University of Groningen

Costs of minor bleeds in atrial fibrillation patients using a non-vitamin K antagonist oral anticoagulant

Mitrovic, Darko; Plomp, Marlies; Folkeringa, Richard; Veeger, Nic; Feenstra, Talitha; van Roon, Eric

Published in:
Current Medical Research and Opinion

DOI:
[10.1080/03007995.2021.1929893](https://doi.org/10.1080/03007995.2021.1929893)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Mitrovic, D., Plomp, M., Folkeringa, R., Veeger, N., Feenstra, T., & van Roon, E. (2021). Costs of minor bleeds in atrial fibrillation patients using a non-vitamin K antagonist oral anticoagulant. *Current Medical Research and Opinion*, 37(9), 1461-1466. <https://doi.org/10.1080/03007995.2021.1929893>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Costs of minor bleeds in atrial fibrillation patients using a non-vitamin K antagonist oral anticoagulant

Darko Mitrovic, Marlies Plomp, Richard Folkeringa, Nic Veeger, Talitha Feenstra & Eric van Roon

To cite this article: Darko Mitrovic, Marlies Plomp, Richard Folkeringa, Nic Veeger, Talitha Feenstra & Eric van Roon (2021) Costs of minor bleeds in atrial fibrillation patients using a non-vitamin K antagonist oral anticoagulant, Current Medical Research and Opinion, 37:9, 1461-1466, DOI: [10.1080/03007995.2021.1929893](https://doi.org/10.1080/03007995.2021.1929893)

To link to this article: <https://doi.org/10.1080/03007995.2021.1929893>

Published online: 04 Jun 2021.

Submit your article to this journal [↗](#)

Article views: 66

View related articles [↗](#)

View Crossmark data [↗](#)

ORIGINAL ARTICLE

Costs of minor bleeds in atrial fibrillation patients using a non-vitamin K antagonist oral anticoagulant

Darko Mitrovic^a, Marlies Plomp^a, Richard Folkerling^b, Nic Veeger^{c,d}, Talitha Feenstra^e and Eric van Roon^{d,e}

^aDepartment of Hospital Pharmacy, Tjongerschans, Heerenveen, Netherlands; ^bDepartment of Cardiology, Medical Centre Leeuwarden, Leeuwarden, Netherlands; ^cDepartment of Epidemiology, University of Groningen University Medical Centre, Groningen, Netherlands;

^dDepartment of Clinical Pharmacy, Medical Centre Leeuwarden, Leeuwarden, Netherlands; ^eDepartment of Pharmacotherapy, -Epidemiology and Economy, Faculty Pharmacy, University of Groningen, Groningen, Netherlands

ABSTRACT

Background: A very common side effect of non-vitamin K antagonist oral anticoagulant (NOAC) is (minor) bleeding. Data about impact and costs of minor bleeds in NOAC therapy is still limited or not present in current literature. In this patient orientated study, we aim to provide an estimate of the costs of minor bleeds in patients with atrial fibrillation (AF) treated with a NOAC.

Methods: A retrospective observational cohort study was conducted. Patients with AF and on NOAC therapy were included. Data was obtained by questionnaires and information from electronic patient records. Reference prices were used to calculate the costs per patient. Furthermore, cost of minor bleeds per patient is compared with literature-based costs of minor and major bleeding.

Results: 139 patients were included. A total of 94 minor bleed were reported by 71 patients. The sum of minor bleeding costs from societal perspective were €9,851.49, or on average €70.87 (95% CI €54.37– €85.68) per patient with AF. The biggest cost drivers were rectal and vaginal bleeds, epistaxis was most commonly reported.

Conclusion: Total costs of minor bleeds from a societal perspective, in AF patients using NOACs, are non-trivial and exceed the costs presented in existing literature.

ARTICLE HISTORY

Received 24 December 2020

Revised 23 April 2021

Accepted 5 May 2021

KEYWORDS

Anticoagulant agents; bleeding; health care costs; atrial fibrillation; Netherlands

Introduction

A common side effect of non-vitamin K antagonist oral anti-coagulant (NOAC) is bleeding. These bleeds can be divided into major and minor bleeds. In this, minor bleeds includes clinically relevant but non-major bleeds in accordance with the definitions of Kaatz et al¹. Major bleeds are defined as having a symptomatic presentation, a fatal bleeding, a bleeding in a critical area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial) or a intramuscular bleeding with compartment syndrome. Furthermore, the bleed causes a fall in haemoglobin level of ≥ 20 g/L (1.24 mmol/L), or has been treated with a transfusion of ≥ 2 units of whole blood or red cells. The minor but clinically relevant bleeds, i.e. clinically relevant non-major bleeds, are defined as a bleed requiring medical intervention by a healthcare professional and/or leading to hospitalization or increased level of care and/or prompting a face to face evaluation.

