SUPPLEMENTAL MATERIAL
Supplemental Methods

Study design and data sources

This study was conducted using the ‘target trial’ principles. Briefly, we specified the protocol of a target trial (a hypothetical randomized experiment) to estimate the effectiveness and safety of NOAC vs. warfarin in atrial fibrillation patients with aortic stenosis and then attempted to emulate this trial using observational data from the Danish nationwide registries. This approach has the advantage of avoiding pitfalls that can occur when conducting comparative effectiveness analyses using observational data. The specifications of each component in the target trial and the emulated trial are provided in Table S1.

Longitudinal observational data from four Danish nationwide registries was used: i) The Danish Civil Registration System, which holds information on sex, date of birth, vital and emigration status of all persons living in Denmark, ii) the National Prescription Registry, which contains data on all prescriptions dispensed from Danish pharmacies, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System, iii) the Danish National Patient Registry, which has registered dates of hospital admissions and discharges, outpatient and emergency room contacts, and discharge diagnoses classified according to the 10th revision of the International Classification of Diseases (ICD) for more than 99% of hospital admissions in Denmark, iv) the Danish National Laboratory Register, which includes information on laboratory values from 4 out of 5 regions in Denmark. The Danish National Patient Registry also holds information about surgical procedures and clinical examinations coded according to the Danish version of the Nordic NOMESCO Classification of Surgical Procedure provided by the Danish Health Data Agency. Data from these registries were linked via a unique personal identification number, which is used across all Danish national registries.
Eligibility criteria

We identified patients in the Danish nationwide registries who met the target trial eligibility criteria (Table S1). The study population included patients with a diagnosis of both atrial fibrillation and aortic stenosis at baseline or within 30 days after baseline; both diagnoses could be primary or secondary diagnoses given during a hospital admission or at an outpatient clinic. To ensure that patients were eligible for stroke prevention with oral anticoagulant therapy according to contemporary guidelines,(28) a CHA2DS2-VASc score level threshold of ≥1 for males and ≥2 for females was also an eligibility criterion. The score is comprised of congestive heart failure, hypertension, age ≥75 years [doubled], diabetes mellitus, prior stroke/transient ischemic attack/systemic embolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65-74 years, sex category [female].

Patients with other indications for oral anticoagulant therapy were excluded, such as patients with a venous thromboembolism within the last year (or more than one previous diagnosis of venous thromboembolism) and patients undergoing knee/hip surgery within the last 3 months. Patients with potential contraindications for NOAC or warfarin treatment were excluded, including patients with mitral stenosis, any mechanical heart valve replacement, registered cancer diagnosis within the last 6 months (to reflect active cancer), or severe renal insufficiency (defined by creatinine clearance <15 mL/min, prior dialysis, or kidney transplantation). Patients with dispensation of both a NOAC and warfarin within the first 30 days after baseline were excluded. Lastly, only patients who were alive and event-free after the first month were included (see Figure 1 for a flowchart of the study population). See Table S2 for details on the definition of atrial fibrillation, aortic stenosis, contraindications, comorbidities, and co-medication.
**Outcomes**

The effectiveness outcome was a hospital diagnosis of ischemic stroke and/or systemic embolism defined as a composite endpoint of ‘thromboembolism’. Given the severity of the diagnosis of ischemic stroke/systemic embolism, we only considered events if the patient was admitted to the hospital. Additionally, we only considered primary diagnoses of thromboembolism. An event of ‘unspecified stroke’ was included as an outcome since outcome adjudication assessment was not performed and since most strokes coded as such are of ischemic origin. The safety outcome was a major bleeding leading to hospital admission (either intracranial bleeding, gastrointestinal bleeding, major or clinically relevant bleeding in other anatomic sites). We did not consider outpatient diagnoses for this outcome, but both primary and secondary inpatient diagnoses of major bleeding were included because of clinical coding practice. For both the effectiveness and safety outcomes, emergency room codes were not included due to a general low positive predictive value (see Table S2 for details about the definition of the outcomes).

**Follow-up period**

Each patient was followed up in the registries for the outcomes of interest. Follow-up started 30 days after treatment assignment (baseline) and ended at outcome diagnosis, death, administrative end of follow-up (3 years or December 2018), or emigration (loss to follow-up), whichever occurred first.

