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Anticoagulation and use of services in patients with atrial fibrillation in Finland

BACKGROUND Direct anticoagulants and warfarin are used to prevent strokes associated with non-valvular atrial fibrillation, but there is only limited information on Finnish patients.

METHODS Here, we report the use of primary, specialized and social care services, medication and profile of Finnish AF-patients with anticoagulation therapy based on real-world registry data. In addition, we observed in more detail those AF-patients who had used a particular anticoagulant for at least one full year, disaggregated by age and medication. For this, we looked at the service use and costs, as well as primary and specialized care visits and treatment days due to a selected event (brain events and gastrointestinal bleeding) during the year 2018.

RESULTS Warfarin and apixaban are prescribed, on average, to older and higher-risk patients than other anticoagulants. The total costs of AF-patients' service use in 2018 were around 2 billion euros. Strokes and post-stroke conditions were behind most of the primary and specialized visits and treatment days.

CONCLUSIONS The treatment of AF-patients incurs significant costs to society. Patients taking direct anticoagulants and warfarin differ in terms of patient profile and service use and its costs.

Correctly implemented anticoagulant therapy is important for the prognosis of atrial fibrillation patients (1). In recent years, direct oral anticoagulants (rivaroxaban, apixaban, dabigatran etexilate and edoxaban) have overtaken warfarin in the initiation of anticoagulation therapy to prevent strokes associated with nonvalvular atrial fibrillation. In 2018, drug reimbursements for warfarin use were paid in all patient groups to approximately 105,000 patients and for direct oral anticoagulant use to approximately 140,000 patients (2).

For the moment, there are very few studies based on real-life data from Finnish atrial fibrillation patients on anticoagulant therapy. Earlier studies have investigated the use of anticoagulants among patients with atrial fibrillation, and the costs of social and health care services for atrial fibrillation patients after complications (3, 4). Finnish register data has also been used to evaluate the treatment and complication risks of patients on warfarin: according to the Fin-WAF study, particularly the patient's time in therapeutic range (TTR) has a great significance for the risk of thrombosis or bleeding (5). According to the same study, cardiovascular mor-

tality was 50% lower and the risk of myocardial infarction one-third lower in patients whose TTR (time in therapeutic range) was > 80% compared with patients whose TTR was 60–70% (5). No corresponding register study has been carried out with direct oral anticoagulants.

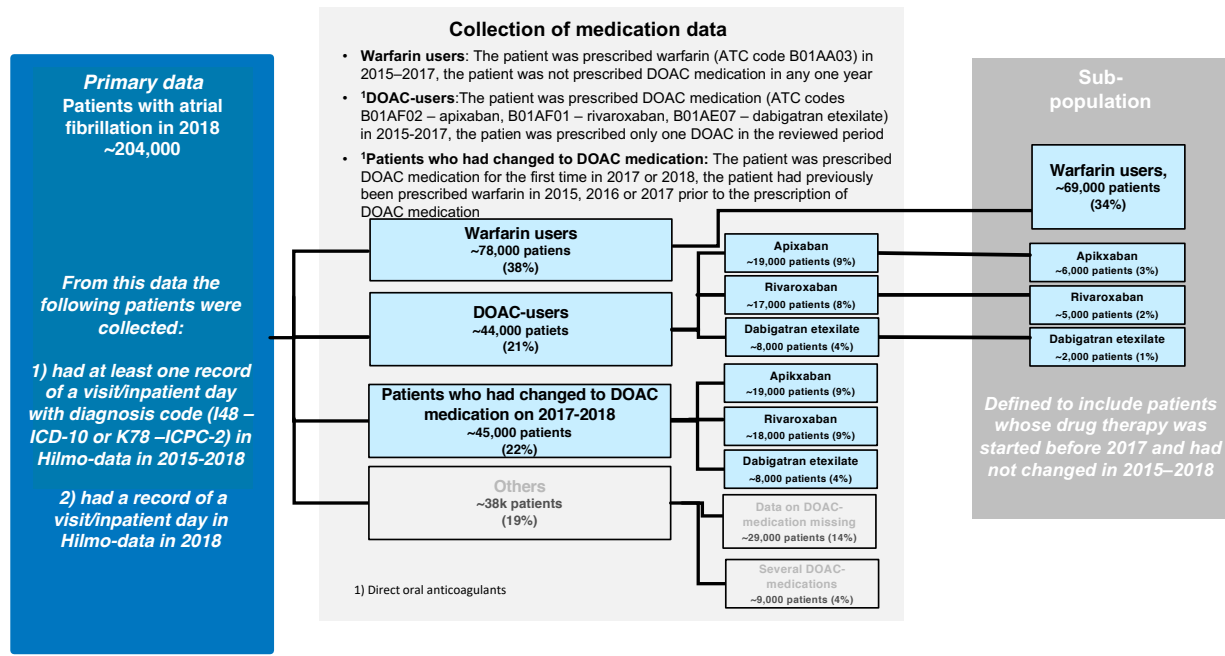
Based on the register data from the data on inpatient care (Hilmo), outpatient care (Avo-hilmo) and social benefits (SosiaaliHilmo), our study examines the medication (warfarin and direct oral anticoagulants), profile, and the use of services in Finnish atrial fibrillation patients. The Hilmo-registers are national social and health care data collection and reporting systems, which collect data on the use of services, access to treatment, and treatment practices (6). They are based on care notifications collected from the electronic systems of service providers.

