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ORIGINAL ARTICLE

Risk of overanticoagulation during acute kidney injury in patients treated with vitamin K antagonists

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ABSTRACT

Background. Vitamin K antagonists (VKAs) are still in use for oral anticoagulation, but not all indications allow their replacement by direct oral anticoagulants. Although formal dose reduction is not required in patients with impaired kidney function, case reports indicate that acute kidney injury (AKI) might be associated with derailment of VKA therapy.

Methods. The study retrospectively collected patients from a tertiary nephrology care centre who experienced AKI while being treated with VKA. In these individuals, the international normalized ratio (INR) as a measure of anticoagulant effect during renal failure was compared with a reference time point with stable kidney function.

Results. A total of 100 patients with AKI and ongoing VKA therapy met the inclusion criteria. The majority (76%) of patients had AKI with CKD. Volume depletion ($n = 43$), septic renal failure ($n = 22$), decompensated heart failure ($n = 18$) and toxic renal damage ($n = 11$) were the most important causes of AKI. The average INR values at the time of AKI were higher than at the reference time point [median 3.17 (range 1.10–13.0) versus 2.24 (1.07–5.17); $P < 0.0001$]. Fifty-four patients had INR values above the recommended therapeutic range for their indication at the time point of AKI. Bleeding complications occurred in 24 patients during AKI and the VKA dose had to be reduced in 55. Women, patients with low body mass index and patients with diabetes were predisposed to overanticoagulation during AKI.

Conclusions. The effect of AKI on anticoagulation by VKA has not been systematically described. This risk should be considered in patients at high risk for AKI.

Keywords: acute kidney injury, anticoagulant therapy, bleeding, chronic kidney disease, drug interactions

INTRODUCTION

Until the introduction of direct thrombin inhibitors for oral anticoagulation in 2008, vitamin K antagonists (VKAs) were the mainstay of this treatment. Still today, quite a number of patients remain on warfarin or phenprocoumon and there are indications, such as prosthetic heart valves, for which there is no oral therapeutic alternative.

Due to their narrow therapeutic index, treatment with VKA should be monitored by periodic measurement of the international normalized ratio (INR) to ensure proper efficacy while avoiding excess risk of bleeding.

The commonly used VKAs, warfarin and phenprocoumon, are mainly metabolized by the liver. Dosing recommendations do not suggest adapting the dose to kidney function, however, their use is not encouraged in patients with severe renal failure. Limdi et al. [1] described an increased frequency of supratherapeutic INR levels in patients with chronic renal failure treated with warfarin. Although their use is not recommended in dialysis patients, VKAs are frequently prescribed in these patients as well. However, end-stage renal disease is associated with reduced dosing requirements to achieve the target INR as well as the need for more intense INR monitoring to avoid dangerous overanticoagulation [2]. The clinical effect of VKAs is highly dependent on liver function and interactions with drugs influencing liver metabolism. Further, heart failure and several food interactions are known to interfere with VKA activity.

Patients with chronic renal failure often have indications for long-term oral anticoagulation, mostly due to the high incidence of atrial fibrillation. Traditionally these patients were treated with VKAs; direct oral anticoagulants (DOACs) were introduced only reluctantly due to complex dose reduction rules. Further, DOACs should be used with caution at a glomerular filtration rate (GFR) <30 mL/min and should not be used at a GFR <15 mL/min. Several risks of VKA other than haemorrhage have been identified in patients with severe chronic renal failure and on dialysis [3], among them progressive vascular calcification or uremic calcifying arteriolopathy.

Until now, potential risks that incur with episodes of acute kidney injury (AKI) in patients chronically treated with VKAs have not been reported systematically. A case report from 2009

KEY LEARNING POINTS

What is already known about this subject?

- Formal dose reduction according to renal function is not required when prescribing vitamin K antagonists (VKAs).
- Excretion of warfarin, acenocoumarol and phenprocoumon mainly depends on hepatic function.

What this study adds?

- Acute impairment of renal function is associated with overanticoagulation in patients who are on long-term VKA therapy.
- Women, patients with low body mass index and diabetic patients are at particular risk for overanticoagulation during AKI.

What impact this may have on practice or policy?

- Awareness of this particular risk may lead to avoidance of VKA in patients with high risk for AKI (if possible) and attention to coagulation parameters in patients with VKA who happen to have AKI.

[4] described a patient on stable warfarin treatment who experienced overshooting INR levels during an episode of AKI.

This series of patients with AKI and pre-existing phenprocoumon therapy was compiled to determine if there is a systematic interaction between AKI and complications of VKA therapy.

