Decoding definitions of major bleeding in retrospective observational studies on direct oral anticoagulants for atrial fibrillation: A targeted literature review

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PURPOSE

- Major bleeding is an adverse event associated with using direct oral anticoagulants (DOACs) for prevention of stroke in patients with atrial fibrillation (AF)[1]
- Incidence rates of major bleeding vary between randomised controlled trials (RCTs) and real-world evidence (RWE) studies[2]
  - This may be attributable to inconsistent major bleeding definitions across RWE studies[3]
- RCTs commonly use the International Society on Thrombosis and Haemostasis (ISTH) major bleeding definition, including fatal bleeding, critical area/organ bleeding, bleeding requiring a blood transfusion of 2 or more units, and/or reductions in haemoglobin[4]
  - These parameters may be absent in RWE studies, leading to utilisation of proxy definitions; thus, the components used to define major bleeding in RWE studies remain unclear[2]
- The purpose of this study was to examine major bleeding definitions via a targeted literature review of retrospective observational studies on patients with AF receiving DOACs in routine clinical practice

METHODS

- Studies of patients with AF receiving DOACs published between 2012 and 2023 were identified using keywords and medical subject headings (MeSH) terms in PubMed, screened for inclusion by title and abstract, and subsequently screened by full text
- Data elements extracted and compared across articles included data source, DOACs received by patients, components of major bleeding definitions, and major bleeding incidence rates

RESULTS

- Of 328 articles screened, 42 retrospective observational studies were included in this analysis (**Figure 1**)
- The most common data sources were claims data (n = 24; 57%), followed by electronic medical records (n = 11; 26%) and registry data (n = 7; 17%)
- Sponsor types were industry (n = 16; 38%), nonindustry (n = 16; 38%), and no sponsor reported (n = 10; 24%)
- Of the 42 studies analyzed, 18 (43%) cited a reference for their definition of major bleeding, while the majority (n = 24; 57%) did not use any citation (**Figure 2A**)
- Regardless of whether the definition of major bleeding was cited or not, the leading definitions observed were ISTH (n = 7; 17%), Cunningham, et al (2011) (n = 4; 10%), or definitions derived from Cunningham, et al (2011) (n = 30; 71%) (**Figure 2B**)
  - The primary difference between the two leading definitions is that Cunningham, et al (2011) lacks fatal bleeding and blood transfusion elements
- Among articles that used Cunningham, et al (2011) or its adaptation (n = 34), 20 (59%) were from claims studies, 8 (23%) were from electronic heath record (EHR) studies, and 6 (18%) were from registry studies
- Major bleeding incidence rates varied across studies, reflecting differences in study populations and designs, with rates ranging from a minimum of 0.2 per 100 person-years to a maximum of 22.9 per 100 person-years
- Articles that investigated major bleeding among overall patients with AF were identified and summarised based on the primary definitions employed (**Figure 3**)
- From an operational perspective, many code lists for major bleeding events were uniquely tailored to each study and displayed marked variations when compared, despite sharing common definitions from ISTH or Cunningham, et al (2011) or its adaptations

This targeted literature review of RWE studies decoded proxy use of ISTH major bleeding definitions, highlighting an absence of key elements, such as mortality and the necessity for blood transfusion.

Major bleeding rates were slightly higher for studies that used the ISTH definition, suggesting further research is vital to assess the variation in major bleeding rates reported in RWE studies.

CONCLUSIONS

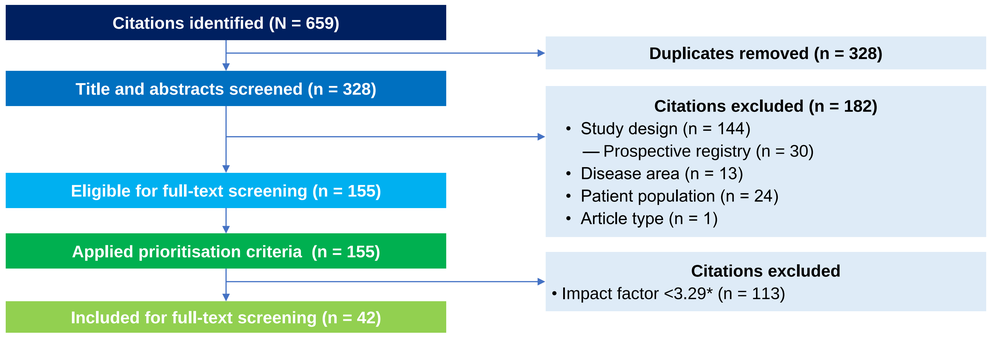
Mortality and the necessity for blood transfusion, which often serve as indicators of bleeding severity, were notably absent in study definitions of major bleeding among retrospective database studies

