Comparative Analysis of Coding Schemas for Assessing Major Bleeding Risk between Non-vitamin K Antagonist Oral Anticoagulants and Warfarin

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Background

- Observational studies frequently depend on diagnosis codes to assess the risk of major bleeding in clinical practice.
- However, the disparities in major bleeding risk observed across observational studies can be attributed to variances in study populations and data sources, **as well as variations in the methodologies employed to identify bleeding events.**

Study Objectives

To investigate how the utilization of different diagnosis coding schemas influences the assessment of major bleeding risk linked to non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin

Methods

- **Data source:** Taiwan's National Health Insurance Research Database between 2012 and 2019
- **Study design:** retrospective cohort study
- **Study population:** Patients diagnosed with atrial fibrillation who were newly prescribed NOACs or warfarin, with or without those who had a previous history of bleeding
- **Study outcomes:** Major bleeding events were identified by four different coding schemas (**Table 1**)[1,2,3]
  - Types of events include gastrointestinal bleeding (GIB), intracranial hemorrhage (ICH), and other major bleeding (OMB)
- **Statistical analysis:**
  - 1:1 propensity score matching to ensure covariate balance between comparison groups
  - Incidence rates were calculated, and Cox proportional hazards modeling was used to evaluate the risk of major bleeding between NOACs and warfarin

Table 1. Four coding schemas for identifying major bleeding events

	Different algorithms and the required diagnostic positions				
	Contents	Cunningham	Mini-Sentinel	Yao	
				Original	Modified
GIB	Shared diagnosis code	Primary	Primary	Primary/secondary	Primary
	Hemorrhoids	Primary	Primary		
	Gastric ulcer, duodenal ulcer, peptic ulcer or gastrojejunal ulcer	Primary but require bleeding indicator	Primary		
	Atrophic gastritis or diverticulosis of colon	Primary but require bleeding indicator			
ICH	Shared diagnosis code (Spontaneous ICH)	Primary	Primary/secondary	Primary/secondary	Primary
	Traumatic ICH (without open wound)		Primary/secondary	Primary/secondary	Primary
	Traumatic ICH (with open wound)			Primary/secondary	Primary
OMB	Shared diagnosis code	Primary	Primary	Primary/secondary	Primary
	Gross hematuria, epistaxis	Primary	Primary		
	Hemarthrosis		Primary	Primary/secondary	Primary
	Hemorrhage into bladder wall			Primary/secondary	Primary
	Anemia, abnormal coagulation profile, or excessive/frequent menstruation	Primary but require bleeding indicator			

Results

- After matching, both the NOAC and warfarin groups comprised 20,704 patients in the overall cohort, with 18,060 patients in the sub-cohort of those without a bleeding history (**Figure 1**).
- NOACs consistently showed significantly lower rates of all major bleeding and ICH compared to warfarin, while rates of GIB were similar between the treatment groups (**Figure 2A**).
- Risk estimates remained consistent when excluding patients with a bleeding history (**Figure 2B**).
- For ICH, focusing on the primary diagnosis or considering only spontaneous cases (excluding traumatic ICH) resulted in a greater risk reduction associated with NOAC (**Figure 3**).

