Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2012. DOI: 10.1056/NEJMoa1207541

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about the AMPLIFY-EXT (Apixaban after the initial management of pulmonary embolism and deep vein thrombosis with first-line therapy – extended treatment; ClinicalTrials.gov number, NCT00633893) study.

Supplementary Appendix

Table of Contents

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INCLUSION AND EXCLUSION CRITERIA

1.1 Study Population

For entry into the study, the following criteria MUST be met.

1.1.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Subjects must be willing and able to give written informed consent.

2) Target Population

a) Subjects who have:

- an unprovoked index event OR a provoked index event with a risk for recurrence as described in the eligibility checklist.
- an objectively documented index event of symptomatic proximal DVT or symptomatic PE;

  (1) Symptomatic proximal DVT is defined as symptomatic DVT with evidence of proximal thrombosis that involves at least the popliteal vein or a more proximal vein, demonstrated by imaging with compression ultrasound (CUS), including grey-scale or color-coded Doppler, or ascending contrast venography.

  (2) Symptomatic PE with evidence of thrombosis demonstrated by imaging as follows:

  - an intraluminal filling defect in segmental or more proximal branches on spiral CT scan; or
  - an intraluminal filling defect or a sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram; or
  - a perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan (VPLS)

- completed approximately 6 to 12 months of standard anticoagulant therapy, or completed assigned CV185056 (AMPLIFY) study treatment, for the treatment of the index event; and
- no objectively documented symptomatic recurrence of VTE after the index event.

b) Subjects should be randomized within approximately 7 days of the last dose of their initial 6-to 12-month treatment. If a VKA was used as standard anticoagulant therapy,

then an INR must be documented as 2 or less before randomization. If the subject received CV185056 (AMPLIFY) study treatment, then a blinded INR must be documented as 2 or less before randomization.

Every attempt should be made to randomize subjects as soon as possible after discontinuation of their initial treatment.

The index DVT and/or PE will be adjudicated by the ICAC according to the adjudication manual. Investigators are encouraged to assemble and to submit imaging dossiers to the ICAC as soon as possible during the period that extends from the beginning of the screening period up to 2 weeks after randomization. Please refer to the diagnostic test manual for details regarding the assembly and submission of dossiers to the ICAC.

3) Age and Sex

a) Men and women, ages 18 years or greater.

Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months; or women on hormone replacement therapy [HRT] with documented serum follicle stimulating hormone [FSH] level >35 mIU/mL). Even women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g., vasectomy) should be considered to be of childbearing potential.

WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.

Women are considered surgically sterile only if they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy. Women are considered postmenopausal only if they have had amenorrhea for ≥12 consecutive months, or for

women on hormone replacement therapy (HRT), if they have a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL.

1.1.2 Exclusion Criteria

1) Sex and Reproductive Status

a) WOCBP who are **unwilling or unable** to use an acceptable method of birth control [such as oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides)] to avoid pregnancy for the entire study

b) Women who are pregnant or breastfeeding

c) Women with a positive pregnancy test on enrollment or prior to investigational product administration

2) Medical History and Concurrent Diseases

a) Subjects with a provoked index event without the existence of a persistent risk factor for recurrence as described in the eligibility checklist. .

b) More than 12 months of anticoagulation planned for the most recent DVT or PE (index event).

c) Subjects with indications for long-term treatment with a VKA, such as:

- Mechanical valve
- Atrial fibrillation or atrial flutter with moderate to high risk of systemic thromboembolism
- Multiple episodes of unprovoked DVT or PE
- Documented anti-phospholipid antibodies, anti-thrombin III deficiency, protein C deficiency, protein S deficiency, homozygous factor V Leiden, or homozygous prothrombin gene mutation.

d) Subjects with cancer who will be treated indefinitely with anticoagulation therapy;

e) The following chart lists examples of conditions for which serious bleeding may occur and the time of exclusion relative to the time of randomization.

