Peer reviewed article

Characteristics of bleeding complications in patients with anticoagulant treatment

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Summary

Background/aims: Anticoagulation treatment is effective in the prevention of stroke as well as deep venous thrombosis (DVT) and pulmonary embolism (PE). Its preventive benefit has to be balanced against possible bleeding complications. We sought to assess risk factors for the severity of bleeding events in patients under anticoagulant treatment.

Methods and patients: Clinical characteristics, type of anticoagulant treatment, bleeding site, risk factors and additional medication taken were analysed in patients with bleeding complications during an observation period of 12 months.

Results: Eighty-seven bleeding complications in 84 patients (mean age, 79 years; 51% female) were observed from January to December 2005 at the Department of Internal Medicine of the Cantonal Hospital of Aargau. Most bleeding complications occurred in the gastrointestinal tract (54%). The median time interval from the beginning of the anticoagulant treatment to the bleeding event was 34 months. Forty-nine percent of events occurred after a treatment time above 36 months. Age was not found to influence the severity of bleeding but the duration of anticoagulant treatment before the occurrence of a complication was significantly longer for older patients ($p = 0.001$).

Conclusions: Our study shows no influence of age on severity of bleeding complications. Furthermore, in patients with advanced age complications occurred later in the treatment course than in younger patients. Overall we assessed various bleeding events in patients treated for over three years. Therefore we emphasize the importance of closely controlling patients on anticoagulant treatment in the later course of treatment and to take account of the anticoagulation when ordering new medication.

Key words: anticoagulants; complications; haemorrhage; risk; warfarin

Introduction

Oral anticoagulation treatment (OAT) has been proven to be effective in the prevention of arterial thromboembolism in patients with potential cardiac sources such as atrial fibrillation (AF) [1], heart valve replacement with a mechanical prosthesis [2] or myocardial infarction with aneurysm [3]. Some of the indications for OAT are particularly frequent in elderly people. In a recent study Miyasaka et al. estimated a prevalence of AF of 13.5% for individuals >75 years of age and 18.2% for those >85 years by the year 2020 [4]. More than one third of all patients reported in an Italian study were older than 70 years when OAT was started and 8% were older than 80 years [5]. Nevertheless, anticoagulation treatment is still underused in elderly patients with AF [6, 7]. In a recent study the use of warfarin at discharge was 54% even amongst those patients considered to be at highest risk [8]. The underuse of anticoagulant treatment can be explained in part by findings that indicate an increased complication rate in patients with OAT with increased age, hypertension, diabetes and previous stroke [9–13]. Overall, the observed rates of major haemorrhage in randomized trials and observational cohorts have been reassuringly low [5, 14–16]. However, published rates may be underestimates, as few patients older than 80 years of age were enrolled. Furthermore many reports do not focus on the severity of bleeding events, which must be compared to the burden of thromboembolic events especially in older people.

The current study on patients with bleeding events was performed to assess the clinical charac-

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teristics of bleeding complications and to assess whether the severity of complications is influenced by the presence or absence of several known risk factors for bleeding complications in patients undergoing anticoagulant treatment.

Material and methods

Study setting and patients

This retrospective study took place in the Department of Internal Medicine at the Cantonal Hospital of Aargau. In the department we treat nearly 5,000 patients in the inpatient and 10,000 patients at the outpatient clinic each year. We retrospectively analysed all patients referred to our clinic between January 2005 and December 2005 with a clinically relevant bleeding event whilst receiving anticoagulation therapy. If patients had multiple bleeding events in the reported time, we collected the data for each event separately.

Anticoagulation treatment

Anticoagulation treatment was defined as oral anticoagulation with a vitamin K antagonist (VKA), application of low molecular weight heparin (LMWH) or unfractionated heparin (UFH). A clinically relevant bleeding event was defined as an event requiring treatment or medical evaluation.

Classification of outcomes

We categorised the events in three subgroups: serious, life-threatening and fatal, as previously defined elsewhere [14].

Examples of serious bleeding: overt gastrointestinal bleeding, occult gastrointestinal bleeding if endoscopic or radiographic studies were done, gross haematuria that prompted cystoscopy or intravenous urography or lasted more than two days, and haemoptysis. If blood was transfused, two units or less were given.

Life-threatening bleeding was defined as follows: leading to cardiopulmonary arrest, surgical or angiographic intervention, or irreversible sequelae, e.g., myocardial infarction, neurological deficit consequent to intracerebral haemorrhage or massive haemothorax. Bleeding was also considered to be life-threatening if it led to at least two of the following consequences: loss of three or more units of blood; systolic blood pressure less than 90 mm Hg, or critical anaemia (haematocrit <0.20).

