


# **Gender Related Differences in Gastrointestinal Bleeding With Oral Anticoagulation in Atrial Fibrillation**

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# Background

- DOACs are characterized by a higher incidence of gastrointestinal bleeding and this may be different among males and females.
- There is uncertainty whether women are at higher risk of adverse events from oral anticoagulation with respect to men, although this evidence derives mostly from studies in the pre-DOAC era.
- Moreover, female patients were underrepresented in the DOAC pivotal trials.

# AIM of the study

- The aim of the study is to provide real-world evidence on gender differences in the gastrointestinal bleeding of DOACs and well-managed warfarin treatment.

# Methods

- Population-based retrospective study: data from regional health information systems including the drug prescription database and the regional inpatients register.
- Patients receiving oral anticoagulants, VKAs or DOACs, in the period July 1, 2013 to September 30, 2017 were enrolled.
- Study endpoint was gender difference for major GI bleeding with DOACs and VKAs.

# Results (I)

- 59880 patients with non-valvular AF.
- 15338 were on DOACs and 44542 on VKAs.
- Female population represented 51.8% of the DOACs group and 47.5% of the VKAs group.
- The mean age of the cohort was 77.8 for male and 80.3 for female in the DOACs group and 77.1 for male and 79.4 for female in the VKAs group.
- Most patients of both genders and among DOAC and VKA belonged to the 75-84 age group.
- HASBLED score was higher among female patients in both DOAC and VKAs group.

**Table 1.** Baseline Characteristics of the Cohort Stratified for Gender, Age and HASBED Score.

	DOACs			VKAs		
	Female, n = 8466	Male, n = 6872	<i>P</i> value*	Female, n = 22451	Male, n = 22091	<i>P</i> value*
Age groups, n (%)						
65-74 yrs	1,955 (23.1%)	2,373 (34.5%)	<i>P</i> < 0.01	5,766 (25.7%)	8,256 (37.4%)	<i>P</i> < 0.01
75-84 yrs	3,854 (45.5%)	3,138 (45.7%)		10,957 (48.8%)	10,540 (47.7%)	
85+ yrs	2,657 (31.4%)	1,361 (19.8%)		5728 (25.5%)	3295 (14.9%)	
HASBED						
1	1019 (12.0%)	928 (13.5%)	<i>P</i> < 0.01	2887 (12.9%)	3428 (15.5%)	<i>P</i> < 0.01
≥2	7447 (88.0%)	5944 (86.5%)		19564 (87.1%)	18663 (84.5%)	

\*Chi-squared test.

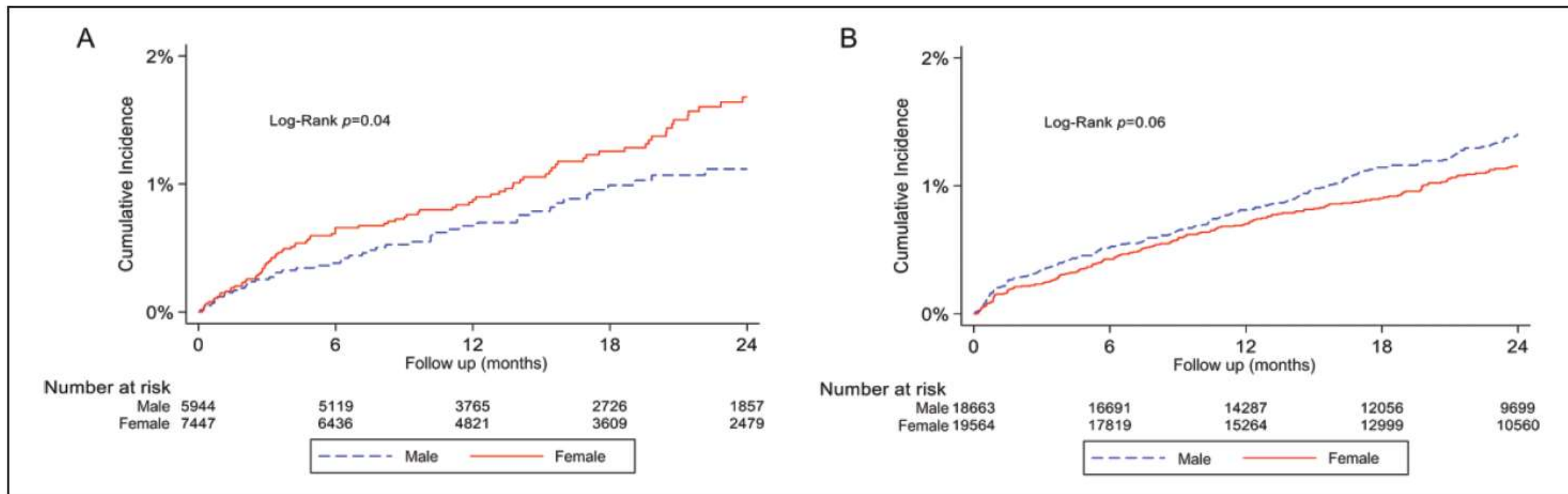
## Results (II)

