RESEARCH ARTICLE

Areas of improvement in anticoagulant safety. Data from the CACAO study, a cohort in general practice

Paul Frappe1,2,3*, Joël Cogneau4, Yoann Gaboreau5,6, Nathan Abenhaîm1, Marc Bayen7, Matthieu Calafiore7, Claude Guichard4, Jean-Pierre Jacquet8, François Lacoin4, Laurent Bertoletti2,3,8, CACAO study investigators¶

1 Department of General Practice, University of Saint-Etienne, Saint-Etienne, France, 2 Inserm U 1059, Sainbiose DVH, University of Saint-Etienne, Saint-Etienne, France, 3 CIC-EC 1408, Saint-Etienne, France, 4 Institut de Recherche en Médecine Générale, Paris, France, 5 Department of General Practice, Grenoble Alpes University, Grenoble, France, 6 TIMC-IMAG UMR 5525, Grenoble Alpes University, Grenoble, France, 7 Department of General Practice, University of Lille, Lille, France, 8 Department of Vascular Medicine and Therapeutics, CHU de Saint-Etienne, Saint-Etienne, France

¶ Investigators participating in the CACAO study are listed in the Appendix.

* paul.frappe@univ-st-etienne.fr

Abstract

Background
Real-world studies on anticoagulants are mostly performed on health insurance databases, limited to reported events, and sometimes far from every-day issues in family practice. We assess the presence of data for safe monitoring of oral anticoagulants in general practice, and compare patients’ knowledge of taking an anticoagulant between vitamin K antagonists (VKA) and direct anticoagulants (DOAC), and the general practitioner’s perception of their adherence to anticoagulation.

Methods
The CACAO study is a national cohort study, conducted by general practitioners on ambulatory patients under oral anticoagulant. In the first phase, investigators provided safety data available from medical records at inclusion. They also evaluated patients’ knowledge about anticoagulation and graded their perception of patients’ adherence.

Results
Between April and December 2014, 463 general practitioners included 7154 patients. Renal and hepatic function tests were respectively unavailable in 109 (7.5%) and 359 (24.7%) DOAC patients. Among patients with atrial fibrillation, 345 patients (6.9%) had a questionable indication of anticoagulant (CHA2DS2-Vasc<2). One hundred and thirty-three VKA patients (2.3%) and 70 DOAC patients (4.9%) answered they took no anticoagulant (p<0.0001). According to general practitioners’ perception, 430 patients (6.1%) were classified as “not very” or “not adherent”, with no difference between groups.
Conclusions
Our results highlight the efforts needed to improve anticoagulant safety in daily practice: decreasing the rate of unknown biological data in patients with DOACs or the rate of patients with VKA with no strong indication of anticoagulation, and improving patient knowledge with regard to their anticoagulant. Patients’ adherence seems highly over-estimated by the general practitioners.

Clinical trial registration
ClinicalTrials.gov NCT02376777

Introduction
In ambulatory care, anticoagulants are involved in 12% of suspected adverse drug reactions (ADR) [1]. In older patients, they constitute the first drug implicated in suspected ADR [1] and the first cause of admission to emergency department for an ADR [2]. Inadequate drug monitoring and ignoring clinical or laboratory results are the most frequent omission errors leading to a preventable ADR in an ambulatory context [3].

Oral anticoagulants are widely prescribed in family practice. Their main indications are atrial fibrillation and venous thromboembolic disease. In France, 2.1% of the population had an oral anticoagulant in 2013 [4]. Since their introduction in 2009, the proportion of direct oral anticoagulants (DOAC) is increasing constantly [5].

Several real-world studies provided results confirming those of phase III studies on DOAC, showing at least similar efficacy and safety [6–9]. However, these studies are mostly performed on health insurance databases, limited to reported events. Other practical issues on anticoagulant management by general practitioners remain. Having available renal and hepatic function tests (in order to adjust drug and regimen choices), performing coagulation tests when appropriate, informing patient, inquiring about adherence and potential interactions are all tasks assigned to the general practitioner, as well as all potential sources of ADR [10,11].