Materials and methods

The primary data (n = 203,988) comprised of Finnish atrial fibrillation patients who had in the Hilmo data in 2015–2018 at least one visit or inpatient day in public health care related to the diagnosis codes ICD-10 (I48) or ICPC-2 (K78) indicative of atrial fibrillation. In addition,

FIGURE 1.

Formation of the primary data and sub-population of atrial fibrillation patients



the patient had to have a service event recorded in Hilmo in 2018 to ensure that the patient was alive in that year (Fig. 1). The basic information collected from the patients included sex, age (age at the time of last Hilmo recording in 2018) and selected comorbidities (Table 1). The patient was interpreted to have a comorbidity if there was at least one recorded visit or inpatient day with a diagnosis code indicative of the disease during 2015–2018 (Table 1). Based on this data, the CHA₂DS₂-VAsc score depicting the average stroke risk was also calculated for the patients (7).

The medication of patients was identified from the ATC (Anatomical Therapeutic Chemical) codes of drug prescriptions recorded in AvoHilmo. The analysis focused on the most common anticoagulant drugs (warfarin, apixaban, rivaroxaban and dabigatran etexilate). Edoxaban was left outside of the study due to the small number of users. On the basis of the drug prescriptions, the patients were divided into three segments: 1) warfarin users with a prescription for warfarin in 2015–2017 and no oth-

er drug prescriptions for anticoagulants within the same time period, 2) users of direct oral anticoagulants who had in 2015–2017 prescriptions for apixaban, rivaroxaban or dabigatran etexilate and no other drug prescriptions for anticoagulants within the same time period, and 3) patients who had changed to a direct anticoagulant and whose first prescription was for apixaban, rivaroxaban or dabigatran etexilate in 2017 or 2018 and a prior warfarin prescription in 2015, 2016 or 2017 (Fig. 1).

A sub-population (n = 82,470) was defined from the primary data, including all the patients on warfarin or direct oral anticoagulants whose drug therapy had been started before 2017 with no changes during 2015–2018 (Fig. 1). This definition made it possible to examine comorbidities and the use of services in each medication segment in patients who had been on the same medication for at least one year prior to the examined year 2018. All data on primary health care and specialized care visits and treatment periods as well data on home care and intensive residential care were collected for

 **TABLE 1.**

Diagnosis codes of associated diseases and adverse events collected for the patients

Diagnosis codes of associated diseases and adverse events, ICD-10 (ICPC-2)

Associated diseases

Systolic cardiac insufficiency	ICD-10: I50 - Cardiac insufficiency ICPC-2: K77: Cardiac insufficiency
Hypertension	ICD-10: I10-I15 – Hypertension ICPC-2: K86: Hypertension, uncomplicated; K87: Hypertension, complicated
Diabetes	ICD-10: E11 – Adult type diabetes, ICD-10 – Diabetes mellitus ICPC-2: T89: Diabetes, type 1; T90: Diabetes, type 2
Stroke or TIA	One of the following ICD-10 diagnoses: I61 – Cerebral hemorrhage, I63 – Stroke, G45 - Transient ischemic attacks and closely related syndromes ICPC-2: K90 – Stroke; K89 – TIA/Transient ischemic attack
Arterial disease	One of the following ICD-10 diagnoses: I21 – Myocardial infarction, I70-I79 Peripheral vascular diseases ICPC-2: K75 – Acute myocardial infarction; K92 – Atherosclerosis/peripheral vascular disease; K99 – Cardiovascular disease other; K06 – Prominent veins

