ORIGINAL RESEARCH

Electronic Alert System for Improving Stroke Prevention Among Hospitalized Oral-Anticoagulation-Naïve Patients With Atrial Fibrillation: A Randomized Trial

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***Background*—**Many patients with atrial fibrillation (AF) do not receive oral anticoagulants (OAC) for the prevention of stroke and systemic embolism. We aimed to improve the prescription of (OAC) among hospitalized patients with AF.

***Methods and Results*—**We developed a computer-based electronic alert system for identifying hospitalized OAC-naïve patients with AF. The alert system contained a CHA_2DS_2-VASc score calculation tool and provided recommendations for OAC prescription. The alert system was tested in a 1:1 randomized controlled trial at the University Hospital Bern: Patients with suspected AF without an active prescription order were allocated to an alert group in which an alert was issued in the electronic patient chart and order entry system or to a control group in which no alert was issued. The primary end point was the rate of adequate OAC prescription at hospital discharge, defined as prescription in OAC-naïve men and women with CHA_2DS_2-VASc score $\geq$1 and $\geq$2, respectively. Overall, 889 OAC-naïve patients (455 from the alert group and 434 from the control group) were eligible for analysis. Although the CHA_2DS_2-VASc score module was used in only 48 (10.5%) patients from the alert group, 100 (22.0%) patients from the alert group versus 69 (15.9%) from the control group received adequate OAC prescription (relative risk 1.38; P=0.021). OAC or antiplatelet therapy was prescribed in 325 (71.4%) patients from the alert group versus 271 (62.4%) from the control group (P=0.004).

***Conclusions*—**Versus standard care, the alert system modestly improved OAC prescription among consecutive hospitalized AF patients.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT02455102. **(*J Am Heart Assoc*. 2016;5: e003776 doi: 10.1161/JAHA.116.003776)**

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Atrial fibrillation (AF) is the most common heart rhythm disorder and its prevalence is consistently increasing.[1,2] One quarter of all 40-year-olds will develop this arrhythmia during the course of their lives.[3] AF increases the risk of stroke by 5 times[4] and doubles the risk of cardiovascular deaths and strokes after just 1 year.[5]

Oral anticoagulation therapy (OAC) with vitamin K antagonists reduces the risk of stroke and systemic embolism by ≈80% compared with placebo.[6] The direct oral anticoagulants are at least as effective as vitamin K antagonists. However, direct oral anticoagulants confer improved safety as compared with vitamin K antagonists in terms of bleeding complications.[7–10]

Current guidelines of the American Heart Association, the American College of Cardiology, and the European Society of Cardiology recommend the calculation of the CHA_2DS_2-VASc score in all patients with AF.[6,11] In patients with a score of $\geq$1 point with the exception of women without additional risk factor, OAC is recommended for the prevention of stroke and systemic embolism.[11] However, many patients with AF do not take OAC as recommended by the guidelines.[12]

Undertreatment can be reduced by increasing adherence rates to medications at the patient level.[13] However, better quality of treatment may also be achieved by making the physicians in charge aware of a problem that needs to be

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Accompanying Tables S1, S2, and Figure S1 are available at http://jaha.ahajournals.org/content/5/7/e003776/DC1/embed/inline-supplementary-material-1.pdf

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addressed. In this respect, computer-based electronic alert systems or clinical decision support systems may improve the prescription of recommended therapy among hospitalized patients.[14,15]

In a randomized controlled clinical trial, a single computer alert to the physician in charge increased the rate of adequate prescriptions of thromboprophylaxis and reduced the rate of venous thromboembolism by 41%.[16] It remains unclear whether computer-based electronic alert systems improve adequate OAC prescription among hospitalized AF patients.

Methods

Alert System

We developed a computer-based electronic alert system for identifying consecutive hospitalized OAC-naïve patients with AF and tested the hypothesis that such an alert system would improve OAC prescription.

