Opinion
12 June 2013

ELIQUIS 2.5 mg, film-coated tablets
B/60 (CIP: 34009 419 456 7 0)
B/60x1 (CIP: 34009 419 457 3 1)

ELIQUIS 5 mg, film-coated tablets
B/60 (CIP: 34009 267 841 0 2)
B/100x1 (CIP: 34009 583 807 3 0)

Applicant: BRISTOL-MYERS SQUIBB

<table>
<thead>
<tr>
<th>INN</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code (year)</td>
<td>B01AF02 (antithrombotic)</td>
</tr>
</tbody>
</table>

Reason for the request

Inclusion for ELIQUIS 5 mg
Extension of indication for ELIQUIS 2.5 mg

List(s) concerned

National Health Insurance (French Social Security Code L.162-17):
- ELIQUIS 2.5 mg and 5 mg: B/60

Hospital use (French Public Health Code L.5123-2):
- ELIQUIS 2.5 mg: B/60x1
- ELIQUIS 5 mg: B/60 and B/100x1

Indication concerned

“Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).”
**Actual Benefit**

Substantial in the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation with one or more risk factors.

**Improvement in Actual Benefit**

The Committee considers that ELIQUIIS does not provide an improvement in actual benefit (IAB V, non-existent) in the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

The patients who would be most likely to benefit from apixaban, as with rivaroxaban and dabigatran, are those whose INR cannot be controlled by VKAs. These patients require close clinical monitoring, but the lack of a need to measure the level of anticoagulation may result in follow-up consultations becoming less frequent; close monitoring must not be forgotten in everyday practice. The clinical data for apixaban in elderly patients (> 75 years), patients with renal impairment or with a low body weight, who are at risk of bleeding, are currently limited. Furthermore, indirect comparisons drawn from three studies, RE-LY, ROCKET AF and ARISTOTLE, which have different methodologies and different patient characteristics on inclusion, cannot enable a hierarchy to be established for these three medicinal products.

**Therapeutic use**

First-line therapy as an alternative to other oral anticoagulants.

**Recommendations**

Request for a study documenting the therapeutic benefit of apixaban (ELIQUIIS) under actual conditions of use in comparison with the usual management of at-risk patients with non-valvular atrial fibrillation.
01 ADMINISTRATIVE AND REGULATORY INFORMATION

| Marketing Authorisation (European centralised procedure) | ELIQUIS 5 mg  
Start date: 19 November 2012  
ELIQUIS 2.5 mg  
Start date (thromboprophylaxis): 18 May 2011  
Extension of indication (prevention of stroke and systemic embolism): 19 November 2012 |
| Prescribing and dispensing conditions/special status | List I |

02 BACKGROUND

ELIQUIS 2.5 mg is already indicated in the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery, and provides a substantial actual benefit and a minor improvement in actual benefit (IAB IV) in comparison with enoxaparin (LOVENOX) in terms of efficacy (Opinion of 18 January 2012).

For the indication “prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation and one or more risk factors,” a new dose of ELIQUIS in the form of 5 mg tablets has obtained marketing authorisation and the company has applied for inclusion. For patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl; (133 µmol/l), the company has applied for inclusion of the 2.5 mg dose in this new indication.

03 THERAPEUTIC INDICATIONS

“- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

- Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.”
**04 DOSAGE**

“The recommended dose is 5 mg taken orally twice daily for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF).

**Dose reduction:**
The recommended dose is 2.5 mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl (133 µmol/l).

Therapy should be continued long term.

**Switching:**
- When converting patients from vitamin K antagonist (VKA) therapy to ELIQUIS, discontinue warfarin or other VKA therapy and start ELIQUIS when the international normalized ratio (INR) is < 2.0.
- When converting patients from ELIQUIS to VKA therapy, continue administration of ELIQUIS for at least 2 days after beginning VKA therapy. After 2 days of co-administration of ELIQUIS with VKA therapy, obtain an INR prior to the next scheduled dose of ELIQUIS. Continue co-administration of ELIQUIS and VKA therapy until the INR is ≥ 2.0.

**Renal impairment:**
- As there is no clinical experience in patients with creatinine clearance < 15 ml/min, or in patients undergoing dialysis, apixaban is not recommended in these patients.
- No dose adjustment is necessary in patients with mild or moderate renal impairment. Patients with serum creatinine ≥ 1.5 mg/dl (133 µmol/l) associated with age ≥ 80 years or body weight ≤ 60 kg should receive the lower dose of apixaban 2.5 mg twice daily.
- Patients with exclusive criteria of severe renal impairment (creatinine clearance 15-29 ml/min) should also receive the lower dose of apixaban 2.5 mg twice daily.

**Hepatic impairment:**
- ELIQUIS is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B). No dose adjustment is required in patients with mild or moderate hepatic impairment.
- Patients with elevated liver enzymes (ALT/AST > 2 × ULN) or total bilirubin ≥ 1.5 × ULN were excluded in clinical trials. Therefore ELIQUIS should be used with caution in this population (see sections 4.4 and 5.2). Prior to initiating ELIQUIS, liver function testing should be performed.

**Body weight:** no dose adjustment required, unless criteria for dose reduction are met.

**Elderly patients:** no dose adjustment required, unless criteria for dose reduction are met.”
05 THERAPEUTIC NEED

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an estimated prevalence of between 1% and 2% of the adult general population. It is characterised by a markedly increased heart rate (350 to 600 beats per minute) and an irregular atrial contraction rhythm, which increases the risk of blood stasis in the left ventricle and thus of the formation of a thrombus that may migrate to the brain or to the peripheral circulation. AF may be immediately life-threatening or life-threatening following complications, the most serious of which is stroke.

Antithrombotic treatment is essential for preventing thromboembolic complications, unless the AF is isolated in a patient aged under 65 years with no associated thromboembolic risk factors. Vitamin K antagonists (VKAs) are the standard antithrombotic treatment in cases of atrial fibrillation in patients at high risk of stroke. According to the most recent expert guidelines, the use of aspirin + clopidogrel, or even aspirin as monotherapy, should only be considered in patients who cannot take an oral anticoagulant and where there are no contraindications.\(^1\),\(^2\),\(^3\),\(^4\)

VKAs are effective at preventing the risk of thromboembolism associated with atrial fibrillation (AF), but come at the cost of an increased risk of major bleeding (particularly intracranial haemorrhage). The individual response varies because there are many interactions with other medicines (NSAIDs, antibiotics, antifungalics, statins, anticonvulsants, glucocorticoids, etc.) and foods (cabbage and asparagus are rich in vitamin K, for example) and because of genetic polymorphism. VKAs must therefore be taken regularly at a fixed time and require regular monitoring of the level of anticoagulation by measuring the INR (International Normalised Ratio) with the maintenance of an INR record. The inherent difficulties and constraints associated with their use help to explain why the prescription and monitoring of these medicinal products are not optimal. In France, up to 50% of patients with AF who require anticoagulant treatment do not receive a VKA. Consequently, a partially met therapeutic need has been identified.

Following dabigatran etexilate (PRADAXA, a direct thrombin inhibitor) and rivaroxaban (XARELTO, a direct factor Xa inhibitor), apixaban (ELIQUIS, a direct factor Xa inhibitor) is the third oral anticoagulant that can be prescribed as an alternative to a vitamin K antagonist in cases of AF to prevent the occurrence of stroke or systemic embolism.

**06 CLINICALLY RELEVANT COMPARATORS**

**06.1 Medicinal products**

- Other non-VKA oral anticoagulants:

<table>
<thead>
<tr>
<th>NAME (INN)</th>
<th>Company</th>
<th>Same TC* yes / no</th>
<th>Indications</th>
<th>Date of opinion</th>
<th>AB</th>
<th>IAB (wording)</th>
<th>Refunded yes/no</th>
</tr>
</thead>
<tbody>
<tr>
<td>XARELTO</td>
<td>Bayer Santé</td>
<td>Yes (Direct factor Xa inhibitor)</td>
<td>Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors</td>
<td>14/03/2012</td>
<td>Substantial</td>
<td>IAB V in comparison with VKAs</td>
<td>Yes</td>
</tr>
<tr>
<td>PRADAXA</td>
<td>Boehringer Ingelheim</td>
<td>No (Direct thrombin inhibitor)</td>
<td>Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors</td>
<td>29/02/2012</td>
<td>Substantial</td>
<td>IAB V in comparison with VKAs</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*therapeutic category

- Oral VKA anticoagulants:

<table>
<thead>
<tr>
<th>INN (proprietary medicinal product)</th>
<th>Indications</th>
<th>Date of TC opinion</th>
<th>AB</th>
<th>IAB (wording)</th>
<th>Refunded (Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINTROM MINI-SINTROM (acenocoumarol)</td>
<td>Embolicogenic cardiopathies: prevention of thromboembolic complications associated with some AF, some mitral valvulopathies and valve prostheses</td>
<td>NR</td>
<td>Substantial</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>PREVISCAN (Fluindione)</td>
<td></td>
<td>NR</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>COUMADINE (Warfarin)</td>
<td></td>
<td>NR</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td></td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Acetylsalicylic acid at a dosage of 75 to 325 mg/day.

**Conclusion**
The comparators listed are all clinically relevant. The standard treatments are vitamin K antagonists where there are no contraindications. The other medical products represent an alternative. Acetylsalicylic acid is also recommended as an alternative to VKAs in patients with a low risk of thromboembolism (CHADS₂ score = 1).
07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

1) Data on whether the medicine is refunded in Europe and North America:

<table>
<thead>
<tr>
<th>Country</th>
<th>YES/NO If no, why</th>
<th>Population(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>Yes</td>
<td>MA or restricted population</td>
</tr>
<tr>
<td>Other European Union countries</td>
<td>Under assessment</td>
<td></td>
</tr>
<tr>
<td>USA (FDA)</td>
<td>(MA since 28/12/2012)</td>
<td>Marketing Authorisation</td>
</tr>
</tbody>
</table>

2) An assessment of ELIQUIS has been conducted by NICE (United Kingdom) and an assessment by IQWIG (Germany) is being finalised. In February 2013, NICE issued a guideline in favour of ELIQUIS, considering it to be an alternative to warfarin, rivaroxaban and dabigatran in patients with non-valvular AF and at least one risk factor for stroke. In April 2013, IQWIG issued an opinion in favour of ELIQUIS in patients eligible for VKAs aged over 65 years and in patients not eligible for VKAs.

