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# Screening for anemia in patients on warfarin facilitates diagnosis of gastrointestinal malignancies and pre-malignant lesions ☆

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ABSTRACT

*Introduction:* The prevalence and etiology of occult bleeding among patients on warfarin who are screened systematically for new anemia is largely unknown. We aimed to estimate the usefulness of following hemoglobin and mean red cell volume (MCV) with INR in order to screen for developing anemia as an indicator of occult bleeding.
*Material and methods:* All patients on warfarin controlled at our institution had measurements of complete blood count (CBC) with INR during 18 months. Patients who fell > 25 g/L and/or decrease of MCV over 5 fL or MCV < 80 fL were contacted with instructions to undergo evaluation of anemia.
*Results:* Overall 3218 patients on warfarin were monitored at our institution and 442 (13.7%) had anemia and 235 (7.3%) had unexplained anemia. A total of 163/235 (69%) who were notified contacted their doctors and 82/163 (50%) were referred for investigation with upper and/or lower endoscopies. Gastrointestinal malignancies were found in 11 patients (10 colorectal cancers, 1 esophageal) and pre-cancerous lesions among 14 other patients. Additional 25/82 patients (30%) had upper and/or lower bleeding lesions such as ulcers and angiodysplasia. Based on 3669 years of observation, 73 patients needed to be screened for one year in order to identify one gastrointestinal lesion causing occult bleeding.
*Conclusions:* Thirty percent of those endoscoped had malignant or pre-malignant diseases. Regular measurement of CBC concomitantly with INR in patients on warfarin therapy led to detection of otherwise asymptomatic diseases in a significant proportion of patients and might lead to earlier diagnosis of malignant and premalignant disease.



## Introduction

Warfarin is widely used for the treatment and prevention of thromboembolism [1–3]. The most common adverse reaction of warfarin is bleeding, most commonly of gastrointestinal (GI) and intracranial origin [4]. Although acute symptomatic GI bleeding problems associated with warfarin have been well characterized [4–7], limited data exists on the prevalence and etiology of occult bleeding among patients on warfarin. A few studies have used fecal occult blood test (FOBT) in patients on warfarin with conflicting results [8–11].

All patients on warfarin are regularly controlled by measurement of the international normalized ratio (INR). It has very rarely been reported that complete blood counts (CBC) are followed on a regular basis concomitantly with INR in these patients. Only a single previous study has assessed the use of CBC monitoring in patients on warfarin. That study reported the yield of clinically important decreases in hemoglobin to be low but the results of the diagnostic work-up and the etiology of anemia were not reported [12].

We hypothesized that surveillance of patients on warfarin for new non-overt anemia by measuring hemoglobin and mean red cell volume (MCV) concomitantly with the INR would reveal important sources of otherwise occult bleeding, particularly GI bleeding.

## Material and Methods

### *Facility*

Ethical approval was obtained from the National Ethical Committee of Iceland and the Icelandic Cancer Registry. The Landspitali National

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University Hospital (NUH) anticoagulation management center (AMC) in Reykjavik monitored approximately 3200 patients with INR measurements and providing drug dosage for these patients using the DAWN anticoagulation management software [13,14]. At the time of the study, CBC was monitored with every INR on average monitoring 15 occasions annually aiming to diagnose new or progressive asymptomatic (ie pre-symptomatic) anemia. In the current practice this is done with every third INR. In our practice, blood counts of patients with hemoglobin or MCV below the normal reference range (women with Hb<108 g/l, men with Hb <120 g/l or MCV<80 fl) or - if within normal range - a hemoglobin or MCV decrease from their baseline of >25 g/l or >5 fl, respectively, are reviewed by a consultant hematologist at the AMC. If these patients do not have a known chronic anemia and/or an obvious cause of anemia (such as recent surgery or cancer therapy), the patients are notified by phone by the AMC staff as well as with an advisory notification letter recommending them to contact their attending physician who then decides upon diagnostic work-up. In many cases, CBC is repeated after the first evident hemoglobin or MCV decrease before notification. However, it must be noted that all patients with symptomatic anemia (eg overt GI bleeding) are attended to by immediate referral to approppriate level care, including the emergency department, and that any patients with overt bleeding were excluded from the current study group. Two examples of hemoglobin and MCV values in patients on warfarin are shown in Fig. 1, ie anemia due to a chronic bleeding (a) and anemia of chronic renal failure (b). The former patient was informed, whereas the latter was not.