**Treatment strategies**

The Danish National Prescription Registry were used to identify patients who redeemed a first-time prescription for a NOAC (apixaban, dabigatran, rivaroxaban, or edoxaban) or warfarin between January 2013 and October 2018 (oral anticoagulation naïve users only). The date of first prescription
claim was used as the baseline date. Shift between NOAC agents and/or changes in dosage during follow-up were left to the treating physician’s discretion. Treatment groups were assumed exchangeable at baseline conditional on covariates that could confound the exposure-outcome association.

Causal contrasts

To compare the two treatment strategies, we estimated the intention-to-treat (ITT) effect and per-protocol (PP) effect.

Statistical analysis

The baseline characteristics of the study population were described according to treatment exposure category (NOAC or warfarin), using means and standard deviation for continuous variables, and proportions for categorical variables. The exposure category (i.e. NOAC or warfarin) of each patient was based on the prescription claim at the baseline date, and this category remained unchanged throughout the study duration.

Counterfactual outcomes were investigated at 3 years and data were arranged such that each patient-month was represented by a single row (maximum of 36 rows per individual, corresponding to 3 years). To account for the non-randomization of the treatment assignment, we derived stabilized inverse probability of treatment weights (IPTW). To compute these weights, we estimated the propensity of being assigned each treatment by a logistic regression including the following baseline confounding factors: age (as a restricted cubic spline) and dichotomous covariates on sex, heart failure, hypertension, diabetes, myocardial infarction, ischemic heart disease, renal disease, prior bleeding, prior thromboembolic event, diagnosis of atrial fibrillation within 60 days before or 30 days after the baseline date, diagnosis of aortic stenosis within 60 days before or 30 days after the baseline
date, valve surgery including bioprosthetic valve implantation within 60 days before or 30 days after
the baseline date, and use of statin or antiplatelet therapy within the last year.

The assessment of outcomes was based on an ITT approach and a PP approach (see details in the
following sections). When estimating the ITT treatment effects, treatment status remained unchanged
throughout follow-up disregarding actual treatment. When estimating the PP treatment effects,
continuous treatment status was assessed using a recommended daily dose and quantity of pills per
pack in each prescription (a 60-day grace period between each prescription claim was allowed). The
variable dose regimen of warfarin was modeled by continuous adaption of an (individual) estimated
daily dose. Patients were considered adherent to the initial treatment strategy (NOAC or warfarin)
unless a clinical event that fully or partly contraindicated treatment or had a major clinical impact on
the anticoagulant therapy strategy occurred. Such an event included primary diagnoses/codes for the
following diseases or procedures: chronic kidney disease or procedure code for dialysis, cancer, mitral
stenosis, procedure code for any mechanical heart valve replacement or any other valve surgery,
major bleeding (when investigating the thromboembolic outcome), or thromboembolism (when
investigating the major bleeding outcome). If such an event occurred, we stopped updating the
censoring weight for that patient, but kept the patient in the analysis. Statistical analyses were
performed using SAS 9.3 (SAS Institute) and Stata version 16 (StataCorp LP).

**Intention-to-treat analyses**

Pooled logistic regression models were used to estimate the average treatment effects by means of
hazard ratios (HRs) for the effectiveness and safety outcomes (with the warfarin group used as
reference). In detail, we derived odds ratios from pooled logistic regressions, which are
approximations of HRs when the outcome investigated is rare in all time intervals.(29) The baseline
hazard rate function was estimated by a linear and a quadratic term of months of follow-up in the
study. In the adjusted analyses, the calculated IPTWs were applied in the weighted pooled logistic regression models. The risks of the effectiveness and safety (counterfactual) outcomes in both treatment groups were also estimated through the weighted pooled logistic regressions models with the additional inclusion of interaction terms on treatment exposure and time variables (in order to construct standardized event-free survival curves, which depict the estimated counterfactual event-free survival had every individual receiving either treatment).

