# Additional file

## Gastrointestinal Safety Profiles Differ Among Non–Vitamin K Antagonist Anticoagulants?

## Evidence from A Network Meta-analysis

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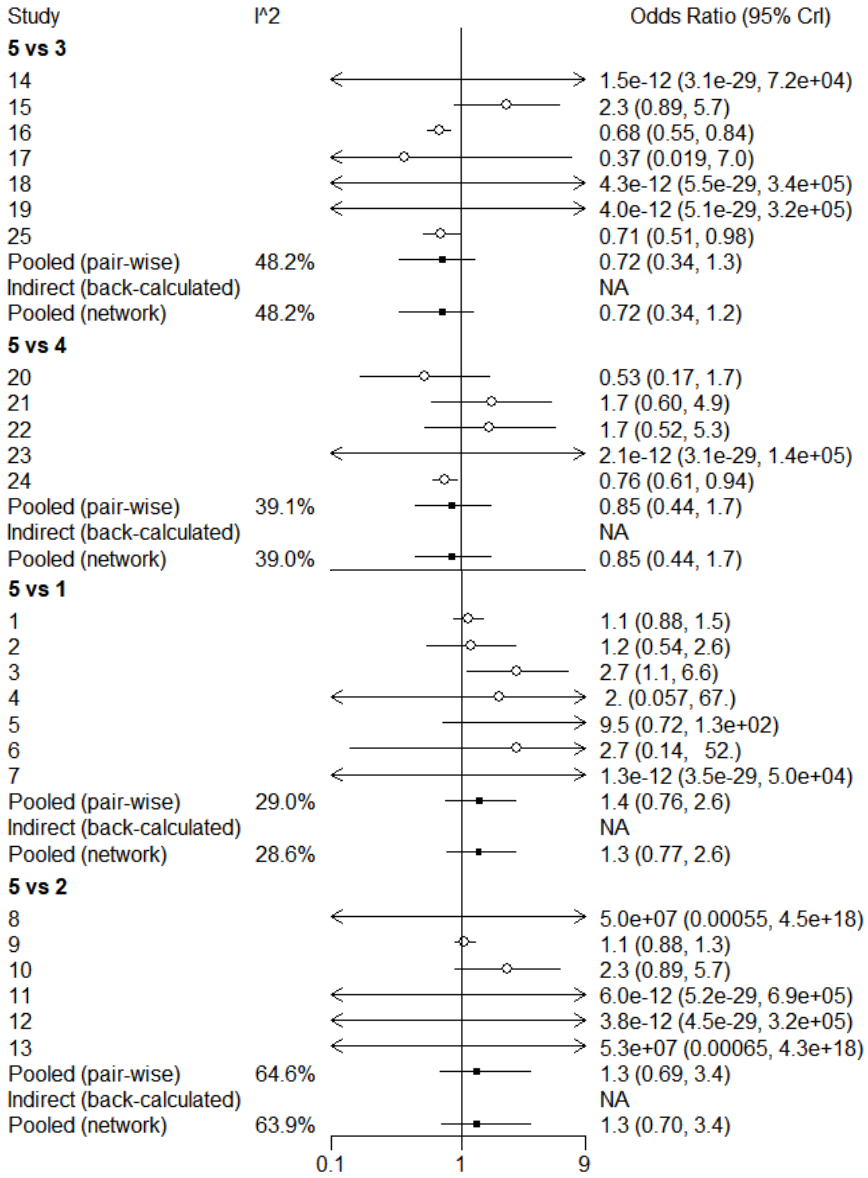
**Fig. S1.** Assessment of the risk of bias of the included studies.

