Routledge
Taylor & Francis Group

ARTICLE

Estimation of the costs attributable to vitamin K antagonist treatment in patients with non-valvular atrial fibrillation from a French societal perspective

Pierre Levy[a], David Smadja[b,c], Julie Dorey[d], Mondher Toumi[e], Anna-Katharina Meinecke[f], Kevin Bowrin[g] and Jean-Baptiste Briere[f]

[a]Department of Economics and Management of Health Organisations, The University of Paris Dauphine, Paris, France; [b]Department of Medicine, The University of Paris Descartes, Paris, France; [c]The European Hospital Georges-Pompidou (HEGP), Assistance Publique - Hôpitaux de Paris, Paris, France; [d]Creativ Ceutical, Paris, France; [e]Medical School, Laboratory of Public Health, The University of the Mediterranean, Marseilles, France; [f]Bayer AG, Berlin, Germany; [g]Bayer Plc, Reading, UK

ABSTRACT

Background: Little is known about the costs associated with vitamin K antagonist (VKA) treatment in patients with non-valvular atrial fibrillation (NVAF) in France.

Objectives: To evaluate monthly per-patient costs attributable to VKA treatment in NVAF patients from a French societal perspective.

Study design: Retrospective data were obtained from 7 international normalised ratio (INR) monitoring centres in France. Patients older than 18 years of age with NVAF treated with VKA were recruited. Additional patient-level data assessing resource use corresponding with VKA treatment were collected via self-completed questionnaires. Unit costs applicable to 2015 were multiplied by resource use and summed to generate VKA treatment costs.

Results: 363 patients were included; 53% were men. The majority of patients received fluindione (72%). The number of INR tests per patient per month was 1.69 (95% CI, 1.59–1.80). The monthly patient cost was €39.72 (€36.23–43.21) from the French societal perspective. Direct medical costs comprised 76% of overall costs, with drug costs representing 7.4% (€2.4); direct non-medical and indirect costs comprised 10% and 14% respectively.

Conclusions: Costs associated with VKA treatment in NVAF cannot be estimated only with drug costs. When direct and indirect attributable costs associated with VKA treatment are considered, the VKA treatment costs are more substantial.

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is independently associated with increased morbidity and mortality [1]. Prevalence rises with age and it has been estimated that 1 in 4 individuals will develop AF during their lifetime. Patients with AF typically have comorbid, high-risk cardiovascular and/or metabolic conditions [2]. AF is associated with serious complications such as stroke, and a reduced quality of life for both patients and their caregivers [3].

Stroke is the most common complication of AF, and prophylactic anticoagulant pharmacotherapy is a treatment mainstay. A number of oral antithrombotic drugs are indicated to prevent stroke and systemic embolism in adults with non-valvular atrial fibrillation (NVAF), the most common type of AF. These include the vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs). Both VKAs and

DOACs have been shown to be effective in preventing stroke in patients with NVAF [4]. No specific antidote is currently available to enable immediate reversal of the anticoagulant effect of DOACs in cases of severe bleeding. However, VKAs have limitations that include multiple drug–food and drug–drug interactions and dietary restrictions [5]. Furthermore, VKA treatment only works optimally when drug concentrations are in the appropriate therapeutic range, assessed using the international normalised ratio [INR]. Patients typically require frequent dose adjustments and INR monitoring during early VKA treatment, as well as regular monitoring thereafter [4,6]. DOACs do not require INR monitoring and are effective and safe. International guidelines, such as the European Society of Cardiology (ESC) guidelines, acknowledge that DOACs have substantial safety benefits and moderately improved efficacy over VKAs [4]. In particular, clinical trials have found that DOACs significantly reduce overall mortality as well as

the incidence of intracranial haemorrhage and haemorrhagic stroke compared with VKAs [7–10]. Additionally, several real-world analyses have confirmed that DOACs offer improved clinical efficacy compared with VKAs [11,12]. Retrospective analyses have also identified improved patient-reported benefit, reduced burden [13], and greater treatment adherence [14] in patients treated with DOACs compared with VKAs. However, the role of DOACs in NVAF treatment in the European Union (EU) and other regions has typically remained secondary, often due to cost considerations [4,6,15]. In France specifically, VKAs such as acenocoumarol, fluindione, and warfarin remain the most common oral anticoagulant therapies used [16].