MATERIALS AND METHODS

Study design and patient selection

The intention of this retrospective case analysis was to identify patients under permanent anticoagulation therapy with VKA who experienced an episode of AKI. To this end we included all patients who were admitted between 1 January 2009 and 31 December 2016 to the Department of Internal Medicine II (Nephrology) of the Martin Luther University Hospital, Halle, Germany and received the primary or secondary International Classification of Diseases, Tenth Revision diagnosis code N17.x (AKI) and the code Z92.1 (permanent anticoagulation), T45.5 (intoxication with anticoagulants) or D68.22 (haemorrhagic complication of coumarins). We verified by individual file analysis if the patients had been on oral anticoagulation with VKA before acute admission and if the creatinine-based Kidney Disease: Improving Global Outcomes (KDIGO) diagnostic criterion for AKI [5] was fulfilled. All patients received phenprocoumon as a VKA, which is the common preparation used in Germany. The study was carried out in accordance with the Code of Ethics of the Declaration of Helsinki and approved by the Ethics Committee of the University of Halle-Wittenberg (approval 2017-41).

Definitions

AKI creatinine was defined as the serum creatinine measured on the day of admission for AKI. The reference creatinine in most cases was a creatinine value that had been measured within a time window of 6 months prior to the admission. The value was determined from the patient's records from the hospital, the outpatient clinic or the patient's general physician. Such reference values could be obtained in 59 patients. In 41 patients, no such value could be found. In these individuals we used the best serum creatinine they achieved within 21 days of recovery after AKI as a reference. Patients who were suspected of having AKI and in whom we did not find a suitable reference value were excluded from the study. Pre-existing chronic kidney disease (CKD) was assumed if the reference creatinine value translated into an estimated GFR (eGFR) <60 mL/min/1.73 m^2 according to the Chronic Lidney Disease Epidemiology Collaboration formula [6], following the KDIGO definition of CKD [7].

The INR values were taken from the day of either AKI creatinine or reference creatinine. If these values were unavailable, the next value within a maximum time window of 24 h was used. All other demographic and laboratory data were taken from the day of admission to the hospital. The recommended therapeutic range for the INR values was individually determined according to the indication for anticoagulation. Therefore a range of INR of –2.5–3.5 was considered adequate for patients with prosthetic heart valves [8] and an INR of 2–3 for all other indications [9].

Statistics

Categorical variables are presented as the percentage of patients. Continuous data are expressed as median and range. They were compared by the Wilcoxon matched pair test. Frequencies were compared with Fisher's exact test. The influence of demographic and clinical variables on the occurrence of an INR increase during AKI was estimated by multivariable logistic regression. Data were computed with SPSS version 24 (IBM, Armonk, NY, USA). The data underlying this article will be shared upon reasonable request to the corresponding author.

RESULTS

From January 2009 to December 2016 there were 100 first admissions with AKI of patients who had concurrent oral anticoagulation and met the study criteria. The patient selection process is described in Figure 1. The demographic data of the patients are listed in Table 1. The majority of patients (76%) already had underlying chronic renal failure with an eGFR <60 mL/min/1.73 m^2 when the AKI episode occurred. The severity of AKI was classified as Stage 1 in 49 patients, Stage 2 in 18 patients and Stage 3 in 33 patients according to the KDIGO definition [5].

The causes of AKI were pre-renal volume depletion ($n=43$), septic renal failure ($n=22$), decompensated heart failure ($n=18$), toxic renal damage ($n=11$), post-renal obstruction ($n=3$) and primary renal disease ($n=3$). Among the patients with pre-renal volume depletion, 12 (28%) had diarrhoea immediately before or at admission. None of the patients

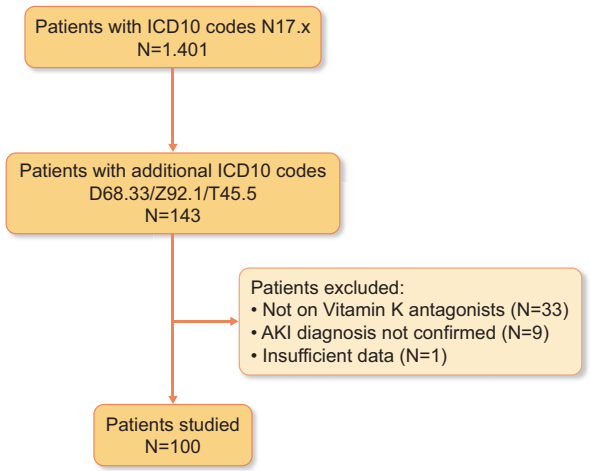

FIGURE 1: Patient selection for the study.

