

Original Article

Discontinuation of warfarin prior to elective invasive procedures

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Dan Med J 2025;72(7):A01250048. doi: 10.61409/A01250048

ABSTRACT

INTRODUCTION. Patients on warfarin are normally required to interrupt treatment for a fixed number of days prior to an invasive procedure. This study aimed to investigate the potential influence of the warfarin maintenance dose and the initial international normalised ratio (INR) level on the duration of the break required to achieve the planned target INR.

METHODS. A total of 120 patients on self-managed warfarin treatment measured INR once daily for five days before the intervention and were guided by the anticoagulation clinic on when to discontinue warfarin. Depending on the bleeding risk of the planned intervention, the target INR on the day of the intervention was ≤ 1.4 , ≤ 2.5 or ≤ 3.0 .

RESULTS. From day 1 to day 5 after interruption of warfarin, the INR ratio ($\text{INR}_{\text{day}x}/\text{INR}_{\text{day}0}$) decreased exponentially, with wide interpatient variation in the rate of decrease. Patients with a maintenance warfarin dose < 25 mg/week decreased significantly less in INR during the first day after stopping warfarin than patients who received a higher maintenance dose (9% vs 15%; $p < 0.04$). The INR half-life after day 1 was 113 hours for patients receiving < 25 mg/week and 101 hours for patients receiving ≥ 25 mg/week.

CONCLUSIONS. The duration of pre-interventional discontinuation of warfarin can be individualised by knowing the maintenance dose, baseline INR and target INR for the planned procedure.

FUNDING. None.

TRIAL REGISTRATION. Quality assessment study approved by the legal department of the Capital Region of Denmark. Approval number: p-2024-15914.

Although warfarin has been used for decades, pre-interventional downregulation of the international normalised ratio (INR) still causes problems [1]. The decrease in INR after pausing warfarin typically takes longer in those with an initial high INR and patients on a low maintenance dose due to factors such as advanced age, decompensated congestive heart failure, active malignancy, CYP2C9 and VKORC1 genotype or interacting comedication [2-6]. One way to overcome the uncertainty as to the rate of decline in INR is to discontinue warfarin for a week or more preoperatively. However, long-term warfarin interruption exposes patients to an unnecessarily high risk of thromboembolic events [7]. Heparin bridging has been proposed to reduce the risk of thrombosis. However, cohort studies, randomised trials and meta-analyses have shown that heparin bridging increases the perioperative incidence of major bleeding without reducing the risk of thrombosis [8, 9].

The interval without anticoagulation therapy should be as short as possible, and the risk of thromboembolic events should be balanced against the risk of bleeding [10]. Many procedures can be performed with a moderately downregulated INR (1.5-2.5), and some procedures can be performed with INR in the therapeutic

range (Table 1) [11-14].

TABLE 1 Risk stratification for procedural bleeding risk. Modified from [14].

Bleeding risk	Suggested pre-interventional INR	Procedures ^a
Minimal	≤ 3.0	Minor dental procedures: dental extractions, restorations, prosthetics, endodontics + dental cleanings, fillings Minor dermatologic procedures: excision of basal and squamous cell skin cancers, actinic keratoses, premalignant or cancerous skin naevi Ophthalmological procedures: cataract Pacemaker or cardioverter-defibrillator device implantation
Low/moderate	≤ 2.5	Abdominal hernia repair Abdominal hysterectomy Arthroscopy Bronchoscopy ± biopsy Colonoscopy ± biopsy Coronary angiography Cutaneous/lymph node biopsies Epidural injections Foot/hand surgery Gastrointestinal endoscopy ± biopsy Haemorrhoidal surgery Laparoscopic cholecystectomy
High	≤ 1.4	Any major operation, procedure duration > 45 min. Bowel resection Cancer surgery, especially solid tumour resection Cardiac, intracranial, or spinal surgery Colonic polyp resection ERCP Major orthopaedic surgery, including shoulder replacement surgery Major surgery with extensive tissue injury Nephrectomy, kidney biopsy Neuraxial anaesthesia PEG placement Reconstructive plastic surgery Surgery in highly vascular organs: kidneys, liver, spleen Transurethral prostate resection, bladder resection, or tumour ablation Urologic or gastrointestinal surgery, especially anastomosis surgery

ERCP = endoscopic retrograde cholangiopancreatography; INR = international normalized ratio; PEG = percutaneous endoscopic gastrotomy.

a) Alphabetical order.