The primary aim of this study was to assess in general practice records the presence of mandatory data for safe monitoring of oral anticoagulants. The secondary objectives were to compare between vitamin K antagonists (VKA) and DOAC, patient knowledge of taking an anticoagulant, and the perception by the general practitioners of their adherence to anticoagulation.

Materials and methods
The CACAO study (Comparison of Accidents and Circumstances with Oral Anticoagulants) is a national cohort study, conducted by general practitioners from all over France on ambulatory patients with an oral anticoagulant. These 463 investigators covered 290 different rural or urban towns, and were distributed over 47 different departments of France. This study was approved by the ethical committee of the University Hospital of Saint-Etienne (IRBN112014/ CHUSTE). Its protocol has been registered in ClinicalTrials.gov (NCT02376777). All patients received written information about the study, emphasizing their right to refuse participation, or to withdraw at any time. No written informed consent was required for inclusion. This cohort is divided into two distinct periods: phase 1 (baseline data) and phase 2 (follow-up data). We report the phase 1 results here.
Study population
Every patient aged 18 years or more, taking an oral anticoagulant, and consulting a general practitioner investigator, whatever his or her reason for consultation, were included. Patients with injectable anticoagulants and those under the age of 18 were not included. Each investigator included all consecutive eligible patients for 3 months, beginning inclusions between April and October 2014.

Data collection
When the patient was eligible, the general practitioner first asked a standardized question, using the following formulation: “Can you tell me if, among your medications, there is an anticoagulant?” Then the general practitioner collected demographic status, personal history, current medications, items of CHA2DS2-Vasc and HAS-BLED scores [12,13] and results of available biological tests performed (renal and hepatic functions, coagulation tests). Co-medications list was built from the ANSM (National agency for medication safety) list [4]. No specific biological sample was asked for this study, as our aim was to assess the prevalence of information available from the patient’s medical record. The general practitioner was finally asked to rate his perception of the patient’s adherence to anticoagulant. Data were collected anonymously by physicians via an e-CRF.

Statistical analysis
We used descriptive statistics with a 95% confidence interval (CI) to analyze the prevalence of available information, patients’ knowledge and their adherence to treatment as perceived by the general practitioners. Normality tests have been performed with quantitative variables. In case of normality, these variables were described by their mean and standard deviation. In other cases, they were described by their median and interquartile range, Q1-Q3. Data were secondarily compared between VKA and DOAC groups, using Chi-squared or Fisher’s exact test for qualitative data, and Student’s t-tests or rank tests for quantitative data. We performed analysis using IBM SPSS Statistics 20® (International Business Machines Corp).

Results
Between April and December 2014, the 463 general practitioners included 7154 patients: 5699 (79.7%) with a VKA and 1455 (20.3%) with a DOAC. For 6824 patients (95.4%), the investigator was their usual physician. Table 1 shows the patients’ characteristics.

Prevalence of information available in patients’ records are shown in Table 2. In patients with DOAC, renal function tests were not available in 109 (7.5% (95% CI, 6.1%-8.9%)) cases, and for hepatic function in 359 cases (24.7% (95% CI, 22.5%-26.9%)). In patients anticoagulated for atrial fibrillation, the CHA2DS2-Vasc score was 0 or 1 in 345 cases (6.9% (95% CI, 6.1%-7.5%)).

At least one medication potentially interactive with anticoagulants was reported for 4146 patients (58.0% (95% CI, 56.9%-59.1%)). Besides the suggested treatments, general practitioners reported 100 other treatments as being at risk of interaction, such as proton-pump inhibitors, diuretics and hemigoxin.

Patients under DOAC responded more frequently “No” to the question “Do you take an anticoagulant?” than patients under VKA (Table 3).