**Fig. S2. The heterogeneity of the network meta-analysis.**




1=apixaban; 2=edoxaban; 3=rivaroxaban; 4=dabigatran; 5=conventional therapy

**Fig. S3. Comparison-adjusted funnel plots in the network meta-Analysis.**

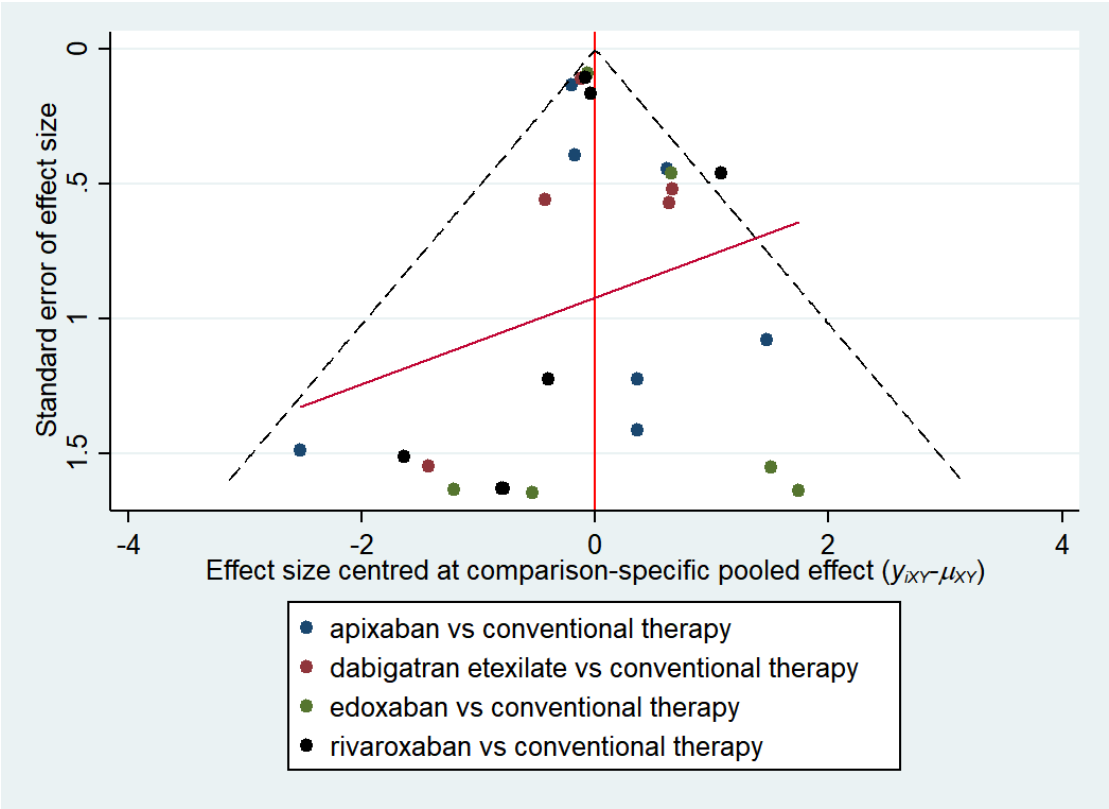


**Table S1. The definition of major bleeding.**

| Study | The criteria for bleeding | Definition of major bleeding |
|---|---|---|
| ADVANCE 2009 | ISTH | Major bleeding was defined as acute, clinically overt bleeding accompanied by one or more of the following events: a decrease in the hemoglobin level of 2 g per deciliter or more within a 24-hour period; a transfusion of 2 or more units of packed red cells; bleeding at a critical site (i.e., intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding); bleeding into the operated joint, requiring an additional operation or intervention; intramuscular bleeding with the compartment syndrome; or fatal bleeding. |
| ADVANCE-2 2010 | ISTH | acute clinically overt bleeding accompanied by one or more of the following: a decrease in blood haemoglobin concentration of 20 g/L or more during 24 h; transfusion of two or more units of packed red blood cells; critical site bleeding (including intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding); bleeding into the operated joint needing reoperation or intervention; intramuscular bleeding with compartment syndrome; or fatal bleeding |
| ADVANCE-3 2010 | ISTH | The definition of major bleeding was acute, clinically overt bleeding accompanied by one or more of the following findings: a decrease in the hemoglobin level of 2 g per deciliter or more over a 24-hour period; transfusion of 2 or more units of packed red cells; bleeding at a critical site (including intracranial, intraspinal, intraocular, pericardial, and retroperitoneal bleeding); bleeding into the operated joint, necessitating reoperation or intervention; intramuscular bleeding with the compartment syndrome; or fatal bleeding. |
| AMPLIFY 2013 | ISTH | Bleeding was defined as major if it was overt and associated with a decrease in the hemoglobin level of 2 g per deciliter or more, required the transfusion of 2 or more units of blood, occurred into a critical site, or contributed to death |
| AMPLIFY EXT 2013 | ISTH | Major bleeding was defined as overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to transfusion of 2 or more units of red cells, occurred in a critical site, or contributed to death |
| ARISTOTLE 2011 | ISTH | as clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g per deciliter or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death |

