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ORIGINAL RESEARCH

Predictors for total hospital and cardiology cost claims among patients with atrial fibrillation initiating dabigatran or acenocoumarol in The Netherlands

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ABSTRACT

Aims: The prevalence of atrial fibrillation (AF) has increased over the past years due to aging of the population, and healthcare costs associated with AF reflect a significant financial burden. The aim of this study was to explore predictors for the real-world AF-related in-hospital costs in patients that recently initiated anticoagulation with acenocoumarol or dabigatran.

Methods: Predictors for claimed total hospital care costs and cardiology costs in AF patients were explored by using hospital financial claims data from propensity score matched patient groups in a large Dutch community hospital. This study analyzed the total dataset ($n = 766$) and carried out a secondary analysis for all matched pairs of anticoagulation naïve AF patients ($n = 590$) by ordinal regression.

Results: Dabigatran was a predictor for significantly lower cardiology and total hospital care costs (Odds Ratio [OR] = 0.43, 95% confidence interval (CI) = 0.33–0.57; and OR = 0.60, 95% CI = 0.46–0.79, respectively). Female gender was a predictor for lower total hospital care costs. Predictors for an increase in total hospital care costs were the occurrence of stroke or systemic embolism, major bleeding, and minor bleeding. The costs predictors were comparable when limiting the analysis to patients that were anticoagulation naïve. Age and CHA_2DS_2-VASc were not predictors for either cardiology or total hospital care costs in both analyses.

Conclusion: Dabigatran treatment was as a predictor for lower cardiology costs and lower total hospital care costs in AF patients that initiated oral anticoagulation.

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia, with a prevalence of 3% in the adult population, increasing with age up to 5.9% above 65 years old[1,2]. The prevalence of AF has increased over the past years, due to aging of the population, and it is expected to increase even further in the next decade[3,4]. By 2030, 120,000–215,000 newly-diagnosed AF patients per year are anticipated in the European Union[2]. The healthcare costs associated with AF reflect a significant financial burden, mainly determined by events occurring as a consequence of the prevailing arrhythmia or as a consequence of the anticoagulant treatment. Several cost studies have identified the annual AF-related medical costs. These costs were more than 1% of the total healthcare expenditures globally, and are still rising[5]. Patients with AF have a 5-fold higher risk for stroke compared to patients without AF, and strokes attributable to AF have a greater severity and higher mortality[6]. Thrombo-embolic events can be reduced by long-term anticoagulation with vitamin K antagonists (VKAs) or non-vitamin K antagonists oral anticoagulants (NOACs)[7]. However, the use of anticoagulants introduces an increased risk of bleeding. Several studies have been conducted focusing on total healthcare costs and healthcare utilization of AF patients, mostly within the US. Cost studies show a wide range in annual costs for AF patients[8–10]. There are a few studies that calculated the differences in total hospital care costs between AF patients on dabigatran compared to acenocoumarol. The results seem controversial in terms of the significance of the differences in costs, and the hospital cost data for Europe are limited.

The aim of this study was to explore predictors for the real-world AF-related in-hospital costs in patients that recently initiated anticoagulation with acenocoumarol or dabigatran by using hospital financial claims data from a large Dutch community hospital.