General practitioners perceived the patient as hardly or not adherent in 430 cases (6.1% (95% CI, 5.5%-6.7%)) (Table 4).
Discussion

We report the results of the first French national cohort study of ambulatory patients under oral anticoagulant therapy, a study designed and conducted by and for general practitioners. Our results emphasize the efforts needed to improve anticoagulant safety in daily practice:

Table 1. Characteristics of patients.

| Characteristics                        | VKA       | DOAC      | p        |
|----------------------------------------|-----------|-----------|----------|
| Patients, No. (%)                      | 5699 (79.7) | 1455 (20.3) |          |
| Age                                    |           |           |          |
| median (IQR), y                        | 78 (69–84) | 75 (67–82) | <0.0001  |
| ≥75 y, No. (%)                         | 3516 (61.7) | 763 (52.4) | <0.0001  |
| Male, No. (%)                          | 3083 (54.1) | 764 (52.5) | 0.278    |
| Weight, median (IQR), kg               | 76 (66–88) | 78 (66–90) | 0.099    |
| BMI, median (IQR), kg/m²               | 27.3 (24.3–31.1) | 27.7 (24.5–31.2) | 0.103    |
| Personnal history, No. (%)             |           |           |          |
| Hypertension                           | 3872 (67.9) | 960 (66.0) | 0.154    |
| DVT and/or PE                          | 1514 (26.6) | 239 (16.4) | <0.0001  |
| Diabetes mellitus                      | 1307 (22.9) | 315 (21.6) | 0.296    |
| Coronaropathy and/or MI                | 1178 (20.7) | 210 (14.4) | <0.0001  |
| Symptomatic heart failure              | 1154 (20.2) | 188 (12.9) | <0.0001  |
| Stroke and/or TIA                      | 931 (16.3) | 219 (15.1) | 0.234    |
| Peripheral arterial disease            | 490 (8.6) | 72 (4.9) | <0.0001  |
| Hemorraghe requiring hospitalization   | 477 (8.4) | 68 (4.7) | <0.0001  |
| Anticoagulant, No. (%)                 |           |           |          |
| Fluindione                             | 4161 (73.0) | - |          |
| Warfarine                              | 1112 (19.5) | - |          |
| Rivaroxaban                            | - | 823 (56.6) |          |
| Dabigatran                             | - | 544 (37.4) |          |
| Acenocoumarol                          | 426 (7.5) | - |          |
| Apixaban                               | - | 88 (6.0) |          |
| Indication for anticoagulation, No. (%) |           |           |          |
| Valvular atrial fibrillation            | 594 (10.4) | 60 (4.1) | <0.0001  |
| Non-valvular atrial fibrillation       | 3274 (57.4) | 1111 (76.4) | <0.0001  |
| DVT/PE                                 | 1257 (22.1) | 208 (14.3) | <0.0001  |
| Surgery                                | 36 (0.6) | 29 (2.0) | <0.0001  |
| Heart valve prothesis                  | 524 (9.2) | 5 (0.3) | <0.0001  |
| Other                                  | 459 (8.1) | 83 (5.7) | 0.003    |
| Unknown                                | 13 (0.2) | 1 (0.1) | 0.326    |
| Duration of anticoagulant treatment >1 year, No. (%) | 4848 (85.1) | 788 (54.2) | <0.0001  |
| CHA2DS2- Vasc / atrial fibrillation (n = 5039) | | | |
| 0                                      | 44 (1.1) | 40 (3.4) | <0.0001  |
| 1                                      | 187 (4.9) | 74 (6.3) |          |
| ≥2                                     | 3637 (94.0) | 1057 (90.3) |          |
| HASBLED / atrial fibrillation (n = 5039) | | | |
| ≤3                                     | 3017 (78.0) | 1040 (88.8) | <0.0001  |
| >3                                     | 851 (22.0) | 131 (11.2) |          |

VKA: vitamin-k antagonists, DOA: direct oral anticoagulants, BMI: body mass index, DVT: deep vein thrombosis, PE: pulmonary embolism, MI: myocardial infarction, TIA: transient ischemic attack

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decreasing the rate of unknown biological data in patients with DOACs (renal and hepatic functions) or the rate of patients with VKA but with no formal indication of anticoagulation, and improving patient knowledge with regard to their anticoagulant therapy.

