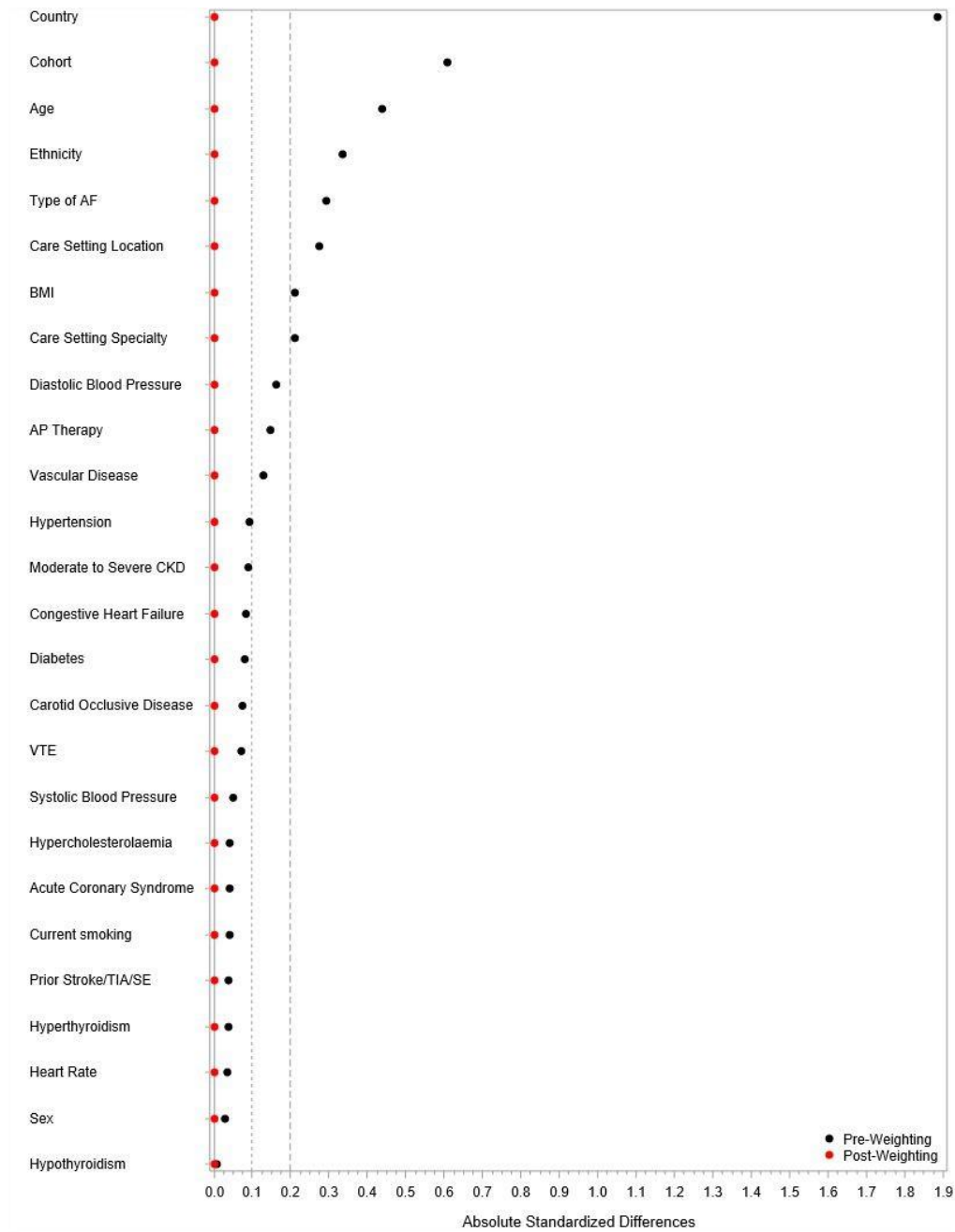


**Supplementary Figure S1.** Balance of variables associated with apixaban treatment in reference to VKA treatment at baseline before and after propensity score weighting, in apixaban and VKA users eligible for ARISTOTLE