Condition	Exclusion Relative to Time of Randomization			
	6 Months	1 Month	2 Weeks	Time of Randomization
Intracranial bleeding	X			
Intra-ocular bleeding	X			
Gastrointestinal bleeding and/or endoscopically verified ulcer disease	X			
Head trauma or other major trauma		X		
Major surgery		X		
Stroke of any type			X	
Neurosurgery			X	
Gross hematuria				X
Evidence of poor healing of a major wound or major trauma				X
Planned major surgery during trial				X
Intracranial neoplasm, arteriovenous malformation or aneurysm				X
Overt major bleeding (defined in Section 6.3.1)				X
Documented hemorrhagic tendencies or blood dyscrasias				X

f) Active and clinically significant liver disease (eg, hepatorenal syndrome);

g) Life expectancy <12 months;

h) Bacterial endocarditis;

i) Uncontrolled hypertension: systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg.

3) Physical and Laboratory Test Findings

a) Platelet count <100,000/mm^3;

b) Hemoglobin <9 g/dL;

c) Serum creatinine >2.5 mg/dL [221 umol/L];

d) Calculated creatinine clearance <25 ml/min (see Section 6.3.2.2.);

e) ALT or AST >2 times upper limit of normal;

f) Total bilirubin >1.5 times upper limit of normal (unless an alternative causative factor is identified [eg, Gilbert's syndrome]).

4) Prohibited Treatments and/or Therapies

a) Subjects requiring ASA >165 mg/day at randomization.

b) Subjects requiring dual anti-platelet therapy (such as ASA plus clopidogrel or ASA plus ticlopidine) at randomization. Subjects who transition from dual anti-platelet therapy to monotherapy prior to randomization will be eligible for the trial.

c) Subjects who have used any oral direct factor Xa inhibitor, any oral direct thrombin inhibitor, or any investigational antithrombotic agent during the period between the onset of the index event to randomization. Subjects who participated in the CV185056 (AMPLIFY) study may participate in this study and are exempt from this exclusion (see Section 5.7)

5) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

c) Receiving concurrent investigational agents or has received an investigational agent within the past 30 days prior to the first dose of study treatment (with the exception of approved medications being used for an approved indication, e.g., investigating a new dosing regimen for an approved indication).

Subjects who participated in the CV185056 (AMPLIFY) study may participate in this study and are exempt from this exclusion (see Section 5.7)

d) Any condition, which in the opinion of the investigator, would put the subject at an unacceptable risk from participating in the study; or

e) Any other medical, social, logistical, or psychological reason, which in the opinion of the investigator, would preclude compliance with, or successful completion of, the study protocol

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

OUTCOME DEFINITIONS

VENOUS THROMBOEMBOLISM (VTE)

Pulmonary embolism (PE)

Symptoms of PE with one of the following findings.

- A new intraluminal filling defect in (sub)segmental or more-proximal branches on spiral computed tomography (CT) of the chest.
- A new intraluminal filling defect, or an extension of an existing defect, or a new sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram.
- A new perfusion defect of at least 75% of a segment, with a local normal ventilation result (high probability) on ventilation/perfusion lung scintigraphy (VQ scan).
- Inconclusive spiral CT, pulmonary angiography, or VQ scan evidence of a new or recurrent PE, with demonstration of a new or recurrent deep vein thrombosis (DVT) in the lower extremities by compression ultrasound (CUS) or venography.

Deep vein thrombosis (DVT)

Symptoms of DVT with one of the following findings.

(a) For a NEW DVT:

- abnormal CUS, including grey-scale or color-coded Doppler, or
- an intraluminal filling defect on venography.

(b) For a RECURRENT DVT:

- abnormal CUS where compression had been normal or, if non-compressible during screening, a substantial increase (4 mm or more) in diameter of the thrombus during full compression, or
- an extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of veins in the presence of a sudden cut-off on venography.

DEATH

For all patients who died during the study, the cause of death was adjudicated to one of the following categories.

- VTE-related death

- PE (based on objective diagnostic testing, autopsy)
- Unexplained death (and VTE cannot be ruled out)
- Sudden death (and VTE cannot be ruled out).

- Cardiovascular (CV)-related death
  - Myocardial infarction (MI)
  - Stroke
  - Other CV event (to be specified).
- Other
  - Cancer
  - Bleeding
  - Infectious disease
  - Other known cause (to be specified).

ACUTE MYOCARDIAL INFARCTION

An acute MI was defined as the presence of at least two of the three following conditions.