Various studies exist on the perioperative management of patients receiving warfarin therapy [1]. Most studies have focused on documenting the incidence of bleeding and thromboembolic complications after various interventions at different INR levels. There is, however, a paucity of studies on the decrease in INR after stopping warfarin [2, 15, 16].

Our study aimed to assess the importance of the maintenance dose of warfarin and the level of INR at warfarin discontinuation in achieving the planned target INR on the day of the invasive procedure.

Methods

Patients

Patients included in this retrospective, single-centre study were all on self-managed warfarin therapy. The study was conducted at the Centre of Excellence for Anticoagulant Treatment at Bispebjerg-Frederiksberg University Hospital, Denmark, which is the centre for training in self-management of vitamin K antagonist (VKA) treatment in the Capital Region of Denmark. From February 2020, patients were assisted by the Anticoagulation Clinic in planning warfarin discontinuation prior to planned invasive procedures. Once the date of a planned procedure was known, the patient was sent a form to record the warfarin dose and INR daily for the five days leading up to the procedure, along with instructions on when to discontinue warfarin. The pre-interventional INR target value and the INR level at which they should discontinue warfarin were determined by the physician on duty. On the day of the planned procedure, patients were required to bring their INR measurement results with them so that the interventionalist could assess whether the intervention could be conducted. Any bleeding or thrombosis within two months post-operatively was recorded. The project was approved as a quality assurance and development project by the health authorities of the Capital Region of Denmark, project number p-2024-15914.

Measurements

INR was determined by the patients on CoaguChek XS or CoaguChek INRange. During their education and at outpatient follow-up visits, all patients had their INR measured on a CoaguChek device compared to the INR measured in the hospital laboratory using an ACL TOP 500 from Instrumentation Laboratory or a Cobas t711 from Roche Diagnostics. None of the included patients had clinically significant differences in INR measured with the two methods. During admission for intervention, INR was measured in the hospital laboratory.

Statistics

The ratio between INR on days 1-5 after cessation of warfarin and INR on the day of cessation (day 0) was evaluated using exponential regression analysis in Microsoft Office Excel 2019. Normal distribution of each of the INR ratios ($\text{INR}_{\text{dayX}}/\text{INR}_{\text{day0}}$) was verified by the Kolmogorov-Smirnov test. The unpaired t-test was used to compare the rate of decline in INR after discontinuing warfarin in patients who had a maintenance dose of < 25 mg/week with patients who had a higher maintenance dose.

Trial registration: Quality assessment study approved by the legal department of the Capital Region of Denmark. Approval number: p-2024-15914.

Results

From February 2020 to February 2024, results were obtained from 120 patients. Patient demographics are shown in Table 2.

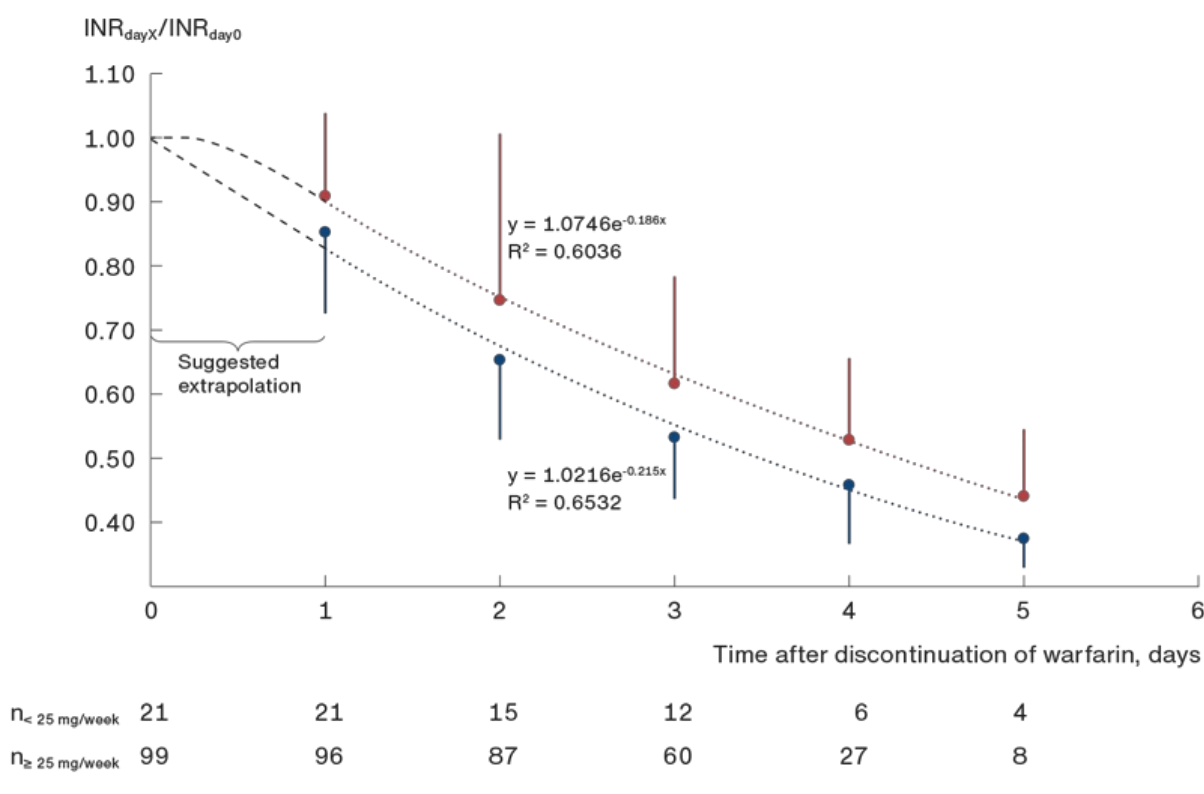
TABLE 2 Patient demographics.