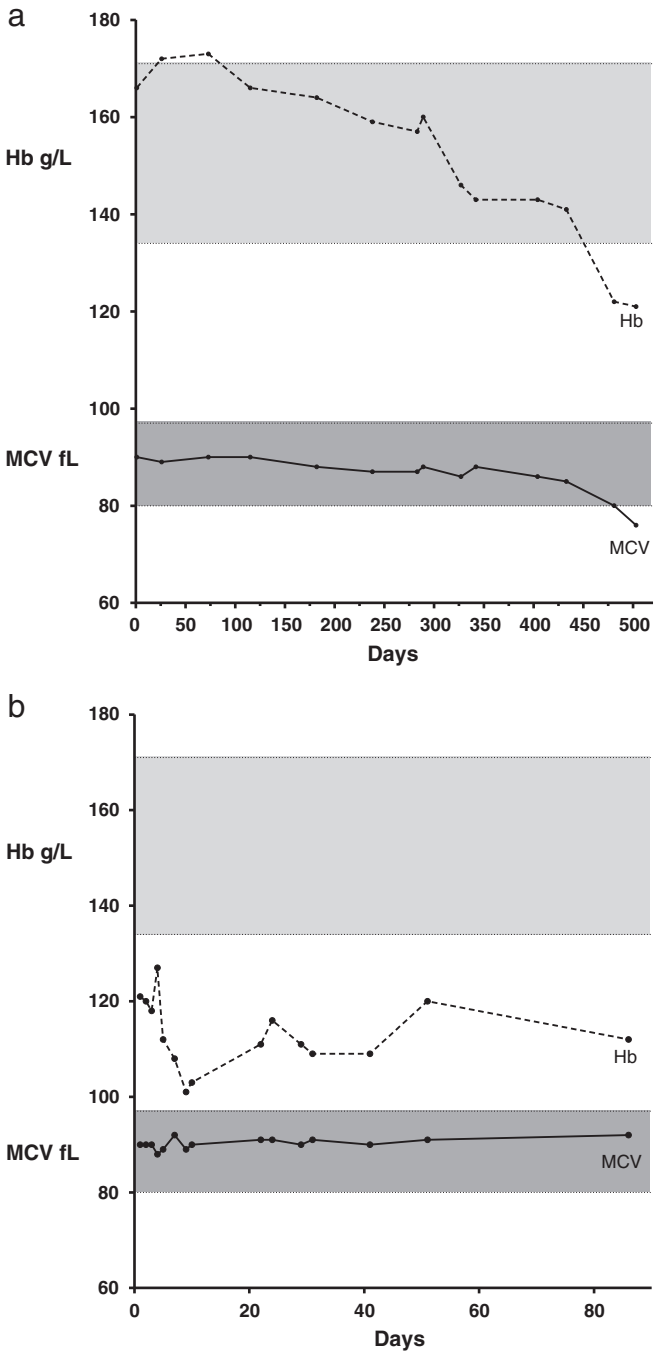


**Fig. 1. a.** Example graphic printout from the laboratory interphase system showing both hemoglobin and MCV gradually falling. The patient developed iron-deficiency anemia was sent a letter with a recommendation of diagnostic work-up. The patient was diagnosed with colorectal cancer. **b.** Example graph from the laboratory information system showing lower than normal hemoglobin during a one year period but MCV was within the normal range. The patient had chronic renal failure and was not notified with a recommendation of diagnostic work-up.

*Data Collection*

All patients on warfarin managed during an 18 month period, from September 2008 to February 2010 were identified. Medical records were reviewed to determine: age, gender, duration of treatment and indications for warfarin, whether or not the patient had developed anemia, if the patient had been been notified of anemia, and whether the patient had sought medical attention following notification, investigations undertaken and treatment if any. Data on outpatients and hospitalized patients was retrieved retrospectively from various sources. If the information was not found in medical records of the NUH, the patients were contacted and information obtained. Information was also sought from general practitioners and specialists in private practice. At the end of follow-up, information was also gathered from the medical record system of the National University Hospital about patients who did not seek medical attention despite notification. This was done to examine whether any serious disorders such as clinically overt malignancies had been detected in these patients during a period of over one year after the patient had been informed about the anemia. Our institution is the only hospital in the referral area that takes care of cancer patients and their management. Furthermore, it is the only hospital in the region of INR monitoring where patients are hospitalized for gastrointestinal (GI) bleeding. Therefore, the NUH medical records should be complete on any serious GI lesions in these patients. However, in order to compare the occurrence of malignancies in patients on warfarin with bleeding detected by our CBC screening and in those on warfarin not developing anemia, all patients on warfarin monitored at our institution were also reviewed in the central Icelandic Cancer registry after the study period.

*Endpoints*

The primary endpoint of the study was the occurrence of a malignancy or a pre-malignant condition in the GI tract detected based on new anemia. The secondary endpoints were other bleeding lesions such as an otherwise asymptomatic ulcer or angiodysplasia. The total duration of treatment with warfarin was calculated (treatment years) in order to analyze the number of patients needed to screen with CBC in order to find a significant lesion.

*Statistics*

The results are expressed as means and range and percentage as appropriate. The proportion of patients with a colorectal and esophageal malignancy detected in the group of patients who developed anemia on warfarin and those who did not was compared with a Chi-square test.