**Per-protocol analyses**
For the PP analyses, a similar approach was used as in the ITT approach with the addition of administratively censoring follow-up if/when subjects deviated from their initial treatment. Because this censoring may be informative if post-baseline time-varying prognostic factors are not included into the analytic strategy, we calculated stabilized inverse probability of censoring weights to account for the dependence between measured post-baseline time-varying prognostic factors and censoring.(30) To compute these weights, we estimated the propensity of being censored by a logistic regression including post-baseline time-varying prognostic factors (heart failure, hypertension, diabetes, ischemic heart disease, myocardial infarction, and use of statin or antiplatelet therapy (all included as dichotomous covariates)) for each patient month. The calculated weights to account for this censoring process were multiplied by the IPTWs of baseline confounding factors and applied in the weighted pooled logistic regression models to estimate the PP treatment effects. Similarly, as in the ITT approach, the per-protocol standardized event-free survival curves were also estimated.

**Sub-analysis and sensitivity analyses**
Some patients had an aortic valve surgery/procedure before inclusion in the study, which may affect the treatments effects, especially if the surgery/procedure were performed close to the baseline date. Therefore, we performed a sub-analysis in which we restricted the population to the following
subpopulations and repeated the main analyses: i) those who had an aortic valve surgery/procedure within 60 days before or 30 days after baseline, ii) those who had an aortic valve surgery/procedure at any time before or 30 days after baseline, and iii) those who never had an aortic valve surgery/procedure.

Two sensitivity analyses were performed to investigate the robustness of the analytical strategy in the main analyses. In the PP analysis, a grace period of 60 days was allowed. However, we performed a sensitivity analysis in which we changed the assessment of continuous treatment status by allowing a grace period of 90 days as treatment gap. Additionally, two ‘falsification outcomes’ were examined, which were expected to have a null association with the exposure. In detail, we emulated an individual target trial with pneumonia as the outcome and an individual target trial with cancer as the outcome using the described features from the ITT analyses.
Table S1. Specifications of the target trial and the emulated trial using observational data.

| Protocol component | Target trial specifications | Emulated trial specifications |
|--------------------|-----------------------------|-------------------------------|
| **Eligibility criteria** | Diagnosis of both atrial fibrillation and aortic stenosis.  
Age ≥18 years.  
A CHA2DS2-VASc score ≥1 for males, and ≥2 for females.  
No previous prescription of oral anticoagulants (oral anticoagulant naïve participants).  
No other indications for oral anticoagulant treatment, including:  
  - A diagnosis of venous thromboembolism within the last year or several diagnoses at earlier times.  
  - Knee or hip procedure within last three months.  
Potential contraindications for NOAC treatment, including:  
  - Diagnosis of mitral stenosis or heart valve replacement.  
  - Cancer diagnosis within last 6 months.  
  - Renal insufficiency defined as creatinine clearance <15 mL/min, prior dialysis, or kidney transplantation. | Same as for target trial with the following specifications:  
Residents of Denmark for at least 1 year and with valid identifier information between January 2013 and October 2018.  
Diagnosis of atrial fibrillation before first prescription claim or up to 30 days later (using ICD-10 codes, both primary and secondary diagnoses given during hospitalization or in outpatient clinics) [see Table S2 for details].  
Diagnosis of aortic stenosis before first prescription claim or up to 30 days later (using ICD-10 codes, both primary and secondary diagnoses given during hospitalization or in outpatient clinics) [see Table S2 for details].  
Exclude participants with dispensation of both a NOAC and warfarin within the first 30 days after baseline.  
Other indications for oral anticoagulant treatment or potential contraindications were defined on the basis of recorded ICD-10 codes or procedure codes [see Table S2 for details]. |
| **Treatment strategies** | 1. Initiation of warfarin  
2. Initiation of a NOAC (apixaban, edoxaban, dabigatran, or rivaroxaban)  
The treatment strategy allows for shift in NOAC agent or dosage after initial assignment (left to physician’s discretion).  
Patients were considered adherent to the initial treatment strategy unless a clinical event that fully or partly | First prescription claim of either:  
warfarin (ATC: B01AA) or NOAC (ATC: B01AE07; B01AF01; B01AF02; or B01AF03).  
Shift between NOAC agents or dosage during follow-up was allowed.  
Same accepted reasons for treatment non-adherence as in target trial (using ICD-10 codes or procedure codes to identify these deviations) [see Table S2 for details]. |
contraindicated treatment or had a major clinical impact on the anticoagulant therapy strategy occurred, including:

- Development of chronic kidney disease or need for dialysis.
- Primary diagnosis of cancer.
- Diagnosis of mitral stenosis.
- Mechanical heart valve replacement.
- Any valve-related operation.
- Major bleeding (for the effectiveness outcome).
- Thromboembolism (for the safety outcome).

| Assignment procedure | Study participants were randomly assigned to receive either warfarin or a NOAC. The participants and investigators were aware of the treatment (no blinding). |
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Follow-up            | For each participant, follow-up started at treatment assignment and ended at diagnosis of outcome, death, administrative end of follow-up (3 years or December 2018), or emigration (loss to follow-up), whichever occurred first. |
| Outcomes definitions | Effectiveness outcome: A diagnosis of ischemic stroke and/or systemic embolism defined as a composite endpoint of ‘thromboembolism’ leading to a hospital admission. Safety outcome: A diagnosis of major bleeding (either intracranial bleeding, gastrointestinal bleeding, and major or clinically relevant bleeding in other anatomic sites) leading to a hospital admission. |

The exposure category (i.e. NOAC or warfarin) of each study participant was based on first prescription claim during the study period, and this category remained unchanged throughout the study duration.

Randomization was emulated by estimating stabilized inverse probability of treatment weights to adjust for pre-baseline prognostic factors [see details in Statistical methods].

Same as for the target trial, but follow-up started at prescription claim using ATC codes. Information of follow-up were obtained from the registries.

Same as for target trial with the following specifications:

Outcomes were defined by records of ICD-10 codes [see Table S2 for details].

Given the severity of the diagnosis of ischemic stroke/systemic embolism, an event was only considered if the participant was admitted to the hospital. Additionally, only a primary diagnosis of thromboembolism was considered. An event of ‘unspecified stroke’ was included as an outcome since outcome adjudication assessment was not performed.

A major bleeding event was only considered if the participant was admitted to the
hospital; thus, outpatient diagnosis of a major bleeding event was not included, but both primary and secondary diagnoses of major bleeding were included due to clinical coding practice. For both outcomes, emergency room codes were not included due to a general low positive predictive value.

| Causal contrasts | Intention-to-treat effect and per-protocol effect. | Average treatment effect in the population estimated with observational analogue of the intention-to-treat effect and per-protocol effect. |
|------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| Statistical analyses | Estimation of the intention-to-treat effect comparing risk of the outcomes among participants assigned to NOAC vs. risk of the outcomes among participants assigned to warfarin. Estimation of the per-protocol effect with censoring of participants if/when they deviate from their assigned treatment strategy, unless a clinical event that fully or partly contraindicated treatment or had a major clinical impact on the anticoagulant therapy strategy occurred. Stabilized inverse probability of censoring weights was used to adjust for post-baseline time-varying prognostic factors associated with treatment adherence to avoid potential selection bias from informative censoring. | Same intention-to-treat and per-protocol effect analyses as for the target trial. However, the analyses only included participants who were alive and outcome-free 30 days after baseline due to data setup. In both the intention-to-treat and per-protocol analyses, stabilized inverse probability of treatment weights were used to adjust for pre-baseline prognostic factors. When estimating the per-protocol treatment effects, continuous treatment status was assessed using a recommended daily dose and quantity of pills per pack in each prescription (a 60 days grace period between each prescription claim was allowed). If an event with a major clinical impact on the anticoagulant therapy strategy occurred, we stopped updating the censoring weight for that patient, but kept the patient in the analysis. |
Table S2. ICD-codes, procedure codes, and ATC-codes used to define study population, interventions, contraindications, comorbidities, medical therapies, and outcomes.