The alert system automatically identified hospitalized patients with AF without an active OAC prescription in the electronic order entry system. The alert system was incorporated into the electronic medical chart and order entry system of the University Hospital in Bern, Switzerland. It recognized AF by permanently searching diagnosis lists and physician notes of the entire electronic patient chart database for free text entries of AF or its various abbreviations. Alerts were issued 24 hours after the onset of hospital stay if the following 4 criteria for an individual patient were present: (1) AF detected by search criteria; (2) no active prescription order for anticoagulants, including unfractionated or low-molecular-weight heparin, fondaparinux, direct oral anticoagulants, or vitamin K antagonists; (3) at least 1 electronic drug prescription order other than an anticoagulant had to be in place in the order entry system; and (4) the patient was randomized to the alert group. Once the criteria were fulfilled, the alert was issued in the electronic patient chart. The alert was visible to physicians and nurses, but only physicians were enabled to respond to the alert. In the first alert screen (Figure 1), the physician was notified that this patient had suspected AF without an active OAC prescription. In addition, the physician was asked to confirm the presence of AF. The physician in charge had the option to complete the CHA_2DS_2-VASc score electronically or to reject the alert if there was no AF. If AF was present but the physician was unable to complete the CHA_2DS_2-VASc score, he or she was able to postpone the action 3 times. During this time, the alert remained active. After 3 times of rejecting the alert, the physician in charge was informed that the alert would permanently disappear from the electronic patient chart. If the physician in charge agreed to calculate the CHA_2DS_2-VASc score, a new screen with the CHA_2DS_2-VASc score items opened (Figure S1). The system automatically entered the information for the score items sex and age. The system also calculated the score once the remaining items of the score were entered. In men with a calculated score <1 and women with a score <2, no further information was provided to the physician and the alert disappeared. For all other patients with increased CHA_2DS_2-VASc score, an additional screen opened, containing the current recommendations from the European Society of Cardiology for stroke prevention in patients with AF with the following text.[11]

The alert system was tested and adjusted in a passive run-in phase in collaboration with the IT Department of the University Hospital (Inselspital) Bern. Instructions for use of the alert system were provided in the electronic medical chart

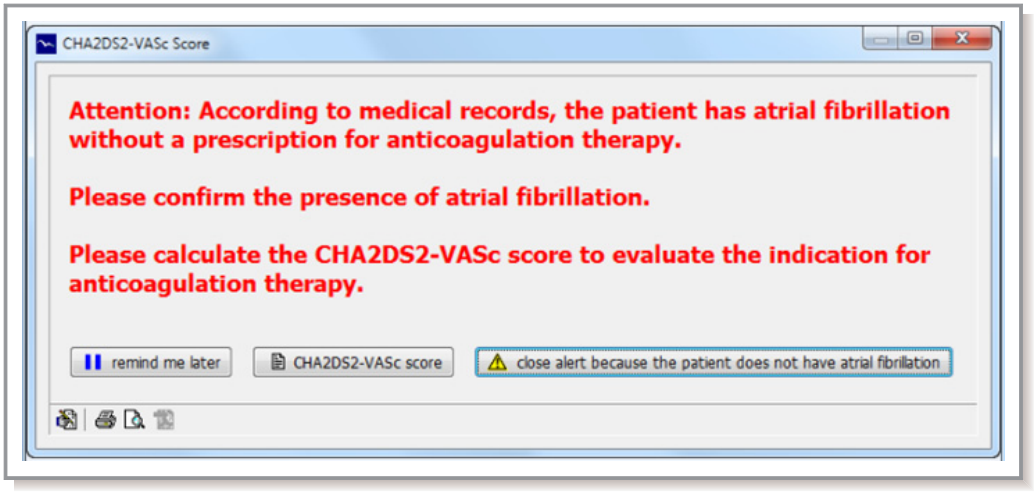

Figure 1. Electronic alert screen that is sent to physicians in charge of patients with atrial fibrillation but without oral anticoagulation treatment.

and order entry system. In addition, the heads of the medical departments were asked to inform their medical staff about the study.

Study Design

From September 2014 until October 2015 at the University Hospital Bern, we randomly assigned 1707 patients in a 1:1 fashion to the alert group (n=877) and to the control group (n=830) where no alert was issued. Randomization was performed electronically by automatically generating a number between 1 and 65 535 for each eligible patient. Patients with odd numbers were randomized to the alert group, whereas patients with even numbers were randomized to the control group.

All hospitalized patients aged ≥18 years with AF but without an active OAC prescription in the order entry system were included. There were no exclusion criteria.