- An appropriate clinical situation suggestive of an MI (e.g. abnormal history, physical examination, or new electrocardiogram changes).
- Elevation of CK-MB or troponin T or I ≥2 × upper limit of normal (ULN); if no CK-MB or troponin values are available, a total CK ≥2 × ULN.
- New, significant (≥0.04 seconds) Q waves in ≥2 contiguous leads.

If possible, confirmed acute MI was classified as ST-elevation MI or non-ST elevation MI.

STROKE

An acute stroke was defined as a new, focal neurologic deficit of sudden onset, lasting at least 24 hours, not due to a readily identifiable nonvascular cause (i.e. brain tumor, trauma). All strokes during the study were assessed by imaging or autopsy, and classified as primary hemorrhagic, non-hemorrhagic, infarction with hemorrhagic conversion, or unknown, as defined by the American College of Cardiology.

- Primary hemorrhagic: a stroke with documentation on imaging (e.g. CT scan or magnetic resonance imaging) of hemorrhage in the cerebral parenchyma, or a subdural or subarachnoid hemorrhage. Evidence of hemorrhagic stroke obtained from lumbar puncture, neurosurgery, or autopsy can also confirm the diagnosis.

- Non-hemorrhagic: a focal neurological deficit that results from a thrombus or embolus (and not due to hemorrhage) that appears and is still partially evident at 24 hours.
- Infarction with hemorrhagic conversion: no evidence of hemorrhage on an initial scan, but found on a subsequent scan.
- Unknown type/no imaging performed: the type of stroke could not be determined by imaging or other means (lumbar puncture, neurosurgery).

BLEEDING EVENTS

Major bleeding event

A major bleeding event was defined as a bleeding event (as per International Society on Thrombosis and Haemostasis guidelines), as follows.

- Acute clinically overt bleeding accompanied by one or more of the following.
  - A decrease in hemoglobin of 2 g/dl or more
  - A transfusion of 2 or more units of packed red blood cells
  - Bleeding that occurs in at least one of the following critical sites:
    - intracranial
    - intraspinal
    - intra-ocular (within the corpus of the eye; thus, a conjunctival bleed is not an intra-ocular bleed)
    - pericardial
    - intra-articular
    - intramuscular with compartment syndrome
    - retroperitoneal
  - bleeding that is fatal.

Clinically relevant non-major bleeding event

The definition of clinically relevant non-major bleeding was acute clinically overt bleeding that consists of:

- any bleeding compromising hemodynamics
- any bleeding leading to hospitalization
- subcutaneous hematoma larger than 25 cm^2, or 100 cm^2 if there was a traumatic cause
- intramuscular hematoma documented by ultrasonography

- epistaxis that lasted for more than 5 minutes, was repetitive (i.e. two or more episodes of bleeding more extensive than spots on a handkerchief within 24 hours), or led to an intervention (e.g. packing or electrocoagulation)
- gingival bleeding occurring spontaneously (i.e. unrelated to eating or tooth brushing) or lasting for more than 5 minutes
- hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after instrumentation (e.g. catheter placement or surgery) of the urogenital tract
- macroscopic gastrointestinal hemorrhage, including at least one episode of rectal blood loss, if more than a few spots on toilet paper
- hemoptysis, if more than a few speckles in the sputum and not occurring within the context of PE, or
    - any other bleeding type considered to have clinical consequences for a patient such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug, or associated with pain or impairment of activities of daily life.