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Methods

Study design and population

This was a retrospective, single-center, observational cohort study conducted in the Martini Hospital Groningen, The Netherlands. The Martini Hospital is a top clinical teaching hospital with 35 different disciplines, with ~377,000 outpatient visits per year and roughly 26,000 hospitalizations per year. Our study is a follow-up of a previous study conducted by Korenstra *et al.*[11], which included all consecutive patients with AF who started with oral anticoagulation in the outpatient clinic from January 1, 2010 to December 31, 2012. These patients were selected by a computerized search for the combination AF (diagnosis code) and initiated medication of acenocoumarol or dabigatran within the study period. Patients that were already using a VKA before January 2010 and switched to dabigatran during the study period were included in the dabigatran group. Patients were followed during time on therapy, with a maximum follow-up of 2 years, until they switched to another anticoagulant, ceased to use the anticoagulant, had a first event (stroke/systemic embolism (SE) or minor/major bleeding) or deceased. To address selection bias, 1:1 propensity score matching for both anticoagulation groups was applied. The variables included in the propensity score matching consisted of: Age (quintiles), gender, type AF (paroxysmal, persistent, permanent), cerebrovascular event/transient ischemic attack/embolism, myocardial infarction, bleeding, heart failure, diabetes mellitus, hypertension, vascular disease, alcohol use, platelet inhibitor use, angiotensin receptor blocker or angiotensin converting enzyme inhibitor use, beta-blocker use, amiodarone use, statin, proton pump inhibitor use, H2-receptor antagonist use, verapamil use, and non-steroidal anti-inflammatory drugs use.

A sub-set of the total dataset was established which only included the newly-diagnosed AF patients, i.e. excluding 88 patients from the dabigatran treatment group who had used a VKA for >2 months before dabigatran initiation. The matching pairs were also excluded from the acenocoumarol treatment group to balance the dataset.

We obtained the real-world effectiveness and safety data from the matched patients of Korenstra *et al.*[11] and used these data as a basis for our real-world hospital care cost analysis. The Dutch Diagnosis Treatment Combination (DTC or DBC in Dutch; Diagnose Behandel Combinatie) claims system was used to determine real-world hospital costs among AF patients using anticoagulation. In this claims system, hospitals are paid a case-mix based tariff for the entire treatment of a patient. Every DTC has a unique performance code including all information on the main specialist seeing the patient, the type of care, the demand for care, the diagnosis, the procedure performed, the treatment setting, and the length of cost follow-up (which includes acute hospitalization, re-admission for the same event, hospital allied health services, and hospital outpatient visits in the same hospital). If the patient is seen after exceeding the follow-up period, a new DTC will be opened. The medical specialist decides which DTC will be initiated upon first contact with a patient[12].

Study outcomes

The total hospital care costs were defined as the total claimed costs to the Martini Hospital within the study period, and the cardiology costs were defined as the total claimed costs only from the discipline cardiology within the study period. To define the real-world costs of events related to AF or events related to the use of oral anticoagulants, the combined end-point of ischemic stroke (IS) and SE was used as the primary efficacy outcome, and major bleeding was used as the primary safety outcome. Specific definitions of the outcomes were adopted from the aforementioned, retrospective, observational study that assessed the effectiveness and safety of dabigatran and acenocoumarol[11]. Minor bleeding was used as a secondary safety outcome.

Study procedure

This study was approved by the local Medical Ethics Committee of the Martini Hospital, and need for informed consent was waived by this committee. The total hospital care costs and total cardiology costs of AF patients initiating anticoagulation therapy with dabigatran or acenocoumarol were calculated using real-world in-hospital cost claims. The total claimed costs from the period 2010–2014 were retrospectively collected per patient by an independent person not involved in the study. All cost data were reviewed by two investigators independently (MSJ and MWJL) to determine which costs were made during the study period. Potential differences were resolved by consensus and, where needed, an expert opinion of a third investigator was asked (RGT). A DTC was included in the costs if the initiation date was within the study period. The end date of the DTC was allowed to be outside the study period, so that the cost follow-up period can be different from the clinical patient follow-up. The claimed costs were standardized to 1 year by adjusting the declared costs to 365 days, based on the cost follow-up period, since not all patients had a follow-up of 1 year. A disadvantage of this method is that the costs could be under- or over-estimated in the few patients with a very short follow-up and could, therefore, bias the results. The median follow-up time between treatment groups was significantly different[11].

Statistical analyses

Statistical analyses were performed using R (R Foundation for Statistical Computing, software version 3.3.2, Vienna, Austria). The costs for the total patient population and for the newly-diagnosed AF patient population were described as median + tertiles, because of their property of skewness.