When it comes to the impact and costs of bleeding most “evidence based medicine” registration studies focused mainly on major bleeds^{2,3}. There are few studies discussing the costs of (clinically relevant) minor bleeds. Most describe the costs of a minor bleed due only to GP-consultation (acute care costs of €32)^{4,5}. The small observational study from Franco et al. concluded that in terms of management, duration of hospitalisation and in-hospital mortality, the

burden arising from minor bleeds occurring in clinical practice in patients taking NOAC was not trivial⁶. However, in the current literature data about impact and costs of minor bleeds in NOAC therapy is still limited.

From the Dresden NOAC Atrial Fibrillation (AF) registry we know that more than 90% of all rivaroxaban associated bleeding complications were found to be non-major bleeds⁷. The incidence rate was 35.8 (95% Confidence Interval 32.2–39.7) per 100 patient years for minor bleeding (excluding clinically relevant minor bleeds), 20.7 (CI 18.1–23.5) for clinically relevant minor bleeding and 3.1 (CI 2.2–4.3) for major bleeds. This high occurrence of minor bleeds could have a major impact on quality of life.

In this patient orientated study, we aim to provide an estimate of all costs (from a social perspective) of minor bleeding in AF patients treated with NOAC. In this, the estimated costs of minor bleeds are driven by the need for medical interventions, requested by the patient suffering from a minor bleed.

Materials and methods

Patient population

This study was conducted in a population of AF patients under control of a NOAC outpatient clinic. This NOAC outpatient clinic was part of the thrombosis service of the

Figure 1. Flowchart of the inclusion and exclusion of patients.

Leeuwarden Medical Centre in cooperation with the cardiologists of the Leeuwarden Medical Centre. The clinic operated in accordance with Dutch guidelines governing integrated anticoagulation services (LSKA 2.0)⁸.

Study design

The retrospective study was conducted between November 2019 and February 2020. The patients were asked to describe any bleed from the start of anticoagulation therapy with NOACs. Data on the costs of the management of bleeding were collected from the electronic patient record (EPIC) and semi-structured questionnaires by telephone. Patients were asked for their willingness to take part in this study by the nurses of the NOAC outpatient clinic during routine follow-up visits. The inclusion by the nurses took place between 18 October 2019 and 8 January 2020, and all included patients provided written informed consent.

Inclusion/exclusion criteria

All patients using a NOAC under control of the NOAC outpatient clinic with an indication of non-valvular Atrial Fibrillation (nvAF) were included in this study. These NOACs included: apixaban, dabigatran, rivaroxaban and edoxaban. Patients with another indication than nvAF and temporary NOAC therapy for scheduled cardioversion or pulmonary vein isolation were excluded. Furthermore, patients with memory complaints and patients unsuitable for a 20-minute consultation by telephone were excluded, based on the estimation of the nurses of the outpatient NOAC clinic.

Ethics

The Regional ethical committee reviewed the study protocol prior to the start of the study and decided that, in accordance with Dutch laws, for this study a full medical ethical review was not required.

Definitions

For the purpose of this costs-related study, all non-major bleeds are considered minor, either clinically relevant are not. According to definition, a minor bleed becomes a clinically relevant non-major bleed (CRNMB) when the patient him- or herself decides to contact a healthcare professional subsequently leading to healthcare costs¹.

Costs

The primary study endpoint was to determine the immediate costs related to minor bleeds per patient in nvAF patients using NOAC from a societal perspective. Therefore, according to the definition of the Dutch health Care Institute⁹ not only healthcare costs (such as for visits to general practitioner or hospital) but also the costs made by patient, patient family and other sectors than healthcare are taken into account. In our study we focused on the immediate event related costs of minor bleeds.

The costs were distinguished into 3 categories: healthcare costs (GP costs and hospital related costs), patient or patient family related costs (travelling costs, etc.) and other costs (costs of informal caregivers or loss of productivity). Costs were calculated by multiplying volumes by unit costs. Unit costs were determined from recent reference prices⁹.

