Witt DM, et al. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. Arch Intern Med. 2012:[Published online Sept 17 2012].

Clinical question posed by this trial: For patients who sought hospital treatment for a GI bleed while taking warfarin, do the benefits of restarting warfarin outweigh the risks?

Methodology

Study design	Retrospective registry cohort
Biases	**Efforts to Minimize Them**
Confounding	Design • Restricted to warfarin users (in last 2 months) with GIB diagnosed in hospital Analysis • Multivariable regression adjustment of HRs including: propensity score, age, sex, CDS, indication for warfarin use, prior HF diagnosis, location of GIB, ICU admission, HTN, prior stroke dx, pre-GIB target INR, pre-GIB TTR, reception of LMWH, acute GIB treatment (blood transfusions) ○ **Propensity score**: Age; sex; CDS; indication for warfarin use; INR TTR; LOS; time since warfarin initiation; ASA dose; treated in ER only; ICU admission; reception of LMWH, FFP, vit K; hx HF, VTE, renal disease, HTN, DM, stroke, cancer & alcoholism
Allocation	• Propensity score in multivariable regression
Performance	• Multivariable regression
Misclassification	• Events identified by ICD-9 code had confirmed by objective evidence
Detection	Use of mortality as an outcome
Interviewer/ Observer	N/A
Attrition	Included only patients with continued HMO membership
Intervention	• Resume warfarin (median 4 days after GIB) • Or not
Outcomes	• **Death** ○ Death certificate & medical record review • **Thrombosis** • **Recurrent GI bleed**
Duration	90 days
Sensitivity analysis	• Analysis of time-to-death excluding patients who died ≤1 week of index GIB • Analysis of outcomes stratified by days of warfarin interruption (0, 1-7, 8-14, 15-90, not resumed) • Analysis of time-to-event excluding patients who did not interrupt warfarin & had index GIB at rectum-anus; all patients who did not interrupt warfarin • Analyses comparing who did/didn't experience a recurrent GIB & did/didn't die

Participants

Setting	Colorado, USA (2005-2008)
Eligibility criteria	• Kaiser Permanente Colorado (HMO) member 180 days prior to & 90 days after index GI bleed • Hospitalized or ER visit for GI bleed (index GIB) identified by ICD-9 code in clinical database • Outpatient purchase of warfarin in 60 days prior to index GIB (based on pharmacy database) • INR in the 60 days prior to the index GIB based on clinical pharmacy anticoagulation service database • No GIB diagnosis within 6 months prior to index GIB
Study size	442 patients (260 restarted warfarin, 182 didn't)
"Average" patient	• Male 50% • Thrombosis/bleed risk factors (based on ICD-9 code) ○ CHF 25% ○ HTN 55% ○ Diabetes <5% ○ Prior CVA 10% ○ Renal insufficiency 10% ○ Prior bleed – not reported ○ ASA use 45%; other antiplatelets, NSAIDs, corticosteroids not reported ○ Alcoholism 1% ○ Cancer <2% • Age mean 74 y • Indication for warfarin ○ Afib (median CHADS2 = 2) 50% ○ VTE 25% ○ Prosthetic heart valve 10% ○ Other 15% • % of INR in range in last 90 days 30% • Median INR on presentation = 3 • Location of bleed ○ Stomach-duodenum 30% ○ Colon 25% ○ Rectum-anus 15% ○ Others 10% ○ Not identified 20% • Treated in ER only 25% • Treated in ICU 30%

Patients who restarted warfarin were:
- Younger
- More likely to be using warfarin for a prosthetic heart valve
- Less likely to have HTN
- More likely to have index GIB be identified and in the rectum-anus
- Longer-term users of warfarin
- Less likely to be given fresh-frozen plasma and transfusions
- More likely to be treated in ER only & for a shorter length-of-stay
- More likely to be given LMWH

Results				
	Warfarin restarted (median 4 days)	Not restarted	Adjusted HR	NNT/NNH*
Death	5.8%	20.3%	0.31 (0.15-0.62)	8
Thrombosis	0.4%	5.5%	0.05 (0.01-0.58)	20
Recurrent GI bleed	10%	5.5%	1.32 (0.50-3.57)	18
				**Calculated by applying adjusted HR to control group rate*
• Of those who resumed warfarin, lowest risk of death if resumed between 15-90 days after the index GIB • No thrombotic events occurred within 7 days				

Major Limitations:

Methods

- Confounding – Did not adjust for smoking status, BMI, actual renal function (only assessed ICD-9 code), hepatic dysfunction, use of non-ASA antiplatelets, corticosteroid use, SSRI use, prior bleeding >6 months, new dx of malignancy following GIB
  - *Consequence: These factors may account for the apparent lower risk of mortality beyond CV mortality in the "resume" group*
- Allocation – Patients perceived to be at higher risk of recurrent GIB more likely to not resume warfarin, and patients perceived to be at higher risk of thrombosis more likely to resume warfarin
  - *Consequence: Underestimation of the increased risk of GIB and reduced risk of thrombosis with warfarin resumption*
- Detection bias – Patients who resume warfarin are likely to receive more thorough monitoring for recurrent GIB (and perhaps overall)
  - *Consequence: Overestimation of recurrent GIB risk in "resume" group*

Results

- Cause of death – Most deaths (34/37) were not attributable to thrombosis (3) or recurrent GIB (0); malignancy (11), infection (8)
  - *Consequence: Likely that there is still significant residual confounding leading to uncertainty of the estimate of mortality reduction with resumption of warfarin*

Generalizability

- Mean INR control was poor, with TTR ~30% in the 3 months prior to GIB
- Only includes patients with HMO coverage

Conclusions:

- In patients with GIB while on warfarin with low % of time at therapeutic INR, the risk of recurrent GIB does not appear to outweigh the benefits of lowering thrombotic events.
- Unmeasured confounding may account for some or all of the apparent mortality benefit found in this study.