Oral anticoagulation and vitamin K deficiency

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Summary
A 61-year-old woman with atrial fibrillation developed macrohaematuria during anticoagulant treatment with a direct oral factor Xa inhibitor for stroke prevention. Abnormal results of coagulation assays were first interpreted as an effect of the anticoagulant. However, upon further testing diagnosis of vitamin K deficiency was established. After vitamin K supplementation, coagulation tests normalized and macrohaematuria disappeared. Treatment with broad spectrum antibiotics for urinary tract infection was finally interpreted as an effect of the anticoagulant.

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A 61-year-old woman with atrial fibrillation had been treated with a vitamin K antagonist (phenprocoumon, Marcoumar®) for prevention of ischaemic stroke and systemic embolism. Her CHA2DS2-Vasc score was 5 because of a history of transitory ischaemic attack, diabetes mellitus, arterial hypertension, and female sex, translating into an estimated annual risk of stroke of 6.7% (1).

During the first year of treatment she had very unstable international normalized ratios with time in therapeutic range of less than 40%. She was switched to a direct oral factor Xa-inhibitor and had no further complaints. Her medical history was otherwise uneventful. She took metformin, an angiotensin convertin enzyme inhibitor, and diuretics.

One year later, she developed macrohaematuria and was initially managed by her general practitioner. The macrohaematuria disappeared but recurred after two weeks and she was admitted to the hospital.

Upon admittance her blood count and differential blood count were normal except of mild normochromic and normocytic anaemia with a haemoglobin of 10.5 g/dl. Her renal function was impaired with a serum creatinine of 1.99 mg/dl and a calculated creatinine clearance (Cockroft-Gault) of 35.5 ml/min (body weight 75 kg). Liver function parameters were all within normal limits.

Coagulation assays showed a severe prolongation of the activated partial thromboplastin time (aPTT) as well as of the prothrombin time.

Discussion
Direct oral factor Xa-inhibitors affect global coagulation assays in a concentration dependent manner with a stronger effect on the prothrombin time than on the aPTT (2, 3). Thus, the abnormal test results were initially interpreted as an effect of the direct oral anticoagulant. However, the patient’s prothrombin time was seemingly too prolonged as to be explained by use of a factor Xa-inhibitor at standard dose. An analysis of clotting factors influencing the prothrombin time was performed and showed very low concentrations of clotting factors II, VII, IX, X while factor V was near normal (►Tab. 1). This pattern was indicative of vitamin K deficiency and the patient was treated with vitamin K, first orally (10 mg) and later intravenously (10 mg) upon which the concentration of all vitamin K dependent clotting factors increased, prothrombin time as well as aPTT normalized and macrohaematuria disappeared.

The potential causes of vitamin K deficiency are listed (►Tab. 2). Based on her medical history malabsorption as well as biliary dysfunctions could be excluded. The patient had previously been treated with a vitamin K antagonist. To exclude unintended or intended vitamin K antagonist intake, the patient’s blood was tested for presence of vitamin antagonists, but results were normal. Intake of extremely high

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Phenprocoumon, haematuria, direct oral anticoagulant, bleeding, vitamin K deficiency

Schlüsselwörter
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doses of vitamin E or D was unlikely, and there were no other signs of an overdose of the respective vitamins.

Treatment with antibiotics is a rare cause of vitamin K deficiency. Broad spectrum antibiotics affect intestinal bacteria growth. A number of microorganisms in the colon and distal ileum produce vitamin K. Broad spectrum antibiotic therapy diminishes this population of bacteria, limiting vitamin K production thereby contributing to vitamin K deficiency (4, 5).

Some broad-spectrum antibiotics in particular those with antibiotics containing the N-methylthiotetrazole side chain are associated with hypoprothrombinaemia and have a weak coumarin-like effect in patients with low vitamin K stores (6). Upon further questioning the patient recalled that initially she had been treated with antibiotics for two weeks by her general practitioner because of a urinary tract infection which most likely was the underlying cause for her first episode of macrohaematuria.

### References