	Warfarin maintenance dose		All
	< 25 mg/week	≥ 25 mg/week	
Patients, n	21	99	120
Sex, n (%)			
Male	13 (62)	63 (64)	76 (63)
Female	8 (38)	36 (36)	44 (37)
Age, mean (range), yrs			
Male	70 (50-86)	63 (32-87)	68 (32-87)
Female	61 (22-80)	67 (32-80)	63 (22-80)
Indication for anticoagulation, n (%)			
Mechanical heart valve	8 (38)	40 (40)	48 (40)
Venous thromboembolism	8 (38)	36 (36)	44 (37)
Atrial fibrillation	5 (24)	23 (23)	28 (23)
Therapeutic INR range, n (%)			
2.0-3.0	16 (76)	88 (89)	104 (87)
2.5-3.5	5 (24)	11 (11)	16 (13)
Warfarin weekly dose, median (IQR), mg			
Therapeutic INR range: 2.0-3.0	20 (17-22)	45 (32-53)	41 (27-53)
Therapeutic INR range: 2.5-3.5	20 (17-23)	48 (35-59)	35 (23-56)
INR at baseline, median (range)			
Planned target INR: ≤ 1.4	2.7 (1.9-3.9)	2.5 (1.7-3.5)	2.5 (1.7-3.9)
Planned target INR: ≤ 2.5	2.3 (1.6-2.8)	2.3 (1.5-3.1)	2.3 (1.5-3.1)
Planned target INR: ≤ 3.0	2.0 (1.9-2.6)	2.3 (2.1-2.4)	2.1 (1.9-2.6)
Planned target INR at intervention, n (%)			
≤ 1.4	10 (48)	61 (62)	71 (59)
≤ 2.5	8 (38)	34 (34)	42 (35)
≤ 3.0	3 (14)	4 (4)	7 (6)
Duration of warfarin pause, median (range), days			
Planned target INR: ≤ 1.4	4 (3-5)	3 (2-5)	4 (3-5)
Planned target INR: ≤ 2.5	3 (2-5)	2 (1-4)	3 (2-5)
Planned target INR: ≤ 3.0	2 (2-3)	2 (0-2)	3 (1-4)

INR = international normalized ratio; IQR = interquartile range.

The initial decline in INR from day 0 (first day without warfarin) to day 1 was significantly slower among patients with a maintenance dose < 25 mg/week (21/120 = 17.5%) than among patients with a higher maintenance dose (9% versus 15%, $p < 0.04$). From day 1 to day 5, the decrease in INR had an exponential course in both groups (Figure 1). From day 1 to day 5, the half-life of INR was 113 hours among patients with a maintenance dose <25 mg/week and 101 hours in patients with a higher maintenance dose. The 25 mg/week cut-off was defined post-hoc due to the few patients with a very low maintenance dose. None had a maintenance dose <10 mg/week.