The study (ClinicalTrials.gov. Identifier: NCT02455102) was approved by the institutional review board at the University of Bern. Informed consent by the patients was waived for the following reasons: (1) The study did not involve an intervention to patients but to physicians. The intervention served to remind the responsible physician to assess the stroke risk in patients with AF and to consider the prescription of preventive measures if an increased risk of stroke was present. Therefore, the alert was regarded as a clinical decision support system to help the physician to comply with current international consensus guidelines. However, the responsible physician solely carried the responsibility for ordering or not ordering measures to prevent stroke in patients with AF; (2) there was no direct or indirect patient contact during the study (chart review from the hospital stay only; and (3) a consent procedure in control group patients without alert was regarded as unethical and would have confounded the outcome.

As this was a hospital-wide quality improvement initiative, which involved all departments except pediatrics, approval was also obtained from the hospital management.

End Points

The primary end point of the study was the rate of adequate OAC prescription at hospital discharge, defined as prescription of any of the recommended drug regimens in OAC-naïve men with CHA_2DS_2-VASc score ≥1 and in OAC-naïve women with CHA_2DS_2-VASc score ≥2. Patients were considered OAC-naïve if they were not receiving OAC within 30 days prior to randomization. The secondary end point was the use of the CHA_2DS_2-VASc score calculation tool by the physician in charge. We also collected data to calculate the HASBLED score. This score indicates bleeding risk and includes the risk factors hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile INR, elderly, and drugs or alcohol abuse.[17]

Statistical Analysis

For sample size calculation, we assumed a 30% rate of adequate OAC prescription in the alert group and a 20% rate in the control group. Using a power of 90% and a 2-sided alpha of 5%, at least 412 OAC-naïve AF patients per group were required to reject the null hypothesis. During the recruitment phase, we continuously monitored all randomized patients whether they were OAC naïve and had confirmed AF by medical record review. We planned to terminate the patient recruitment phase once at least 412 OAC-naïve AF patients per group were eligible for analysis.

Data for baseline characteristics and the primary and secondary end points are presented as absolute numbers and percentages or as means and standard deviations for categorical or continuous variables, respectively. *P*-values for differences between the groups with regard to end points are calculated with χ^2 tests. All *P*-values are 2-sided and *P*-values <0.05 were considered significant. For the primary end point, we additionally calculated the relative risk for ordering adequate OAC prescription comparing the alert and control groups. All analyses were performed with IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp, Armonk, NY).

Results

Patient Characteristics

A total of 889 OAC-naïve AF patients were eligible for analysis (Figure 2). Mean (SD) age was 73.9 (11.3) years. Overall, 359 (40.3%), 48 (5.4%), and 31 (3.5%) patients had paroxysmal, permanent, and persistent AF, respectively, whereas in 451 (50.7%) patients, the type of AF was unknown. Both groups were balanced with respect to baseline characteristics with the exception of a higher rate of systemic hypertension, a trend toward a higher rate of transient ischemic attack, and a trend toward a lower rate of renal dysfunction in the alert group (Table 1). The most frequent reasons for hospital admission were acute coronary syndrome or other cardiovascular disease (30.0%), cancer (10.6%), nonpulmonary infection (7.9%), stroke (6.9%), and heart failure (6.4%) (Table 2). The mean duration of the hospital stay was 9.4 (10.8) days.

Very few patients had a CHA_2DS_2-VASC score of 0, and there were only 10 women with a CHA_2DS_2-VASC score of 1 (Table S1). Overall, 856 (96.3%) of the patients were OAC candidates based on the CHA_2DS_2-VASC score. There was no difference in the proportion of OAC candidates based on the CHA_2DS_2-VASC score between the alert (443; 97.4%) and the