Ordinal regression analysis was used to determine which variables influenced the cardiology costs and total hospital care costs. This method was chosen because the cost data were too skewed to include as the dependent variable in

Table 1. Descriptive table of patient characteristics included in the ordinal regression models for the total patient population that initiated acenocoumarol or dabigatran ($n = 766$) and the anticoagulation naïve population ($n = 590$).

Variable	Primary analysis ($n = 766$)	Secondary analysis ($n = 590$)
Female	48%	48%
Age (years), mean ± SD	71.5 ± 9.1	71.8 ± 9.3
CHA_2DS_2-VASc score, mean ± SD	3.1 ± 0.9	3.1 ± 1.4
HAS-BLED score, mean ± SD	1.5 ± 0.9	1.5 ± 0.9
Stroke + SE, *n**	11	9
Major Bleeding, *n**	38	29
Minor Bleeding, *n**	92	78
Cardiology costs, median (tertiles)	€685 (€0∼€432; €432∼€1,297; €1,297∼€256,058)	€704 (€0∼€456; €456∼€1,403; €1,403∼€256,058)
All hospital costs, median (tertiles)	€1,400 (€0∼€792; €792∼€2,411; €2,411∼€106,345)	€1,518 (€0∼€834; €834∼€2,530; €2,530∼€106,345)

*Number of events observed in the observational study of Korenstra *et al.*[11].
CHA_2DS_2-VASc, Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); HAS-BLED, Hypertension, Abnormal renal/liver function (1 point each), Stroke, Bleeding history or predisposition, Labile INR, Elderly (> 65 years), Drugs/alcohol concomitantly (1 point each); SE, Systemic Embolism.

linear regression analysis. In addition, as there were 10% of patients who had the value of zero of either cardiology costs or total hospital care costs, the generalized linear model with gamma distribution can not be performed unless the cost data is properly transformed. Ordinal regression is the most direct and easy-to-fit approach to conduct when zero values exist, as recommended by Min and Agresti[13]. The assumption of proportional odds was not met when using the quartile costs data as the dependent variable in our ordinal regression model. We, therefore, used the tertile costs data as the dependent variable in our regression models. Multi-colinearity was assessed by the correlation matrix of all independent variables ($r > 0.80$ indicates multi-colinearity) and the variance inflation factor (a value >10 indicates multi-colinearity). The following independent variables were included: Gender, Age, Therapy, CHA_2DS_2-VASc score, HASBLED score, stroke + SE, major bleeding, and minor bleeding. Stroke + SE was the composite primary efficacy outcome, and major bleeding was the primary safety outcome. The CHA_2DS_2-VASc score was used instead of the $CHADS_2$ score because the CHA_2DS_2-VASc score performs better in predicting patients at high risk for stroke[14,15]. The primary analysis included all patients that initiated dabigatran or acenocoumarol ($n = 766$ patients), the secondary analysis included the matched pairs that were newly-diagnosed within the study period ($n = 590$ patients). When setting up the regression, the independent variable "Therapy" (dabigatran or acenocoumarol) was found to not meet the proportional odds assumption for the newly-diagnosed AF patients when using the tertile costs. To relax this assumption in the regression model, the effect of therapy was allowed to be varied across the tertile cost intervals (tertiles 1 and 2 and tertiles 2 and 3). The factors were considered statistically significant coefficients in the regression analyses if the two-tailed *p*-value was <0.05.

Results

A total of 766 patients were included in the primary analysis. The mean age of the population was 71.5 years, with 48% being female. The average CHA_2DS_2-VASc score was 3.1, and 11 patients of the total population experienced a stroke and/or systemic embolism (SE). The median cardiology costs were €685 per year, and median total hospital costs were €1,400 per year (mean costs: €3,703 and €3,580, respectively). The secondary analysis included a total of 590 newly-diagnosed AF patients who were anticoagulant naive. The mean age of this population was 71.8 years, with 48% being female. The median cardiology costs were €704, and the total hospital costs were €1,518 (mean costs = €3,649 and €3,945, respectively). Table 1 summarizes these costs + tertiles and the descriptive statistics of the patient population.