- GI bleeding was more frequent among females as compared to males in DOAC users (0.90 per 100 patient-years vs 0.59 per 100 patient-years, HR 1.51, 95%CI 1.05- 2.19).
- This finding was statistically significant after adjustment for the variables correlated with the outcome at univariate analysis: HR 1.48, 95%CI 1.02-2.16.
- In the VKAs group, GI bleeding was more frequent among males as compared to females (0.61 per 100 patient-years vs 0.50 per 100 patient-years, HR 0.82, 95%CI 0.67-1.01), although the finding was not statistically significant.

**Table 2.** Cox Regression Analysis for Overall GI Bleeding in Female Compared With Male Patients: DOAC Group.

	Rate of GI bleeding (%)	HR (95%CI)	P value	Adjusted HR (95%CI)	P value
Gender					
Male	0.59	1.00		1.00	
Female	0.90	1.51 (1.05-2.19)	0.03	1.48 (1.02-2.16)	0.04
Age groups					
65-74	0.45	1.00		1.00	
74-84	0.73	1.61 (0.98-2.64)	0.06	1.47 (0.90-2.42)	0.121
>85	1.27	2.73 (1.66-5.56)	<0.01	2.28 (1.36-3.85)	0.01
Comorbidities					
History of GI disease	1.99	2.56 (1.19-5.50)	0.02	1.89 (0.87-4.09)	0.10
Congestive heart failure	1.14	1.87 (1.16-2.99)	0.01	1.46 (0.90-2.35)	0.11
Neoplastic disease	0.85	1.10 (0.61-1.95)	0.74		
Diabetes	0.64	0.80 (0.49-1.31)	0.39		
Hypertension	0.78	1.28 (0.70-2.32)	0.41		
Stroke	0.71	0.92 (0.61-1.38)	0.69		
History of bleeding	2.37	3.28 (2.64-7.30)	<0.01	3.27 (1.86-5.73)	<0.01
Myocardial infarction	2.03	2.77 (1.40-5.43)	<0.01	2.23 (1.12-4.43)	0.03
Peripheral artery disease	3.73	4.90 (2.39-10.0)	<0.01	4.63 (2.24-9.56)	<0.01
Renal disease	1.21	1.65 (0.67-4.04)	0.27		
Hepatic disease	1.87	2.45 (0.90-6.64)	0.08		
Medications					
Aspirin	0.67	0.85 (0.57-1.19)	0.30		
Clopidogrel	0.61	0.80 (0.37-1.72)	0.57		
NSAIDs	0.92	1.26 (0.82-1.93)	0.28		
PPI	0.77	1.02 (0.72-1.46)	0.87		





**Figure I.** Kaplan-Meier curves for overall GI bleeding in patients with HASBED  $\geq 2$  in DOAC (A) and VKA (B) users.

# Conclusions

- This study suggests that female patients treated with DOACs have a higher risk of GI bleeding versus male patients; this difference is not observed in VKA patients.
- When treated with DOACs, female patients with multiple comorbid conditions should be actively followed with frequent complete blood cell count and stool tests.
- While this study might help clinicians tailor their choice of anticoagulants in men and women, further studies exploring possible mechanisms and predictors are warranted.