Table 1. Demographic characteristics of the patients included in this study

Variables	Values
Age (years), median (range)	75.4 (37.9–93.1)
Gender (male/female), *n*/*n*	56/44
BMI (kg/m^2), median (range)	27.7 (17.1–48.4)
Diabetes mellitus (yes/no), *n*/*n*	57/43
Chronic heart failure New York Heart Association II+ (yes/no), *n*/*n*	56/44
Liver disease (yes/no),[a] *n*/*n*	32/68
Baseline serum creatinine (µmol/L),[b] median (range)	135 (61–468)
Baseline kidney function before AKI[b], *n*	
eGFR ≥60 mL/min/1.73 m^2	14
CKD 3a	27
CKD 3b	33
CKD 4	22
CKD 5	4
Indication for oral anticoagulation, *n*	
Atrial fibrillation	82
Deep vein thrombosis/pulmonary embolism	7
Valvular prosthesis	6
Cardiac support system	2
Left ventricular thrombus	1
Arteriovenous bypass	1
Stroke of undetermined source	1

[a]Liver disease was assumed if a chronic severe liver condition was mentioned in the patient's records or serum levels of aspartate aminotransferase, alanine aminotransferase or gamma-glutamyl transferase were elevated >2 ULN.
[b]In 41 patients, the creatinine before AKI could not be determined. In these patients, the best creatinine that was achieved within 21 days of recovery of AKI was used instead [median 122 (range 61–468) µmol/L].

from the other etiologic groups had diarrhoea or gastrointestinal infection. Five patients received antibiotic treatment at the time of AKI diagnosis and first INR measurement. All other patients either did not receive antibiotics or their treatment was initiated only after the relevant blood sample for diagnosing AKI was obtained.

The average INR values measured at the time of AKI were significantly higher than the INR values measured together with the reference creatinine [median 3.17 (range 1.10–13.0) versus 2.24 (1.07–5.17); $P < 0.0001$; Figure 2]. At the time of reference creatinine, 49 patients had an INR value within the boundaries of the therapeutic recommendation for their indication, in 37 patients the value was below and in 14 patients the value was above that range. The number of patients with INR ·'s above the recommended range for their indication in-ɜed with AKI (Figure 3). Across all stages of AKI, 54% of ɔatients had INR levels above the recommended range for · indication. In 57 patients the INR at the time of AKI was standard deviation higher than the INR at the reference point.

ımong the 100 individuals who were admitted with AKI, anticoagulation was acutely modified in 55 patients while therapy remained unchanged in 45 patients. Among those 54 patients with INR above therapeutic range during AKI, the VKA was paused in 28. Five patients received vitamin K and one patient received prothrombin concentrate. In eight patients, oral anticoagulation was permanently stopped because the physicians concluded that the risk–benefit analysis was not in favour of such therapy.

Any bleeding complication was noted in 24 patients and nine of these episodes were classified as severe (requiring blood transfusion). Severe bleeding was bleeding from the upper ($n = 5$) or lower ($n = 2$) gastrointestinal tract, severe bleeding from an arterial cannulation and severe soft tissue haematoma. Among the patients with bleeding, 12 (50%) had INR levels above the target range and 9 had comedication with acetylsalicylic acid. Among these patients, three had both predisposing conditions, INR above target range and acetylsalicylic acid medication.

Overanticoagulation during AKI occurred more frequently in female compared with male patients (Figure 4). Several concurrent conditions of the patients were tested if they enhanced the risk of overanticoagulation associated with AKI (Table 2). Diarrhoea at presentation or antibiotic treatment before the diagnosis of AKI did not influence the association between AKI and overanticoagulation; however, the number of patients with these conditions was very low. Multivariate analysis confirmed that female gender, a low body mass index (BMI <25) and diabetes mellitus predisposed the patients for enhanced effects of VKA during AKI. Other factors such as higher age, chronic heart or liver disease or pre-existing CKD did not have an effect on this risk.

DISCUSSION

With this study we describe for the first time that acute deterioration of kidney function in patients treated with VKA is associated with a high risk of overanticoagulation. This effect was suspected in a case report [4] but had not yet been systematically analysed. Our data show that 73% of patients experience an increase in the INR value during AKI when compared with a reference time point with better renal function. Such overshooting anticoagulation is linked to a significant risk of haemorrhage [10]. Women, diabetic patients and those with a BMI