Figure 1. Flow chart of patient selection

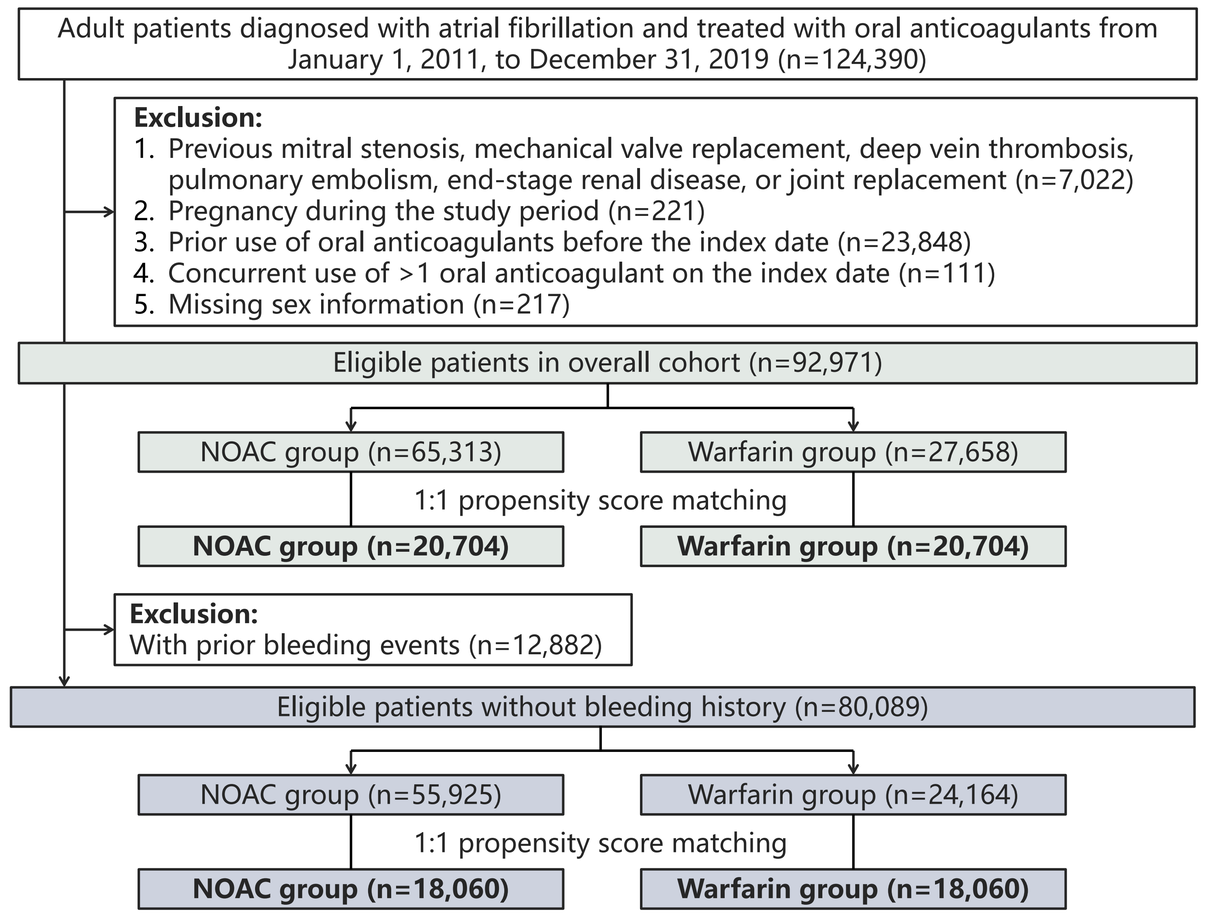
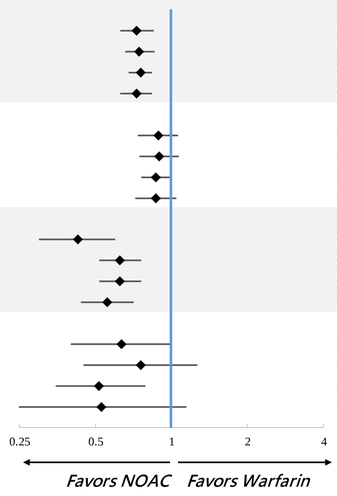


Figure 2. Major bleeding risk between NOACs and warfarin based on different coding schemas