Our data show large differences with patients’ characteristics in phase III trials. Patients are older (mean age = 73 years in DOAC group vs 55 to 57 years in trials) with a higher rate of

Table 2. Safety data in patients’ records.

| Data, No. (%)                        | VKA (n = 5699) | DOAC (n = 1455) | p   |
|--------------------------------------|--------------|----------------|-----|
| Date of the last INR                 |              |                |     |
| <1 month                             | 5039 (91.4)  | -              |     |
| 1–3 months                           | 391 (7.1)    | -              |     |
| >3 months                            | 84 (1.5)     | -              |     |
| Renal failure                        |              |                |     |
| No failure (clearance ≥ 60 mL/min)   | 3506 (61.5)  | 1037 (71.3)    |     |
| Moderate (30 mL/min ≤ clearance < 60 mL/min) | 1549 (27.2)  | 301 (20.7)     |     |
| Severe (15 mL/min ≤ clearance < 30 mL/min) | 175 (3.1)    | 8 (0.5)        |     |
| Terminal (clearance < 15 mL/min)     | 13 (0.2)     | 0 (0.0)        |     |
| Unknown                              | 456 (8.0)    | 109 (7.5)      | 0.549|
| Hepatic function                     |              |                |     |
| AST and/or ALT >3N                   | 29 (0.5)     | 3 (0.2)        |     |
| Bilirubin >2N                        | 4 (0.1)      | 1 (0.1)        |     |
| Unknown                              | 1645 (28.9)  | 359 (24.7)     | 0.002|
| Concomitant medications              |              |                |     |
| Statin                               | 2310 (40.5)  | 561 (38.6)     |     |
| Amiodaron                            | 829 (14.5)   | 263 (18.1)     |     |
| Antiplatelet                         | 599 (10.5)   | 115 (7.9)      |     |
| Serotonin reuptake inhibitors        | 328 (5.8)    | 85 (5.8)       |     |
| Fibrate                              | 154 (2.7)    | 35 (2.4)       |     |
| Vérapamil                            | 134 (2.4)    | 33 (2.3)       |     |
| NSAID                                | 56 (1.0)     | 29 (2.0)       |     |
| Quinidine                            | 14 (0.2)     | 4 (0.3)        |     |
| Carbamazepine                        | 12 (0.2)     | 2 (0.1)        |     |
| Tocrofillin                          | 11 (0.2)     | 1 (0.1)        |     |
| Ciclosporin                          | 7 (0.1)      | 0 (0.0)        |     |
| Anticoagulant                        | 6 (0.1)      | 0 (0.0)        |     |
| Systemic antifungal therapy          | 2 (0.0)      | 0 (0.0)        |     |
| Rifampin                             | 1 (0.0)      | 0 (0.0)        |     |
| Protease inhibitors                  | 1 (0.0)      | 0 (0.0)        |     |
| At least 1 medication                | 3310 (58.1)  | 836 (57.5)     | 0.677|

INR: international normalized ratio, AST: aspartate transaminase, ALT: alanine transaminase, NSAID: non-steroidal anti-inflammatory drug

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Table 3. Patient’s knowledge of taking an anticoagulant.

| Variable, No. (%)                       | VKA (n = 5642) | DOAC (n = 1437) | p   |
|-----------------------------------------|--------------|----------------|-----|
| "Do you take an anticoagulant?"         |              |                |     |
| Yes                                     | 5083 (90.1)  | 1248 (86.8)    | <0.0001|
| No                                      | 131 (2.3)    | 70 (4.9)       |     |
| Do not know                             | 428 (7.6)    | 119 (8.3)      |     |