08 ANALYSIS OF AVAILABLE DATA

This assessment of apixaban (ELIQUIS) in the prevention of stroke and systemic embolism in patients with atrial fibrillation is based on the results of two international phase III clinical trials, one versus warfarin (target INR 2.0-3.0) (ARISTOTLE study\(^5\)) and one versus acetylsalicylic acid (AVERROES study\(^6\)). The safety results of a phase IIb study comparing apixaban to warfarin are also presented.

An indirect comparison of the results of the RE-LY (dabigatran etexilate versus warfarin), ROCKET AF (rivaroxaban versus warfarin) and ARISTOTLE studies was carried out.

08.1 Efficacy

8.1.1 ARISTOTLE study

**Study objectives:**
- To determine whether apixaban at a dosage of 5 mg (or 2.5 mg) twice daily is non-inferior to warfarin at a dosage adjusted to INR (target INR between 2.0 and 3.0) in preventing stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) and at least one other risk factor for stroke.
- Secondarily, to determine whether apixaban is superior to warfarin in terms of efficacy and/or safety in the same patients.

**Study design** (see Figure 1):
Comparative, double-blind, double-placebo study randomised into 2 parallel groups: apixaban versus warfarin. The randomisation was stratified by study centre and patient status, i.e. whether patients were naïve to VKA treatment or not. Patients were still considered to be naïve if they had


taken a VKA for less than 30 consecutive days. Each centre had to randomise a minimum of 40% naïve patients.

**Inclusion criteria:**
- Patients aged at least 18 years with AF or atrial flutter, diagnosed on the basis of two episodes documented by ECG performed at least two weeks apart during the previous 12 months;
- Associated with at least one of the following risk factors:
  - previous stroke, TIA or systemic embolism
  - age ≥ 75 years
  - symptomatic congestive heart failure in the previous three months, or left ventricular dysfunction with a documented left ventricular ejection fraction ≤ 40%
  - diabetes
  - hypertension requiring treatment.

**Non-inclusion criteria included:**
- high risk of bleeding that could contraindicate anticoagulant treatment
- severe renal impairment defined as serum creatinine > 221 µmol/l or creatinine clearance < 25 ml/min
- concomitant treatment with acetylsalicylic acid (> 165 mg/day) or combining acetylsalicylic acid and thienopyridine.

**Dosage of the anticoagulant therapy:**
- Apixaban: 5 mg twice daily, or 2.5 mg twice daily in patients considered at higher risk of bleeding because they met at least two of the following three criteria on inclusion:
  - age ≥ 80 years
  - weight ≤ 60 kg
  - impaired renal function (serum creatinine ≥ 133 µmol/l).
- Warfarin: administered as a single dose per day, at the dose required to achieve a target INR between 2.0 and 3.0.

**Primary efficacy endpoint:**
- time to occurrence (proportion per year) of stroke or systemic embolism during the intended treatment period.

**Secondary efficacy endpoints included:**
- time to occurrence (proportion per year) of the following clinical events during the intended treatment period:
  - death of any cause
  - individual components of the composite criteria for stroke (haemorrhagic, ischaemic or unspecified), systemic embolism or death of any cause
  - stroke (haemorrhagic, ischaemic or unspecified), systemic embolism, major bleeding, myocardial infarction (MI) or death of any cause
  - stroke, systemic embolism or major bleeding, defined as net clinical benefit.

**Method and strategy for the analysis of the results:**
The choice of non-inferiority threshold aimed to preserve at least 50% of the relative reduction in the risk of stroke or systemic embolism associated with warfarin. Non-inferiority was established if:

---

A diagnosis of stroke was made in cases of sudden-onset focal neurological deficit, not caused by trauma, which persisted for at least 24 hours. Retinal ischaemia was considered to be a stroke. A TIA was defined as the sudden, non-traumatic onset of focal neurological symptoms persisting for less than 24 hours. The severity of these events was evaluated using the modified Rankin Scale. Strokes were classified into three categories: ischaemic, ischaemic progressing to haemorrhagic, haemorrhagic or unspecified. Haemorrhagic strokes were sub-classified as subdural haematoma, subarachnoid haemorrhage or intraparenchymal haemorrhage.
- the upper limit of the 95% confidence interval (95% CI) for relative risk (RR) was below 1.38 with a unilateral alpha risk of 0.025
- the upper limit of the 99% CI for RR was below 1.44 with a unilateral alpha risk of 0.005.

The number of patients required was calculated based on the following hypotheses:
- The study would have a power of at least 90% if one stroke or systemic embolism occurred per 448 patients.
- On the basis of a sample of 18,000 patients distributed with a 1:1 ratio between the apixaban and warfarin groups, assuming an incidence of stroke and systemic embolism of 1.20 per 100 patient-years, and estimating that 1% of patients will be “lost to follow-up,” a mean follow-up duration of 2.1 years would be required to achieve the number of primary endpoint events.

Non-inferiority was tested in the ITT population, and secondarily in the per-protocol population (sensitivity analysis).

In accordance with the study’s statistical analysis plan, after analysis of non-inferiority on the primary efficacy endpoint, successive tests were performed following a predefined hierarchical order until statistical significance was no longer achieved, as follows (Figure 1):

**Figure 1: Sequential tests procedure – ARISTOTLE Study**

- **Non-Intériorité sur le critère principal d'efficacité** (population ITT)
- **Supériorité sur le critère principal d'efficacité** (population ITT)
- **Supériorité sur le critère principal de tolérance** (hémorragies majeures, selon NIH) (population de tolérance)
- **Supériorité sur le critère secondaire majeur d'efficacité** (décès toutes causes) (population ITT)

**ITT: intention to treat**

It should be noted that a per-protocol analysis to test non-inferiority was planned.

**Subgroup analyses:**

The protocol provided for the analysis of the primary efficacy and safety endpoints in several subgroups (interaction test), primarily defined by:
- patient demographics (age; sex; weight, BMI) and geographical region on inclusion
- history of treatment with warfarin; history of treatment with acetylsalicylic acid
- dose of apixaban taken
- cardiovascular risk (CHADS2 score; history of stroke or TIA)
- presence of renal impairment, diabetes, treated hypertension, heart failure

Post-hoc analyses were also performed in patients considered at higher risk of bleeding due to their age (≥ 75 and < 80 years; ≥ 80 years) and due to severe renal impairment (creatinine clearance 15-29 ml/min), as well as in patients who had received apixaban at the dose of 5 mg twice daily and met just one of the three criteria for a reduced apixaban dose.

The percentage of time spent within the therapeutic range of 2.0 to 3.0 (TTR) was evaluated using the Rosendaal method. In order to evaluate the effect of apixaban compared with different levels of TTR, the study centres were classified into four quartiles according to their median TTR, calculated from the INRs of patients treated with warfarin at that centre.

**Results:**
The study took place between December 2006 and May 2011. It involved 1,034 centres in 40 countries (Europe, North America, Asia-Pacific and Latin America), including seven centres in France.

Three populations were defined for analysis (Table 1):
- ITT population: randomised patients (18,201 patients)
- per-protocol population (PP): patients from the ITT population with no major deviation from the protocol
- safety population: patients who received at least one dose of treatment.

Table 1: Populations defined for analysis – ARISTOTLE study

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population, n</td>
<td>9,120</td>
<td>9,081</td>
</tr>
<tr>
<td>Safety population, n (%)</td>
<td>9,088 (99.6)</td>
<td>9,052 (99.7)</td>
</tr>
<tr>
<td>PP population, n (%)</td>
<td>8,518 (93.4)</td>
<td>8,475 (93.3)</td>
</tr>
</tbody>
</table>

The proportion of patients who stopped treatment before the end of the study (more than a quarter of patients) was lower in the apixaban group (25.3%) than in the warfarin group (27.5%). The proportion of patients who completed the study was similar in both groups: 88.2% in the apixaban group and 87.4% in the warfarin group.

Characteristics of the evaluated population

The characteristics of patients in the two groups were similar on inclusion. The majority of patients were male (65%) and Caucasian (83%), with a mean age of 69.1 years; almost one third (31.2%) were aged over 75 years and 13.4% were aged over 80 years. 42% of patients included had mild renal impairment (creatinine clearance between 51 and 80 ml/min), 15% had moderate renal impairment (creatinine clearance between 30 and 50 ml/min) and 1.5% had severe renal impairment (creatinine clearance < 30 ml/min).

The level of thromboembolic risk evaluated by the CHADS\textsuperscript{2} score\textsuperscript{8} was 2.1 in both groups; 35% of patients had a CHADS\textsuperscript{2} score of 2 and 30% had a score ≥ 3. Almost 70% of patients in both groups had at least 2 thromboembolic risk factors on inclusion. The proportion of patients with risk factors was similar in the subgroups of patients naïve and non-naïve to VKA treatment. The most common risk factors were hypertension (87.4%), heart failure (35.4%) and age ≥ 75 years (31.2%). More than 19% of patients had a history of stroke/TIA or systemic embolism. About 57% of randomised patients had been previously treated with a VKA, for at least 6 months in over 45% of cases.

About 57% of randomised patients had been previously treated with a VKA, for at least 6 months in over 45% of cases.

Treatments evaluated:

The majority of patients in the apixaban group (95.4%) received the dose of 5 mg twice daily at the time of randomisation, bearing in mind that 22.3% of patients in the apixaban group and 22.2% of patients in the warfarin group met just one of the three predefined criteria for a dose reduction.

The reduced dose of 2.5 mg twice daily therefore applied to 4.6% of patients. These were primarily women with a mean age of over 82 years. Less than 1% of them had normal renal function and more than 80% had moderate or severe renal impairment. More than 80% of these patients had a high risk of thromboembolism with a CHADS\textsuperscript{2} score ≥ 2.

The mean duration of exposure to treatment during the double-blind phase was about 1.7 years (mean of 20 months) in each group, corresponding to a total duration of exposure of 15,534

\textsuperscript{8} The CHADS\textsuperscript{2} score takes into account age > 75 years, congestive heart failure, diabetes, hypertension and a history of stroke or TIA.
patient-years in the apixaban group and 15,184 patient-years in the warfarin group. The mean duration of exposure was comparable in patients who were naïve to VKA treatment and those who were not.