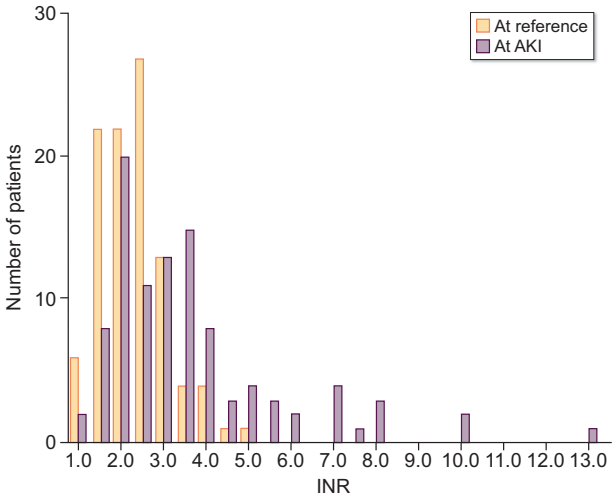

FIGURE 2: Distribution of INR values at the time point of AKI and at the reference time point.

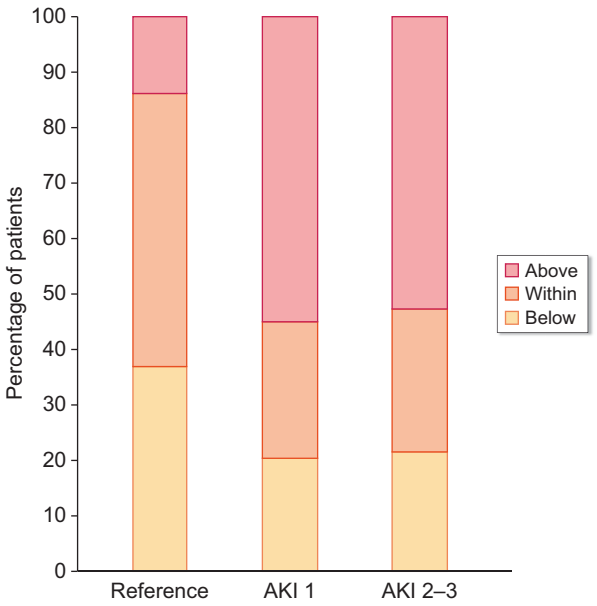

FIGURE 3: Percentage of patients with INR values below, within or above the respective recommended target range for their indication. The number of patients with INR values above therapeutic range was higher at the time of AKI (54%) than at the reference time point [14%; odds ratio 7.21 (95% confidence interval 3.62–14.35)].

<25 are particularly at risk. In the majority (55%) of patients on VKA, the dose of the anticoagulant had to be modified or the substance discontinued when AKI occurred. Bleeding complications were noted in 24% of patients.

All patients in this series from Germany were treated with phenprocoumon. In other parts of the world, acenocoumarol and particularly warfarin are used as VKAs. All these substances have high plasma protein binding (99%). They are metabolized via the cytochrome P450 system in the liver. Hepatic clearance is the main elimination pathway. Warfarin and

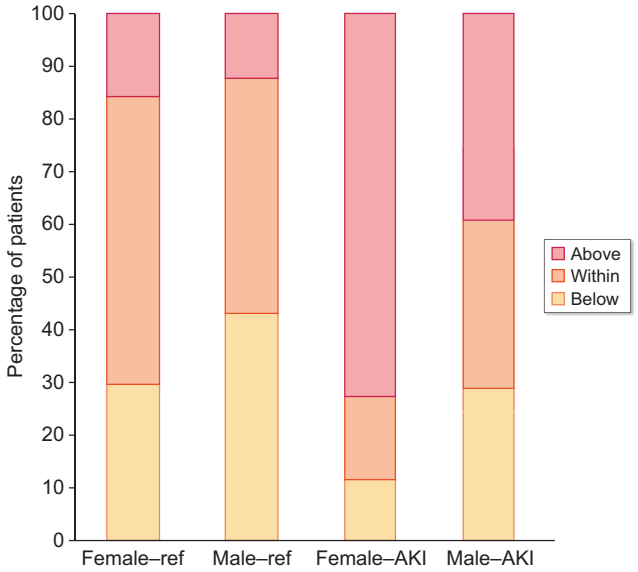

FIGURE 4: Influence of gender on the percentage of patients with INR values below, within or above target range. Overanticoagulation during AKI was more frequent in female than in male patients [odds ratio 4.12 (95% confidence interval 1.76–9.67)].

acenocoumarol are mostly metabolized via the 2C9 isoenzyme, while both 2C9 and 3A4 isoenzymes are important for the metabolism of phenprocoumon [11]. Although there is some renal excretion of phenprocoumon, but not acenocoumarol or warfarin, dosing recommendations do not consider renal function except for severe renal failure.