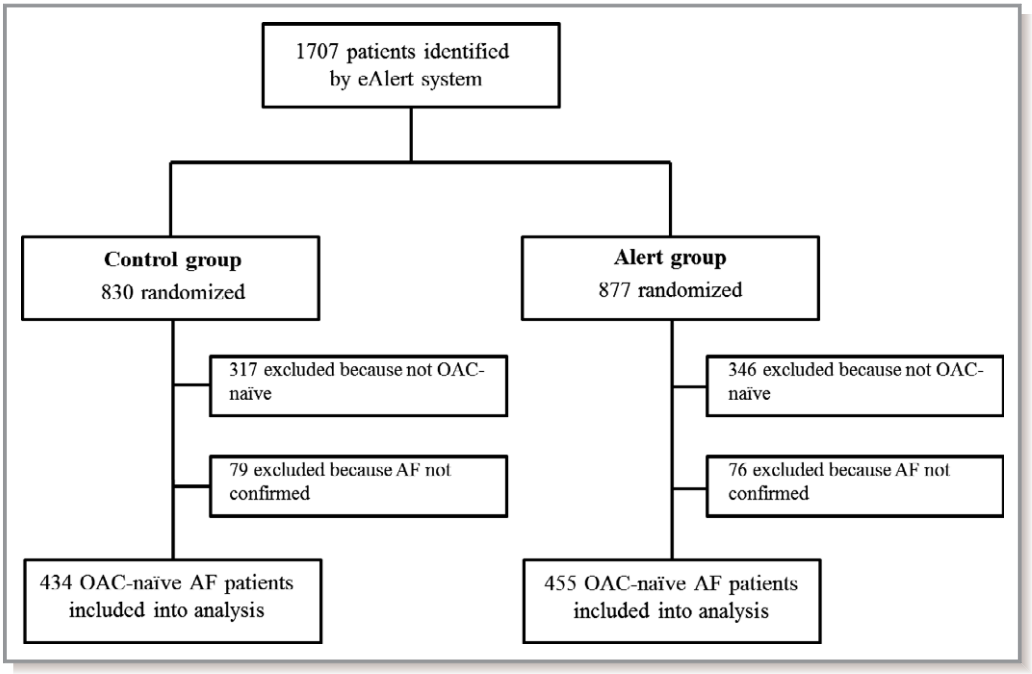

Figure 2. Flow chart of the patients whose physicians in charge received electronic alerts reminding them about patients with atrial fibrillation without ongoing oral anticoagulant treatment. AF indicates atrial fibrillation; OAC, oral anticoagulation therapy.

control (413; 95.2%) groups (P=0.083). On the other hand, 391 (44.0%) patients had a HASBLED score of ≥3. There was no difference in the proportion of patients with HASBLED score of ≥3 between the alert (208; 45.7%) and the control (183; 42.2%) groups (P=0.287). There were only 32 (3.6%) patients with a HASBLED score ≥5 (Table S2). There was no difference in the proportion of patients with HASBLED score of ≥5 between the alert (16; 3.5%) and the control (16; 3.7%) groups (P=0.892).

End Points

Overall, 100 (22.0%) patients from the alert group versus 69 (15.9%) from the control group received an adequate OAC prescription (Table 3) (relative risk 1.38; P=0.021). In patients who did not receive an adequate OAC prescription at discharge, aspirin 100 mg per day was ordered in 199 (56.1%) patients from the alert group and 183 (50.3%) patients from the control group (P=0.12); an adenosine diphosphate-receptor antagonist was ordered in 81 (22.8%) versus 81 (22.3%), respectively (P=0.86); dual antiplatelet therapy was ordered in 55 (15.5%) and 63 (17.3%), respectively (P=0.51). OAC or antiplatelet therapy was prescribed in 325 (71.4%) patients from the alert group versus 271 (62.4%) from the control group (P=0.004).

In 48 (10.5%) patients from the alert group, physicians used the electronic entry system to calculate the CHA_2DS_2-VASc score. Among these, 19 (39.6%) calculations were identical as compared with data obtained from discharge letters and 16 (37.5%) calculations differed by 1 point. Only 1 patient judged to have an increased score according to information from the discharge letter was classified as a low-risk patient by the physician in charge. In patients from the alert group, an OAC prescription was present in 11 (22.9%) patients whose physicians used the CHA_2DS_2-VASc score calculation tool and 89 (21.9%) patients whose physicians did not use it (P=0.87).

Discussion

In this randomized controlled clinical trial, the computer-based alert system increased adequate OAC prescription rates as compared to standard of care among consecutive hospitalized OAC-naïve patients with AF.

The finding is in agreement with the results of a previous study from our group testing the effectiveness of a clinical decision support system in the prevention of venous thromboembolism.[16] Taken the findings from these 2 randomized trials together, there is increasing evidence supporting the implementation of computerized decision support systems in cardiovascular medicine. Both alert systems significantly increased adequate prescription rates. In the present study, the observed rates of adequate OAC prescription of 22.0% in the alert group and 15.9% in the control group were somewhat lower than expected (30% versus 20%), respectively.