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| AVERROES 2011 | ISTH | defined as clinically overt bleeding accompanied by one or more of the following: a decrease in the hemoglobin level of 2 g per deciliter or more over a 24-hour period, transfusion of 2 or more units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding |
| RE-COVER 2009 | ISTH | Bleeding was defined as major if it was clinically overt and if it was associated with a fall in the hemoglobin level of at least 20 g per liter, resulted in the need for transfusion of 2 or more units of red cells, involved a critical site, or was fatal |
| RE-COVER II 2014 | ISTH | Bleeding was defined as major if it was clinically overt and if it was associated with a fall in the hemoglobin level of at least 20 g per liter, resulted in the need for transfusion of 2 or more units of red cells, involved a critical site, or was fatal |
| RE-MEDY 2013 | ISTH | Bleeding was defined as major if it was clinically overt and associated with a fall of the hemoglobin level of 20 g/L or required transfusion of at least 2 units of red cells or, involved a critical organ or was fatal |
| RE-SONATE 2013 | ISTH | Bleeding was defined as major if it was clinically overt and associated with a fall of the hemoglobin level of 20 g/L or required transfusion of at least 2 units of red cells or, involved a critical organ or was fatal |
| RELY 2009 | ISTH | Major bleeding was defined as a reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least 2 units of blood, symptomatic bleeding in a critical area or organ or falal blleding |
| Chung, et al 2011 | ISTH | Major bleeding was defined as overt if it was fatal, bleeding associated with ≥2 g/dl drop in haemoglobin, transfusion ≥800 ml of packed red blood cells or whole blood, and bleeding into a critical area or organ (retroperitoneal, intracranial, intraocular, intraspinal, intra-articular or pericardial or intramuscular with compartment syndrome) |
| ENGAGE-AF-TIMI 48 2013 | ISTH | Bleeding was defined as major if it was clinically overt and if it was associated with a fall in the hemoglobin level of at least 20 g per liter, resulted in the need for transfusion of 2 or more units of red cells, involved a critical site, or was fatal |
| Fuji, et al 2014 | ISTH | Major bleeding was defined as fatal bleeding, clinically overt bleeding accompanied by a decrease in hemoglobin of N2 g/dL, clinically overt bleeding requiring transfusion (excluding predonated autologous blood) with more than 4 units of blood (1 unit = approximately 200 mL), retroperitoneal bleeding, intracranial bleeding, intraocular bleeding or intrathecal bleeding, and bleeding requiring repeat surgery |
| Hakusai-VTE 2013 | ISTH | Bleeding was defined as major if it was overt and was associated with a decrease in hemoglobin of 2 g per deciliter or more or required a transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death |

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| STARS E-3 2014 | ISTH | Major bleeding was defined as fatal bleeding, clinically apparent bleeding with a decrease in haemoglobin of more than 2 g/dL, clinically apparent bleeding that requires transfusion of more than 4 units (1 unit = approximately 200 mL) of blood (excluding transfusion of stored autologous blood), retroperitoneal bleeding, intracranial bleeding, intraocular bleeding, or intrathaecal bleeding, or bleeding necessitating additional surgery |
| STARS J-V 2015 | ISTH | Major bleeding was defined as fatal bleeding; clinically overt bleeding accompanied by a decrease in hemoglobin of >2 g/dL; clinically overt bleeding requiring hemotransfusion with more than four units of blood (1 unit = approximately 200 mL); retroperitoneal, intracranial, intraocular, or intrathecal bleeding; or bleeding requiring repeat surgery |
| COMPASS 2017 | ISTH and consider bleeding that led to presentation to an acute care facility or hospitalization as major bleeding | fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalization (including presentation to an acute care facility without an overnight stay). All bleeding that led to presentation to an acute care facility or hospitalization also as major bleeding |
| EINSTEIN 2010 | ISTH | Bleeding was defined as major if it was clinically overt and associated with a fall in the hemoglobin level of 20 g per liter or more, or if it led to transfusion of two or more units of red cells, or if it was retroperitoneal, intracranial, occurred in a critical site, or contributed to death. |
| J-ROCKET AF 2012 | ISTH | Major bleeding was defined as clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), fall in hemoglobin concentration >2 g/dL, transfusion of >2 units of whole blood or packed red blood cells, or permanent disability |
| RECORD1 2008 | ISTH | Major bleeding was defined as bleeding that was fatal, occurred in a critical organ (e.g., retroperitoneal, intracranial, intraocular, and intraspinal bleeding), or required reoperation or extrasurgical-site bleeding that was clinically overt and was associated with a fall in the hemoglobin level of at least 2 g per deciliter or that required transfusion of 2 or more units of whole blood or packed cells |
| RECORD2 2008 | ISTH | Major bleeding was defined as bleeding that was fatal, was into a critical organ (eg, retroperi toneal, intracranial, intraocular, intraspinal), required re-operation, or clinically overt extra-surgical-site bleeding associated with a fall in haemoglobin of 20 g/L or more, calculated from the day 1 post-operative baseline value, or requiring infu sion of two or more units of whole blood or packed cells |

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|---|---|---|
| RECORD4 2009 | ISTH | Major bleeding was defi ned as clinically overt bleeding that was fatal, occurred in a critical organ (eg, retroperitoneal, intracranial, intraocular, or intraspinal), necessitated operation, was outside of the surgical site and associated with a fall in haemoglobin of 2 g/dL or more (calculated from the postoperative haemoglobin baseline value before the event), or required an infusion of two or more units of blood |
| ROCKET AF 2011 | ISTH | Major bleeding was defined as clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), fall in hemoglobin concentration >2 g/dL, transfusion of >2 units of whole blood or packed red blood cells, or permanent disability |

ISTH= International Society on Thrombosis and Haemostasis

**Table S2. The results of network meta-regression.**

| Variables | Interaction term |
|---|---|
| age group | -0.24(-0.72-0.31) |
| the proportion of male | 0.14(-0.40-0.79) |
| the indication for taking NOAC | 0.20(-0.24-0.61) |
| Follow-up time | 0.17(-0.35-0.62) |