

Outcomes from gastrointestinal hemorrhage in oral anticoagulated patients with atrial fibrillation. is there a target for left atrial appendage closure?

Introduction

Atrial Fibrillation (AF) is the most frequent cardiac arrhythmia and its prevalence is even larger in older population. Patients with AF are at an increased risk of thromboembolic stroke with an average yearly risk of 5%.¹ AF related stroke is associated to woeful neurologic outcomes and duplicates the risk of death.² Current guidelines recommend antithrombotic therapy with Vitamin K antagonists (VKAs) or Novel Oral Anticoagulants (NOAC) to reduce the risk of stroke and death if the CHA₂DS₂-VASc score is more than 2 points.³ However, this treatment needs to be balanced against the risk of bleeding complications.

Gastrointestinal Bleeding (GIB) is the more frequent location of major or compromising vital status bleeding in anticoagulated patients and occurs up to 12% of cases.⁴ Obscure Gastrointestinal Bleeding (OGIB) includes all GIB's of unknown cause and that cannot be explained following full endoscopic and radiographic examinations.⁵ When GIB requires hospitalization its prognosis is ominous, with around 50% of bleedings considered major and associated with a rate of in-hospital mortality of 9.5%.⁶ The objective of the present study was to describe the outcomes and adverse events of AF-OGIB population in the ELIGIBLE (Efficacy of Left atrial appendage closure after Gastrointestinal Bleeding) Registry.

OGIB patients were screened to be included in the ELIGIBLE study (NCT01628068) to randomize left atrial appendage (LAA) closure versus medical management. In case they were excluded from the study, they were asked to join this Registry. Acute OGIB was defined as any bleeding manifested by hematemesis, melena, hematochezia or rectal bleeding and complete endoscopic and radiographic evaluation did not find any treatable source of bleeding. The Registry complies with Spanish data protection laws and has been approved by a central ethics board. Informed consent was signed by all participants. We retrospectively assessed the digital records of each patient to determine the occurrence of adverse clinical events and vital status. In case information was not available we contacted by telephone survey.

The characteristics of the study population and clinical presentation are reported in Table 1. A total of 89 patients were included in the Registry in 6 participant centers. Mean age was 82.5±6.4 years and 44 (49.4%) were women. The most common cardiovascular risk factor was high blood pressure and previous stroke in 76 (85%) and 16 patients (18%), respectively. The bleeding was located in the low GI tract in 55.3% and in the high GI tract in 44.7% of the patients. Mean hemoglobin and INR levels at admission were 9.9±2.8mg/dL and 2.37±1.33, respectively. Mean CHA₂DS₂-VASc score was 4.24±1.27 and mean HASBLED score was 3.9±0.96.

Table 1 Population demographics and clinical presentation

Population demographics	n=89
Age, mean ± SD	82.5±6.4
Female gender (n; %)	44 (49.4)

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High Blood Pressure (n; %)	76 (85.4)
Diabetes (n; %)	33 (37.1)
Dislipidemia (n; %)	40 (44.9)
Previous stroke (n; %)	16 (18)
Peripheral vascular disease (n; %)	14 (15.7)
Previous AMI (n; %)	19 (21.3)
Previous CABG (n; %)	13 (14.6)
Previous PTCA (n; %)	8 (9)
Clinical presentation	
GI Bleeding Origina (n; %)	
Low	47 (55.3)
High	38 (44.7)
Hemoglobin, mean±SD	9.9±2.8
Creatinine, mean±SD	1.17±0.6
Platelet count, mean±SD	227±77
INR, mean±SD	2.37±1.33
CHA ₂ DS ₂ score, mean±SD	4.24±1.27
HASBLED score, mean±SD	3.9±0.96
GFR <30%, mean±SD	5±5.6

SD, Standard Deviation; AMI, Acute Myocardial Infarction; CABG, Coronary Artery Bypass Graft; PTCA, Percutaneous Transluminal Coronary Angioplasty; GI, Gastro-intestinal; GFR, Glomerular Filtration Rate.

^aData only available in 85 patients.

Four patients (4.5%) died at the index hospitalization and 1 had a major stroke (1.2%). Thirty-five patients had a major bleeding and 36 required blood transfusions. Discharge treatment with acenocumarol was reported in 71.4% of the patients, Acetylsalicylic Acid (ASA) plus acenocumarol in 6%, ASA plus clopidogrel in 9.5%, ASA alone in 8.3%, clopidogrel alone in 3.3% and no antithrombotic treatment just in 1 patient. In a total of 77.1% patients, acenocumarol was restarted at discharge.