Other treatments:
Concomitant treatments were similar in both groups in the 30 days preceding randomisation, and then during the study. It should be noted that 31.7% of patients in the apixaban group and 30.3% in the warfarin group took acetylsalicylic acid for a mean duration of 54 weeks.

INR monitoring in the warfarin group:
In patients randomised into the warfarin group, the median percentage of time spent in the target therapeutic range (TTR) was 66%. The limit between the 1st and 2nd quartiles was 52.4% and the limit between the 3rd and 4th quartiles was 76.5%.

Reminder:
- In the ROCKET AF study (XARELTO), the mean percentage of time spent in the therapeutic range (TTR) by patients receiving warfarin was 55.16% and the median time was 57.83%. The TTR was 70.18% for an INR range of 1.8 to 3.2. Patients who were “ naïve to VKAs” on inclusion had poorer control of their INR and a lower percentage of time in the therapeutic range. The TTR was also lower in cases of congestive heart failure (present in 62% of patients, who had a mean percentage of 52.9% vs. 59.6% when this risk factor was absent). Large regional differences were noted, with the median time in the therapeutic range being greater in North America (64.13%) and in Western Europe (60.62%). In the other regions, TTR was lower than expected (with INR < 2).
- In the RE-LY study (PRADAXA), the mean percentage of time spent in the target range was 64.4% (median 67%), which is close to values from earlier studies in which patients were treated with warfarin [SPORTIF-V (59%), SPORTIF III (66%), ACTIVE-W (64%), AMADEUS (63%) and AFFIRM (62%)].

Efficacy results:

Primary efficacy endpoint
Apixaban was demonstrated to be non-inferior to warfarin in the ITT population (HR = 0.79; 99% CI [0.62; 1.00]; p = 0.0001).
This result is confirmed by analysis of the PP population (HR = 0.69; 99% CI [0.52; 0.92]; p = 0.0001).

Table 3: Primary efficacy endpoint (intended treatment period / PP and ITT populations) – ARISTOTLE study

<table>
<thead>
<tr>
<th></th>
<th>PP population</th>
<th>ITT population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apixaban</td>
<td>Warfarin</td>
</tr>
<tr>
<td>N</td>
<td>8,518</td>
<td>8,475</td>
</tr>
<tr>
<td>Stroke and systemic embolism, n (%)</td>
<td>138 (1.62)</td>
<td>200 (2.36)</td>
</tr>
<tr>
<td>Incidence (%/year)</td>
<td>0.96</td>
<td>1.39</td>
</tr>
<tr>
<td>Hazard ratio [99% CI]</td>
<td>0.69 [0.52; 0.92]</td>
<td>0.79 [0.62; 1.00]</td>
</tr>
<tr>
<td>Unilateral non-inferiority test (p)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Absolute risk reduction vs. warfarin (%/year, 95% CI)</td>
<td>0.43 [0.41; 0.44]</td>
<td>0.33 [0.30; 0.35]</td>
</tr>
<tr>
<td>NNT [95% CI]</td>
<td>-</td>
<td>303 [286; 333]</td>
</tr>
</tbody>
</table>

NNT: number needed to treat
Secondary efficacy endpoints
As non-inferiority had been demonstrated on the primary efficacy endpoint in the ITT and PP populations, the following different secondary efficacy endpoints were tested in accordance with the hierarchical statistical testing procedure stipulated in the protocol:

- **Superiority analysis for the primary efficacy endpoint:** The risk of occurrence of a stroke or systemic embolism during the intended treatment period was 1.27%/year in the apixaban group and 1.60%/year in the warfarin group. Apixaban was more effective than warfarin, with an annual relative risk reduction for the incidence of stroke and systemic embolism of 21% (HR = 0.79; 95% CI [0.66; 0.95]; p = 0.01 for superiority) and an absolute risk reduction of 0.33%/year. An average of 303 patients would need to be treated with apixaban for one year to prevent one stroke or one systemic embolism in comparison with warfarin. This reduction in strokes and systemic embolisms was comparable in the subpopulations of patients naïve and non-naïve to VKA treatment.

- **Superiority analysis for major bleeding as defined by ISTH:** The risk of occurrence of major bleeding was 2.13%/year in the apixaban group and 3.09%/year in the warfarin group. The risk of occurrence of major bleeding (ISTH) was lower on apixaban than on warfarin, with an annual relative risk reduction of 31% (HR = 0.69; 95% CI [0.60; 0.80]; p < 0.001) and an absolute risk reduction of 0.96%/year. An average of 104 patients would need to be treated with apixaban for one year to prevent one case of major bleeding in comparison with warfarin.

- **Superiority analysis for all-cause mortality:** The risk of death was 3.52%/year in the apixaban group and 3.94%/year in the warfarin group. Apixaban reduced the risk of death from any cause more than warfarin, with an annual relative risk reduction of 11% (HR = 0.89; 95% CI [0.80; 1.00]; p = 0.0465) and an absolute risk reduction of 0.42%/year. An average of 238 patients would need to be treated with apixaban for one year to prevent one death from any cause in comparison with warfarin.

**Summary of the results of the sequential tests:**

**Figure 2: Results of the sequential tests – ARISTOTLE study**

| Non-inferiority on the primary efficacy endpoint (ITT population) N=18,201 (9,120 apixaban; 9,081 warfarin) | Non-inferiority of apixaban demonstrated (p<0.0001) Incidence of events: apixaban 1.27%/year; warfarin 1.60%/year HR= 0.79; 95% CI [0.66; 0.95] ARR: 0.33%; 95% CI [0.30; 0.35] |
| Superiority on the primary efficacy endpoint (ITT population) N=18,201 (9,120 apixaban; 9,081 warfarin) | Superiority of apixaban demonstrated (p<0.0114) |
| Superiority on major bleeding (safety population) N=18,140 (9,088 apixaban; 9,052 warfarin) | Superiority of apixaban demonstrated (p<0.0001) Incidence of events: apixaban 2.13%/year; warfarin 3.09%/year HR=0.69; 95% CI [0.60; 0.80] ARR: 0.96%; 95% CI [0.91; 1.00] |
| Superiority on all-cause mortality (ITT population) N=18,201 (9,120 apixaban; 9,081 warfarin) | Superiority of apixaban demonstrated (p<0.0465) Incidence of events: apixaban 3.52%/year; warfarin 3.94%/year HR=0.89; 95% CI [0.80; 1.00] ARR: 0.42%; 95% CI [0.35; 0.49] |

CI: confidence interval; ITT: intention-to-treat; ARR: absolute risk reduction; RRR: relative risk reduction.
Other secondary efficacy endpoints
The majority of primary efficacy endpoint events that occurred during the study were strokes. Haemorrhagic strokes occurred less frequently in the apixaban group than in the warfarin group (HR=0.51; 95% CI [0.35; 0.75]). It should be noted that, in comparison with warfarin, apixaban reduced the annual relative risk of disabling strokes (Rankin score 3 to 6) by 29% (p=0.0178) and the risk of fatal strokes by 41% (p=0.0172).

The annual incidence of MI did not differ statistically between the apixaban and warfarin groups, with an annual incidence of MI of 0.53% in the apixaban group versus 0.61% in the warfarin group (HR = 0.88; 95% CI [0.77; 1.13]), a non-significant difference.

Table 4: Main secondary efficacy endpoints (intended treatment period and ITT population) – ARISTOTLE study

<table>
<thead>
<tr>
<th>Event</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>Apixaban versus warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=9,120 (N=9,081)</td>
<td>Incidence (%)/year</td>
<td>Incidence (%)/year</td>
<td>HR [95% CI]</td>
</tr>
<tr>
<td><strong>Ischaemic or unspecified stroke</strong></td>
<td>162 (1.78)</td>
<td>0.97</td>
<td>175 (1.93)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>40 (0.44)</td>
<td>0.24</td>
<td>78 (0.86)</td>
</tr>
<tr>
<td>SE</td>
<td>15 (0.16)</td>
<td>0.09</td>
<td>17 (0.19)</td>
</tr>
<tr>
<td>MI</td>
<td>90 (0.99)</td>
<td>0.53</td>
<td>102 (1.12)</td>
</tr>
<tr>
<td><strong>Stroke, SE, MI or death of any cause</strong></td>
<td>810 (8.88)</td>
<td>4.85</td>
<td>906 (9.98)</td>
</tr>
<tr>
<td><strong>Consequences of stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rankin score missing</td>
<td>59 (0.65)</td>
<td>0.35</td>
<td>62 (0.68)</td>
</tr>
<tr>
<td>Non-disabling stroke (Rankin 0-2)</td>
<td>63 (0.69)</td>
<td>0.37</td>
<td>70 (0.77)</td>
</tr>
<tr>
<td>Disabling stroke (Rankin 3-6)</td>
<td>85 (0.93)</td>
<td>0.50</td>
<td>118 (1.30)</td>
</tr>
<tr>
<td>Death (Rankin 6, fatal)</td>
<td>32 (0.35)</td>
<td>0.19</td>
<td>54 (0.59)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>603 (6.81)</td>
<td>3.52</td>
<td>669 (7.37)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>308 (3.38)</td>
<td>1.80</td>
<td>344 (3.79)</td>
</tr>
<tr>
<td>Non-vascular death</td>
<td>196 (2.15)</td>
<td>1.14</td>
<td>208 (2.29)</td>
</tr>
<tr>
<td>Death from unknown cause</td>
<td>99 (1.09)</td>
<td>0.58</td>
<td>117 (1.29)</td>
</tr>
<tr>
<td><strong>Net clinical benefit</strong></td>
<td>N=9,088 (N=9,052)</td>
<td>Incidence (%)/year</td>
<td>Incidence (%)/year</td>
</tr>
<tr>
<td>Stroke, SE or major bleeding</td>
<td>521 (5.71)</td>
<td>3.17</td>
<td>666 (7.33)</td>
</tr>
<tr>
<td>Stroke, SE, major bleeding or death from any cause</td>
<td>1,009 (11.06)</td>
<td>6.13</td>
<td>1,168 (12.86)</td>
</tr>
</tbody>
</table>

SE: systemic embolism; CI: confidence interval; MI: myocardial infarction
Analysis of efficacy in subgroups:

Pre-specified analyses: The results for the primary efficacy endpoint in the various pre-specified subgroups were comparable with those in the overall study population.