| Variable definition            | Data source                      | ATC drug code* | Registry sources               |
|-------------------------------|----------------------------------|----------------|--------------------------------|
| **Comorbidities**             |                                  |                |                                |
| Atrial fibrillation           | Yes/no                           | I48            | Danish National Patient Registry|
| Aortic stenosis / Aortic valve surgery | Yes/no | DI350; DI352; DI060; DI062; DQ230; KFMD10; KFMD11; KFMD12A; KFMD14; KFMA00; KFMA10; KFMA20; KFMA32; KFMA32A; KFMA96 | | Danish National Patient Registry |
| Heart failure                 | Yes/no                           | I501; I509; I110; I130; I132; I420; I50 or | C03C and C09 | Danish National Patient Registry National Prescription Registry |
| Hypertension                  | Yes/no                           |                | Minimum 2 of: C02A; C02B; C02C; C02DA; C02L; C03A; C03B; C03D; C03EA; C03X; C07C; C07D; C08G; C09BA; C09DA; C09XA52; C02DB; C02DD; C02DG; C04; C05; C07; C07F; C08; C09BB; C09DB; C09 | National Prescription Registry |
| Diabetes mellitus             | Yes/no                           | E100; E101; E109; E110; E111; E119 or | A10 | Danish National Patient Registry National Prescription Registry |
| History of thromboembolism    | Yes/no                           | I63; I64; I74; |                                | Danish National Patient Registry |
| Vascular disease              | Yes/no                           | I21; I23; I700; I702-I709; I71; I739 | | Danish National Patient Registry |
| Ischemic heart disease        | Yes/no                           | I20; I21; I22; I23; I24; I25 | | Danish National Patient Registry |
| Myocardial infarction         | Yes/no                           | I21; I23 | | Danish National Patient Registry |
| Cancer                        | Yes/no                           | C | Internal Medicine and Surgery or | Danish National Patient Registry |
| Liver disease                 | Yes/no                           | B150; B160; B162; B190; K704; K72; K766; I85 | | Danish National Patient Registry |
| Condition                                      | Yes/no | ICD Codes                                                                 | Registry                        |
|-----------------------------------------------|--------|---------------------------------------------------------------------------|---------------------------------|
| Alcohol abuse                                 | Yes/no | E244; E529A; F10; G312; G621; G721; I426; K292; K70; K860; L278A; O354; T51; Z714; Z721 | Danish National Patient Registry |
| Chronic obstructive pulmonary disorder        | Yes/no | J40-J47; J60-J65; J67; J684; J701; J703; J841; J920; J921; J982; J983 | Danish National Patient Registry |
| Chronic kidney disease                        | Yes/no | I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61 | Danish National Patient Registry |
| Venous thromboembolism                        | Yes/no | I26; I801; I802; I803; I808; I809; I828; I829; I822; I823; O223; O229; O871; O879; O882 | Danish National Patient Registry |
| Mitral stenosis                               | Yes/no | I050; I052; I081A; I342; Q232 | Danish National Patient Registry |
| Total hip or knee arthroplasty                | Yes/no | KNGB; KNGC; KNGU; KNFB; KNFK; KNFU | Danish National Patient Registry |
| Coronary artery bypass graft                  | Yes/no | KFNA; KFNC; KFND; KFNE | Danish National Patient Registry |
| Percutaneous coronary intervention            | Yes/no | KFNG | Danish National Patient Registry |
| Bioprosthetic valve implantation              | Yes/no | KFMD10; KFKD10; KFJF10; KFGE10 | Danish National Patient Registry |
| Mechanical prosthetic valve implantation      | Yes/no | KFMD00; KFKD00; KFJF00; KFGE00 | Danish National Patient Registry |
| Kidney transplantation                        | Yes/no | KKAS00; KKAS10; KKAS20 | Danish National Patient Registry |
| **Outcomes**                                  |        |                                                                           |                                 |
| Thromboembolism                               | Yes/no | I63; I64; I74 | Danish National Patient Registry |
| Major bleeding (composite outcome)            | Yes/no | I60-I62; I690-I692; I850; I864A; K226; K228F; K250; K252; K254; K256; K260; K262; K264; K266; K270; K272; K274; K276; K280; K282; K284; K286; K290; K298A; K625; K638B; K638C; K661; K838F; K868G; K920; K921; K922; S063C; S064; S065; S066; S068B; S068D; S141C; S141D; S141E; S241D; S241E; S241F; S341D; S341E; S341F; E078B; E274B; G951A | Danish National Patient Registry |
| Condition                                      | Yes/no | Danish National Patient Registry |
|------------------------------------------------|--------|----------------------------------|
| Intracranial bleeding                           | Yes/no | I60-I62; I690-I692                |
| Gastrointestinal bleeding                       | Yes/no | I850; I864A; K226; K228F; K250; K252; K254; K256; K260; K262; K264; K266; K270; K272; K274; K276; K280; K282; K284; K286; K290; K298A; K625; K638B; K638C; K661; K838F; K868G; K920; K921; K922 |
| Major clinically relevant bleeding located elsewhe | Yes/no | S063C; S064; S065; S066; S068B; S068D; S141C; S141D; S141E; S241D; S241E; S241F; S341D; S341E; S341F; E078B; E274B; G951A; I312; I319A; I230; J942; M250; R04; S259A; S368A; S368B; S368D; T143C; T144A; D500; D62; D683; D698; D699; R58; T792A; T792B |