How could AKI lead to a strong increase in the phenprocoumon effect if renal excretion is not very relevant for its excretion? As mentioned, all VKAs are highly bound to plasma proteins, while only the unbound fraction is actively inhibiting hepatic synthesis of vitamin K–dependent coagulation factors. Animal studies on experimental AKI suggest that warfarin can be displaced from protein binding [12–14] by acidosis and retained uremic toxins. This might lead to a higher active fraction of the VKA. Such effects have been described for other pharmaceuticals in renal failure as well (review in Dreisbach and Lertora [15]).

Uremic toxicity may also influence the activity of the cytochrome P450 system [16]. Dreisbach *et al.* [17] showed that end-stage renal disease leads to reduced activity, particularly of the CyP 2C9 isoenzyme. More importantly in the case of phenprocoumon, Dowling *et al.* [18] also demonstrated a lower activity of the 3A4 isoenzyme under uremic conditions.

Could other reasons rather than acutely diminished renal function play a role in the effect we observed in our patients? Therapy with VKA aims at a narrow therapeutic index and overanticoagulation occurs frequently. Froom *et al.* [19] pointed out that older age is an important risk factor for too high INR values. Sixty-seven per cent of the patients from our series were at least 70 years old. Thus age may have accelerated the risk of VKA in this population, although we did not identify this parameter as a risk factor in the multivariate analysis.

In an analysis of prescription and health insurance data, Clark *et al.* [20] pointed out that comedication of warfarin with

Table 2. Influence of patient conditions on the increase of INR associated with AKI

Variable	Exp(B)	95% confidence interval	P-value
Age (≥70 years versus younger)	1.245	0.402–3.852	0.704
Gender (female versus male)	3.339	1.226–9.092	0.018
BMI (>25 versus ≤25)	0.315	0.100–0.994	0.049
Diabetes mellitus (yes versus no)	3.614	1.308–9.986	0.013
Chronic heart failure (yes versus no)	1.023	0.399–2.627	0.962
Liver disease (yes versus no)	1.884	0.664–5.345	0.234
Pre-existing CKD (eGFR <60 versus ≥60 mL/min/1.73 m^2)	0.482	0.126–1.841	0.286

The table gives the results of multivariate logistic regression analysis with an increase in INR by at least 1 standard deviation (0.78 units) relative to the INR measured at the reference time point.

antibiotics more than doubles the risk of overshooting anticoagulation. Such interaction may be particularly pertinent with cephalosporins [21]. Although there were several patients in our series in whom infection contributed to the pathogenesis of AKI, only five patients received antibiotic treatment before blood sampling for the diagnosis of renal dysfunction and the measurement of INR. Further, the effect described by van Walraven *et al.* [22] that hospitalization itself is a risk factor for derailment of VKA therapy due to altered comedication, nutrition and care is not relevant to our patients since AKI was diagnosed before admission to the hospital.

VKA and AKI are often linked via the observation of warfarin-induced nephropathy [23]. Intrarenal microbleeding can lead to acute deterioration of kidney function that appears clinically as AKI. In this case, overanticoagulation would be the primary event, followed by AKI. In addition, a Spanish group [24] recently described an association between VKA intake and the prevalence of immunoglobulin A nephropathy. In our patients, a distinct pathogenesis could be identified to explain AKI. None of the cases was suggestive of VKA-induced AKI and only very few patients were reported to have initiated VKA recently before AKI or to have changed their VKA dose. Nevertheless, we cannot completely rule out that VKA-related nephropathy might have played a role in our patient group.

LIMITATIONS

Our study has several limitations. As a retrospective series, we cannot derive causality from the association between AKI and overanticoagulation in VKA-treated patients. Further, although being the largest report on this issue, the series is quite small. In addition, due to the retrospective nature, we cannot provide pharmacokinetic measurements to confirm the suggested mechanisms. In spite of these limitations, our series may provide grounds for further research and highlight a relevant risk in everyday therapy that is worth being considered when caring for patients with AKI.

FUNDING

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AUTHORS' CONTRIBUTIONS

L.S. discussed the protocol, performed data acquisition and evaluation and drafted the manuscript. D.G. discussed the protocol and contributed to the manuscript. M.G. designed the protocol, supervised data acquisition and statistical evaluation and drafted the manuscript.

CONFLICT OF INTEREST STATEMENT

M.G. reports speakers compensation from Amgen, Bayer, Daiichi Sankyo, Novartis, Roche and Sanofi unrelated to this topic. Further, he receives a grant for a clinical study unrelated to this work from Daiichi Sankyo. L.S. and D.G. have nothing to disclose. The results presented in this article have not been published previously in whole or part, except in abstract format.

DATA AVAILABILITY STATEMENT

Original data are available from the corresponding author upon request.

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