Through a specifically developed semi-structured questionnaire the amount and type of minor bleeds were collected as well as information about volumes for the three different cost categories. Total costs from societal perspective were calculated as costs per type of minor bleed, multiplied by the number of patients reporting this bleed. Costs of minor bleeding per patient were then calculated by dividing total costs by the total amount of included patients. Hence averaging over all patients with and without bleeds, to find the mean costs of minor bleeds per patient with AF.

Sensitivity analysis

Sensitivity analyses (univariate and probabilistic) were conducted to evaluate the influence of uncertainty in input parameters on the total costs. In the univariate sensitivity analysis input parameters (prices and the prevalence of the different bleeds) were varied one by one over their 95% CI, to examine the influence on the total costs per person for each parameter separately. Probabilistic sensitivity analysis (PSA) is used to determine the level of confidence in the output considering all uncertainties of the model parameters (prices and the prevalence of the different bleeds). In PSA the parameters were varied simultaneously over their 95%

confidence intervals and total costs per patients were calculated during 1000 simulations.

Results

Inclusion and baseline characteristics

An overview of the inclusion of patients is shown in Figure 1. A board description of the non-valvular AF population is presented in Table 1.

A total of 94 bleeds were reported by 71 patients (mean 1.3 bleeds per person) (Table 2). The majority of bleeds were hematomas (50%) and epistaxis (22.3%). Rectal, eye and vaginal bleeds were reported once.

Costs

A total number of 17 patients out of 139 reported a single minor bleed that was considered clinically relevant and for which a healthcare professional was contacted and costs were made. The total costs for these 17 clinically relevant bleeds was €9851.49, that is, on average €70.87 per patient. (Table 3). In this, the rectal and vaginal bleeds were associated with the highest costs.

Using these data we can make a comparison between the costs of major and minor bleeding incorporating the prevalence of both types of bleeding and translating the costs to a population of 1000 patients. (Table 4). To calculate the costs of major bleeding only data from Dutch studies were used^{4,10,11} The prevalence of major bleeds was 0.5–3%,

based on existing literature¹¹. We therefore used a prevalence of 0.5, 1, and 3%, respectively to calculate the costs of major bleeding per 1000 patients and to compare these costs with minor bleeding (95% CI; €54.37–€85.68).

Prevalence of minor bleed was based on data from this study (minor bleedings 38.8% + CRNMB 12.2%, total 51.1%), (Table 2).

Subsequently, major bleeding costs €20,455,300 to €122,732,300 per 1000 persons and minor bleeding €2,778,300 to €4,378,200 per 1000 persons (Table 3). While this may seem a small amount of money compared to the costs of major bleeding, at the scale of all patients using NOACs, the costs are non-negligible.

In 2020, the estimated number of patients using a NOACs in the Netherlands is 300,000¹². If we consider that costs of minor bleeding per treated patient is between €54.37 and €85.65, this could result in a total costs between €16,311,000–€25,695,000

Sensitivity analysis

Figure 2 shows a Tornado diagram (Univariate Sensitivity Analysis) illustrating the impact of varying the unit costs as well as the incidence of the bleeds. The costs and incidence of the rectal bleeds, eye bleeds and vaginal bleeds were combined due to low patient numbers and were labelled as “others”. The parameters with the most influence on uncertainty of the cost of bleeds per patient were the incidence of other bleeds (mainly rectal and vaginal bleeds) and epistaxis.

Table 1. Baseline characteristics of the study population of non-valvular atrial fibrillation patients.

	Apixaban N = 56	Rivaroxaban N = 55	Dabigatran N = 27	Edoxaban N = 1	Total N = 139
Age	71 ± 8	74 ± 8	72 ± 7	77 ± 0	72 ± 8
Male	36 (64.3%)	37 (67.3%)	8 (29.6%)	1 (100%)	82 (59.0%)
Female	20 (35.7%)	18 (32.7%)	19 (70.4%)	0 (0.0%)	57 (41.0%)
Renal function (ml/min)					
eGFR <50	10 (17.9%)	8 (14.5%)	2 (7.4%)	0 (0.0%)	20 (14.4%)
eGFR 50–80	29 (51.8%)	38 (69.1%)	18 (66.7%)	1 (100%)	86 (61.9%)
eGFR >80	17 (30.4%)	9 (16.4%)	7 (25.9%)	0 (0.0%)	33 (23.7%)
Duration of use					
1–3 months	2 (3.6%)	4 (7.3%)	0 (0.0%)	0 (0.0%)	6 (4.3%)
3–6 months	0 (0.0%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	2 (1.4%)
6–12 months	5 (8.9%)	3 (5.5%)	0 (0.0%)	0 (0.0%)	8 (5.8%)
1–2 years	15 (26.8%)	14 (25.5%)	5 (18.5%)	1 (100%)	35 (25.2%)
>2 years	34 (60.7%)	32 (58.2%)	22 (81.5%)	0 (0.0%)	88 (63.3%)

Table 2. Overview of the reported minor bleeds.