Table 1. Clinical Baseline Characteristics of the Patients Stratified for Randomization Group

	Randomization Group	
	Control	Alert
Number	434	455
Sex		
Male	292 (67.3)	300 (65.9)
Female	142 (32.7)	155 (34.1)
Age (y)	73.3 (11.8)	74.4 (10.9)
Type of atrial fibrillation		
Paroxysmal	174 (40.1)	185 (40.7)
Permanent	25 (5.8)	23 (5.1)
Persistent	15 (3.5)	16 (3.5)
Unknown	220 (50.7)	231 (50.8)
History of stroke	27 (6.2)	41 (9.0)
History of transient ischemic attack	13 (3.0)	26 (5.7)
History of venous thromboembolism	25 (5.8)	35 (7.7)
History of systemic embolism	4 (0.9)	3 (0.7)
Vascular disease*	154 (35.5)	179 (39.3)
Congestive heart failure†	134 (30.9)	137 (30.1)
Diabetes mellitus	93 (21.4)	104 (22.9)
Systemic hypertension	229 (52.8)	276 (60.7)
Bleeding‡	143 (32.9)	140 (30.8)
Renal dysfunction§	100 (23.0)	80 (17.6)
Hepatic impairment‖	16 (3.7)	15 (3.3)
Alcohol intake¶	23 (5.3)	20 (4.4)
Antiplatelet or nonsteroidal antirheumatic drug	235 (54.1)	265 (58.2)

Values are numbers and percentages for categorical data or means with standard deviation for continuous data.
*Myocardial infarction, peripheral artery disease, or aortic plaque.
†Chronic heart failure or left ventricular ejection fraction ≤40%.
‡History of major bleeding and predisposition (anemia).
§Creatinine clearance <30 mL/min.
‖Aminotransferase >3× upper limit of normal.
¶≥Eight units alcohol per week.

Of note, the tool to calculate the CHA_2DS_2-VASc score was used in a minority of patients. Nevertheless, a simple reminder of untreated AF has obviously increased awareness and improved treatment quality offered by the physicians in charge.

Due to the poor use of the CHA_2DS_2-VASc score tool, we were only able to evaluate the accuracy of the CHA_2DS_2-VASc score calculation in about 10% of the patients from the alert group. As compared with our calculations of the CHA_2DS_2-VASc score based on information from discharge letters, the CHA_2DS_2-VASc scores calculated with the tool were quite accurate. Only 1 patient was classified as low risk by the tool

Table 2. Diagnoses, Which Were the Main Reason for Hospital Admission, Stratified by Randomization Group

	Group	
Reason	Control	Alert
Cardiovascular disease/rhythm disorder	129 (29.7)	138 (30.3)
Heart failure (NYHA III and IV)	31 (7.1)	26 (5.7)
Acute stroke (ischemic or hemorrhagic)	27 (6.2)	35 (7.7)
Cancer	48 (11.1)	46 (10.1)
Nonpulmonary infection or sepsis	35 (8.1)	35 (7.7)
Gastrointestinal bleeding	11 (2.5)	6 (1.3)
Pneumonia	8 (1.8)	6 (1.3)
COPD	3 (0.7)	0 (0.0)
Renal failure*	8 (1.8)	5 (1.1)
Inflammatory or rheumatic disease	4 (0.9)	4 (0.9)
Liver cirrhosis or hepatobiliary disease	2 (0.5)	7 (1.5)
Endocrine disease (including diabetes)	1 (0.2)	3 (0.7)
Hematological disease (nonmalignant)	0 (0.0)	1 (0.2)
Other medical condition	127 (29.3)	143 (31.4)

Values are numbers and percentages. COPD indicates chronic obstructive pulmonary disease; NYHA, New York Heart Association.
*Creatinine clearance <30 mL/min.

but as high risk by information from the discharge letter. Interestingly, the use of the CHA_2DS_2-VASc score calculation tool had no impact on the OAC prescription rate. Reasons for not using the CHA_2DS_2-VASc score tool may include knowledge of the CHA_2DS_2-VASc score prior to the alert, time constraints, the high rate of non-sense alerts, and known contraindication to OAC because of an increased risk of bleeding. In this respect it was notable that ≈40% of the

Table 3. Vitamin K Antagonist and Direct Oral Anticoagulant Therapy Stratified for Randomization Group

	Group		
	Control	Alert	*P* Value*
Any prescription			
Vitamin K antagonist	32 (7.4)	52 (11.4)	0.039
Direct oral anticoagulant	38 (8.8)	48 (10.5)	0.366
Total	70 (16.1)	100 (22.0)	0.027
Adequate prescription			
Vitamin K antagonist	32 (7.4)	52 (11.4)	0.039
Direct oral anticoagulant	37 (8.5)	48 (10.5)	0.305
Total	69 (15.9)	100 (22.0)	0.021