The results of the ordinal regression analyses are listed in Table 2. No multi-colinearity among regression coefficients was detected. Dabigatran treatment was a predictor for significantly lower cardiology costs compared to patients using acenocoumarol in the total patient population (Odds ratio [OR] = 0.43, 95% confidence interval [95% CI] = 0.33–0.57). Female gender and dabigatran treatment were associated with significant lower total hospital care costs compared to male gender (OR = 0.75 [95% CI = 0.56–1.00]) and acenocoumarol treatment (OR = 0.60 [95% CI = 0.46–0.79]). In contrast, the occurrence of stroke + SE, major bleeding and minor bleeding were associated with a significant increase in total hospital costs in the primary analysis. In the secondary analysis focusing on the newly-diagnosed AF patient population, a higher HAS-BLED score and dabigatran treatment were predictors for significantly lower cardiology costs (OR = 0.82 [95% CI = 0.68–0.99] for HAS-BLED score and OR = 0.49 [95% CI = 0.36–0.66] for dabigatran treatment). Across the first and second tertiles of total hospital costs, patients initiating dabigatran show significantly lower total hospital costs compared to patients initiating acenocoumarol (OR = 0.56 [95% CI = 0.39–0.81] for tertiles 1 and 2). This significant treatment effect was not found across the second and third tertiles of total hospital costs. The occurrence of stroke + SE, major bleeding, and minor bleeding were associated with a significant increase in total hospital costs.

Discussion

This cost analysis showed that, in this specific population where patients recently initiated dabigatran or acenocoumarol for stroke prevention in AF, dabigatran treatment is a predictor for lower cardiology costs and total hospital cost claims in the total patient population and in the newly-diagnosed AF patient population. Dabigatran was also a predictor for lower in-hospital costs when a fair share of patients (23%) from the treatment group were not newly-diagnosed.

Table 2. Ordinal regression model results for cardiology costs and total hospital costs for the total patient population that initiated acenocoumarol or dabigatran ($n = 766$) and the anticoagulation naïve population ($n = 590$).

	Primary analysis ($n = 766$), Odds ratio (95% CI)		Secondary analysis ($n = 590$), Odds ratio (95% CI)	
	Cardiology costs	Total hospital costs	Cardiology costs	Total hospital costs
Age, years	1.01 (0.99–1.02)	1.02 (1.00–1.04)	1.00 (0.98–1.02)	1.01 (0.99–1.03)
Gender, Female	0.97 (0.73–1.28)	**0.75 (0.56–1.00)**	0.98 (0.71–1.35)	0.76 (0.55–1.06)
$CHADS_2$-VASc score	1.00 (0.88–1.14)	1.02 (0.89–1.15)	0.96 (0.83–1.11)	1.02 (0.88–1.18)
HAS-BLED score	0.90 (0.77–1.06)	0.94 (0.80–1.11)	**0.82 (0.68–0.99)**	0.87 (0.71–1.05)
Therapy, Dabigatran	**0.43 (0.33–0.57)**	**0.60 (0.46–0.79)**	**0.49 (0.36–0.66)**	**0.56 (0.39–0.81) (tertile 1 and 2)** 0.87 (0.60–1.26) (tertile 2 and 3)
Stroke + SE	0.99 (0.34–2.86)	**4.98 (1.29–24.30)**	0.99 (0.31–3.12)	**4.24 (1.05–21.05)**
Major bleeding	1.31 (0.72–2.44)	**24.61 (8.57–104.01)**	1.09 (0.55–2.17)	**29.63 (8.59–186.50)**
Minor bleeding	1.48 (0.97–2.26)	**3.93 (2.53–6.20)**	1.14 (0.73–1.79)	**3.43 (2.13–5.60)**

CHA_2DS_2-VASc, Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); HAS-BLED, Hypertension, Abnormal renal/liver function (1 point each), Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly (1 point each); SE, Systemic Embolism.
bold numbers indicate significant odds ratios.