Minor bleeding events

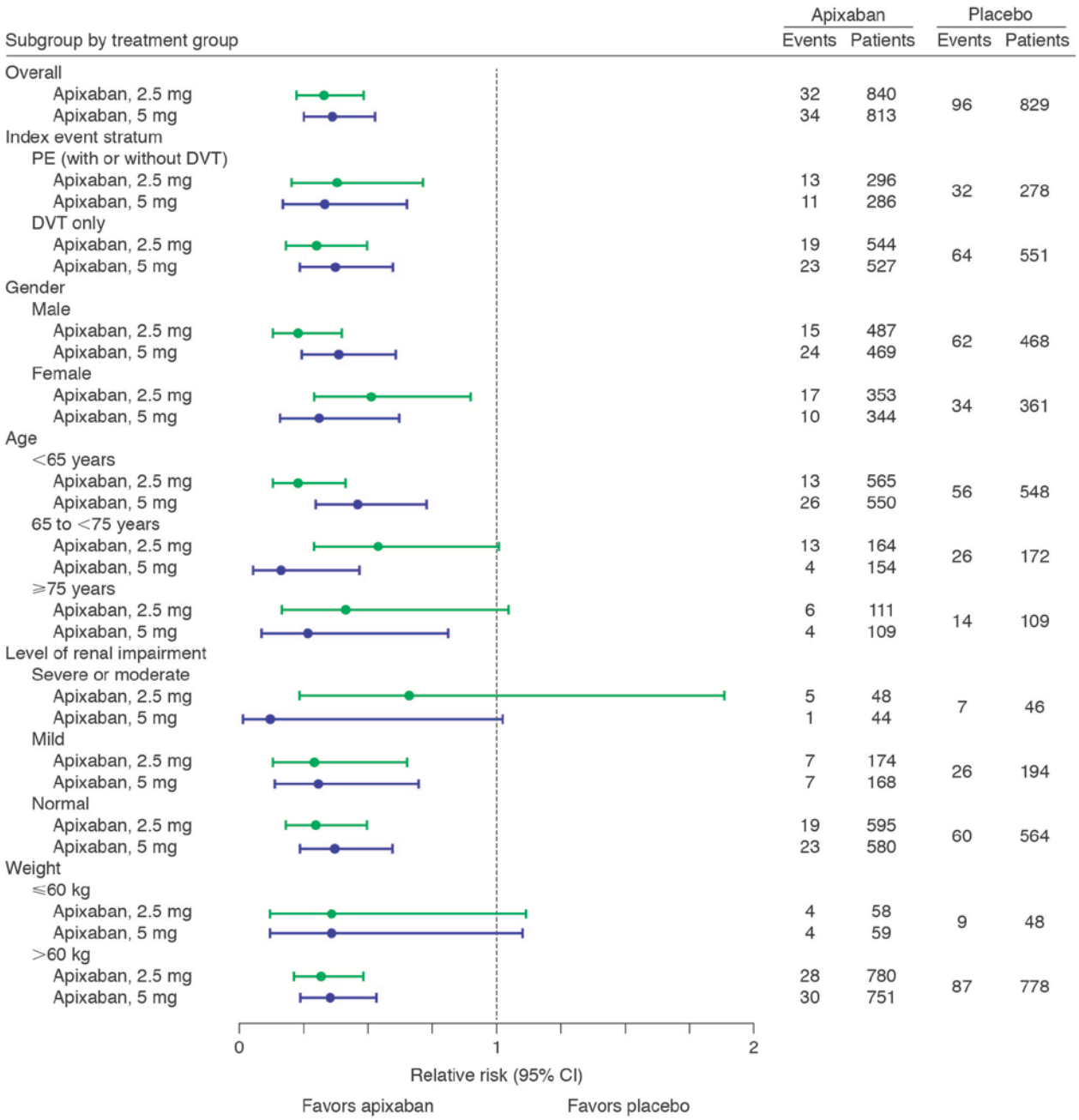
All acute clinically overt bleeding events not meeting the criteria for either major bleeding or clinically relevant non-major bleeding were classified as minor bleeding.

Fatal bleeding event

A fatal bleeding event was defined as a bleeding event that the independent adjudication committee determined was the primary cause of death or contributed directly to death.

FIGURES AND TABLES

Figure S1. Relative Efficacy in the Pre-specified Subgroups for the Composite Outcome of Symptomatic Recurrent Venous Thromboembolism and All Cause Death.*



*Patients who withdrew consent or were lost to follow-up were counted as having had a primary outcome.

Figure S2. Relative Safety in the Pre-specified Subgroups for the Composite Outcome of Major and Clinically Relevant Non-Major Bleeding.