FIGURE 1 Relative decrease in international normalised ratio (INR) from discontinuation of warfarin in patients with a maintenance dose < 25 mg/week (red) and ≥ 25 mg/week (blue). Number of patients, means and standard deviations (SD) are shown. SD is only shown one way to avoid overlap. The exponential regression lines and correlation coefficients were calculated using all data from day 1 to day 5 in both groups. Extrapolation of the regression lines suggests that patients on a maintenance dose < 25 mg/week have an initial slow INR decline.



The maintenance dose of warfarin decreased with age from an average of 50 mg/week among patients < 60 years to 38 mg/week in patients > 80 years of age ([Supplementary figure S1](#)). Only a few of the elderly patients received < 25 mg/week, and there was no significant correlation between age and INR decrease from day 0 to day 5. The INR at baseline, planned target INR levels and duration of pre-procedural warfarin pause are presented in Table 2.

All but two patients underwent the planned procedures. A colonoscopy was postponed because the doctor inexplicably required a five-day break from warfarin. The patient had only taken a three-day break, and the INR was 1.3. Another patient had an elective operation postponed for one week due to many emergency operations. All other procedures were performed, although the INR in 10/120 (8%) of the patients was higher than planned (median INR units above threshold: 0.2; range: 0.1-0.7). In all these cases, the target INR was ≤ 1.4. Major bleeding and clinically relevant non-major bleeding (according to the International Society on Thrombosis and Haemostasis definition [17]) occurred in five patients. One of the patients had mistakenly been assigned a target INR of < 3.0. ([Supplementary table S1](#)). None of the patients had post-operative thromboembolism.

[Tables S2 and S3 in the online-only data supplement](#) show a count of when the patients reached the target INR based on the baseline INR and the planned target INR. Based on these tables, we revised our estimate of when the target INR is likely to be achieved. All seven patients with a target INR ≤ 3.0 were already at the desired INR

level from day 0. **Table 3** shows our suggestions for individualised duration of pre-interventional warfarin interruption based on the maintenance dose, the initial INR and the planned target INR.

TABLE 3 Suggested duration of warfarin interruption to reach target INR. Add 1-2 days if the maintenance dose is < 25 mg/week. With the suggested number of days of pre-interventional warfarin discontinuation, approximately 95% of patients will reach INR target level or lower, while the remaining patients will be close to the target INR. If all patients were to reach the target INR or a lower level, a large number of patients would be exposed to an unnecessarily long break, thus increasing the risk of thrombosis unnecessarily.

Target INR	Initial INR	Pause, days
≤ 1.4	3.0-3.9	5
	2.0-2.9	4
	1.5-1.9	3
≤ 2.5 or ≤ 3.0	3.0-3.9	2
	2.0-2.9	1
	< 2.0	0

INR = international normalized ratio.

Discussion

Although warfarin has been used for decades, there is still no consensus on how the treatment should be downregulated prior to invasive procedures. Previously, it was recommended to reduce INR to below 1.5 for most procedures. Higher INR levels are now accepted for interventions with a moderate and low bleeding risk [11-13]. Since the risk of post-operative thromboembolism increases with the duration of the pre-interventional warfarin break, it is essential that the break is as short as possible [7, 10].

Discontinuation of warfarin before an invasive procedure is often based on fixed schedules, where the duration of the break is adjusted according to the risk of bleeding during and after the procedure, but without knowledge of the INR at the start of the break. Measuring INR 5-7 days rather than weeks before the planned intervention provides a safer assessment of how long the break should be. We therefore suggest that the duration of the break be adjusted according to the INR measured within a week before the intervention. The duration of the break is then decided based on the measured INR, the patient's maintenance dose and the planned target INR. The INR should always be measured again before the invasive procedure unless the bleeding risk is negligible.

We found that the initial decrease in INR after discontinuation of warfarin was significantly slower from day 0 to

day 1 in patients with a maintenance dose < 25 mg/week than in patients with a higher maintenance dose. After day 1, INR decreased exponentially with parallel-spaced regression lines for patients with maintenance doses ≥ 25 mg/week and < 25 mg/week. None of our patients had a maintenance dose < 10 mg/week. In patients with a very low maintenance dose, an even longer period of slow decline in the initial INR is likely. Further studies are warranted on the INR during pre-interventional warfarin interruption in patients with a low warfarin maintenance dose, as these patients are particularly at risk of having a target INR that is higher than planned.