An increase in total claimed hospital care costs could be predicted by the occurrence of a stroke and/or SE, a major bleeding, and minor bleeding in both patient populations.

Several studies have been conducted focusing on total healthcare costs and healthcare utilization of AF patients, mostly within the US. The healthcare costs reported in the literature are mainly based on newly-diagnosed or recently diagnosed AF patients, and show a wide range, with annual costs varying from $3,463–$19,195 per patient on dabigatran. Bancroft *et al.*[10] calculated the mean adjusted 12-month all-cause healthcare costs to be high at $19,195 and $19,815 for dabigatran and warfarin, respectively, in a matched cohort. The reported annual healthcare costs in their study were much higher compared with the calculated hospital care costs in our study, which were €1,400 and €1,518. This could be due to their inclusion of pharmacy costs and outpatient costs. In our study, the drug costs were not included, since the drugs of interest used in the hospital are within the DTC. Patients visiting the outpatient clinic will obtain their medication from the community pharmacy for which associated costs are not within the hospital budget. Bancroft *et al.*[10] also concluded that the newly-diagnosed AF patients treated with dabigatran needed significantly fewer office, outpatient, and emergency department visits compared with those taking warfarin. This is in accordance with the results of our study, where dabigatran was associated with significantly lower cardiology cost and lower total hospital care costs for the total patient population and for the newly-diagnosed AF patients.

There are a few studies that calculated the differences in total hospital care costs between AF patients on dabigatran compared to acenocoumarol. Differences in costs were statistically significant in some studies, while others found no significant difference. Xie *et al.*[8] analyzed the effect of hospital length of stay on hospital care costs for patients using warfarin. They found hospital care costs ranging from $5,797–$22,386, depending on the hospitalization days (0–2 and 8–14 days, respectively). The authors concluded that there might be a positive correlation between hospitalization days and hospital care costs[8]. In our analyses, we did not correct for total hospital length of stay, as we did not monitor hospitalization days for all patients. Deitelzweig *et al.*[9] calculated the theoretical difference in medical costs of dabigatran treated AF patients compared to costs of warfarin in the US, based on event rates from the RE-LY trial. The incremental costs were –$143 and $2 in patients with a CHA_2DS_2-VASc score of 2 and ≥3, respectively, when comparing patients on dabigatran to patients on warfarin. In their study, the medical costs were based on efficacy and safety end-point such as stroke/systemic embolism, myocardial infarction, major bleeding, and non-major bleeding. It can be discussed whether the hospital costs within the US and Europe are comparable since the healthcare systems are quite different, and costs also tend to be higher within the US. In contrast, results from a diverse healthcare setting can be indicative to explore differences in healthcare costs between treatment groups.

The patients on acenocoumarol had a longer follow-up compared to patients on dabigatran, most likely caused by dabigatran being introduced on the market during the study period. Both treatment groups have a follow-up of at least 1 year, wherefore it is expected that higher costs in the initial period after diagnosis are included in both groups. The cost standardization to 1 year was chosen because the initial period is no proper approximation of the costs of stable AF patients, as this period would include more outpatient visits for optimizing the medication and potentially performing expensive procedures like cardioversion. Using all the cost data within the follow-up period makes the cost estimate more generalizable. For patients with a follow-up shorter than 1 year we could not use a multiple imputation method, since the data was not missing at random due to censoring of the follow-up period after an event.