Exploratory post-hoc analyses: The results for the primary efficacy endpoint in patients at higher risk of bleeding (aged over 75 years or with severe renal impairment) were comparable with those observed in the overall study population.

Figure 3: Results for the primary efficacy endpoint in patients ≥ 75 years and patients with severe renal impairment (intended treatment period and ITT population) – ARISTOTLE study

The results of the post-hoc analysis performed in patients meeting only one of the three criteria for apixaban dose reduction are dissimilar from those in the overall study population:

Figure 4: Results for the primary efficacy endpoint in patients meeting only one of the three criteria for dose reduction (intended treatment period) – ARISTOTLE study

Analysis of efficacy according to TTR (time in the therapeutic range)
Apixaban reduced the number of strokes and systemic embolisms in comparison with warfarin for all levels of TTR in the different centres, with a comparable effect size (HR=0.73; 95% CI [0.38; 1.40]) to that of the overall population (HR=0.79) in the upper quartile (median > 76.5%), a non-significant difference.

8.1.2 AVERROES study

Primary objectives of the study:
The study aimed to demonstrate the superiority of apixaban to acetylsalicylic acid in the prevention of stroke or systemic embolism (primary efficacy endpoint) in patients with NVAF and at least one risk factor who are unsuitable for treatment with VKAs. If this superiority hypothesis was proven, the superiority of apixaban to acetylsalicylic acid at preventing major vascular events and reducing all-cause mortality was evaluated using a sequential hierarchical testing procedure.
Study design:
Comparative, double-blind, double-placebo study randomised into 2 parallel groups: apixaban versus acetylsalicylic acid.

Inclusion criteria:
- Patients aged at least 50 years with permanent, paroxysmal or persistent AF documented on inclusion or in the 6 months prior to enrolment and with at least one of the following risk factors: age ≥ 75 years; prior stroke or TIA; heart failure (New York Heart Association [NYHA] class II or greater or left ventricular ejection fraction [LVEF] ≤ 35% documented within 6 months of inclusion); diabetes; hypertension on treatment; documented peripheral arterial disease (previous arterial revascularisation, limb or foot amputation, or intermittent claudication with ankle-arm systolic blood pressure ratio < 0.9).
- Patients unsuitable for VKA therapy:
  - “Demonstrated” to be unsuitable:
    • unsatisfactory laboratory monitoring: INR measurement not done or not maintained in the target range
    • occurrence of bleeding or other adverse effects
    • patient refuses to continue VKA therapy
    • patient unable or unwilling to adhere to INR monitoring or dose adjustments required.
  - “Expected” to be unsuitable:
    • patient unlikely to comply with laboratory monitoring for VKA therapy
    • unlikely to adhere to restrictions on diet (including alcohol) and medications
    • risk of VKA therapy considered to outweigh the potential benefit of preventing stroke or systemic embolism
    • patient is unwilling to take VKAs.

Non-inclusion criteria included:
- high risk of bleeding
- severe renal impairment (creatinine clearance < 25 ml/min).

Dosage of the anticoagulant therapy:
- Apixaban: 5 mg twice daily, or 2.5 mg twice daily in patients with a higher risk of bleeding who met at least two of the following three criteria on inclusion: age ≥ 80 years; weight ≤ 60 kg; serum creatinine ≥ 133 µmol/l.
- Acetylsalicylic acid: between 81 and 324 mg/day (as chosen by investigator).

Endpoints:
- Primary efficacy endpoint: time to occurrence of stroke or systemic embolism during the intended treatment period (1st objective).
- Time to occurrence of stroke, systemic embolism, MI or vascular death during the intended treatment period. This endpoint corresponds to major vascular events (2nd objective).
- All-cause mortality (3rd objective).

Secondary efficacy endpoints included:
- Time to occurrence, during the intended treatment period, of the individual components of the composite criteria.
- Hospitalisations with a cardiovascular cause.
- A composite criterion combining stroke, systemic embolism, MI, vascular death and major bleeding defined as the “net clinical benefit.”
Method and strategy for the analysis of the results:
The study’s three objectives were analysed using a sequential hierarchical method, the method pre-specified in the study protocol, in order to limit the risk of a type I error to 0.05 (bilateral):
- Demonstration of the superiority of apixaban to acetylsalicylic acid on the primary efficacy endpoint (prevention of confirmed stroke [haemorrhagic, ischaemic or unspecified] or systemic embolism).
- If this superiority hypothesis was proven, the objective was to establish the superiority of apixaban to acetylsalicylic acid at preventing major vascular events.
- If superiority was demonstrated on this last endpoint, the objective was to establish the superiority of apixaban to acetylsalicylic acid on all-cause mortality.

The superiority of apixaban on the primary efficacy endpoint was established if the relative risk was less than 1, with relative risk representing the risk on apixaban in comparison with acetylsalicylic acid, measured by the HR. It was estimated that a total of 5,600 patients would need to be randomised into one of the two study arms (2,800 patients in each) on the basis of the following hypotheses:
With an estimated mean follow-up of about 1.6 years, an incidence of stroke of 3.3 per 100 patient-years in the acetylsalicylic acid group, and an estimated incidence of patients lost to follow-up of 1%, the study would have a power of at least 90% for observing a 35% reduction in the relative risk of events on apixaban compared to acetylsalicylic acid, with a unilateral alpha risk of 0.025, if 226 patients had a stroke or systemic embolism.

The study protocol provided for two interim analyses: one after the occurrence of 113 events from the primary efficacy endpoint, i.e. 50% of the 226 events expected, and one after the occurrence of 170 events from this endpoint, i.e. 75% of the events expected.

NB. The primary endpoint was also monitored using the conservative Peto method (modified Haybittle-Peto boundary of 3 standard deviations; bilateral p-value < 0.0026). The effect of treatment was estimated using a Cox model. The relative risk and its 95% CI were calculated using the HR. The proportionality assumption was also tested by supposing that the level of risk was consistent in each of the four pre-specified time periods (0 to < 9 months, 9 to 18 months, 18 to < 27 months, and 27 months onwards). A sensitivity analysis was planned for evaluating the study’s primary endpoint in the PP population.

Subgroup analyses:
The protocol provided for the analysis of the primary efficacy and safety endpoints in several subgroups (interaction test), primarily defined by:
- patient demographics (age; sex; weight, BMI) and geographical region on inclusion
- history of treatment with warfarin; history of treatment with acetylsalicylic acid
- reason for non-use of VKA therapy
- dosages of apixaban and acetylsalicylic acid received
- cardiovascular risk (CHADS2 score; history of stroke or TIA)
- presence and severity of renal impairment, diabetes, treated hypertension, heart failure.

Results:
The study took place between September 2007 and December 2009. It involved 526 centres in 36 countries (Europe, North America, Asia-Pacific and Latin America), including 8 centres in France.

Three populations were defined for statistical analysis:
- Primary analysis population (ITT): randomised patients
- Per-protocol population (PP): randomised patients excluding those with a major deviation from the protocol
- Safety population: patients who received at least one dose of treatment.

9 The figure of 226 patients required in this study is based on an incidence of events estimated from similar clinical trials.
The patient populations defined for analysis are presented below; the proportion of patients in each population was similar in both groups.

Table 6: Populations defined for analysis – AVERROES study

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Acetylsalicylic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population, n</td>
<td>2,807</td>
<td>2,791</td>
</tr>
<tr>
<td>Safety population, n (%)</td>
<td>2,798 (99.7)</td>
<td>2,780 (99.6)</td>
</tr>
<tr>
<td>PP population, n (%)</td>
<td>2,714 (96.7)</td>
<td>2,695 (96.6)</td>
</tr>
<tr>
<td>Patients having stopped treatment, n (%)</td>
<td>558 (19.9)</td>
<td>649 (23.3)</td>
</tr>
</tbody>
</table>

The mean duration of exposure to treatment was about 59 weeks in both groups, corresponding to 3,193 patient-years in the apixaban group and 3,150 patient-years in the acetylsalicylic acid group. A total of 5,598 patients were randomised (ITT population): 2,807 patients randomised into the apixaban group and 2,791 in the acetylsalicylic acid group.

Characteristics of the evaluated population:
On inclusion, the characteristics of the patients in the two treatment groups were similar. The mean age of the patients was about 70 years. More than 69% of patients were aged 65 years and over, and 33.8% were 75 or older. The majority of patients were male (about 58% in both groups) and Caucasian (more than 78% in both groups). Two thirds had impaired renal function, 17% had moderate renal impairment and 2% had severe renal impairment. The mean CHADS\(^2\) score was 2 in both treatment groups; 38% had a CHADS\(^2\) score of 1, 35% had a CHADS\(^2\) score of 2 and 26% had a CHADS\(^2\) score ≥ 3. Furthermore, 61.4% of patients in both groups had at least 2 thromboembolic risk factors.

Treatments evaluated:
- Acetylsalicylic acid: the majority of patients (90.8%) received a low dosage of acetylsalicylic acid, namely 81 mg/day (64.3%) or 162 mg/day (26.2%). About 76% of randomised patients in both groups had taken acetylsalicylic acid before the start of the double-blind period, thus suggesting that a significant proportion of patients in the study were tolerant to acetylsalicylic acid at the time of inclusion. Furthermore, 15% of randomised patients in both groups had been treated with an oral anticoagulant before the start of the double-blind period.
- Apixaban: the majority of patients (93.6%) took apixaban at a dosage of 5 mg twice daily. The characteristics of the patients who received 2.5 mg twice daily were similar in both treatment groups. These patients had a mean age greater than 83 years and were primarily women, and 90% had a high risk of thromboembolism with a CHADS\(^2\) score ≥ 2.