Adverse events

Stroke (ischemic)	ICD-10: I63 – Cerebral infarction, (Sequelae I69.3) ICPC-2: K90 – Stroke/cerebrovascular event
Intracerebral hemorrhages:	ICD-10: I61 – Intracerebral hemorrhage (sequelae I69.1), I62 – Other and unspecified nontraumatic intracranial hemorrhage (sequelae I69.2))
TIA	ICD-10: G45 – Transient cerebral ischemic attacks and related syndromes, ICPC-2: K89 – TIA/Transient ischemic attack
GI bleedings	ICD-10: K92 – Other diseases of digestive system (Hematemesis, Melena, Gastrointestinal hemorrhage, unspecified), K25 – Gastric ulcer, K26 – Duodenal ulcer, K27 – Peptic ulcer, site unspecified, K28 – Gastrojejunal ulcer ICPC-2: D14 – Hematemesis, D15 – Melena, D85 – Duodenal ulcer, D86 – Peptic ulcer, other

the patients. Institutional care in social care was not included in the review. The annual costs related to the use of services were evaluated by multiplying the number of inpatient days and visits in different services by the unit costs according to the monetary value in 2018 (8). Based on the primary data, we also estimated the combined yearly public social and health service cost for atrial fibrillation patients.

We studied separately the service use of resulting from cerebrovascular events (intracerebral hemorrhage, ischemic stroke, transient ischemic attack, sequelae of cerebral events) and gastrointestinal bleedings (GI-bleeding). The service use related to cerebrovascular events and GI-bleeding was identified from Hilmo-registers based on a diagnosis code.

The patient was interpreted to have service use resulting from cerebral events or GI-bleed-

ing, if there was a diagnosis code indicative of these events in the visit or inpatient day recordings in 2018 (Table 1). Diagnoses were not restricted to the main diagnoses because the purpose was to describe the entire use of services caused by adverse events. Statistical methods used in the study included direct distributions, mean values, and relative proportions.

Results

Patient profiles in the primary data and in the sub-population defined from it as well as the medication data are described in Table 2. The average age of patients was 76 years in the entire material and 77.9 years in the sub-population.

In 2018, 38% of all the patients had warfarin medication. Approximately every fifth patient used either apixaban or rivaroxaban (Table 2).

TABLE 2.

Finnish atrial fibrillation patients with an ICD-10 or ICPC-10 diagnosis code related to atrial fibrillation in 2015–2018 and at least one service event in public health care or social care in 2018 (n = 203,988)

The sub-population included only those patients using warfarin and direct oral anticoagulants whose drug therapy was started before 2017 and had not been changed during 2015–2018 (n = 82,470).

Materials	Primary data	Sub-population
n	203,988	82,470
Gender (female)	47 %	47 %
Age		
Average age	76.0	77.9
<65 years	14 %	9 %
65–75 years	27 %	26 %
>75 years	59 %	65 %
Diagnosis of associated disease in 2015–2018		
Cardiac insufficiency	29 %	32 %
Hypertension	63 %	65 %
Diabetes	28 %	30 %
Cerebrovascular disorder (stroke or TIA)	17 %	17 %
Arterial disease	20 %	21 %
Drug segments according to data from 2018		
Warfarin	38 %	84 %
Apixaban	18 %	7 %
(Patients who switched from warfarin to apixaban in 2015–2018)	(9%)	
Rivaroxaban	17 %	6 %
(Patients who switched from warfarin to rivaroxaban in 2015–2018)	(9%)	
Dabigatran etexilate	8 %	3 %
(Patients who switched from warfarin to dabigatran etexilate in 2015–2018)	(4%)	
No medication data available or several prescriptions of direct oral anticoagulants within one year	19 %	-

The drug or prescription data was not available for 19% of patients – no prescription for an anticoagulant was found for most of them. In addition, there were patients with several prescriptions for direct oral anticoagulants during the same one year in the Hilmo data.