Fatal bleeding was defined as that leading directly to the death of the patient.

Statistical methods

Descriptive statistics (mean, median, proportions) were calculated to characterise the patient, disease and treatment features. Fisher's exact test was used to compare differences in discrete variable. The non-parametric Mann-Whitney U test was used for continuous variables. The overall survival probabilities were estimated using the Kaplan-Meier product-limit method. Differences were examined using the log-rank test. Durations were calculated from the date of diagnosis. *P*-values <0.05 are considered statistically significant. All statistical analyses were performed using SPSS 13 (SPSS Inc., Zurich, Switzerland).

Results

Patient characteristics

In 2005 we treated 84 patients with 87 bleeding complications of anticoagulant treatment. Three patients had two events in the observed time period. Forty four events (51%) occurred in women and 43 in men (49%). Gender does not correlate with the severity of the bleeding event (p = 0.1). The median age at the time when anticoagulant treatment was started was 74 years (range, 44-92 years). Thirty per cent of the patients were older than 80 years and 56% older than 70 years when treatment was initiated. The median age at the time of the bleeding event was 79 years (range, 55-93 years). There were 21 events (25%) in patients younger than 70 years and 66 bleeding complications (75%) in patients older than 70

Table 1

Baseline characteristics of patients and type of anticoagulant treatment.

Characteristic	Serious bleeding events (n = 65)	Life-threatening bleeding events (n = 21)	All bleeding events (n = 87)
Female (%)	46	62	51
Male (%)	54	38	49
Median age (yrs) at beginning of anticoagulant treatment (range)	73 (44–92)	75 (61–91)	74 (44–92)
Median age (yrs) at bleeding event (range)	78 (55–93)	81 (62–92)	79 (55–93)
VKA (%)	75	86	78
VKA + LMWH (%)	12	10	12
LMWH (%)	6	5	6
UFH (%)	6	0	5
VKA + Platelet aggregation inhibitor (%)	11	10	10

Table 2
Indications for anticoagulant treatment (all variables in percent).

Indication for anticoagulant treatment (target INR)	Serious bleeding events (n = 65)	Life-threatening bleeding events (n = 21)	All bleeding events (n = 87)
Atrial fibrillation (INR 2–3)	52	52	53
Pulmonary embolism (2–3[a])	14	19	15
Mechanical heart valve prosthesis (INR 2.5–3.5)	12	0	9
Deep vein thrombosis (INR 2–3)	3	10	5
Myocardial infarction (INR 2–3)	6	0	5
Arterial thrombosis (INR 2–3)	3	10	5
Others	9	10	9

[a] 4 patients with a target INR of 2.5–3.5

Table 3
Sites of bleeding (all variables in percent).

Bleeding site	Serious bleeding events (n = 65)	Life-threatening bleeding events (n = 21)	All bleeding events (n = 87)
Gastrointestinal tract	45	86	54
– Upper gastrointestinal bleeding	26	62	35
– Lower gastrointestinal bleeding	14	14	14
– Upper and lower gastrointestinal bleeding	5	10	6
Skin and muscle	17	10	15
Urogenital tract	14	0	10
Nose	11	5	9
Lung	11	0	8
Joint	3	0	2
Retroperitoneum	0	10	2
Intracranial	0	0	1
Others	3	0	2

years, respectively. Forty one events (47%) were documented in patients older than 80 years. Age does not correlate with the severity of the bleeding complication (p = 0.2) but is significantly correlated to the duration of anticoagulant treatment before the occurrence of a bleeding complication (p = 0.002).

Type of anticoagulant treatment

Sixty eight events (78%) occurred in patients treated with oral anticoagulation with a VKA (phenprocoumon) alone, 10 events (12%) occurred in patients receiving phenprocoumon and concomitant a LMWH (dalteparin) in the initial phase of anticoagulant treatment. Five events (6%) occurred in patients receiving a LMWH (dalteparin) alone. Four patients were treated with a therapeutic dosage whilst one patient received LMWH as prophylaxis. A further four bleeding events (5%) occurred in patients treated with UFH (heparin). In nine (12%) of the 78 events in patients treated with phenprocoumon, the patient was taking a platelet inhibitor (acetylsalicylic acid, clopidogrel) at the same time. The type of anticoagulant treatment was not significantly associated with severity of bleeding.

Indication for anticoagulant treatment

Most events occurred in patients treated for atrial fibrillation (46 patients, 53%). Further indications were pulmonary embolism in 13 patients (15%), deep vein thrombosis in 4 patients (5%), mechanical heart valve prosthesis in 8 patients (9%), myocardial infarction in 4 patients (5%) and others in 12 patients (14%). We found a statistically non significant trend for more severe complications in patients treated for mechanical heart valve prosthesis (p = 0.08).