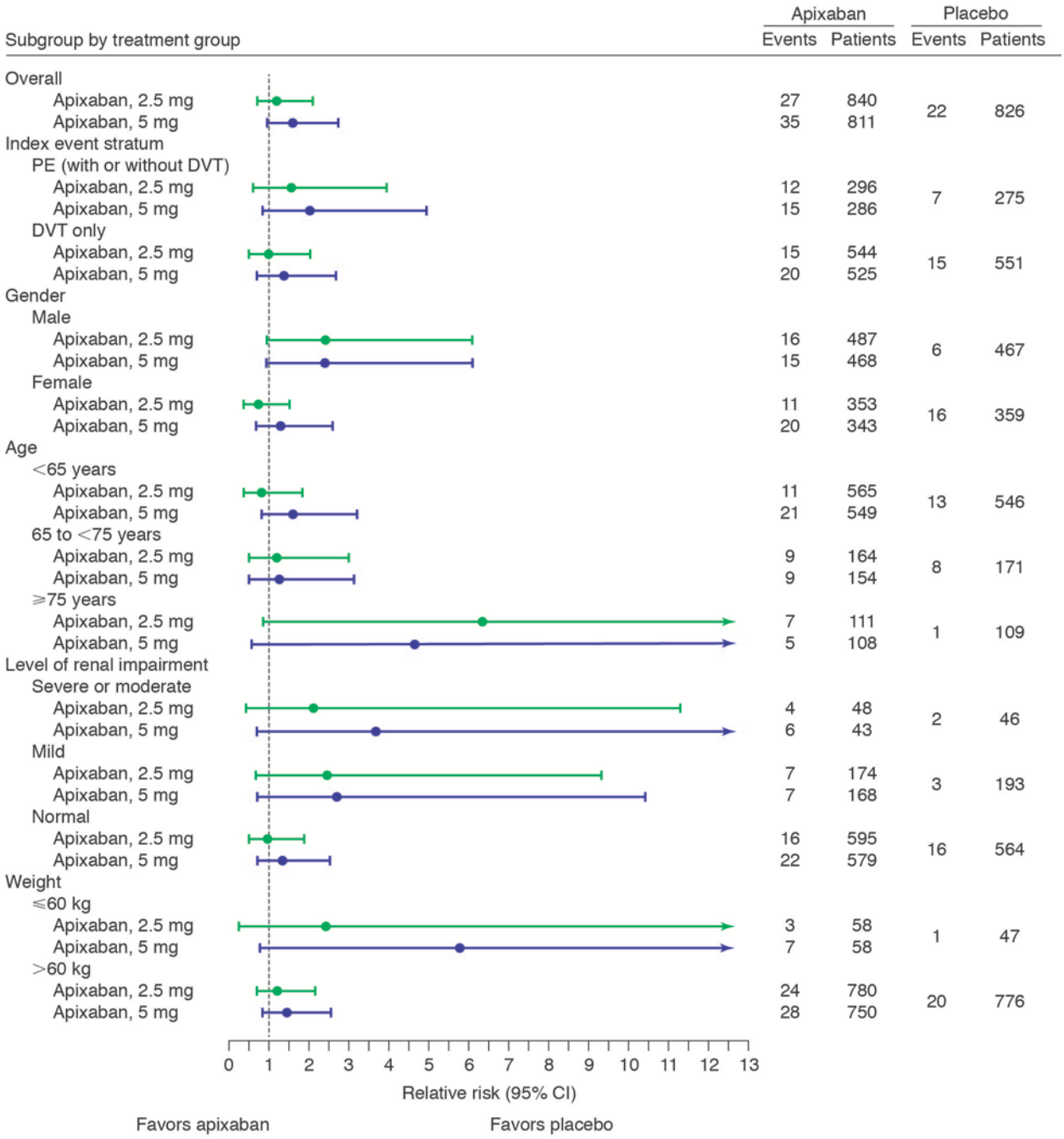


Table S1. Additional Demographic and Clinical Characteristics of the Patients.*

	Apixaban, 2.5 mg (N=840)	Apixaban, 5 mg (N=813)	Placebo (N=829)
Mean body mass index – kg/m^2	29.3±6.1	29.2±5.7	29.2±5.9
Duration of anticoagulant treatment prior to randomization – no. (%)			
<6 months	2 (0.2)	4 (0.5)	6 (0.7)
6–12 months	828 (98.6)	797 (98.0)	811 (97.8)
>12 months	10 (1.2)	12 (1.5)	12 (1.5)
Participated in AMPLIFY	282 (33.6)	272 (33.5)	282 (34.0)
Comorbid conditions – no. (%)			
Obesity	228 (27.1)	224 (27.6)	219 (26.4)
Diabetes mellitus	100 (11.9)	82 (10.1)	93 (11.2)
Hypercholesterolemia	243 (28.9)	261 (32.1)	241 (29.1)
Hypertension	336 (40.0)	324 (39.9)	356 (42.9)
Cigarette smoking – no. (%)	156 (18.6)	149 (18.3)	158 (19.1)