Table 3 shows patient profiles by drug segments. Patients on warfarin and apixaban were on average older and had higher CHA₂DS₂-VASc scores than patients on rivaroxaban or dabigatran etexilate. In all drug segments, the mean CHA₂DS₂-VASc score was three or higher.

The most common comorbidity in all segments was hypertension (Table 3). The second most common comorbidity was heart failure in

warfarin and apixaban users, and diabetes in dabigatran etexilate and rivaroxaban users.

In age groups, there were significant differences in the costs of atrial fibrillation patients: the total costs of service use for patients under the age of 75 years were on average 4,900 euros and approximately 13,000 euros for patients over the age of 75 years (Fig. 2). The costs for patients over the age of 75 years were in all drug segments on average about 2.5-fold compared with those for patients under the age of 75 years. Based on the primary data, the estimated combined public social and health service cost for atrial fibrillation patients in 2018 were approximately 2 billion euros.

The share of social services of the costs was pronounced for patients over the age of 75 years and they comprised about half of the total costs in all drug segments (Fig. 2). For patients under the age of 75 years, the share of social services was about one fourth of the costs.

In all segments (with the exception of rivaroxaban patients under the age of 75 years), the most visits to specialized and primary health care were due to ischemic strokes (Fig. 3 and 4). In addition to ischemic strokes, sequelae of cerebrovascular events were often also the reason for atrial fibrillation patients' use of services. In relation to the number of patients, patients on warfarin had the most visits to specialized and primary health care due to the combined number of cerebral events in patients under the age of 75 years, and patients on rivaroxaban had the least visits. In patients over the age of 75 years, patients on apixaban had the most visits due to the number of cerebral events.

In relation to the number of patients, patients on dabigatran etexilate had the most visits to special and primary health care due to GI-bleeding in patients under the age of 75 years, and patients on rivaroxaban had the least visits (Fig. 3). In patients over the age of 75 years, patients receiving warfarin had the most visits and patients on rivaroxaban the least visits.

Patients under the age of 75 years receiving warfarin and patients over the age of 75 years receiving dabigatran etexilate had the largest number of GI-bleeding related treatment days.

The dosage sizes of direct oral anticoagulants were also examined from the sub-population by age groups. In patients under the age of 75, four percent of apixaban users, six percent of ri-

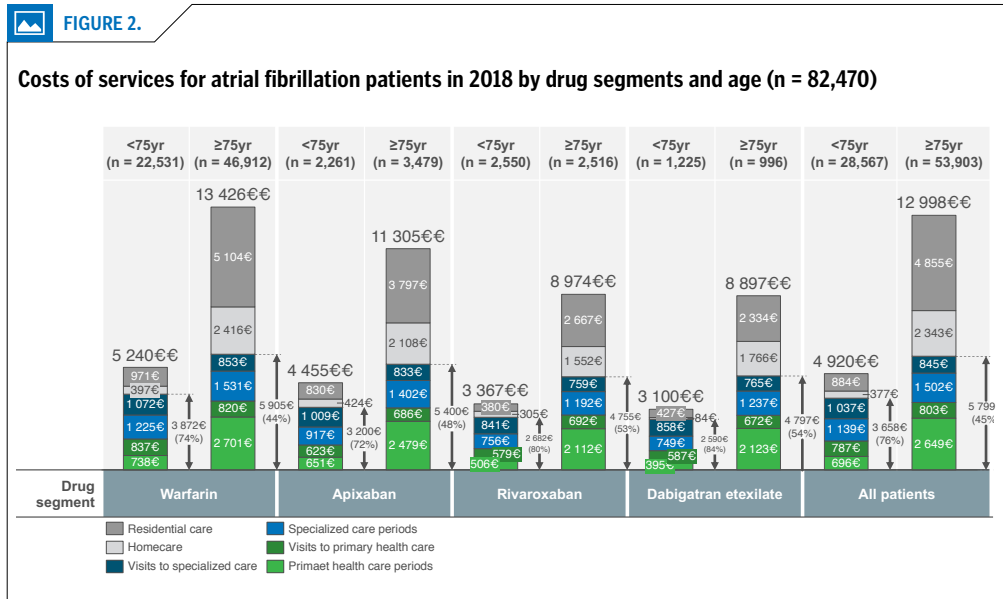


TABLE 3.

