. Effect of a multifaceted intervention on use of evidence-based therapies in patients with acute coronary syndromes in Brazil: the BRIDGE-ACS randomized trial. *JAMA* 2012; 307: 2041–49.
- 29 Lip GY, Laroche C, Boriani G, et al. Regional differences in presentation and treatment of patients with atrial fibrillation in Europe: a report from the EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace* 2015;
- 30 Hendriks JM, de Wit R, Crijns HJ, et al. Nurse-led care vs usual care for patients with atrial fibrillation: results of a randomized trial of integrated chronic care vs routine clinical care in ambulatory patients with atrial fibrillation. *Eur Heart J* 2012; 33: 2692–99.