Values are numbers and percentages.
*Calculated with χ^2 test.

patients in the study had a HASBLED score ≥3, indicating increased bleeding risk.[11] This may also be a reason for the overall low OAC prescription rate in the study. Of relevance, a considerable amount of patients received antiplatelet therapy, and as compared with the control group more patients from the alert group received OAC or antiplatelet therapy. A previous clinical decision support system was developed to facilitate clinical decision making with regard to OAC treatment in AF patients.[18] This system included both the calculation of the CHA_2DS_2-VASc and the HASBLED scores. However, it did not include what we think is the main benefit of our electronic alert system, namely, to issue alerts to patients with suspected AF without an active OAC prescription.

A limitation of our alert system was the high rate of non-sense alerts for patients who were not OAC-naïve because alerts were often issued before anticoagulation treatment was ordered through the electronic prescription system. Prior to the randomization phase, the rate of non-sense alerts was reduced by issuing alerts not directly on admission but 24 hours after the onset of the hospital stay. Very few departments at the Inselspital did use the electronic patient chart only for entering diagnoses but not for prescription of pharmaceutical treatments. This problem was then solved through sending alerts only if at least 1 drug has been prescribed through the alert system at 24 hours. Another problem was that many patients had paused OAC therapy due to planned surgical procedures. Patients with paused OAC therapy were identified by reviewing medical discharge letters and then excluded from the analysis. In addition, alerts were issued for several patients in whom AF was identified by the alert system but not confirmed by the treating physician. We think that the use of the CHA_2DS_2-VASc score calculation tool and the rate of adequate OAC prescription can be further improved by reducing the rate of non-sense alerts. We plan to continuously improve the identification of OAC-naïve patients and integrate the alert system in routine clinical practice. Further limitations of our study were the single-center setting, and the lack of systematic evaluation of why anticoagulation was not given. Physicians' acceptance of the alert was not assessed systematically either, nor was the potential impact of other electronic alert systems on the present alert system considered. The strengths of the present study include its randomized design and chart reviews of bleeding and stroke risks. The intervention was designed to modify physician behavior, but randomization was at the patient level. Since individual physicians may have treated several patients, the observations are not independent, and the outcome analysis typically should account for clustering of patients within physicians. However, since more than 500 physicians were involved in the study, such a cluster analysis was deemed less helpful.

An increase in the prescription rate of anticoagulant treatment in AF may translate into a reduction of the future risk of stroke. We did not collect data to investigate the effect of the alert system on the risk of stroke and systemic embolism. A prospective multicenter trial testing the effects of the alert system on end points is therefore encouraged. The total cost for the entire project was US $230 000, of which the majority was used for developing and testing of the alert system. Therefore, the implementation of the alert system in other hospitals seems feasible.

In conclusion, we developed and tested a novel electronic decision support system for improving adequate stroke prevention measures among hospitalized OAC-naïve patients with AF. In comparison to routine clinical practice, this alert system modestly increased adequate OAC prescription. Our results suggest that hospitals with electronic patient chart and order entry systems may consider implementing similar computer-based alerts to increase physician awareness of untreated AF.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. The categories of the CHA_2DS_2-VASC-Score stratified for randomization group

	Group	
CHA_2DS_2VASC-Score	**Control**	**Alert**
0	15 (3.5)	8 (1.8)
1 (women)	6 (1.4)	4 (0.9)
1 (men)	38 (8.8)	39 (8.6)
2	69 (15.9)	57 (12.5)
3	89 (20.5)	98 (21.5)
4	87 (20.0)	97 (21.3)
5	75 (17.3)	63 (13.8)
6	30 (6.9)	57 (12.5)
7	19 (4.4)	24 (5.3)
8	6 (1.4)	8 (1.8)
9	0 (0.0)	0 (0.0)

Values are numbers and percentages.