A. Overall cohort (including those with a bleeding history)

	NOAC (n=20,704) Events	NOAC (n=20,704) Incidence rate	Warfarin (n=20,704) Events	Warfarin (n=20,704) Incidence rate	Hazard Ratio (95% CI)
All major bleeding					
Cunningham et al.	325	2.58 (2.31-2.88)	370	3.59 (3.24-3.98)	**0.73 (0.63-0.85)**
Mini-Sentinel dabigatran protocol	447	3.56 (3.24-3.91)	496	4.82 (4.42-5.27)	**0.75 (0.66-0.86)**
Yao et al. (Original - Primary/Secondary)	621	4.96 (4.58-5.37)	688	6.72 (6.23-7.24)	**0.76 (0.68-0.84)**
Yao et al. (Modified - Primary only)	347	2.75 (2.48-3.06)	398	3.86 (3.50-4.26)	**0.73 (0.63-0.84)**
Major gastrointestinal bleeding					
Cunningham et al.	244	1.93 (1.71-2.19)	230	2.23 (1.96-2.54)	0.89 (0.74-1.06)
Mini-Sentinel dabigatran protocol	242	1.92 (1.69-2.18)	226	2.19 (1.92-2.49)	0.90 (0.75-1.07)
Yao et al. (Original - Primary/Secondary)	414	3.29 (2.99-3.63)	400	3.89 (3.52-4.29)	0.87 (0.76-1.00)
Yao et al. (Modified - Primary only)	226	1.79 (1.57-2.04)	217	2.10 (1.84-2.40)	0.87 (0.72-1.05)
Major intracranial hemorrhage					
Cunningham et al.	51	0.40 (0.32-0.53)	99	0.95 (0.78-1.16)	**0.43 (0.30-0.60)**
Mini-Sentinel dabigatran protocol	182	1.44 (1.25-1.67)	243	2.35 (2.07-2.66)	**0.63 (0.52-0.76)**
Yao et al. (Original - Primary/Secondary)	182	1.44 (1.25-1.67)	243	2.35 (2.07-2.66)	**0.63 (0.52-0.76)**
Yao et al. (Modified - Primary only)	112	0.89 (0.74-1.07)	165	1.59 (1.37-1.86)	**0.56 (0.44-0.71)**
Other major bleeding					
Cunningham et al.	31	0.24 (0.17-0.35)	41	0.40 (0.29-0.54)	0.64 (0.40-1.01)
Mini-Sentinel dabigatran protocol	28	0.22 (0.15-0.32)	31	0.30 (0.21-0.43)	0.76 (0.45-1.27)
Yao et al. (Original - Primary/Secondary)	38	0.09 (0.05-0.16)	60	0.58 (0.45-0.75)	**0.52 (0.35-0.79)**
Yao et al. (Modified - Primary only)	11	0.30 (0.22-0.41)	17	0.16 (0.10-0.26)	0.53 (0.25-1.15)



B. Sub-cohort of patients without a bleeding history

	NOAC (n=18,060) Events	NOAC (n=18,060) Incidence rate	Warfarin (n=18,060) Events	Warfarin (n=18,060) Incidence rate	Hazard Ratio (95% CI)
All major bleeding					
Cunningham et al.	241	2.18 (1.92-2.48)	274	3.03 (2.69-3.41)	**0.73 (0.61-0.87)**
Mini-Sentinel dabigatran protocol	355	3.22 (2.90-3.58)	390	4.32 (3.91-4.78)	**0.76 (0.66-0.87)**
Yao et al. (Original - Primary/Secondary)	506	4.61 (4.25-5.03)	544	6.05 (5.56-6.59)	**0.78 (0.69-0.87)**
Yao et al. (Modified - Primary only)	268	2.43 (2.15-2.74)	306	3.39 (3.03-3.79)	**0.73 (0.62-0.86)**
Major gastrointestinal bleeding					
Cunningham et al.	185	1.67 (1.45-1.93)	164	1.81 (1.55-2.11)	0.94 (0.76-1.16)
Mini-Sentinel dabigatran protocol	185	1.67 (1.45-1.93)	162	1.79 (1.53-2.09)	0.95 (0.77-1.18)
Yao et al. (Original - Primary/Secondary)	322	2.92 (2.62-3.26)	296	3.28 (2.92-3.67)	0.92 (0.78-1.07)
Yao et al. (Modified - Primary only)	169	1.53 (1.31-1.78)	155	1.71 (1.46-2.00)	0.91 (0.73-1.13)
Major intracranial hemorrhage					
Cunningham et al.	40	0.36 (0.26-0.49)	78	0.86 (0.69-1.07)	**0.42 (0.29-0.62)**
Mini-Sentinel dabigatran protocol	157	1.42 (1.21-1.66)	206	2.27 (1.98-2.61)	**0.63 (0.52-0.78)**
Yao et al. (Original - Primary/Secondary)	157	1.42 (1.21-1.66)	206	2.27 (1.98-2.61)	**0.63 (0.52-0.78)**
Yao et al. (Modified - Primary only)	87	0.79 (0.64-0.97)	140	1.54 (1.31-1.82)	**0.51 (0.39-0.67)**
Other major bleeding					
Cunningham et al.	16	0.14 (0.09-0.24)	32	0.35 (0.25-0.50)	**0.41 (0.23-0.75)**
Mini-Sentinel dabigatran protocol	14	0.13 (0.07-0.21)	24	0.26 (0.18-0.39)	**0.48 (0.25-0.93)**
Yao et al. (Original - Primary/Secondary)	36	0.32 (0.23-0.45)	51	0.56 (0.43-0.74)	**0.56 (0.36-0.87)**
Yao et al. (Modified - Primary only)	12	0.11 (0.06-0.19)	12	0.13 (0.07-0.23)	0.82 (0.37-1.82)