Emerging international data suggest that the cost of VKA treatment dramatically increases when INR monitoring and relevant medical expenses beyond drug costs are taken into account [17,18]. To address this question, the present study evaluates the attributable costs associated with VKA treatment in patients with NVAF from the societal perspective in France, a country where approximately 200,000 new cases of NVAF occur per year [19].

Study design

Study setting

The study was a retrospective INR monitoring centre chart review linked with a patient self-completion questionnaire. Patients were recruited from French INR monitoring centres ('laboratoires d'analyses medicales') located in urban areas across France. To be eligible for study participation, INR monitoring centres were required to perform at least 75 INR tests per week.

Patient data were obtained from two sources: (a) retrospective information from INR monitoring centres; and (b) patient input via a self-completion questionnaire. Patients usually travelled to monitoring centres for INR testing, but in some cases, patients could not travel due to disability. Therefore, medical professionals who performed blood collection from these patients were asked to screen and recruit them at patient homes or at nursing homes instead of at the INR monitoring centre as for the others.

Study population

Patients were required to be ≥18 years of age, with a diagnosis of NVAF, and taking VKA medication (acenocoumarol, fluindione, or warfarin). Additionally, patients had to receive INR testing at least once during the data collection period. Patients were excluded from the analysis if they were participating in another clinical study, had valvular heart disease or valvular prosthesis, or were being treated with injectable anticoagulants or DOACs, including apixaban, dabigatran, rivaroxaban, or edoxaban.

Data collection

INR monitoring centres were asked to complete a questionnaire for each patient providing information within the last 6 months on frequency of INR testing, frequency of concomitant biologic tests, frequency of patient blood sampling performed at home, prescriber of INR testing, healthcare provider who performed INR testing and tariffs invoiced for the last INR.

Patients were asked to complete a self-completion questionnaire providing information on resource use associated with VKA treatment. Patients were asked to report on direct medical, non-medical, and indirect costs associated with their treatment; these cost components are summarised in detail below in the section entitled 'Endpoints'. Patients were asked to complete and return the form in person or by mail using a prepaid envelope.

The INR monitoring centres used provisional identification (ID) information to connect centre questionnaires and patient questionnaires. Following this, the ID was removed from both documents and all information obtained was forwarded to a third-party organisation responsible for data entry and management.

Endpoints

The primary study endpoint was costs attributable to VKA treatment in patients with NVAF, calculated from the French societal perspective. Attributable costs composed the sum of direct medical costs, direct non-medical costs, and indirect costs. Direct medical costs included: costs associated with INR testing, physician consultations (general practitioner or cardiologist) related to VKA monitoring, costs associated with VKA pharmacy consultations and VKA drug costs. Direct non-medical costs included costs associated with transportation for INR testing. Indirect costs included lost productivity, patient opportunity costs and patient's relative opportunity costs.

Total costs associated with INR monitoring were obtained by multiplying identified resource use by 2015 national unit costs obtained from L'Assurance Maladie, the official French health insurance organisation [20]. Productivity loss costs were calculated based on hourly mean labour cost in France, whereas opportunity costs associated with patients and relative time spent on VKA monitoring were calculated based on the French minimal hourly net wage. The Supplemental Material summarises in detail all unit costs and related references.

Attributable costs were defined as costs directly attributable to VKA treatment, including costs of physician consultations during which only follow-up of VKA treatment was discussed, and costs of associated travels and time. Likewise, activities of INR testing (e.g. blood collection and management of blood sample) that were shared by the INR test and concomitant tests were not considered in the cost calculation. Finally, costs of patient travel to INR monitoring centre when concomitant tests were performed were not considered.

INR test costs were calculated based on tariffs reported for previous INR tests, with the average of reported tariffs used as unit cost. Two average unit costs were calculated: one for INR tests performed at the INR monitoring centre and one for INR tests performed outside the INR monitoring centre. INR test costs were then calculated by multiplying the number of tests by unit costs. The study questionnaire did not collect the distinction between consultations at a physician's office or other locations. The proportion of consultation locations was assumed to be the same as the proportion of INRs performed at home versus those performed at the INR monitoring centre.