Table S2. The categories of the HASBLED-Score stratified for randomization group

	Group	
HASBLED-Score	**Control**	**Alert**
0	32 (7.4)	25 (5.5)
1	79 (18.2)	84 (18.5)
2	140 (32.3)	138 (30.3)
3	112 (25.8)	136 (29.9)
4	55 (12.7)	56 (12.3)
5	13 (3.0)	14 (3.1)
6	3 (0.7)	2 (0.4)
7	0 (0.0)	0 (0.0)
8	0 (0.0)	0 (0.0)
9	0 (0.0)	0 (0.0)

Values are numbers and percentages.

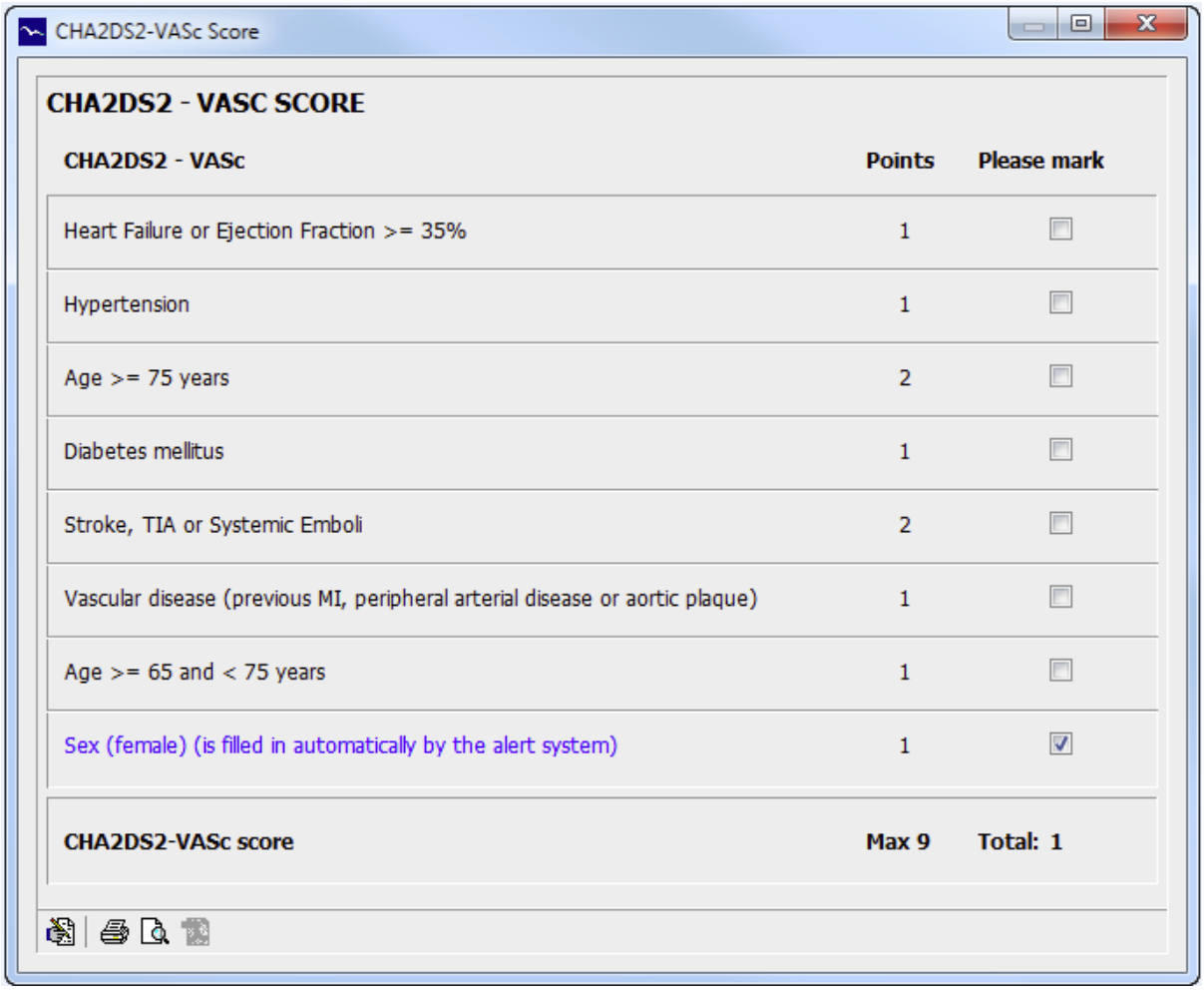

Figure S1. CHA_2DS_2-VASc score calculation tool for physicians in charge of patients with atrial fibrillation but without ongoing oral anticoagulant treatment