Comorbidities of atrial fibrillation patients and CHA₂DS₂-VASc scores in 2018 by drug segments (n = 82,470)

Anticoagulant	Warfarin	Apixaban	Rivaroxaban	Dabigatran etexilate
n	69,443	5,740	5,066	2,221
Average age	78,1	77,0	74,3	73,3
65–74 years of age	24 %	28 %	35 %	38 %
Over 75 years of age	68 %	61 %	47 %	45 %
Female	46 %	52 %	47 %	46 %
Cardiac insufficiency	34 %	29 %	20 %	19 %
Hypertension	65 %	67 %	63 %	64 %
Diabetes	31 %	28 %	25 %	25 %
Cerebrovascular disturbance	16 %	18 %	13 %	21 %
Arterial disease	23 %	17 %	13 %	13 %
CHA ₂ DS ₂ -score (average)	3,9	3,7	3,1	3,2

varoxaban users, and seven percent of dabigatran etexilate users were on a reduced drug dose (apixaban: Eliquis, 5mg large dose; 2.5mg reduced dose; rivaroxaban: Xarelto, 20mg large; ≤15mg reduced; dabigatran etexilate: Pradaxa, 150mg large, ≤110mg reduced). Respectively, in patients over the age of 75 years and older, 44 percent of apixaban users, 28 percent of rivaroxaban users and 69 percent of dabigatran etexilate users were on a reduced dose.

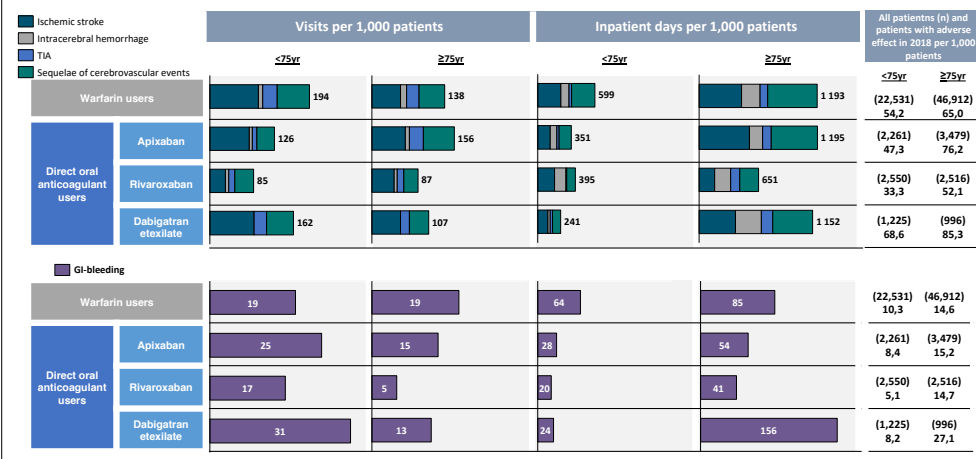
Conclusions

This is the first study based on real-world data of patient profiles and use of services related to Finnish atrial fibrillation patients on warfarin and direct oral anticoagulants. The primary data of the study was used to examine the medication and profile of atrial fibrillation patients and their total costs of using public social welfare and health care services in 2018. In addition, the patient profiles, the use of services and re-

FIGURE 3.

Visits and inpatient days due to ischemic stroke, intracerebral hemorrhage, TIA, sequelae to cerebrovascular events, and GI bleeding in atrial fibrillation patients in 2018 by drug segments and age groups (n = 82,470)

More detailed numbers of cerebral events are in Fig. 4. Column on the right displays the total number of patients and the number of those patients/1,000 patients, who had at least one visit or treatment day associated with ischemic stroke or GI-bleeding registered in Hilmo in 2018.



lated costs and the number of visits and inpatient days in special and basic health care due to cerebral events and GI bleedings were analyzed in the sub-population defined from the primary data, according to the age and drug segment.

Significant costs are accrued to the society from the atrial fibrillation patient population. The combined costs of visits and inpatient days in specialized and primary health care and of residential care and home care were in the atrial fibrillation patients included in the primary data about 2 billion euros in 2018. In atrial fibrillation patients over 75 years of age using the same medication for at least one year, the average service-related costs per person were over 13,000 euros in 2018. This is approximately 3,000 euros more than the average for a Finnish person of the same age (9). In earlier studies, it has been shown that particularly the occurrence of stroke increases the treatment costs significantly: in the year following the stroke, the average costs of patients for the above-mentioned services were about 39,000 euros per year (4).