Reasons for unsuitability for VKA therapy
These reasons were similar in both randomised groups, as well as in the subgroups of patients naïve and non-naïve to VKA therapy. Almost 40% of randomised patients in both groups had already been treated with a VKA, prescribed in 37.7% of cases for AF. The mean duration of treatment was less than 6 months for 17.8% of patients and more than 24 months for 12.3% of patients.
Among the patients who had previously received VKA therapy, 48.4% had had poor INR control, 23.5% had been outside the target therapeutic range (INR: 2.0-3.0) over half of the time and 23.9% had experienced bleeding on VKAs, sometimes major bleeding (4.3% of them). The reason for stopping VKA therapy was primarily explained by the doctor’s decision (20.4%), the patient’s decision (19.7%), poor INR control (19.1%) or the occurrence of bleeding (11.9%).

Efficacy results:
The AVERROES study was stopped after the second interim analysis provided for in the protocol and following the recommendations of the Independent Data Monitoring Committee for the following reasons: a greater reduction in the risk of stroke and systemic embolism in patients treated with apixaban in comparison with those treated with acetylsalicylic acid, p<0.00006 in both analyses, with a similar safety profile in both groups.
Primary efficacy endpoint

Table 7: Primary efficacy endpoint (stroke or systemic embolism) (intended treatment period / PP and ITT populations) – AVERROES study

<table>
<thead>
<tr>
<th></th>
<th>PP population</th>
<th>ITT population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apixaban</td>
<td>ASA</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>2,714</td>
<td>2,695</td>
</tr>
<tr>
<td><strong>Stroke or SE, n (%)</strong></td>
<td>48 (1.77)</td>
<td>105 (3.90)</td>
</tr>
<tr>
<td><strong>Incidence, %/year</strong></td>
<td>1.57</td>
<td>3.48</td>
</tr>
<tr>
<td><strong>Hazard ratio [95% CI]</strong></td>
<td>0.45 [0.32; 0.64]</td>
<td>0.45 [0.32; 0.62]</td>
</tr>
<tr>
<td><strong>Bilateral superiority test (p)</strong></td>
<td>&lt;0.00001</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td><strong>Absolute risk reduction vs. ASA (%/year, 95% CI)</strong></td>
<td>2.01 [1.9; 2.12]</td>
<td>2.01 [1.9; 2.13]</td>
</tr>
<tr>
<td><strong>NNT [95% CI]</strong></td>
<td>-</td>
<td>50 [47; 53]</td>
</tr>
</tbody>
</table>

ASA: acetylsalicylic acid; CI: confidence interval; NNT: number needed to treat

Secondary efficacy endpoints

As superiority had been demonstrated on the primary efficacy endpoint in the ITT population, the following secondary efficacy endpoints were tested in accordance with the hierarchical statistical testing procedure stipulated in the protocol:

- **Major vascular events (composite endpoint combining stroke, systemic embolism, MI and vascular death):** the annual incidence was 4.21% in the apixaban group and 6.35% in the acetylsalicylic acid group. Apixaban showed a 34% reduction in these events compared to acetylsalicylic acid (HR = 0.66; 95% CI [0.53; 0.83]; p = 0.00026), i.e. an absolute risk reduction of 2.14%. An average of 47 patients would need to be treated with apixaban for one year to prevent one major vascular event in comparison with acetylsalicylic acid.

- **All-cause mortality:** the difference between the two groups was not significant. It should be noted that the number of events observed was lower in the apixaban group than in the acetylsalicylic acid group, as was the number of vascular and non-vascular deaths.
Other secondary efficacy endpoints:

Table 8: Components of the primary endpoints (intended treatment period and ITT population) – AVERROES study

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Acetylsalicylic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2,807</td>
<td>2,791</td>
</tr>
<tr>
<td>Ischaemic or unspecified stroke, n (%)</td>
<td>43 (1.53)</td>
<td>97 (3.48)</td>
</tr>
<tr>
<td>Incidence, %/year</td>
<td>1.37</td>
<td>3.11</td>
</tr>
<tr>
<td>Hazard ratio [95% CI]</td>
<td></td>
<td>0.44 [0.31; 0.63]</td>
</tr>
<tr>
<td>Absolute risk reduction vs. ASA (%/year, 95% CI)</td>
<td></td>
<td>1.74 [1.6; 1.8]</td>
</tr>
<tr>
<td>Haemorrhagic stroke, n (%)</td>
<td>6 (0.21)</td>
<td>9 (0.32)</td>
</tr>
<tr>
<td>Incidence, %/year</td>
<td>0.19</td>
<td>0.28</td>
</tr>
<tr>
<td>Hazard ratio [95% CI]</td>
<td></td>
<td>0.67 [0.24; 1.88]</td>
</tr>
<tr>
<td>Absolute risk reduction vs. ASA (%/year, 95% CI)</td>
<td></td>
<td>0.09 [0.07; 0.11]</td>
</tr>
<tr>
<td>SE, n (%)</td>
<td>2 (0.07)</td>
<td>13 (0.47)</td>
</tr>
<tr>
<td>Incidence, %/year</td>
<td>0.06</td>
<td>0.41</td>
</tr>
<tr>
<td>Hazard ratio [95% CI]</td>
<td></td>
<td>0.15 [0.03; 0.68]</td>
</tr>
<tr>
<td>Absolute risk reduction vs. ASA (%/year, 95% CI)</td>
<td></td>
<td>0.35 [0.33; 0.37]</td>
</tr>
</tbody>
</table>

Table 9: Secondary endpoints and composites (intended treatment period and ITT population) – AVERROES study

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Acetylsalicylic acid</th>
<th>Apixaban versus acetylsalicylic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=2,807</td>
<td>n (%) Incidence (%/year)</td>
<td>N=2,791</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 (0.86)</td>
<td>0.76</td>
<td>28 (1.00)</td>
<td>0.89</td>
</tr>
<tr>
<td>Consequences of stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-disabling stroke (Rankin 0-2)</td>
<td>18 (0.64)</td>
<td>0.57</td>
<td>35 (1.25)</td>
</tr>
<tr>
<td>Disabling stroke (Rankin 3-6)</td>
<td>31 (1.1)</td>
<td>0.98</td>
<td>72 (2.58)</td>
</tr>
<tr>
<td>Death (Rankin 6, fatal*)</td>
<td>13 (0.46)</td>
<td>0.41</td>
<td>16 (0.57)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>111 (3.95)</td>
<td>3.51</td>
<td>140 (5.02)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>84 (2.99)</td>
<td>2.65</td>
<td>96 (3.44)</td>
</tr>
<tr>
<td>Non-vascular death</td>
<td>27 (0.96)</td>
<td>0.85</td>
<td>44 (1.58)</td>
</tr>
<tr>
<td>Hospitalisation with a cardiovascular cause</td>
<td>367 (13.07)</td>
<td>12.50</td>
<td>455 (16.3)</td>
</tr>
<tr>
<td>Net clinical benefit*</td>
<td>128 (4.57)</td>
<td>4.03</td>
<td>198 (7.12)</td>
</tr>
</tbody>
</table>

*: Net clinical benefit: major vascular events and major bleeding
Analysis of efficacy in subgroups:
The effect of apixaban versus acetylsalicylic acid at reducing primary efficacy endpoint events observed in the overall study population was uniform regardless of the predetermined patient sub-population. None of the interaction analyses were significant, with the exception of the analysis for weight: RR = 0.84, 95% CI [0.44; 1.58] for weight < 60 kg and RR = 0.36, 95% CI [0.24; 0.53], p = 0.02.

8.1.3 Indirect comparisons

Methodology

Three studies were included, bearing in mind that the data selected came from phase III randomised clinical trials with a control treatment that enabled comparisons with the apixaban vs. warfarin study to be made: RE-LY (dabigatran etexilate 110 mg and 150 mg), an open-label non-inferiority study; ROCKET AF (rivaroxaban, 20 mg), a double-blind non-inferiority study; and ARISTOTLE (apixaban 5 mg), a double-blind non-inferiority study.

The method of combining odds ratios through random-effects meta-analysis was applied to obtain an overall odds ratio with a 95% CI. Bucher’s method for adjusted indirect comparisons was used. Data from the intention-to-treat analyses were used for the calculations.

A total of 50,578 patients were included: 18,113 patients in the RE-LY study, 14,264 in the ROCKET AF study and 18,201 in the ARISTOTLE study.

Patient demographics and risk of stroke were similar on inclusion in the RE-LY and ARISTOTLE studies (with mean CHADS\(_2\) scores of 2.2 and 2.1 respectively). However, the patients in the ROCKET AF study were slightly older and had a higher mean CHADS\(_2\) score than patients in the other two studies.

Table 5: Main characteristics of patients in the RE-LY, ROCKET AF and ARISTOTLE studies

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>RE-LY(^{10}) N=18,113</th>
<th>ROCKET AF(^{11}) N=14,264</th>
<th>ARISTOTLE N=18,201</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.5 ± 8.7</td>
<td>73 (65-78)</td>
<td>69.1 ± 9.61</td>
</tr>
<tr>
<td>Female (%)</td>
<td>36.4</td>
<td>39.7</td>
<td>35.3</td>
</tr>
<tr>
<td>Mean CHADS(_2) score</td>
<td>2.2</td>
<td>3.5</td>
<td>2.1</td>
</tr>
<tr>
<td>CHADS(_2) &gt; 3 (%)</td>
<td>32.5</td>
<td>87.0</td>
<td>30.2</td>
</tr>
<tr>
<td>History of stroke, TIA or ES (%)</td>
<td>20.0</td>
<td>54.8</td>
<td>19.7</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>32.0</td>
<td>32.5</td>
<td>35.4</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>23.3</td>
<td>40.0</td>
<td>24.9</td>
</tr>
<tr>
<td>Treated hypertension (%)</td>
<td>78.9</td>
<td>90.5</td>
<td>87.6</td>
</tr>
</tbody>
</table>

The ROCKET AF and ARISTOTLE studies were double-blind trials while RE-LY was an open-label study. As open-label comparisons may lead to an overestimation of the effect size of treatment,\(^{12}\) an exploratory ancillary analysis has been performed to take this bias into account. An empirical estimation of this bias (and its distribution) has been obtained by calculating the ratio of odds ratios estimating the effect size in open-label studies to odds ratios measured in double-blind studies (open-label studies overestimate the effect of treatment if the ratio of odds ratios is below 1). This method takes into account the size of the bias and the uncertainty as to the bias (through its distribution). Two estimations of bias were used:


- An “empirical bias” estimated to be 14%, derived from a meta-epidemiological study that compared the results of open-label studies with those of double-blind studies on the same subject (the same treatment for a defined pathology);
- A “specific bias” estimated to be 25%, derived from studies using ximelagatran in the prevention of stroke and systemic embolism in patients with NVAF and one or more risk factors.