	Apixaban n = 56	Rivaroxaban n = 55	Dabigatran n = 27	Edoxaban n = 1	Total n = 139
Patients with minor bleeds	26 (46.4%)	34 (61.8%)	11 (40.7%)	0 (0.0%)	71 (51.1%)
CRNMB	5 (8.9%)	9 (16.4%)	3 (11.1%)	0 (0.0%)	17 (12.2%)
Site of bleeding					
Hematoma	19 (54.3%)	19 (43.2%)	9 (60.0%)	0 (0.0%)	47 (50.0%)
Epistaxis	7 (20.0%)	12 (27.3%)	2 (13.3%)	0 (0.0%)	21 (22.3%)
Eye	4 (11.4%)	5 (11.4%)	1 (6.7%)	0 (0.0%)	10 (10.6%)
Gingival	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Vaginal	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Haematuria	1 (2.9%)	2 (4.5%)	0 (0.0%)	0 (0.0%)	3 (3.2%)
Haemorrhoids	2 (5.7%)	1 (2.3%)	1 (6.7%)	0 (0.0%)	4 (4.3%)
Rectal	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
Bleed after injury	0 (0.0%)	3 (6.8%)	2 (13.3%)	0 (0.0%)	5 (5.3%)
Total	35	44	15	0	94

Overall, the incidence of bleeding influenced the costs per patient more than the unit costs of the different bleeds.

Furthermore a Probabilistic Sensitivity Analysis (PSA) was conducted in order to determine the impact of the different

Table 3. Acute event costs of different type of minor bleeds from societal perspective**.

Type of minor bleed (n)	Mean costs per event	Total costs
Epistaxis (7)	€ 512.26	€ 3585.85
Haemorrhoid (3)	€ 284.86	€ 854.58
Bleeding after injury (4)	€ 409.79	€ 1693.17
Rectal (1)	€ 2316.94	€ 2316.94
Eye (1)	€ 35.244	€ 35.24
Vaginal (1)	€ 1419.71	€ 1419.71
Total costs		€ 9,851.49
Costs per patient*		€ 70,87

*Costs of minor bleed per patient in total population of 139 patients.

**See Appendix 1 for unit costs and volumes.

parameters on the price per patient. All the parameters were combined in one model and a Monte Carlo Simulation with 1000 simulations. The results of the PSA are displayed as a histogram in Figure 3. The 5 percentile was €54.37 and the 95 percentile was €85.68. This indicates that, with 90% probability, costs per person were between €54.37 and €85.68.

Discussion

To our knowledge, this is the first study determining the societal costs of minor bleeds by using data directly derived from patient contact instead of large study registries. Our estimation the of the costs of minor bleeds is €70.87 per patient on a NOAC for nvAF

Table 4. Estimations of the costs of major and minor bleeds per 1000 patients.

	Prevalence (%)	Bleeds/ 1000 patients	Costs/person	Total costs/1000 patients
Minor bleeding	51.1	511	€ 70,87 (95% CI € 54,37–85,68)	€ 36.214,57 (€ 27.783,08–€ 43.782,48)
Major bleeding	0.5	5	€ 40.910,77	€ 204.553,85
Major bleeding	1	10	€ 40.910,77	€ 409.107,70
Major bleeding	3	30	€ 40.910,77	€ 1.227.323,11

Figure 2. *Univariate sensitivity analysis. The figure depicts the influence of uncertainty in different input parameters on costs of minor bleeds. *With this analysis, we tried to emphasize the amount of uncertainty around our cost estimates related to the small study size. The parameters with the most influence on uncertainty of the cost of bleeds per patient were the incidence of other bleeds (mainly rectal and vaginal bleeds) and epistaxis. Overall, the incidence of bleeding influenced the costs per patient more than the unit costs of the different bleeds

Figure 3. Probabilistic sensitivity analysis histogram.

Baseline characteristics of our study population (age 73 ± 8 ; men 66%) correspond to the baseline characteristics in major trials like ARISTOTLE (age $70[63-76]$; men 64.5%)¹³ and RE-LY (age 71.4 ± 8.6 ; men 64.3%)¹⁴. None of the patients lost productivity due to their bleeding. This can be explained by the high age in our study population resulting in a high percentage of retired patients.