Statistical methods

Descriptive data analyses were performed using summary statistics for categorical and continuous data. Results were used to describe overall attributable VKA treatment costs, as well as specific cost components, from the French societal perspective. Continuous data were described by mean, standard deviation, and 95% confidence intervals (CIs). Categorical data were described using absolute and relative frequencies.

The following procedures were used to handle missing data: (a) for categorical variables, the most frequent response in the sample was imputed; and (b) for continuous variables, the sample average for the variable was imputed. No imputation was performed for variables not considered in cost calculations (i.e. sociodemographic variables, medical history and comorbidities). Data management and primary statistical analyses were conducted using the SAS Analytics Pro release 9.3.

The targeted sample size was 400 patients; this was calculated based on a 95% CI margin of error of 10% for the primary outcome.

Results

INR monitoring centre site description

Data from participating INR monitoring centres were collected between 18 January 2015 and 14 February 2016.

Seven INR monitoring centres (located in Grenoble, Montpelier, Narbonne, Nîmes, Paris, Rennes, and Toulon) participated in the study. Patients were recruited on a consecutive basis by healthcare professionals working at participating INR monitoring centres. The recruitment window was 6 weeks, with the exception of the Montpelier centre that was willing to participate only for 4 weeks.

Patient baseline demographic characteristics

A total of 415 patients were recruited; 51 did not meet the inclusion criteria (46 patients did not report NVAF and 5 reported participating in a clinical study). Additionally, 1 patient was excluded due to missing INR testing data. Therefore, the target analysis group included 363 patients.

Table 1 shows the patients' sociodemographic and clinical characteristics; 53% were male and >80% were >70 years of age. Almost all patients (96%) were retired. More than 80% lived in an urban area (with >5,000 inhabitants). The majority (58%) lived with family, 30% lived alone, and slightly less than 10% lived in a nursing home. On average, patients reported having NVAF for 6.5 years.

In terms of VKA treatment, 72% of patients were treated with fluindione, 21% with warfarin, 6% with acenocoumarol, and <1% with a combination of warfarin and fluindione. Almost all patients (99%) had been taking VKA therapy for longer than 3 months.

Table 1. Patient sociodemographic characteristics.

Variables	N = 363
Sex	**N = 290[a]**
Female	135 (46.55%)
Age (years)	**N = 360**
≤20–40	0
41–60	11 (3.06%)
61–70	34 (14.16%)
71–80	114 (31.67%)
81–90	149 (41.39%)
>90	35 (9.72%)
Work status	**N = 358**
Full-time employed	12 (3.35%)
Part-time employed	1 (0.28%)
Retired/pensioner	344 (96.09%)
Student	0
Unemployed	1 (0.28%)
Living area	**N = 363**
Rural area (<5,000 habitants)	59 (16.25%)
Urban area (>5,000 habitants)	297 (81.82%)
Not reported	7 (1.93%)
Family status	**N = 360**
Live alone	117 (32.50%)
Live with partner/family	210 (58.33%)
Live with friends	0
Live in a nursing home	33 (9.17%)
Homeless	0
Time since NVAF diagnosis (years)[b]	6.53 (5.30–7.77)

[a]73 (20.11%) patients did not report their sex.
[b]Mean (95% confidence interval).
NVAF: non-valvular atrial fibrillation.

Resource use

The average number of VKA tablets taken per day in patients on fluindione 20 mg, warfarin 2 mg, warfarin 5 mg, acenocoumarol 4 mg and acenocoumarol 1 mg were 0.85 (95% CI, 0.78–0.91), 1.44 (1.24–1.63), 0.93 (0.84–1.02), 0.74 (0.50–0.98) and 1.94 [CI not calculated because of small number of patients taking acenocoumarol 1 mg tablets (N = 5)] respectively. Seventy-one percent of patients reported receiving their VKA prescription from their general practitioner (GP), whereas 29% had their medication prescribed by a cardiologist.

The number of INR tests per patient per month was 1.69 (95% CI, 1.59–1.80), as is shown in Figure 1. Eighty-three percent of INR tests were performed without concomitant medical testing, and 36% showed out-of-range results. Forty percent of INR tests were performed outside of the INR monitoring centre. Fifty-two percent of patients seen at the centre had to return to the INR monitoring centre to obtain results.