Results without bias correction

Efficacy: the results do not offer evidence of a difference in efficacy between apixaban, dabigatran etexilate 110 mg/150 mg and rivaroxaban on the incidence of stroke and systemic embolism.

Adverse effects:
Apixaban was shown to have a lesser risk of:
- major bleeding:
  - versus dabigatran etexilate 150 mg (OR=0.74; 95% CI [0.61; 0.90]; p=0.003)
  - versus rivaroxaban (OR=0.67; 95% CI [0.55; 0.82]; p=0.0001).
- gastrointestinal haemorrhage:
  - versus dabigatran etexilate 150 mg (OR=0.58; 95% CI [0.40; 0.83]; p=0.003)
  - versus rivaroxaban (OR=0.60; 95% CI [0.43; 0.84]; p=0.003).
- myocardial infarction versus dabigatran etexilate 110 mg (OR=0.64; 95% CI [0.42; 0.99]; p=0.046) and dabigatran etexilate 150 mg (OR=0.62; 95% CI [0.41; 0.96]; p=0.03).

The risk of stopping treatment was lower on apixaban:
- versus dabigatran etexilate 110 mg (OR=0.66; 95% CI [0.59; 0.75]; p<0.0001) and dabigatran etexilate 150 mg (OR=0.64; 95% CI [0.57; 0.71]; p<0.0001)
- versus rivaroxaban (OR=0.83; 95% CI [0.75; 0.92]; p=0.0003).

Other works typically confirm this absence of a difference in efficacy between apixaban, dabigatran etexilate 110 mg/150 mg and rivaroxaban, as well as the lesser risk of major bleeding on apixaban than on dabigatran etexilate 150 mg and rivaroxaban, of gastrointestinal haemorrhage than on dabigatran etexilate 150 mg, and of myocardial infarction than on dabigatran etexilate 150 mg.

Results with correction of bias related to the open-label design of RE-LY on the primary efficacy endpoint: the bias correction method applies both to the odds ratios for dabigatran etexilate versus warfarin, and to the comparison of apixaban vs. dabigatran etexilate:

Comparison of dabigatran etexilate versus warfarin:
- The superiority of dabigatran etexilate 150 mg to warfarin in the RE-LY study was no longer established for the primary efficacy endpoint (incidence of stroke and systemic embolism):
  - Reminder of results without bias correction: OR = 0.67; 95% CI [0.54; 0.83]
  - Correction with “empirical bias” (14% overestimation of effect): OR = 0.78; 95% CI [0.60; 1.01]
  - Correction with “specific bias” (25% overestimation of effect): OR = 0.89; 95% CI [0.64; 1.24]
- The superiority of dabigatran etexilate 110 mg to warfarin was not established on efficacy (with or without bias correction).

Comparison of dabigatran etexilate versus apixaban:
- The indirect comparison corrected for “empirical bias” offers no evidence of a difference in efficacy between apixaban and dabigatran etexilate 110 mg/150 mg on the primary efficacy endpoint.
- However, the indirect comparison corrected for “specific bias” suggests that apixaban is superior to dabigatran etexilate 110 mg in the prevention of stroke or systemic embolism: OR = 0.65; 95% CI: [0.45; 0.95].

**08.2** Adverse effects

**8.2.1** ARISTOTLE study

The overall incidence of discontinuations of treatment related to adverse effects was 1.8% in the apixaban group and 2.6% in the warfarin group. The percentage of patients who experienced an adverse effect was 27.8% in the apixaban group versus 34.2% in the warfarin group.

Risk of bleeding:

**Table 10: Secondary endpoints in patients with atrial fibrillation in the ARISTOTLE study**

<table>
<thead>
<tr>
<th></th>
<th>Apixaban N = 9,088 n (%/year)</th>
<th>Warfarin N = 9,052 n (%/year)</th>
<th>Relative risk (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding-related results</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major*</td>
<td>327 (2.13)</td>
<td>462 (3.09)</td>
<td>0.69 (0.60; 0.80)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Fatal</td>
<td>10 (0.06)</td>
<td>37 (0.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>52 (0.33)</td>
<td>122 (0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major + CRNM**</td>
<td>613 (4.07)</td>
<td>877 (6.01)</td>
<td>0.68 (0.61; 0.75)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total</td>
<td>2356 (18.1)</td>
<td>3060 (25.8)</td>
<td>0.71 (0.68; 0.75)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Other endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>603 (3.52)</td>
<td>669 (3.94)</td>
<td>0.89 (0.80; 1.00)</td>
<td>0.0465</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>90 (0.53)</td>
<td>102 (0.61)</td>
<td>0.88 (0.66; 1.17)</td>
<td></td>
</tr>
</tbody>
</table>

* Major bleeding defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria.
** Clinically relevant non-major bleeding (CRNM)

The most common types of treatment-related bleeding (> 5%) were epistaxis (6.2% on apixaban and 7.5% on warfarin) and contusions (3.3% on apixaban and 5.3% on warfarin).

In accordance with the sequential statistical analysis stipulated in the protocol, superiority on major bleeding as defined by the ISTH criteria\textsuperscript{19,20} was tested. The risk of its occurrence was reduced


\textsuperscript{20} According to the International Society of Thrombosis and Haemostasis (ISTH), major bleeding is defined as follows: acute, clinically significant bleeding associated with a fall in haemoglobin level \( \geq 2 \text{ g/dl} \) over a
more in the apixaban group, with an incidence of 2.13%/year, than in the warfarin group with an incidence of 3.09%/year, namely a relative risk reduction of 31% and an absolute risk reduction of 0.96%/year, HR = 0.69; 95% CI [0.60; 0.80]; p < 0.0001. Bleeding as defined by the GUSTO\(^{21}\) and TIMI\(^{22}\) criteria (consisting of more severe bleeding than the ISTH criteria) was also reduced more in the apixaban group than in the warfarin group, p < 0.0001. The results relating to major bleeding in the pre-specified subgroups, which were primarily defined by CHADS\(_2\) score, age, body weight, sex, renal function status, history of stroke or TIA and diabetes, were consistent with the results in the overall study population.

Fatal bleeding (haemorrhage and haemorrhagic stroke): this occurred less frequently in the apixaban group (10 patients, 0.06%/year) than in the warfarin group (37 patients, 0.24%/year). Bleeding in critical areas: intraocular haemorrhage occurred more frequently in the apixaban group (28 patients, 0.18%/year) than in the warfarin group (19 patients, 0.13%/year). However, the incidence of major bleeding in other critical areas was lower or comparable between the two groups. In particular, intracranial haemorrhage occurred less frequently in the apixaban group (52 patients, 0.33%/year) than in the warfarin group (122 patients, 0.80%/year), HR=0.42; p < 0.0001. Gastrointestinal haemorrhage had a lower incidence in the apixaban group (0.76%/year) than in the warfarin group (0.86%/year).

The results in the European subgroup of patients were not favourable to apixaban. This result, from one of the many subgroup analyses performed, was discussed by the EMA. No explanation has been found.

Several post-hoc analyses were performed. In patients considered at higher risk of bleeding, reduction in major bleeding still favours apixaban whatever the age bracket. Similar results were found in the subgroup of patients with renal impairment who received apixaban at the dose of 2.5 mg twice daily, with the exception of patients with mild renal impairment, in whom major bleeding occurred less frequently in the warfarin group (2.47%/year) than in the apixaban group (9.23%/year), 95% CI [0.74; 19.69]. Apixaban’s effect at reducing major bleeding as defined by the ISTH was not affected by the use of a reduced dose of apixaban (2.5 mg twice daily).

With regard to the median TTR of patients randomised into the warfarin group excluding the first 7 days of the study and discontinuations of treatment, the study centres were classified into 4 quartiles according to their median TTR, calculated from the INRs of patients treated with warfarin at that site: Q1: < 52.35%; Q2: ≥ 52.35% and < 65.99%; Q3: ≥ 65.99% and < 76.50%; Q4 ≥ 76.50%. The incidence of major bleeding was compared in these different quartiles. The reduction in major bleeding on apixaban versus warfarin was comparable to that demonstrated in the overall study population.

### 8.2.2 AVERROES study

Any interpretation of the data presented below must take into account the fact that the AVERROES study was ended prematurely. The overall incidence of discontinuations of treatment related to adverse effects was 1.5% in the apixaban group and 1.3% in the ASA group. The percentage of patients who experienced an adverse effect was similar in both groups: 16.6% on apixaban versus 16.7% on acetylsalicylic acid. A total of 206 deaths were reported during the treatment period: 91 in the apixaban group (3.3%) and 115 in the acetylsalicylic acid group (ASA: 4.1%).

period of 24 hours and/or leading to transfusion of two or more units of red cells; bleeding in a critical area (such as intracranial, intraspinal, intraocular, pericardial, intramuscular with compartment syndrome, retroperitoneal or intra-articular); and any fatal bleeding.

\(^{21}\) In the GUSTO classification (Global Use of Strategies to Open Occluded Coronary Arteries), either intracranial haemorrhage or bleeding that causes haemodynamic compromise and requires intervention is considered as severe.

\(^{22}\) In the TIMI classification (Thrombolysis in Myocardial Infarction), an intracranial haemorrhage or a ≥ 5 g/dl decrease in the haemoglobin concentration or a 15% absolute decrease in the haematocrit is considered to be major bleeding.
Risk of bleeding:

Table 11: Incidence of bleeding in the AVERROES study

<table>
<thead>
<tr>
<th></th>
<th>Apixaban N = 2,798 n (%/year)</th>
<th>ASA N = 2,780 n (%/year)</th>
<th>Relative risk (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISTH major</td>
<td>45 (1.41)</td>
<td>29 (0.92)</td>
<td>1.54 (0.96, 2.45)</td>
<td>0.0716</td>
</tr>
<tr>
<td>Fatal, n</td>
<td>5 (0.16)</td>
<td>5 (0.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial, n</td>
<td>11 (0.34)</td>
<td>11 (0.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major + CRNM*</td>
<td>140 (4.46)</td>
<td>101 (3.24)</td>
<td>1.38 (1.07, 1.78)</td>
<td>0.0144</td>
</tr>
<tr>
<td>Total</td>
<td>325 (10.85)</td>
<td>250 (8.32)</td>
<td>1.30 (1.10, 1.53)</td>
<td>0.0017</td>
</tr>
</tbody>
</table>

* Clinically relevant non-major bleeding (CRNM)

The risk of occurrence of ISTH major bleeding in the predetermined sub-populations was comparable to that observed in the overall study population.