Jakobsen et al¹⁵. conducted an incidence-based cost-of-illness study to estimate the healthcare costs attributable to major intracranial and gastrointestinal bleeding in patients with AF. But the study population consisted of patients using all types of oral anticoagulants and not specific NOACs. Furthermore, only major bleeds were used in this study and the data was derived from a healthcare administrative database, information of patients was not involved. The study of Ramagopalan et al¹⁶. used the same study design as Jakobsen et al. but only estimated the healthcare costs of gastrointestinal bleeds in patients with non-valvular AF. In the study of de Jong et al⁵. acute care costs of CRNMB were estimated at €31.73 (€23–€43). This amount was based only on General Practitioners (GP) costs and hence probably an underestimation of costs since hospital-related costs were left out of the analysis.

Our results suggest that the mean costs of minor bleeds (€70.87 per patient) is much higher than the are now used in current literature (€31.73). This is mainly due to considering other costs than GP, such as hospital and patient related costs.

This study has two limitations. Most patients used their NOAC over 1 year and sometimes over 2 or 3 years, so potential recall bias needs to be noted. It is possible that we may have missed minor bleeds as we asked about bleeding during the whole period they used NOACs. Another limitation is that our study sample was small, resulting in a higher degree of uncertainty. However, we addressed the level of uncertainty by performing a Probabilistic Sensitivity Analysis, in addition to the Univariate Sensitivity Analysis.

The main strength of our study is that our data is based on direct contact with the patient instead of data derived from a database. Especially for minor bleeds this is important, since many of the costs related to minor bleeds are not well identifiable in a database. Furthermore by contacting all patients (by telephone performing a semi-structured interview), whether or not they had a bleed, we could get an estimate of the prevalence of minor bleeds in a real-world setting. The decision to contact patients by telephone instead of sending a questionnaire by mail, or interview patients in real life was well considered. It is well known that the response rate of a questionnaire by mail is lower than by telephone¹⁷. Furthermore the quality of the answers is better by telephone because of the opportunity to ask for more information and in that way get more context. Lastly, the patients population consists of older, most of them retired, patients who are easily reached by the telephone.

Since our study sample was relatively small, we added elaborate sensitivity analyses. However, future research is needed, to determine the societal costs of minor and major bleeds in a larger population.

Conclusion

Based on our data the costs of minor bleeds from societal perspective, in AF patients using NOACs, are not trivial and exceed the costs reported in existing literature.

Transparency

Declaration of funding

This paper was not funded.

Declaration of financial/other relationships

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. A reviewer on this manuscript has disclosed the following, although none are specific to this manuscript: Consulting fees from Abbott, AbbVie, ACI Clinical, Alexion Pharmaceuticals, Aplagon Ltd, Bayer, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, BTG, Cambridge Healthcare Research, Daiichi-Sankyo, EmstoPA Ltd, EPG Health, Guidepoint Global, Gulf Coast Developments, Janssen, Johnson & Johnson, Leo Pharma, LifeSciences Consulting, Medscape, McKinsey, Navigant, North Star Communications, ONO Pharmaceuticals, Pfizer, Portola Pharmaceuticals, Sanofi, Takeda, Total CME, Windrose Consulting Group; advisory board membership with Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Johnson and Johnson, Pfizer, Portola, Sanofi; payments for lectures, payments for preparation of reports and payment for development of educational presentations from Aspen, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Johnson & Johnson, Medscape, Pfizer and Portola. They have advised the UK Government Health Select Committee, the all-party working group on thrombosis, the Department of Health, and the NHS, on the prevention of VTE. He is also an advisor to Lifeblood: the thrombosis charity and is the founder of the European educational charity the Coalition to Prevent Venous Thromboembolism. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Acknowledgements

None stated.

References

- [1] Kaatz S, Ahmad D, Spyropoulos AC, the Subcommittee on Control of Anticoagulation, et al. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: Communication from the SSC of the ISTH. *J Thromb Haemost.* 2015;13(11):2119–2126.
- [2] Xu Y, Schulman S, Dowlatsahi D, et al. Healthcare resource utilization and costs among patients with direct oral anticoagulant or warfarin-related major bleeding. *Thromb Res.* 2019;182(July): 12–19.
- [3] Rozjabek HM, Coleman CI, Ashton V, et al. Healthcare costs of stroke and major bleeding in patients with atrial fibrillation treated with non-vitamin K antagonist oral anticoagulants. *J Med Econ.* 2019;22(8):751–759.
- [4] Stevanović J, Pompen M, Le HH, et al. Economic evaluation of apixaban for the prevention of stroke in non-valvular atrial fibrillation in the Netherlands. *PLoS One.* 2014;9(8):e103974.
- [5] de Jong LA, Groeneveld J, Stevanovic J, et al. Cost-effectiveness of apixaban compared to other anticoagulants in patients with

atrial fibrillation in the real-world and trial settings. *PLOS One*. 2019;14(9):e0222658–17.