Seventy-one percent of patients indicated that they discussed their INR results with a physician at some time, but the majority (86%) initiated discussion only when INR results were out of range; these conversations usually took place by phone (82.5%). Only 4% of patients (n = 15) reported any pharmacy consultations within the last 6 months. Most patients travelled to physician offices by car (n = 186, 51%) and to the INR monitoring centre and pharmacy on foot (n = 130, 54%; n = 10, 67%; respectively). Patients reported spending an average of 22, 15, and 13 minutes at the physician office, INR monitoring centre, and pharmacy respectively, and 22, 17, and 10 minutes of travel time for these visits respectively. Patients did not report any lost work time for themselves or their relatives, with the exception of 1 patient who reported 1 hour lost.
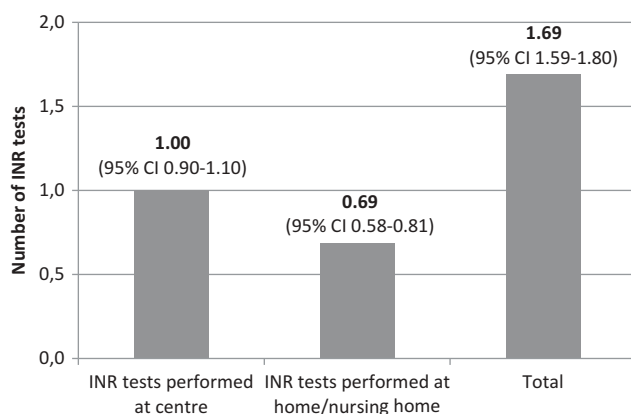
Figure 1. Number of INR tests per patient per month. INR: international normalised ratio.

Costs

As shown in Table 2, the assessed monthly attributable cost of VKA treatment from the French societal perspective was €39.72 per patient (95% CI, €36.23–43.21). Direct medical costs composed 76% of total costs (€30.36), direct non-medical costs were 10% (€4.01), and indirect costs were 14% (€5.68). Cost of VKA drugs represented 7.4% of total costs (€2.94). When evaluating direct medical costs, INR tests were the most costly component, representing 83% (€25.15) of the category sub-total, whereas VKA drugs represented 9.7% (€2.94).

Discussion

Results synthesis/interpretation

This study evaluated the attributable costs associated with VKA treatment for NVAF from a French societal perspective and found that total costs are not adequately approximated when only drug is considered. Specifically, VKA drug costs were less than €3 per patient per month, but the total direct medical, direct non-medical, and indirect costs related to VKA treatment and INR monitoring were approximately €40 per patient per month.

There is a common perception that because VKAs are generic they offer a less expensive alternative to DOACs. However, our results call this into question and align with recent research conducted in France and elsewhere.

Table 2. Breakdown of monthly costs attributable to VKA treatment from French societal perspective.

Cost component (€)	Mean € (SD)	95% CI
Direct medical costs	**30.36 (18.76)**	**28.42–32.29**
VKA drugs[a]	2.94 (1.74)	2.76–3.12
INR tests[b]	25.15 (18.05)	23.28–27.01
Pharmacy consultations	0.28 (1.35)	0.14–0.42
Physician consultations[c]	1.99 (3.53)	1.63–2.35
Direct non-medical costs	**4.01 (20.03)**	**1.94–6.07**
Transportation costs[d]	4.01 (20.03)	1.94–6.07
Indirect costs	**5.36 (5.68)**	**4.77–5.94**
Productivity loss[e]	0.02 (0.31)	–[f]
Time for transportation and time spent at INR monitoring centre, physician office, pharmacy by patient	4.94 (4.45)	4.48–5.40
Time for transportation and time spent at INR monitoring centre, physician office, pharmacy by relative	0.40 (2.26)	0.16–0.63
Total	**39.72 (33.80)**	**36.23–43.21**

[a]Only drug costs.
[b]INR tests costs included INR tests costs and nurse travel costs when relevant.
[c]Physician consultation costs included general practitioner and cardiologist consultations costs and travel when relevant.
[d]Transportation costs included transportation of patient to INR monitoring centre, physician office, pharmacy.
[e]One patient lost 1 hour of work within the last 6 months, valued at French hourly labour cost €35.
[f]CI not calculated because of small number of patients with such costs (N = 1).
CI: confidence interval; INR: international normalised ratio; SD: standard deviation; VKA: vitamin K antagonist.