The most frequently adopted definitions apart from the ISTH, originated from Cunningham, et al (2011) or were adapted from it

The incidence of major bleeding was slightly higher when using the ISTH definition compared with that of Cunningham, et al (2011) or its adapted definitions across the overall AF population

FIGURES

Figure 1. Selection of analysed articles



*Since the top 20% of medical journals have an impact factor of 3.29 and above, journals with impact factors less than 3.29 were excluded from the study.[5]

Figure 2. Studies using cited or non-cited definitions of major bleeding (A) and the leading major bleeding definitions (B)

(B)

1. ISTH[4] (n = 7)

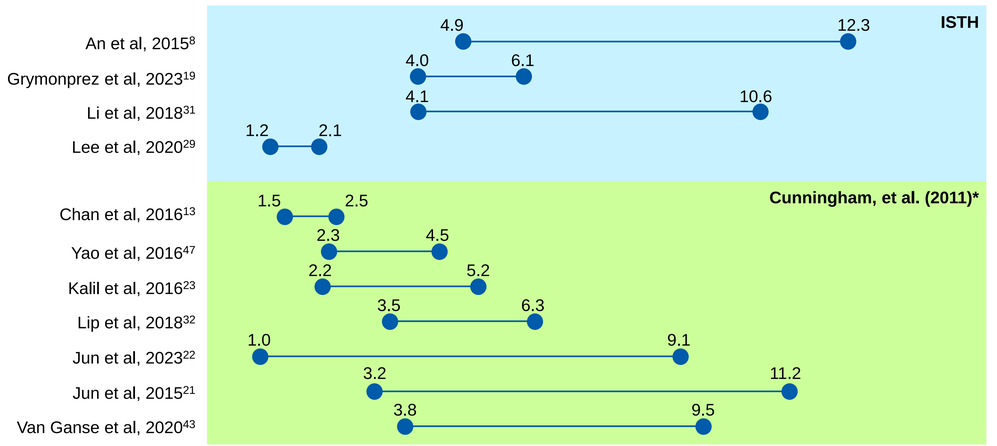
- Fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin levels of 1.24 mmol/L (20 g/L or greater) or more, or leading to a transfusion of 2 units or more of whole blood or red cells.

2. Cunningham, et al. (2011)[6] or its adaptation (n = 34)

- The definition identified inpatient stays with diagnoses and/or procedures that indicated the hospitalisation was related to a current episode of bleeding. We focused on hospitalisations because these are unambiguous and generally represent serious events. The types of serious bleeding events considered included gastrointestinal bleeding, haemorrhagic strokes and other intracranial bleeds, genitourinary bleeding, and bleeding at other sites (n = 4)
- Adaptive definitions derived from Cunningham et al:
  - Hospitalisation with intracranial, gastrointestinal, or other sites of bleeding (n = 19)
  - Hospitalisation with intracranial or gastrointestinal bleeding (n = 4)
  - Hospitalisation with intracranial or extracranial bleeding. Extracranial major bleeding was defined as bleeding with anaemia, haemothorax, haematuria, epistaxis, and bleeding in the eye (n = 2)
  - Hospitalisation with a code list (ICD codes) without specific sites being mentioned (n = 5)

*Studies using cited definition: references 8–11, 13, 14, 17–19, 28, 29, 31, 37, 39–40, 42–43, 46.
†Studies using non-cited definition: references 7, 12, 15–16, 20–27, 30, 32–36, 38, 41, 44–45, 47–48.
ICD, International Classification of Diseases; ISTH, International Society on Thrombosis and Haemostasis.

Figure 3. Minimum and maximum major bleeding incidence rates per 100 person-years with studies stratified by the definition used



*Including adaptations of Cunningham, et al. definition.
ISTH, International Society on Thrombosis and Haemostasis.

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DECLARATION OF INTEREST

RW, **CC**, **XY**, and **MU**: employees of Daiichi Sankyo, Inc.; **NS**: employee of HEORStrategies; **JWC**, **AS**, and **CW**: employees of PRECISIONheor; **RS**: employee of Daiichi Sankyo Europe GmbH; **PBN**: received consulting fees from Daiichi Sankyo, Inc. and grant support from Daiichi Sankyo Europe GmbH.