Considering only the 78 events occurring in patients treated with VKAs, the majority of events occurred in patients with a target INR value of 2.0–3.0 (64 patients, 82%). Thirteen events (17%) occurred in patients with a target INR level of 2.5–3.5 and only one patient who was treated for a not further specified thrombophilia received phenprocoumon in subtherapeutic dosage with a target INR value of <2.0.

Characteristics of bleeding complication

The median time interval from the beginning of the anticoagulant treatment to the bleeding event was 34 months (range, 0–275 months). Sixty five events (75%) were classified as serious and 21 (24%) were life threatening. We observed one fatal event in an 80 year old female patient with non small cellular lung cancer, who was treated with a VKA because of atrial fibrillation. She developed an intracranial bleed after 62 months of oral anticoagulation at an INR level of 4.6. She died several hours after admission to hospital.

The median haemoglobin level at the first visit to our emergency unit was 89 g/l (range, 49–181 g/l). The median haematocrit at the same time was 0.27 (range, 0.15–0.52). A total of 189

red blood cell units were transfused in 58 events (67%). Fifteen events (17%) required treatment in the intensive care unit. The overall treatment time at the ICU was 26 days for all cases.

Gastrointestinal bleeding was the major bleeding site with 47 events (54%), wherefrom 30 events (35%) were in the upper GI-tract, 12 events (14%) in the lower GI-tract und 5 events (6%) with simultaneous bleeding in the upper and lower GI-tract. Other bleeding sites were muscle/skin in 13 events (15%), urogenital tract in 9 events (10%), nose in 8 events (9%), and lung in 7 events (8%). Bleeding in the upper GI-tract resulted in more severe complications with 59% life threatening and 26% serious bleeding events ($p = 0.009$). Other bleeding sites did not lead to more severe complications.

In patients treated with VKAs 34 events (44%) occurred with an INR >3.5, 14 events (18%) with an INR >7.0. Only an INR >7.0 was highly significantly associated with more life threatening events ($p = 0.0001$). Thirteen events were seen in patients with a subtherapeutic INR (INR <2.0). With the exception of one event all patients with an INR <2.0 sustained non life-threatening bleeds ($p = 0.01$). In the four patients treated with UFH the aPTT at the time of bleeding complication was in the therapeutic range.

All but one patient with a bleeding event caused by a VKA were treated with vitamin K, in most of the cases given intravenously. In 26 events (30%) patients received fresh frozen plasma (FFP). The median dose was two units (range, 1–4). In four events (5%) patients were additionally treated with prothrombin complex concentrates. All of these events were classified as life threatening bleeds in the GI-tract with an INR >7.0. One patient who presented with a serious bleed whilst anticoagulated with LMWH was treated with protamine.

The anticoagulant treatment was continued in 51 cases (59%). The decision to continue the treatment was not associated with the severity of bleeding ($p = 0.2$). In thirty patients (59%) who were continued on anticoagulant treatment atrial fibrillation was the indication for the treatment, seven patients (14%) had a pulmonary embolism and a mechanical heart valve prosthesis, respectively. Only one patient who continued his anticoagulant treatment had a deep vein thrombosis as indication for the treatment.

We found an event accumulation in patients treated for longer than 36 months (43 events, 49%). Fifteen patients (17%) had a bleeding event within the three first months of anticoagulant treatment. Treatment time was not associated with the severity of bleeding. We found a positive correlation between the age at beginning of anticoagulant treatment and the duration of treatment until the bleeding event ($p = 0.001$)

Risk factors for bleeding complications

In 84 events (97%) we found associated risk factors for bleeding complications. Forty five cases (52%) were associated with more than two risk factors. The most frequently risk factors were hypertension (77%), renal insufficiency (49%), cancer (33%), and heart failure (30%). Neither the evaluated risk factors nor the number of risk factors in one patient was found to be related to the severity of bleeding.

In 85 events (98%) patients took other drugs beside the anticoagulant treatment. Age was significantly correlated with the quantity of prescribed drugs ($p = 0.04$). The mean number of drugs taken was 5 (range, 0–13). In 20 cases (23%) patients took an NSAID and in 18 cases (21%) platelet aggregation inhibitors. Four patients (5%) received anticoagulant treatment together with an NSAID and a platelet aggregation inhibitor. CYP 450 3A4 inhibitors – e.g. clarithromycin, diltiazem, verapamil, and amiodarone – were taken in 12 cases (14%) and CYP 450 2C9 inhibitors – e.g. amiodarone, fluvastatin, and sertraline – in 7 cases (8%). The concurrent use of a NSAID was significantly associated with more severe bleeding ($p = 0.007$). However, neither other drugs nor the number of drugs were associated with the severity of the bleeding complication.