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renal impairment (21.2% of patients had a clearance < 60mL/min vs 1 to 8% with a clearance < 50mL/min in trials), highlighting the need to evaluate safety issues in “real-world” studies [14–17]. Efforts are needed to increase the presence of biological data in DOACs patients: in patients with VKA, 1.5% had a date of last INR of over 3 months, whereas in DOACs patients, general practitioners did not know the renal function tests in one of 13 patients or the hepatic function tests in one of 4 patients. These data are particularly important: severe renal impairment is a contra-indication for all DOACs, moderate renal impairment implies adapting DOAC dosages, and hepatic impairment is a contra-indication for rivaroxaban and apixaban. These findings probably reflect the difficulties of appropriation of the monitoring modalities of this new pharmacological class.

Several situations reveal contra-indications where the general practitioner has its role of stopping harmful treatment. This is for example the case for the 84 patients with atrial fibrillation (1.7%) having a CHA2DS2-Vasc score of 0, which is not an indication of anticoagulant.

At first sight, associations with a medication at risk of interaction are frequent and concern more than half patients with anticoagulants. Associated medications can be distinguished by their type of interaction. Pharmacokinetic interaction, which constitutes the highest risk of interaction, modifying the medication concentration, is mainly represented by statin and amiodarone, involved in about 55% of cases. These medications can however be justified in this population with cardiovascular history, and occur as often as in the populations included in the phase III studies [14–18]. The clinical impact of such interactions is debatable. Strong inhibitors/inductors such as antifungals, verapamil or quinidine, are rare (< 5%). Pharmacodynamic interactions, with potential effect and no modification of compound concentration, are represented first by antiplatelet association. This occurred in 10% of cases, a frequency similar to that of the population of phase III trials [14–17]. This combination is associated with a 2-fold increase in the risk of major bleeding [19] and the recent 2016 ESC guidelines restrain indications of this combination [20]. The increased bleeding risk with selective serotonin reuptake inhibitor has recently been specified [21]. Prevalence of this combination (5.8%) matches the usual prescription data in France, where psychoanaleptics represent 2.1% of the drug sales market share [22]. Given these points, the data provided by our study do not ring alarm bells as to a large risk of interactions in daily practice. Efforts should probably be more focused on the one hundred supplementary treatments stated by the physicians that highlight the difficulty of identifying the risk of interaction in a practical context. Simple alerts of “at-risk patients” should be developed, rather than software which usually indicates situations of at-risk “drug-drug interaction” irrespective of the risk. The follow-up of the CACAO cohort should provide valuable data on this topic.

With twice as many patients under DOAC as VKA who think they are not taking an anticoagulant, our data confirmed the presentiment of many physicians. From the patient’s point of view, the apparent simplicity of DOAC monitoring can give them the impression of a harmless

| Variable, No. (%) | VKA (n = 5644) | DOAC (n = 1429) | p |
|------------------|---------------|----------------|---|
| Patient adherence as perceived by GP |               |                |   |
| Not adherent     | 41 (0.7)      | 13 (0.9)       | 0.224 |
| Not very adherent| 288 (5.1)     | 88 (6.2)       |   |
| Rather adherent  | 1856 (32.9)   | 486 (34.0)     |   |
| Completely adherent | 3459 (61.3) | 842 (58.9)     |   |

GP: general practitioner

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treatment which, added to the drug novelty, make them forget they are taking anticoagulant therapy. Such oblivion potentiates the risk of this treatment, especially in an emergency context or when the physician does not know the patient and has no access to their usual treatment, leading for example to the prescription of contra-indicated drugs. Several studies have reported patient adherence to oral anticoagulation. Under VKA, the proportion of non-adherent patients varies between 22% and 58% [23]. Regarding DOACs, in phase III studies, adherence varied between 71% and 98% and the rate of discontinuation for non-adherence under DOAC was similar or even higher than warfarin [23]. Adherence of patients appears much higher in our study, which could be explained by its indirect measurement mode, based on the perception of the general practitioner. This less reliable method is however closer to real-world practice, where the physician does not have the tools to measure actual patient adherence, and can only go by his feelings to adapt the treatment. The one year results of the CACAO study should allow us to compare this adherence perceived by the physician to adherence auto-assessed by the patient and to the incidence of thromboembolic events.