We identified several factors that significantly influenced the cardiology and total hospital care costs. Dabigatran was a predictor for significantly lower cardiology costs and total hospital care costs. This could possibly be explained by the fewer office, outpatient, and emergency department visits for dabigatran treated patients, as aforementioned[16]. This same trend associated with dabigatran was seen in the newly-diagnosed AF patients. Comparing the total patient population with the newly-diagnosed patient population results in a slight increase of cardiology costs (€685–€704) and total hospital costs (€1,400–€1,518). The influence on costs of patients

that were not newly-diagnosed (88 of 766 patients) is not as comprehensive as expected in advance.

Predictors for an increase in total hospital care costs in our model were the occurrence of stroke + SE, major bleeding, and minor bleeding. Age and CHA_2DS_2-VASc score showed no association with either total cardiology or total hospital care costs on both the primary and secondary analysis. However, female gender was a predictor for lower total hospital costs in the total population, and a higher HAS-BLED score was a predictor for lower cardiology costs in the newly-diagnosed patients. This counterintuitive finding of the HAS-BLED could be due to the fact that costs associated with bleeding are mostly allocated to non-cardiology disciplines like internal medicine. The influence of female gender on costs could possibly be indicative for a more restrained care-seeking attitude of women[17]. Also, the number of total hospitalizations and the number of patients days, irrespective of the reason for admission, is lower for women in the Netherlands[18]. The same pattern of a lower number of hospitalizations is seen in women when focusing on cardiovascular disease in The Netherlands, although this is not reflected in our regression results. The higher total hospital costs after a primary efficacy or primary safety end-point might be explained by a majority of the events costs not being included within the discipline cardiology. Costs related to stroke mostly belong to the discipline neurology, and not cardiology. This would imply that the occurrence of stroke is mainly associated with an increase in total hospital care costs, which is in line with our results. Previous studies showed that patients with AF experienced ischemic strokes that were more severe, resulting in greater neurological disability, longer inpatient stays, and higher hospital costs than patients with normal sinus rhythm[19,20]. Major bleeding is often intracranial or gastrointestinal, and treated outside the cardiology department; therefore, the impact is higher on total hospital care costs. Different costs levels were calculated for intracranial hemorrhage in the literature, varying from €12,042 in Scotland to €12,748 in France[21,22]. In The Netherlands, the reported costs for intracranial hemorrhage show a wide range from €5,521–€21,284 depending on the severity of the bleeding[23]. A systematic review of the impact of upper and lower gastrointestinal blood loss on healthcare utilization and costs reported mean hospital costs per blood loss event for The Netherlands between €11,900 for a bleeding ulcer and €26,000 for a perforated ulcer[24]. However, there are only limited numbers of studies that have calculated the impact of GI bleeding on healthcare resource utilization and costs. Older age, lower GI blood loss, as well as length of stay were found to be predictors for increased costs in another study[25]. All these costs do not belong to the discipline cardiology, and are mostly allocated to neurology or internal healthcare, and, therefore, influence the total hospital care costs.

Limitations

Direct comparisons of the reported cardiology and total hospital care costs from our study with the costs in other studies may be limited due to differences in healthcare delivery systems and differences in standard of care. In addition, DTCs only covers in-hospital care, resulting in lower total costs due to the exclusion of costs outside the hospital (e.g. general practitioners, nursing home care, anticoagulation clinics, and rehabilitation centers). It is challenging to compare the hospital care costs and cardiology costs between studies. Studies comparing healthcare costs normally vary in methodology, as cost claims differ between countries. In some studies, there was a differentiation between hospitalization costs and outpatient costs, whilst other studies also included drug costs. The reported AF-related events were low in our study population, which makes it difficult to identify a significant association between efficacy and safety outcomes with cardiology or total hospital care costs.

Conclusion

Dabigatran treatment is a predictor for lower cardiology costs and total hospital cost claims in AF patients that recently initiated oral anticoagulation with acenocoumarol or dabigatran. Female gender is a predictor for lower total hospital care costs. The occurrence of stroke + SE, major bleeding, and minor bleeding are predictors for higher total hospital care costs.

Transparency

Declaration of funding

None.

Declaration of financial/other interests

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