- [6] Franco L, Becattini C, Vanni S, et al. Clinically relevant non-major bleeding with oral anticoagulants: Non-major may not be trivial. *Blood Transfus*. 2018;16(4):387–391.
- [7] Beyer-Westendorf J, Förster K, Pannach S, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. *Blood*. 2014;124(6):955–962.
- [8] van Ommen CH, Piersma-Wichers G, van Diermen DE, et al. Landelijke Standard Keten Antistolling 2.0 voor de eerste- en tweedelijns zorg. Kennis instituut van Medisch Specialisten 2014. https://www.nhg.org/sites/default/files/content/nhg_org/uploads/lska.pdf.
- [9] Hakkaart-van Roijen L, van der Linden N, Bouwmans C, et al. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Zorginstituut Ned. 2016;1:1–73.
- [10] Baeten SA, van Exel NJA, Dirks M, et al. Lifetime health effects and medical costs of integrated stroke services - a non-randomized controlled cluster-trial based life table approach. *Cost Eff Resour Alloc*. 2010;8(1):21.
- [11] Central Bureau voor Statistiek (CBS). StatLine - Jaarmutatatie HICP; Nederland, eurozone en Europese Unie, 2015=100 [Internet] [cited 2020 Jan 31]. Available from: <https://opendata.cbs.nl/statline/#/CBS/nl/dataset/83135NED/table?ts=1580124435578>.
- [12] Stichting Farmaceutische Kerngetallen. Pharmaceutisch Weekblad. Jaargang 154 Nr 37. Available from: <https://www.sfk.nl/publicaties/PW/2019/anticoagulantia-doac-blijft-terrein-winnen-op-vka>.
- [13] Hylek EM, Hanna M, Al-Khalidi HR, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981–992.
- [14] Pisano E, Gatsonis C, Boineau R, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *Heart Fail*. 2005;361:225–237.
- [15] Jakobsen M, Kolodziejczyk C, Klausen FE, et al. S. Costs of major intracranial, gastrointestinal and other bleeding events in patients with atrial fibrillation – a nationwide cohort study. *BMC Health Serv. Res*. 2017;17(1):398.
- [16] Ramagopalan SV, Samnaliev M, Weir S, et al. Costs of gastrointestinal bleeding events in atrial fibrillation: a UK clinical practice research datalink study. *Future Cardiol*. 2019;15(5):367–375.
- [17] Nota SPFT, Strooker JA, Ring D. Differences in response rates between mail, e-mail, and telephone follow-up in hand surgery research. *Hand*. 2014;9(4):504–510.

Appendix 1. Unit reference costs and volumes

Reference unit costs in 2019 (in Euro's)		
Healthcare costs		
Epistaxis bleed		394.41
Haemorrhoid bleed		369.89
Gynaceology examination		1379.22
Polyp examination		2276.87
Emergency department visit		532.32
General practitioner consultation		35.24
GP home visit consult		53.40
GP consultation by phone		17.44
GP consult after working hours		145.12
Patient or patient family related costs		
Taxi boarding rate		3.15
Taxi per km		2.84
Own transportation per km		0.20
Parking costs per visit		3.20
Care costs per hour		14.95
Total costs per bleed		
Bleed	Total costs in Euro's	Total mean costs in Euro's
Epistaxis #1	470.14	
Epistaxis #2	35.24	
Epistaxis #3	629.28	
Epistaxis #4	476.59	
Epistaxis #5	1102.50	
Epistaxis #6	435.50	
Epistaxis #7	436.60	512.26
Haemorrhoid #1	413.90	
Haemorrhoid #2	405.44	
Haemorrhoid #3	35.24	
Wound after injury #1	52.34	
Wound after injury #2	184.22	
Wound after injury #3	1332.12	
Wound after injury #4	70.49	
		409.79
Rectal #1	2316.94	2316.94
Eye #1	35.24	35.24
Vaginal #1	1419.71	1419.71
Total costs	9851.489	