The multicenter nature and the large size of the study may help improve the generalizability of the findings. Given that the investigator was the usual physician in 95% of cases, the data were easier to access, with easy filling in of the questionnaire. However, the data do remain declarative and not objectively verifiable, representing a potential measurement bias. It is possible that physicians who agreed to participate in the study were more sensitive to continuing medical education, medical information and/or to the anticoagulant topic than the average general practitioner. This possible recruitment bias should have a tendency to underestimate the result of our outcomes which are nevertheless significant for practice.

Conclusions

In a context of appropriation of new monitoring practices, this study puts forward concrete ways of improvement, such as knowledge of the liver and kidney function in patients under DOAC, simplification of discourse on drug interactions, and patient information to minimize iatrogenic risks in real life. Moreover, patients’ adherence seems highly over-estimated by the general practitioners subjective perception, and may prompt general practitioners to use validate tools to assess patients’ adherence.

Appendix

The members of the CACAO Study Group were as follows (n = 463, all in France):

Nathan Abenhaïm, Sophie Ackermann, Maryse Adam Blanpain, Xavier Andreu, Céline Arnould, Audrey Atlan-Cottin, Jean-Pierre Aubert, Isabelle Aubin-Augier, Jacques Aubry, Julien Augueux, Veena Augustin, Annick Bakry, Marine Baldesi, Eric Banoun, Eric Barberet, Rémi Bardet, Florence Barriere, Dan Baruch, Nicolas Baude, Marc Bayen, Sabine Bayen, François Bayle, Yannick Beaufils, Alain Beaupin, Julie Bedel-Chauvaud, Raphael Bel, Martine Bellier, Farouk Bendamene, Philippe Berard, Cédric Berbé, Christophe Berkhout, Jacques Berland, Charles-Edouard Béthembos, Pierre-Yves Billiard, Olivier Bisch, Aurélie Bizeau, Paul Blanchard, Guy Blanquart, Aurélie Boch, Isabelle Bodein, Emmanuel Boige, Claude Bonin, Anne-Laure Bonis, Marie-Pierre Bonnard, Pascal Bonnet, Pierre-André Bonnet, Gérard Bosse-lut, Anne Bottet, Philippe Bouche, Bérengère Boucherle, Audrey Bougeard, Serge Bouhana, Mourad Boukeloul, Jean Boulet-Gercourt, Jean-Marie Boulongne, Lionel Bouniol, Jean-Jacques Bourcart, Michel Bourgoïn, Véronique Bourguignon-Vartanian, Claire Bouteville, Philippe Boutin, Annelore Boutmy, Evelyn Brenner-Girault, Nicolas Breton, Muriel Briand-Fraysse, Marina Brodieck, Olivier Brunet, Ariel Buchinger, Anne Buffaz-Sutra, Marc Bur, Philippe Cabourdin, Philippe Cachere, Eric Cailliez, Matthieu Calafiore, Denis Calvet, Pierre
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Author Contributions

**Conceptualization:** PF JC YG NA MB MC CG JPJ FL.

**Data curation:** PF.

**Formal analysis:** PF.

**Funding acquisition:** JC MB JPJ FL.

**Investigation:** PF JC YG NA MB MC CG JPJ FL.

**Methodology:** PF JC LB.

**Project administration:** PF JC.

**Resources:** PF JC NA.

**Software:** PF NA.
Supervision: PF JC.

Validation: PF JC.

Visualization: PF JC.

Writing – original draft: PF LB.

Writing – review & editing: PF JC YG NA MB MC CG JPJ FL.

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