Discussion

We have shown that age is not correlated to the severity of the bleeding events in patients with anticoagulant therapy. Interestingly, we found a significantly positive correlation between age and the time interval from the beginning of anticoagulant treatment to the bleeding event ($p = 0.001$). The missing correlation between age and severity of bleeding is at least partially contradictory to the figures in the literature, were many prospective studies found more events and more severe complications in older patients [12, 13, 17]. The fact that complications in older people occur later in the treatment course could be due to an increasing prevalence of co-morbid conditions and increasing number of prescribed drugs. This hypothesis is substantiated by several studies, which show a higher risk of bleeding complications in elderly patients with anticoagulant treatment [18]. One reason why our study fails to show a correlation between the age of the patients and the severity of bleeding events may be the advanced mean age of our study cohort. The mean age at the time of the bleeding event was 79 years with 47% of patients older than 80 years at the time of the bleeding event, which differs from the published data, where differences between patients younger

than 70 years and older patients have been reported.

In accordance with the literature we emphasise the importance of being aware of the reported higher risk of bleeding complications in elderly patients treated with anticoagulants. Older patients on anticoagulants should be monitored closely to keep their INR within the therapeutic margin. Furthermore, conditions and new drugs that may interfere with anticoagulant treatment should be carefully considered.

In our study nearly 50% of all bleeding episodes occurred after a treatment course longer than three years. There is a second peak in patients with newly started anticoagulant treatment within the first 90 days (23%). A higher frequency of bleeding early in the course has been reported in many [13, 19–21], but not all [22, 23] studies. Several factors may contribute to the increased risk of early bleeding. Firstly, anticoagulant therapy can unmask a previously undetected lesion. Secondly, dose adjustment may be less well-controlled at the start of treatment and, thirdly, at the beginning of anticoagulant treatment the use of two different antithrombotic drugs (heparin and phenprocoumon) increases the risk of over-treatment. We can only speculate on the reasons for the numerous bleeding events in the later course. There could be individual factors, such as the increasing prevalence of co morbid conditions and, therefore, the increasing number of interacting drugs. Possibly, the decreased compliance of intake and the longer control intervals are also time dependent factors. Patient compliance has been shown to be an independent risk factor for bleeding complications [24, 25]. Maybe there is also a diminished degree of alertness on the part of the physicians. Independent of these reasons, physicians prescribing anticoagulant drugs should be aware of the risks of anticoagulant therapy and should consider this fact in decisions made when diagnosing and treating a new disease.

Elevated INR is a firmly established risk factor for haemorrhage. We found a highly significant association between an INR >7.0 and life-threatening bleeding events. On the other hand only 44% of complications occurred in patients with an INR >3.5 and more than half of the events occurred at a therapeutic or even subtherapeutic (17%) INR level. This circumstance is in contradiction to the recommendation to use lower INR targets to offset bleeding risk [26, 27].

In patients with a mechanical heart valve prosthesis we found a non-significant trend for more severe bleeding complications, which is in accordance with other studies [12, 17]. An explanation for this finding may be the higher target INR for patients with a mechanical heart valve prosthesis. The target INR for this indication in our population was 2.5–3.5. Another explanation might be that some valvular diseases requiring heart valve replacement also lead to vascular malformations in the gut (Heyde syndrome), leading in turn to more gastrointestinal haemorrhage [28].

The major limitation of this study is its retrospective design based on a historical case series. Thus, the results could be biased because only bleeding complications leading to hospital admission were reported. Although we are confident that a representative number of patients with serious or even life-threatening bleeding events were reported because as a definition of a serious event, these patients need hospital admission and further treatment. For further evaluation of risk factors associated with bleeding complications in patients with anticoagulant treatment a prospective cohort design would be appropriate.

There are several studies that have identified the use of multiple medications as a risk factor for bleeding complications [29, 30] others show no influence on the complication rate [19, 31]. In our study only 2% of the patients were without additional medication, and the mean number of drugs was five. We could find no association between the number of additional medications and the severity of complications. Only the concurrent use of NSAID was significantly associated with more severe bleeding. Notably there was no association between the severity and the intake of drugs known to interact with the anticoagulant treatment. Maybe the fact, that several studies found an increased complication rate of patients with multiple medications is a consequence of comorbidity rather than of drug interaction.

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