**Comedication**

| Medication                                                                 | BNF Code | National Prescription Registry |
|----------------------------------------------------------------------------|----------|--------------------------------|
| Warfarin                                                                   | B01AA03  |                                |
| Non-vitamin K antagonist oral anticoagulant (Dabigatran)                   | B01AE07  |                                |
| (Rivaroxaban)                                                              | B01AF01  |                                |
| (Apixaban)                                                                 | B01AF02  |                                |
| (Edoxaban)                                                                 | B01AF03  |                                |
| Aspirin                                                                    | B01AC06  |                                |
| Other antiplatelets (Thienopyridines)                                      | B01AC04; |                                |
| (Beta-blockers)                                                            | B01AC24; |                                |
| (Renin-angiotensin system inhibitors (ACEi/ARBs))                         | B01AC22  |                                |
| Renin-angiotensin system inhibitors (ACEi/ARBs)                            | C07      |                                |
| Other antiplatelets (Thienopyridines)                                      | C09      |                                |
| Medication Type                      | Drug Codes          | Source                        |
|-------------------------------------|---------------------|-------------------------------|
| Calcium channel blockers            | C07F; C08; C09BB;   | National Prescription        |
|                                     | C09DB               | Registry                      |
| Amiodarone                          | C01BD01             | National Prescription        |
|                                     |                     | Registry                      |
| Digoxin                             | C01AA05             | National Prescription        |
|                                     |                     | Registry                      |
| Non-loop diuretics                  | C02DA; C02L;       | National Prescription        |
|                                     | C03A; C03B; C03D;   | Registry                      |
|                                     | C03EA; C03X; C07C;  |                               |
|                                     | C07D; C09BA; C09DA; |                               |
|                                     | C09XA52             |                               |
| Loop diuretics                      | C03C; C03EB         | National Prescription        |
|                                     |                     | Registry                      |
| Non-steroidal anti-inflammatory     | M01AA; M01AB; M01  | National Prescription        |
| drugs                               | AC; M01AE; M01AG;   | Registry                      |
|                                     | M01AH; M01AX01      |                               |
| Statin                              | C10                 | National Prescription        |
|                                     |                     | Registry                      |

* Prescription data from 180 days before or 30 days after diagnosis of atrial fibrillation.
Table S3. Sub-analysis (participants with no prior aortic valve operation/procedure before baseline date): Treatment effects of NOAC vs. warfarin on thromboembolism and bleeding after 3 years of follow-up.

| Analytical strategy: | Intention-to-treat analysis | Per-protocol analysis |
|----------------------|----------------------------|----------------------|
|                      | Warfarin | NOAC | Warfarin | NOAC |
| **THROMBOEMBOLISM**  |           |      |           |      |
| Event count          | 23       | 71   | 12        | 56   |
| Estimated 3-years event-free survival, % | 96.4 | 92.6 | 97.6 | 93.0 |
| HR (95% CI)          | Ref.     | 2.10 (1.29-3.41) | Ref. | 2.41 (1.25-4.66) |
| **MAJOR BLEEDING**   |           |      |           |      |
| Event count          | 129      | 152  | 87        | 135  |
| Estimated 3-years event-free survival, % | 82.7 | 86.7 | 85.6 | 86.8 |
| HR (95% CI)          | Ref.     | 0.72 (0.56-0.91) | Ref. | 0.78 (0.59-1.04) |

Abbreviations: CI: Confidence interval, HR: Hazard ratio; NOAC: Non–vitamin K antagonist oral anticoagulant.

*Composite of intracranial bleeding, gastrointestinal bleeding, and major or clinically relevant bleeding in other anatomic sites.