A French analysis published in 2016 examined this question from the national health insurance perspective and reported that substantial monitoring costs are incurred with VKA treatment. The analysis found that while VKA drug costs in 2013 were €40 million, INR measurements cost €156 million and hospitalisations for VKA complications €90 million. The author concluded that total annual direct costs in France for AF treatment with VKAs probably exceed €300 million per year when the costs of complications due to VKA dosing miscalculations are considered [21]. However, the author did not evaluate direct non-medical costs, indirect costs, or certain direct medical costs (e.g. physician visits related to INR testing), which means that the results of the analysis cannot readily be extrapolated to a societal perspective. Furthermore, the analysis was conducted from a national perspective using a top-down method to calculate costs in the population of VKA-treated patients, which makes it difficult to compare the results with those of the study published here, because our study evaluated costs per patient with NVAF.

It is important to emphasise the conservative nature of this analysis. To be included, direct and indirect costs had to be directly attributable to VKA treatment. For example, a patient consultation in which medical issues other than VKA were discussed was not considered in the primary analysis. Likewise, costs associated with treatment-related hospitalisations were not assessed. Attributable costs as measured in this study are in line with the French Haute Autorité de Santé (HAS) guidelines because they relate to the production cost of care, wherein costs associated with time spent by patients are to be included [22].

An exploratory analysis was conducted to evaluate the financial impact of VKA treatment when all costs were considered and not only attributable cost. When these cost assumptions were applied, total per-patient per-month costs for VKA management rose to €56.25 from the societal perspective.

Limitations

To our knowledge, this study is the first to evaluate the costs attributable to VKA treatment in NVAF management in France from a societal perspective. Several potential limitations to this analysis should be noted. Patient selection was conducted by healthcare professionals responsible for blood collection (i.e. technicians or nurses); this approach may be less reliable than patient selection by a physician. To limit any bias or error, and to confirm patient diagnosis, patients were asked to self-report their reasons for VKA treatment on the self-completion questionnaire.

As with any patient self-completion questionnaire, recall bias might occur. To limit this, the recall period was limited to a maximum of 6 months.

INR test costs were calculated using the tariffs reported only for the last patients' INR tests, because it was not feasible to collect tariff data for all INR tests performed within the last 6 months. However, the last tariffs are likely to be representative of the 6-month tariffs.

It was assumed that the location of consultations (physician office versus patient home) was similar to the location of INR tests (centre versus home). This assumption seems reasonable because locations depend only on patients' ability to move; patients are not reimbursed for consultations or other medical resource use at home if they are able to move in order to get the medical services at dedicated medical locations.

In terms of the generalisability of results, the study sample closely corresponds to a stable French NVAF population. For example, 70% of the sample was older than 76 years. In France, two-thirds of NVAF patients are older than 75 years [19]. However, some differences between our sample and the overall population should be noted. This study included only 59 patients (16% of sample) residing in rural areas (defined as a town of fewer than 5,000 inhabitants). Therefore, these patients were slightly under-represented based on 2007 estimates indicating that 22.5% of French residents live in a rural area [23]. No data are available on the incidence of NVAF in France in rural areas compared with urban areas, and this is a further limitation of the study. Lastly, only 5 patients reported initiating VKA medication within the last few months. This makes it possible that patients with incident NVAF might be under-represented. If this is the case, the overall costs observed in this study are likely to have been underestimated because incident patient costs are typically higher [4].

Conclusions

This study confirms that the cost of VKA treatment from the French societal perspective should not be assessed based on drug costs alone. In light of the clinical benefits of DOACs and the costs associated with VKA treatment, our results suggest that DOACs may represent a better option for first-line treatment for French patients with NVAF. This conclusion is in line with European Society of Cardiology recommendations [4], but would require confirmation in a fuller comparison of the costs involved in treatment with VKAs and DOACs.