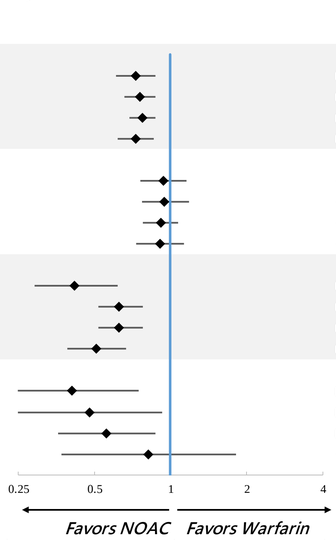
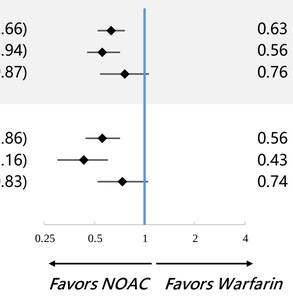


Figure 3. Effect of coding schema on major intracranial hemorrhage (ICH) risk comparison

	CUN	Mini-S	YAO	NOAC (n=20,704) Events	NOAC (n=20,704) Incidence rate	Warfarin (n=20,704) Events	Warfarin (n=20,704) Incidence rate	Hazard Ratio (95% CI)
Primary+secondary code								
Major intracranial hemorrhage (total)				182	1.44 (1.25-1.67)	243	2.35 (2.07-2.66)	0.63 (0.52-0.76)
Spontaneous ICH		V	V	116	0.92 (0.76-1.10)	173	1.67 (1.44-1.94)	0.56 (0.45-0.71)
Traumatic ICH (without open wound)		V	V	66	0.52 (0.41-0.66)	72	0.69 (0.55-0.87)	0.76 (0.54-1.06)
Traumatic ICH (with open wound)			V	0	0	0	0	-
Primary code only								
Major intracranial hemorrhage (total)				112	0.89 (0.74-1.07)	165	1.59 (1.37-1.86)	0.56 (0.44-0.71)
Spontaneous ICH	V			51	0.40 (0.31-0.53)	99	0.95 (0.78-1.16)	0.43 (0.30-0.60)
Traumatic ICH (without open wound)				61	0.48 (0.37-0.62)	68	0.66 (0.52-0.83)	0.74 (0.52-1.05)
Traumatic ICH (with open wound)				0	0	0	0	-



Conclusions

Different coding schemas had a marginal impact on the comparison of major bleeding between NOACs and warfarin, with the exception of ICH. Solely relying on the primary diagnosis and considering only spontaneous ICH yielded a more significant risk difference in favor of NOACs over warfarin.

References: 1. Go AS, Singer D, Cheetham TC, et al. Mini-Sentinel medical product assessment: a protocol for assessment of dabigatran. **2.** Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. J Am Heart Assoc. 2016;5(6). **3.** Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. Pharmacoepidemiol Drug Saf. 2011;20(6):560-566.