8.2.3 SPC data

Risk of bleeding

“As with other anticoagulants, patients taking ELIQUI S are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. ELIQUIS administration should be discontinued if severe haemorrhage occurs. Although treatment with apixaban does not require routine monitoring of exposure, the Rotachrom® anti-FXa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery.”

The SPC also states that:

- “In patients with atrial fibrillation and conditions that warrant mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with ELIQUIS. In a clinical trial of patients with atrial fibrillation, concomitant use of ASA increased the major bleeding risk on apixaban from 1.8% per year to 3.4% per year and increased the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.1%) use of concomitant dual antiplatelet therapy. In a clinical trial of high-risk post acute coronary syndrome patients, characterised by multiple cardiac and non-cardiac comorbidities, who received ASA or the combination of ASA and clopidogrel, a significant increase in risk of ISTH (International Society on Thrombosis and Haemostasis) major bleeding was reported for apixaban (5.13% per year) compared to placebo (2.04% per year).”

- “There is very limited experience with the use of thrombolytic agents for the treatment of acute ischaemic stroke in patients administered apixaban.”
08.3 Summary & discussion

Results of clinical trials
In non-valvular atrial fibrillation with at least one thromboembolic risk factor, apixaban (ELIQUIS) has been evaluated through two international randomised, double-blind studies, one versus warfarin (ARISTOTLE study) and one versus acetylsalicylic acid (AVERROES study). A total of 29,397 patients were included. An indirect comparison study of apixaban, dabigatran and rivaroxaban was also provided.

Study versus warfarin
In the 18,201 patients included, apixaban was superior to warfarin at reducing:
- strokes/systemic embolisms (primary endpoint): 1.27% vs. 1.60%, i.e. an absolute risk reduction of 0.33%/year and a relative risk reduction of 21%/year (HR = 0.79 [0.66; 0.95]; p < 0.001 for non-inferiority; p = 0.01 for superiority)
- major bleeding: 2.13%/year vs. 3.09%/year, i.e. an absolute risk reduction of 0.96%/year and a relative risk reduction of 31% (HR = 0.69 [0.60; 0.80]; p < 0.001)
- deaths: 3.52%/year vs. 3.94%/year, i.e. an absolute risk reduction of 0.42%/year and a relative risk reduction of 11% (HR = 0.89 [0.80; 1.00]; p = 0.0465).

In comparison with warfarin, the mean numbers of patients who would need to be treated with apixaban for one year are:
- 303 patients to prevent one stroke or systemic embolism
- 104 patients to prevent one case of major bleeding
- 238 patients to prevent one death.

The incidence of discontinuations of treatment for adverse effects was 1.8% with apixaban vs. 2.6% with warfarin, and the incidence of major gastrointestinal haemorrhage was 0.76%/year with apixaban vs. 0.86%/year with warfarin.

The efficacy results and results relating to major bleeding in pre-specified subgroups, primarily defined by CHADS\textsubscript{2} thromboembolic risk stratification score, age, weight, sex, renal function status and history of stroke or TIA, were comparable with those in the overall study population.

Study versus acetylsalicylic acid
This study was stopped after the second interim analysis provided for in the protocol and following the recommendations of the Independent Data Monitoring Committee, due to evidence of a reduction in strokes and systemic embolisms together with an acceptable safety profile.

In the 5,598 patients included and considered by investigators to be unsuitable for VKA therapy, apixaban was superior to acetylsalicylic acid (81-324 mg/day) at reducing:
- strokes/systemic embolisms (primary efficacy endpoint): 1.62%/year vs. 3.63%/year, i.e. an absolute risk reduction of 2.01%/year and a relative risk reduction of 55% (HR = 0.45 [0.32; 0.62]; p < 0.00001); the effect observed in the overall study population was comparable with that in the various predetermined subgroups
- strokes/systemic embolisms/MI/vascular deaths: 4.21%/year vs. 6.35%/year, i.e. an absolute risk reduction of 2.14%/year and a relative risk reduction of 34% (HR = 0.66 [0.53; 0.83]; p = 0.00026).

- Apixaban did not differ from acetylsalicylic acid in terms of:
- all-cause mortality: 3.51%/year vs. 4.42%/year; HR = 0.79 [0.62; 1.02]
- discontinuations of treatment related to adverse effects: 1.5% vs. 1.3%
- the incidence of major bleeding: 1.41%/year vs. 0.92%/year; HR = 1.54 [0.96; 2.45].

Net clinical benefit, evaluated from an endpoint combining stroke, systemic embolism and major bleeding, favoured apixaban in both studies:
- versus warfarin: 3.17%/year vs. 4.11%/year, i.e. a relative risk reduction of 23% per year [0.69; 0.86], p < 0.001
- versus acetylsalicylic acid: 4.03%/year vs. 6.32%/year, i.e. a relative risk reduction of 36% per year [0.51; 0.80], p < 0.0001.

No data evaluating quality of life are available.

**Results of indirect comparisons**

An indirect comparison study showed:
- In terms of efficacy: there was no difference between apixaban, dabigatran etexilate and rivaroxaban for preventing the occurrence of strokes and systemic embolisms, both with and without bias correction.
- In terms of safety, apixaban may involve a lesser exposure to the risk of major bleeding and gastrointestinal haemorrhage than dabigatran etexilate 150 mg and rivaroxaban. This result was obtained before bias correction.

**Main discussion points regarding the data:**

1) Methodology:
The ARISTOTLE and AVERROES studies did not pose any particular methodological problems. In particular, the sequential hierarchical testing procedure means that the results of the multiple comparisons are acceptable, and a double-blind design was used as in the ROCKET AF study (rivaroxaban versus warfarin). Nonetheless, the results of the AVERROES study (apixaban versus acetylsalicylic acid) must be interpreted with caution as it was stopped early, after the 2nd interim analysis provided for by the protocol. An overestimation of the apixaban effect size and an underestimation of the bleeding risks in both groups cannot be ruled out.

Furthermore, the choice of warfarin (the standard VKA treatment) because of its efficacy demonstrated in numerous clinical trials\(^{23,24}\) seems to be justified even though it is not the most commonly used VKA in France: “The advantage that indanediones (PREVISCAN) have over coumarins (COUMADINE, SINTROM) is their high protein affinity, which makes them more susceptible to certain drug interactions. Their drawback is that they are sometimes implicated in immunological adverse effects involving the blood, kidneys or liver. The advantage of coumarin derivatives is their good safety profile, even though drug interactions are a little more pronounced. In addition, few international studies of the indanediones are available. In order to simplify treatment and improve stability, VKAs with a long half-life such as COUMADINE are often recommended. VKAs with a short half-life may be preferable in patients at risk of bleeding or who are very sensitive to these drugs.”

---

\(^{23}\) Utilisations des Antivitamines K en pratique médicale courante. Recommandations du GEHT: 2000
\(^{24}\) Protocoles pluriprofessionnels des soins de premier recours, Haute Autorité de Santé, November 2011, citing warfarin as the recommended standard VKA, page 7.
2) Transferability and data still needed:
The duration of the AVERROES and ARISTOTLE studies was relatively short in comparison with actual durations of prescription. The patients included in these two studies had a lesser risk of stroke and a lesser bleeding risk than patients included in the ROCKET AF study. On this point, the latter study included patients with characteristics more representative of the target population. The action to be taken when severe and/or life-threatening bleeding occurs is empirical and poorly documented. No antidote is available for patients who need the anticoagulant effect to be stopped rapidly. The lack of a need to monitor the level of coagulation makes it difficult to assess bleeding risk, particularly in non-compliant or poorly compliant patients or in cases of drug interaction. Thus, little is known about the longer-term bleeding effects of this drug under actual conditions of use.

For this reason, efficacy and safety data from actual conditions of use will be needed to confirm the expected therapeutic benefit of apixaban (ELIQUIS) in comparison with a VKA, or even with other non-VKA anticoagulants (dabigatran and rivaroxaban).

3) Putting into perspective the results of studies of the three non-VKA oral anticoagulants (apixaban [ELIQUIS], dabigatran [PRADAXA] and rivaroxaban [XARELTO]) in the prevention of stroke and systemic embolism in patients with AF:

Dabigatran (PRADAXA) and rivaroxaban (XARELTO) did not demonstrate any reduction in all-cause mortality in comparison with warfarin. Both are likely to reduce the risk of serious bleeding, particularly intracranial haemorrhage, without any loss of efficacy in comparison with warfarin. They have the same theoretical advantages over VKAs, especially a less variable anticoagulant effect, and share the same disadvantages: no possibility of routine monitoring of biological efficacy, which could complicate the management of certain patients, for example those with poor compliance, and lack of an antidote in the event of bleeding.

An indirect comparison (see XARELTO opinion of 14 March 2012) of the results of the RE-LY (dabigatran) and ROCKET AF (rivaroxaban) studies must take into account a bias that is difficult to quantify, given the open-label design of the RE-LY study (comparing dabigatran to warfarin), which may have led to an overestimation of its efficacy and an underestimation of the bleeding risk, and the fact that rivaroxaban (20 mg/day or 15 mg/day in cases of moderate renal impairment) may be less effective than dabigatran (300 mg/day as two daily doses) at preventing the occurrence of stroke but causes fewer severe gastrointestinal haemorrhages.

Dabigatran is being closely monitored by the EMA and the FDA for risk of bleeding, because serious and/or fatal cases of bleeding have been reported since it started to be marketed in this new indication. The EMA has imposed a contraindication in cases of severe renal impairment and included new precautions for use, in particular an evaluation of renal function prior to the start of treatment and then at least once a year and lower dosages in vulnerable patients (advanced age, moderate renal impairment, low weight). In the ROCKET AF study, rivaroxaban did not appear to expose vulnerable patients to an increased risk of bleeding in comparison to other patients. On the other hand, more strokes occurred after a change from warfarin to rivaroxaban.