Author Contribution

All authors were involved in the design of the study and the interpretation of the results in addition to the drafting of the paper and the critical revision of the content.

Disclosure statement

PL and DS received honorarium for critical input into study design and results interpretations, JD is a employee of Creativ-Ceutical, AKM and JBB are employees of Bayer AG, KB is an employee of Bayer Plc. MT declare no conflict of interest. No potential conflict of interest was reported by the authors.

Transparency

The lead author confirms that this manuscript is an honest, accurate, and transparent account of the study being reported.

References

[1] Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998;98(10):946–952.

[2] Ball J, Carrington MJ, McMurray JJV, et al. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. Int J Cardiol. 2013;167(5):1807–1824.

[3] Rosner GF, Reiffel JA, Hickey K. The concept of "burden" in atrial fibrillation. J Atr Fibrillation. 2012;4(5):400.

[4] Kirchhof, P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893–2962.

[5] Lip GYH, Clementy N, Pericart L, et al. Stroke and major bleeding risk in elderly patients aged ≥75 years with atrial fibrillation: the Loire Valley atrial fibrillation project. Stroke. 2015;46(1):143–150.

[6] Massaro A, Giugliano RP, Norrving B, et al. Overcoming global challenges in stroke prophylaxis in atrial fibrillation: the role of non-vitamin K antagonist oral anticoagulants. Int J Stroke. 2016;11(9):950–967.

[7] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–1151.

[8] Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–2104.

[9] Granger, CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–992.

[10] Patel, MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–891.

[11] Coleman CI, Antz M, Bowrin K, et al. Real-world evidence of stroke prevention in patients with nonvalvular atrial fibrillation in the USA: the REVISIT-US study. Curr Med Res Opin. 2016;32(12):2047–2053.

[12] Coleman CI, Antz M, Ehlken B, et al. REaI-LIfe Evidence of stroke prevention in patients with atrial Fibrillation–the RELIEF study. Int J Cardiol. 2016;203:882–884.

[13] Coleman CI, Haas S, Turpie AGG, et al. Impact of switching from a vitamin K antagonist to rivaroxaban on satisfaction with anticoagulation therapy: the XANTUS-ACTS substudy. Clin Cardiol. 2016;39(10):565–569.

[14] Coleman CI, Tangirala M, Evers T, et al. Treatment persistence and discontinuation with rivaroxaban, dabigatran, and warfarin for stroke prevention in patients with non-valvular atrial fibrillation in the USA. PLoS One. 2016;11(6):e0157769.

[15] Ruff, CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955–962.

[16] Mekaj Y, Mekaj A, Duci S, et al. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Manag. 2015;11:967–977.

[17] Walsh, C, Murphy A, Kirby A, et al. Retrospective costing of warfarin. Ir Med J. 2014;107(5):133–135.

[18] de Pouvourville G. Comment améliorer le suivi des AVK et pour quel coût? [How can we improve the follow-up of VKA and for which cost?]. Arch Card Dis. 2016;8 (2):169–173. French.

[19] Le Heuzey Jym, E., Lepillier, A., Fiorina, L., et al. La fibrillation atriale : données démographiques. Mise au point Rythm ologie Realites-cardiologiques 2010.Available fromhttp://www.realites-cardiologiques.com/wp-content/uploads/2010/03/10.pdf

[20] L'Assurance Maladie en Ligne. *Tarifs conventionnels [Conventional rates]*. Available from: https://www.ameli.fr/medecin/exercice-liberal/facturation-remuneration/tarifs. French.

[21] Detournay B. Coût direct des AVK en France [Direct costs of VKAs in France]. Arch Card Dis. 2016;8(2):174–179. French.

[22] Haute Autorité de Santé. *Choix méthodologiques pour l'évaluation économique à la HAS [Methodological choices for economic evaluation at HAS]*. 2011. Available from: https://www.has-sante.fr/portail/upload/docs/application/pdf/2011-11/guide_methodo_vf.pdf. French.

[23] Institut national de la statistique et des études économiques. Le découpage en unités urbaines de 2010. http://www.insee.fr/fr/themes/document.asp?reg_id=0&ref_id=ip1364%C2