*Plus–minus values are means ± standard deviation. There were no significant differences among the study groups.

Table S2. Additional Clinical Outcomes during the Intended Treatment Period.

Event	Apixaban, 2.5 mg	Apixaban, 5 mg	Placebo
	No. of patients (%)	No. of patients (%)	No. of patients (%)
Type of first recurrent event			
Fatal PE	0	0	0
Death, PE could not be ruled out	2 (0.2)	3 (0.4)	7 (0.8)
Non-fatal PE	8 (1.0)	4 (0.5)	15 (1.8)
DVT	6 (0.7)	8 (1.0)	53 (6.4)
MI	2 (0.2)	3 (0.4)	4 (0.5)
Acute stroke	1 (0.1)	1 (0.1)	5 (0.6)
CV-related death	2 (0.2)	3 (0.4)	10 (1.2)
First major bleed			
Contributing to death	0	0	0
Into a critical site*	2 (0.2)	0	2 (0.2)
Associated with a fall in hemoglobin of ≥2 g/dL, transfusion of ≥2 units, or both**	0	1 (0.1)	2 (0.2)
Site of first clinically relevant non-major bleed***			
Gastrointestinal	3 (0.4)	1 (0.1)	2 (0.2)
Rectal	4 (0.5)	7 (0.9)	3 (0.4)
Epistaxis	3 (0.4)	7 (0.9)	2 (0.2)
Hematuria	7 (0.8)	11 (1.4)	7 (0.8)
Skin	2 (0.2)	6 (0.7)	1 (0.1)
Uterine	4 (0.5)	3 (0.4)	2 (0.2)
Gingival	0	1 (0.1)	0
Conjunctival	0	0	2 (0.2)
Other	2 (0.2)	1 (0.1)	0

CV cardiovascular, DVT deep vein thrombosis, MI myocardial infarction, PE pulmonary embolism.

*The critical site bleeding events in the 2.5 mg apixaban group were intraocular in both patients and in the placebo group were intraocular in one patient and hemorrhagic transformation of a cerebral infarct in one patient.

**Sites of bleeding were gastrointestinal in the 5 mg apixaban group, and gastrointestinal and urogenital in the placebo group.

***A patient may have had more than one event.

Table S3. Death and Adverse Events.

Clinical outcome	**Apixaban, 2.5 mg** n (%)	**Apixaban, 5 mg** n (%)	**Placebo** n (%)
Intent-to-treat population	840	813	829
Total deaths through end of intended treatment	7 (0.8)	4 (0.5)	14 (1.7)
Confirmed fatal PE	0	0	0
Death unexplained, PE could not be ruled out	2 (0.2)	3 (0.4)	7 (0.8)
Bleeding	0	0	0
Cancer	3 (0.4)	1 (0.1)	1 (0.1)
Myocardial infarction	0	0	0
Stroke	0	0	0
Infectious diseases	0	0	2 (0.2)
Other cardiovascular	0	0	3 (0.4)
Other cause	2 (0.2)	0	1 (0.1)
Adverse events			
Safety population	840	811	826
ALT or AST >3 xULN and billirubin >2 xULN	1 (0.1)	0	3 (0.4)
Adverse events resulting in permanent discontinuation of treatment	67 (8.0)	61 (7.5)	134 (16.2)
Any event emerging during treatment	596 (71.0)	542 (66.8)	606 (73.4)
Any serious event emerging during treatment	112 (13.3)	107 (13.2)	158 (19.1)

ALT alanine aminotransferase, AST aspartate aminotransferase, PE pulmonary embolism, ULN upper limit of normal.