The increased risk of myocardial infarction associated with dabigatran does not seem to be associated with rivaroxaban.

Only studies under conditions of actual use will enable these observations to be confirmed. A direct comparison would also be desirable in order to clarify the respective benefits of these three new oral anticoagulants. There is no data on apixaban in this indication beyond 3 years of use, in patients with severe renal or hepatic impairment and in patients with valvular disease or a prosthetic heart valve.
08.4 Planned studies

The Marketing Authorisation for ELIQUIS is accompanied by a European risk management plan (RMP) with the following identified risks: bleeding and potential risks:
- transitory increases in liver function test values in thromboprophylaxis in adults following elective hip or knee replacement surgery
- liver lesions in the prevention of stroke and systemic embolism in adults with NVAF and one or more risk factors
- an evaluation by external hepatologists of certain hepatic events reported during studies has been suggested as "additional pharmacovigilance."

The company has also indicated that two studies of use, intended to retrospectively and descriptively evaluate use of ELIQUIS, should be implemented in the Netherlands and Sweden from insurance databases (the Netherlands) and a register (the National Patient Register in Sweden).

09 THERAPEUTIC USE

Oral vitamin K antagonists are the standard antithrombotic treatment in cases of atrial fibrillation in patients at high risk of stroke.

Vitamin K antagonists are effective at preventing the risk of thromboembolism associated with atrial fibrillation (AF), but come at the cost of an increased risk of major bleeding (particularly intracranial haemorrhage). According to AFSSAPS (now ANSM), they are a major cause of iatrogenic drug-related conditions, which account for 13% of hospital admissions and are responsible for almost 4,000 deaths each year. These medicinal products have several other major drawbacks:
- a narrow therapeutic range: VKAs are, according to AFSSAPS, a major cause of iatrogenic drug-related conditions, which account for 13% of hospital admissions, or 17,000 hospitalisations per year, due to haemorrhagic complications and are responsible for almost 4,000 deaths each year.
- a variable individual response: this may be explained by the existence of interactions with numerous medicinal products (NSAIDs, antibiotics and antimycotics, statins, antiepileptics, glucocorticoids, etc.) and with foodstuffs rich in vitamin K (for example, cabbage or asparagus) or may be linked to genetic polymorphism.

These factors mean that VKAs must be taken regularly at a fixed time and require regular monitoring of the level of anticoagulation by measuring the INR (International Normalised Ratio) with the maintenance of an INR record.

The inherent difficulties and constraints associated with the use of VKAs help to explain why the prescription and monitoring of these medicinal products are not optimal. In France, up to 50% of patients with AF and taking an anticoagulant treatment are not taking VKAs.

Therapeutic use of ELIQUIS (apixaban):
Apixaban, like rivaroxaban and dabigatran, is a new alternative to the prescription of VKAs.

The patients who would be most likely to benefit from apixaban, as with rivaroxaban and dabigatran, are those whose INR cannot be controlled by VKAs. The lack of a need in current practice to measure the level of anticoagulation on apixaban should not result in less clinical monitoring in these patients.

The clinical data for apixaban in elderly patients (> 75 years), patients with renal impairment and patients with a low body weight, who are at risk of bleeding, are currently limited.

Bearing in mind that the characteristics (particularly stroke risk and age) of patients included in the studies evaluating these three medicinal products (versus warfarin) are different, the data from
indirect comparisons suggest that apixaban (ELIQUIS) is as effective as dabigatran (PRADAXA) and rivaroxaban (XARELTO) at preventing stroke or systemic embolism with a lower risk of bleeding. Nonetheless, only longer-term data and data obtained under conditions of actual use can confirm this difference.

As with rivaroxaban (XARELTO) and dabigatran etexilate (PRADAXA), no antidote to apixaban is available and the level of anticoagulation cannot be measured in current practice. Further data are needed to determine optimal management in cases of severe bleeding on apixaban (as well as on dabigatran and rivaroxaban).

Apixaban (ELIQUIS) is an alternative to warfarin, rivaroxaban or dabigatran.
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

**010.1 Actual benefit**

- Atrial fibrillation (AF) is the most common cardiac arrhythmia, and it increases with age. It is the primary cause of cerebral embolism of cardiac origin, and it is responsible for about 50% of cases of ischaemic stroke. AF may be immediately life-threatening or life-threatening following complications; stroke, which is a complication of AF, is characterised by its severity and greatly affects quality of life.

- ELIQUIS is a first-line or second-line (in the case of poor control of the INR with VKA) prophylactic therapy in patients at moderate to high risk of thromboembolism as defined in the indications in the Marketing Authorisation.

- **Public health benefit:**
  
The public health burden represented by stroke and systemic embolism is substantial, because of their frequency and/or the often disabling sequelae that follow. AF is a risk factor for stroke and systemic embolism, the prevalence of which is increasing due to the aging population.

  The availability of a preventive treatment for these events, particularly in at-risk subjects, is a public health need and is included in the National Stroke Plan 2010-2014.

  In view of the available data, which come primarily from a double-blind comparative study (improved efficacy and safety versus warfarin) and an indirect comparison suggesting improved safety versus the proprietary medicinal products XARELTO and PRADAXA, apixaban (ELIQUIS) is expected to have a moderate additional impact on the morbidity and mortality of patients treated in comparison with current management. The impact on quality of life is not documented. An impact on the provision of healthcare is expected, particularly because there is no need for specific monitoring of blood values, in contrast to VKAs, but this impact has not been documented.

  There is no guarantee that the trial data are transferable to actual practice, particularly because of the following factors: the demonstration of efficacy based on a controlled trial versus warfarin, which is not the most used comparator in France (where fluindione is more commonly prescribed); the low number of French patients included in this trial; uncertainty as to the long-term impact; compliance (2 doses/day) in the absence of biological monitoring; and the consequences of the lack of an antidote.

  Thus, the proprietary medicinal product ELIQUIS should be able to provide a partial and supplementary response to the public health need identified.

  Consequently, a public health benefit is expected from the medicinal product ELIQUIS in the prevention of stroke and systemic embolism in adult patients with non-valvular AF and one or more risk factors. This benefit is slight.

- **The efficacy/adverse effects ratio of apixaban is high in this indication.**

- Alternative medicinal products exist: oral vitamin K antagonists, rivaroxaban (XARELTO) and dabigatran etexilate (PRADAXA).
Taking account of these points, the Committee considers that the actual benefit of ELIQUIS is substantial in the Marketing Authorisation indication.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication “Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II)” and at the dosage in the Marketing Authorisation.

Proposed reimbursement rate: 65%.

010.2 Improvement in actual benefit (IAB)

The Committee considers that ELIQUIS does not provide an improvement in actual benefit (IAB V, non-existent) in the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

The patients who would be most likely to benefit from apixaban, as with rivaroxaban and dabigatran, are those whose INR cannot be controlled by VKAs. These patients require close clinical monitoring, but the lack of a need to measure the level of anticoagulation may result in follow-up consultations becoming less frequent; close monitoring must not be forgotten in everyday practice. The clinical data for apixaban in elderly patients (> 75 years), patients with renal impairment or with a low body weight, who are at risk of bleeding, are currently limited. Furthermore, indirect comparisons drawn from three studies, RE-LY, ROCKET AF and ARISTOTLE, which have different methodologies and different patient characteristics on inclusion, cannot enable a hierarchy to be established for these three medicinal products.

010.3 Target population

The target population for ELIQUIS 2.5 mg and 5 mg is defined as adult patients with non-valvular atrial fibrillation and one or more risk factors (CHADS2 score ≥ 1) such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

Estimate

The prevalence of AF is estimated at between 1% and 2% of the general adult population (about 51 million). If this is applied to the general population of France, there would be between 510,000 and 1,020,000 people with atrial fibrillation in France.25

According to the Cegedim observational study (unpublished study), of the 60,328,037 patients who consulted a generalist physician at least once in 2009 for any reason, 569,298 had at least been diagnosed with atrial fibrillation, this being 0.9% of patients who attended consultations in 2009. According to this survey, of the 569,298 patients diagnosed with AF, 88%, or 501,097 patients had at least one risk factor (CHADS2 ≥ 1).

A cross-sectional study using a permanent database supplied by generalist physicians (Longitudinal Patient Data) was conducted by Cegedim for the period 1 July 2010 to 30 June 2011. Of the 15,623 patients in the database with AF, 83% had a CHADS\textsubscript{2} score > 1, which would correspond to 500,000 to 800,000 patients.

**Conclusion:** the target population of ELIQUIS is between 500,000 and 800,000 patients.

### 011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

**Packaging**

Appropriate for the prescription conditions in terms of the indication, dosage and treatment duration.

**Requests for data**

In the light of the results of the ARISTOTLE and AVERROES studies and the questions that they raise, the Transparency Committee would like to have additional data documenting the therapeutic benefit of apixaban (ELIQUIS) under actual conditions of use compared with the standard treatment of at-risk patients with non-valvular AF. These data relate to:

- the characteristics of the patients treated, in particular age, gender, history and cardiovascular risk factors
- the conditions of use of ELIQUIS: reasons for starting treatment (particularly first-line or second-line prescription and risk factors associated with AF), any previous anticoagulant treatment and level of control thus obtained, concomitant treatments (in particular, antiplatelet drugs and medicinal products where there is a risk of interaction), dosage prescribed (dose, amount administered daily and duration of prescription), frequency and reason for any discontinuations of treatment and treatments switched to
- the impact on morbidity and mortality (events avoided and adverse effects, particularly bleeding), treatment compliance and quality of life in the medium and long term
- the impact on the provision of healthcare (specialist biological monitoring, nursing care and transfer of nurses, hospitalisations and reasons for hospitalisation, etc.) Real-life data on the resources used would allow the medical economics assessment to be completed.

If scheduled or ongoing studies, in particular within the remit of the European Risk Management Plan, do not answer all the questions raised by the Transparency Committee, a specific study must be conducted.

**Other requests**

As soon as the results of the post-inclusion studies requested are available, the Committee will re-assess the therapeutic benefit of the new oral anticoagulants (ELIQUIS, PRADAXA and XARELTO) indicated in the prevention of stroke secondary to non-valvular atrial fibrillation.