The in-hospital and follow-up outcomes are presented in Table 2. At 480±230 days follow up, a total of 17 patients (19.1%) died. From them 6 (6.7%) were classified as cardiovascular deaths. The non-cardiovascular deaths were because of fatal bleeding in 4 patients (4.4%), neoplasia in 3 patients (3.3%), infections in 2 cases (2.2%) and other complications in 2 patients.

Table 2 In-hospital and one-year follow-up outcomes

In-hospital outcomes	
Death (n; %)	4 (4.5)
Ischemic stroke (n; %)	1 (1.2)
Hemorrhagic stroke(n; %)	0
TIA (n; %)	0
Bleeding (n; %)	51 (57.3)
Fatal bleeding (n; %)	2 (2.2)
Major Bleeding (n; %)	35 (39.3)
Bleeding requiring transfusion (n; %)	36 (40.4)
Follow-up outcomes (480±230 Days)	
All-cause death (n; %)	17 (19.1)
Cardiovascular death (n; %)	6 (6.7)
Ischemic stroke (n; %)	2 (2.2)
Hemorrhagic stroke(n; %)	2 (2.2)
TIA (n; %)	2 (2.2)
GI Bleeding recurrences (n; %)	
1 recurrence	20 (22.5)
2 recurrences	10 (11.2)
3 recurrences	6 (6.7)
4 recurrences	3 (3.4)
Other site bleedings (n; %)	5 (5.6)

TIA, Transient Ischemic Attack; GI, gastro-intestinal

Six patients (6.6%) had neurological adverse events, 2 patients with ischemic stroke (while on treatment with clopidogrel and acenocumarol, respectively), two patients with hemorrhagic stroke (acenocumarol and clopidogrel, respectively) and 2 with transient ischemic attack (acenocumarol before and after event).

The recurrence of GIB was markedly high among all patients. Twenty (22.5%) of them had one recurrence, 10 (11.6%) had two recurrences, 6 (6.7%) patients had three recurrences and even in 3 (3.4%) patients a fourth recurrence was registered. Forty percent of patients required blood transfusions and more than half of them (52%) required hospitalization during follow-up. Besides, 5.6% of patients had other non GI-bleedings.

At the end of follow-up, 59.3% of patients remained treated with acenocumarol. Among the rest of them 12.8% and 4.7% were treated with AAS and clopidogrel, respectively and 23.3% where without any antithrombotic treatment.

The main findings of this analysis are:

- There is an important drop in patients receiving VKA's from the index bleeding event to the end of the follow-up.
- There is a 6.7% of neurological events in the follow-up.
- There is a high rate of OGIB recurrence in this population.
- There is also a high mortality rate, principally because of non-cardiovascular causes such as bleeding and cancer.

The mean CHA₂DS₂-VASc score of the study population was 4.2 meaning an adjusted stroke rate of 4% per year³ that in our population was lowered because oral anticoagulation was restarted in 77.1% of patients after the index OGIB event. At the end of follow-up this percentage reduced to 59.3%, meaning an 18% drop of VKA treatment in a high thromboembolic risk population. Even so, this was not reflected in the rate of neurological events.

The role of NOAC's such as dabigatran and rivaroxaban in this population it is limited since the rate of GI bleedings has been reported the same or even higher than traditional VKA's.⁷ In our registry only one patient was treated with dabigatran after a non-GI bleeding event.

The HASBLED score of this population was around 4, meaning 8.7 bleeds per 100 patients/year.³ The recurrence of GI bleeding was markedly high in accordance with previous reports of around 30% recurrences.^{8,9} This has clinical relevance since these episodes usually require hospitalizations, blood transfusions and are associated with impaired prognosis.

Percutaneous closure of LAA has proven effectiveness and safety reducing stroke rates in a randomized trial and observational studies.^{10,11} In this regard, we believe that this population could be a target for this minimally invasive procedure and this would reduce the rate of OGIB recurrence and the bleeding related deaths. This study has several limitations that we declare. The observational and retrospective nature of the analysis should be carefully interpreted as only hypothesis generator. Participation in this registry is voluntary, so we cannot rule out bias in patient selection due to unmeasured confounding variables. Events have been adjudicated by each investigator's center. Therefore, a certain degree of underreporting of events cannot be completely ruled out.

Conclusion

In conclusion, this study remarks that OGIB-AF patients have a high mortality in the follow-up and a markedly high bleeding recurrence. Since bleeding deaths and recurrences could be avoided without VKA anticoagulation, this population could be a target for percutaneous LAA closure. There is a mandatory need of randomized trials to confirm this hypothesis.

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