In marketing authorization studies, direct oral anticoagulants have been compared with warfarin but due to the differences in study de-

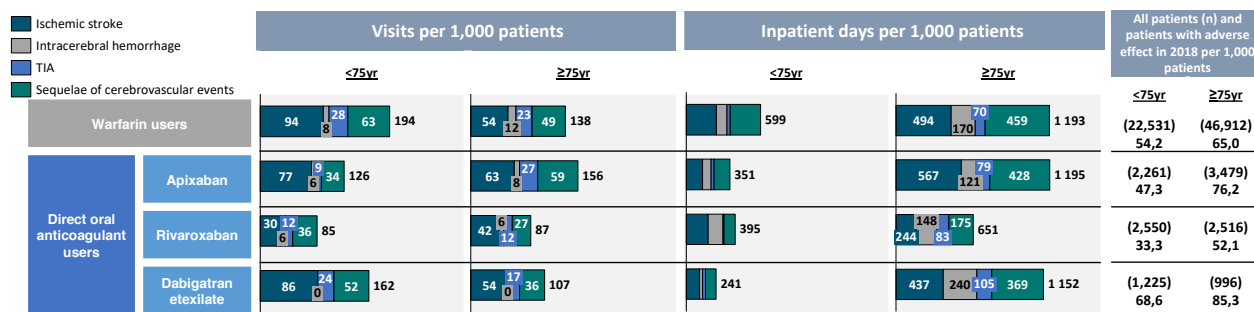
signs and in the patients' risk of thrombosis or bleeding, comparing direct oral anticoagulants with each other is challenging (10–14). Our study shows that in Finland different anticoagulant therapies are prescribed in clinical use to different patient groups in comparison to marketing authorization studies: warfarin and apixaban are prescribed on average to older and higher-risk patients than rivaroxaban and dabigatran etexilate. According to our main finding, there are differences in the patient profiles, use of services and costs related to adverse events in patient groups receiving different anticoagulant therapies. However, it is not possible to make direct conclusions from the data as to the reasons for these differences. The underlying causes may include patient specific matters in drug choice and usage.

The main limitations of the study are related to data. It is possible that by defining the sub-population to so called established anticoagulant users, the data may contain those patients which experience fewer drug related adverse events. This selection might affect warfarin patients in particular. In addition, the examination of visits and inpatient days in specialized

FIGURE 4.

Visits and inpatient days due to ischemic stroke, cerebral hemorrhage, TIA, and sequelae of cerebrovascular events in atrial fibrillation patients in 2018 by drug segments and age groups (n = 82,470)

Column on the right displays the total number of patients and the number of those patients/1,000 patients, which had at least one visit or treatment day associated with cerebral event registered in Hilmo in 2018.



and primary health care includes patients' all events with a diagnosis code for an adverse event. It is not possible to interpret the incidence of individual adverse events based on visits and treatment days. Hilmo-registers might contain inaccuracies due to registry limitations and possibly due to different entry recording practices. In collecting drug data, we use prescriptions recorded to Avohilmo. As in registry studies in general, the data does not allow the possibility to conclude if the patient has also taken the prescribed medicine. In addition, the data does not give an answer on how long the patients on average have had an atrial fibrillation.

Our results emphasize the need for further studies on drug therapy practices for atrial fibrillation and on possible differences in the suitability of different direct oral anticoagulants in the treatment of patients with a high risk of stroke. ●

The study received funding from Bayer Oy.

WHAT WAS KNOWN PREVIOUSLY

- Direct oral anticoagulants have overtaken warfarin in the initiation of anticoagulation therapy to prevent strokes associated with nonvalvular atrial fibrillation.
- According to an earlier study, the patient's treatment balance has a great significance for the risk of thrombosis and bleeding.

WHAT WAS LEARNED FROM THE STUDY

- The costs of public social and health care services for atrial fibrillation patients were approximately 2 billion euros in 2018 - approximately 50% of the costs of one atrial fibrillation patient came from using specialized and primary care services and 50% from residential care and home care costs. Warfarin patients had the highest costs per patient.
- Warfarin and apixaban are prescribed on average to older and higher-risk patients than rivaroxaban and dabigatran etexilate.