Among previous studies of pre-interventional warfarin interruption, the study by White et al. is the most detailed and most frequently cited [15]. They measured INR in 22 patients on the day warfarin was withheld and again after 20, 65, 115 and 185 hours. They found that INR decreased exponentially during the period from 20 to 185 hours. They did not describe the change in INR during the first 20 hours but reported that the onset of maximal decrease began 24-36 hours after discontinuation of warfarin therapy. In our study, we found that a slow initial decline in INR was related to a low maintenance dose. A study of the decrease in INR after excessive anticoagulation with warfarin has also shown that the rate of decrease in INR depends on the maintenance dose [4]. White et al. reported that the mean half-life of INR was 0.9 ± 0.2 days, corresponding to 21.6 ± 4.8 hours. However, judging from the figure in the article showing INR versus duration of warfarin interruption, the half-life was approximately 100 hours, which corresponds to our findings. Furthermore, White et al. found that the INR decrease correlated inversely with the patients' age. We found no significant correlation between age and the decline in INR, likely because most of our elderly patients had a maintenance dose of > 25 mg/week.

In a study focusing on clinical factors influencing INR normalisation after stopping warfarin for six days before surgery, Schulman et al found that 14 of 202 patients (7%) had an INR value of 1.6 or higher on the day of surgery [2]. They found no influence of age on the duration of INR normalisation. Baseline INR was the only variable significantly associated with prolonged INR normalisation. The reason why they found baseline INR to be the all-important factor for INR normalisation may be that 15% of their patients had an INR > 3.0, against 8% among our patients.

Liang et al. investigated the preoperative INR level in 121 patients with mechanical heart valve prosthesis after warfarin interruption. A total of 54 patients paused for three days, 54 for 3-5 days and 13 for > 5 days [16]. They concluded that a three-day break was sufficient to achieve an INR < 1.5. However, it was the average INR (1.46) that was < 1.5. This means that approximately half of the patients had an INR level of ≥ 1.5 . The baseline INR and maintenance dose were not specified. Eight per cent of our patients with a target INR of < 1.5 did not reach the target on the day of intervention. The present study suggests that a four-day break is required to achieve an INR < 1.5 if the baseline INR is in the therapeutic range, and a five-day break if the baseline INR is 3.0-3.9.

Our study has some limitations. The study does not address whether the recommended upper INR thresholds for various interventions are optimal for lowering the risk of bleeding and thromboembolism. The aim was simply to describe the decrease in INR when stopping warfarin. All our patients were treated with warfarin. The results cannot be used to calculate the pre-interventional pause of other VKAs, as these have different pharmacokinetics.

All included patients were on self-managed warfarin treatment, which is typically associated with a more stable course of INR than clinic-managed treatment. With clinic-directed treatment, changes in INR from day 5-7 before the intervention to planned cessation of warfarin may therefore possibly be greater than recorded among our patients.

It has been suggested that an algorithm for determining the rate of decline in INR after stopping warfarin should include the patient's CYP2C9 genotype, because patients with the CYP2C9 variant alleles CYP2C9*2*2 or CYP2C9*2*3 are slow metabolisers and therefore decline in INR more slowly [18]. Slow warfarin metabolism is

also seen with polymorphisms of certain other genes [5, 19]. Characteristic of slow metabolisers due to e.g. genotype, heart failure, liver disease or cancer is that their maintenance dose of warfarin is lower than average. We observed that patients on a maintenance dose < 25 mg/week initially decreased INR more slowly than other patients. A very low maintenance dose is probably as good a marker for slow metabolisers as the investigation of genetic factors, but we cannot know, as genomic factors were not analysed in the present study.

The strength of our study is that the decrease in INR after warfarin discontinuation was investigated by daily INR measurements in a fairly large number of patients. The decrease in INR is expected to be similar in patients on clinic-managed treatment, and our guidelines for pre-interventional pause of warfarin can therefore also be used in clinic-managed patients on stable warfarin treatment. As none of our patients had an INR > 4.0 when stopping warfarin, our suggestions regarding the duration of pre-interventional warfarin discontinuation should be applied only in patients whose INR is below this level.

Conclusions

The optimal duration of the pre-interventional warfarin break depends on the baseline INR, the planned target INR and the patient's maintenance warfarin dose. A proposal for individualising the duration of pre-interventional discontinuation of warfarin was presented. Further studies are warranted to validate our findings.

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Accepted 12 May 2025

Published 26 June 2025

Conflicts of interest TSH reports financial support from or interest in BMS, Organon, Bayer. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. These are available together with the article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2025;72(7):A01250048

doi 10.61409/A01250048

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Supplementary material: <https://content.ugeskriftet.dk/sites/default/files/2025-05/a01250048-supplementary.pdf>

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