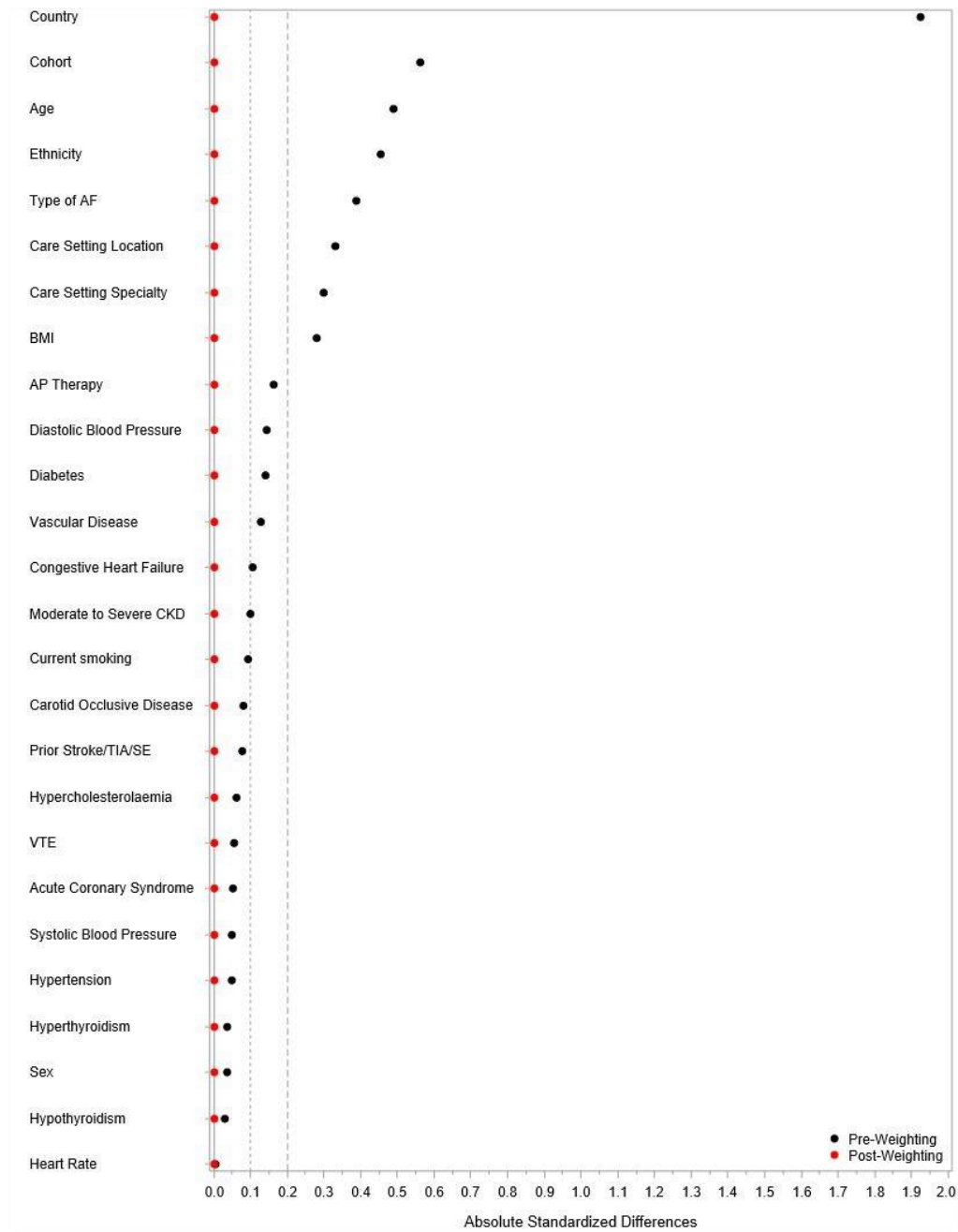
AF, atrial fibrillation; AP, antiplatelet; BMI, body mass index; CKD, chronic kidney disease; SE, systemic embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism

**Supplementary Figure S2.** Balance of variables associated with rivaroxaban treatment in reference to VKA treatment at baseline before and after propensity score weighting, in apixaban and VKA users eligible for ARISTOTLE



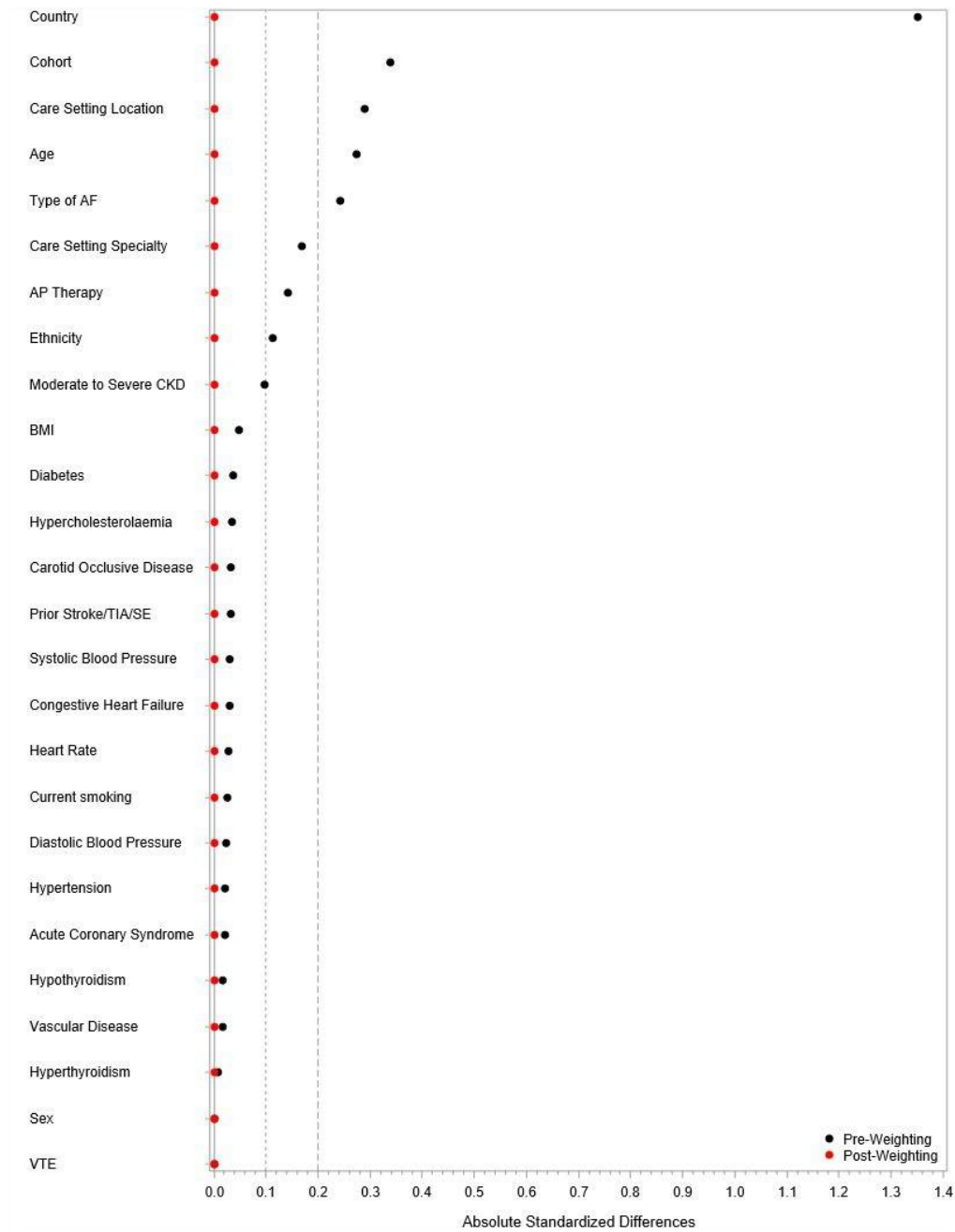
AF, atrial fibrillation; AP, antiplatelet; BMI, body mass index; CKD, chronic kidney disease; SE, systemic embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism

**Supplementary Figure S3.** Balance of variables associated with apixaban treatment in reference to VKA treatment at baseline before and after propensity score weighting, in apixaban and VKA users eligible for ROCKET AF



AF, atrial fibrillation; AP, antiplatelet; BMI, body mass index; CKD, chronic kidney disease; SE, systemic embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism

**Supplementary Figure S4.** Balance of variables associated with rivaroxaban treatment in reference to VKA treatment at baseline before and after propensity score weighting, in apixaban and VKA users eligible for ROCKET AF



AF, atrial fibrillation; AP, antiplatelet; BMI, body mass index; CKD, chronic kidney disease; SE, systemic embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism

**Supplementary Table S1.** Inclusion and exclusion criteria in ARISTOTLE and ROCKET

AF, and their presence and operationalisation in GARFIELD-AF

<b>Trial criteria</b>		<b>ARISTOTLE</b>	<b>ROCKET AF</b>
<b>Inclusion criteria</b>	Age	IC	IC
	Stroke, TIA or systemic embolism history	IC	IC
	Heart failure history	IC <sup>1</sup>	IC
	Hypertension history	IC	IC <sup>2</sup>
	Hypertension treatment	IC <sup>3</sup>	IC <sup>4</sup>
	Diabetes mellitus history	IC	IC
	Diabetes mellitus treatment		IC <sup>5</sup>
	LVEF	IC	IC
<b>Exclusion criteria</b>	Reversible cause for AF	EC <sup>6</sup>	EC <sup>6</sup>
	Pregnancy or breastfeeding	EC	EC
	Uncontrolled hypertension	EC <sup>7</sup>	EC <sup>8</sup>
	Severe renal insufficiency history	EC <sup>9</sup>	EC <sup>10</sup>
	High bleeding risk	EC <sup>11</sup>	EC <sup>11</sup>
	Recent ischemic stroke	EC <sup>12</sup>	EC <sup>12</sup>
	Recent TIA		EC <sup>12</sup>
	Severe prior stroke		EC <sup>13</sup>
	Bleeding history	EC <sup>14</sup>	EC
	Recent gastrointestinal bleeding		EC
	Active internal bleeding		EC
	Planned major surgery	EC	EC
	Recent major surgery	EC	EC
	Alcohol abuse	EC	EC
	Drug abuse	EC	EC
	Simultaneous treatment with both aspirin and a thienopyridine (e.g., clopidogrel, ticlopidine)	EC	EC <sup>15</sup>
	High-dose aspirin treatment	EC <sup>16</sup>	EC <sup>16</sup>
Recent intravenous antiplatelet use		EC	
Chronic NSAID use		EC <sup>17</sup>	

Use of cytochrome P450 3A4 inhibitor		EC
Use of cytochrome P450 3A4 inducer		EC
Anaemia	EC <sup>18</sup>	EC <sup>19</sup>
Thrombocytopenia	EC <sup>20</sup>	EC <sup>21</sup>
Inability to comply with INR monitoring	EC <sup>22</sup>	EC
Heart valve disease history	EC <sup>23</sup>	EC <sup>24</sup>
Atrial myxoma or left ventricular thrombus		EC <sup>25</sup>
Contraindication to VKA		EC <sup>26</sup>
Planned cardioversion therapy		EC <sup>27</sup>
Active liver disease		EC <sup>28</sup>
Liver function tests	EC	EC
Active hepatitis A, B or C		EC
Adequate contraceptive use	EC	EC
Anticoagulation use for chronic condition	EC	
Any indication for anticoagulation other than AF		EC <sup>29</sup>
Active infective endocarditis	EC	EC
Planned AF ablation procedure	EC	
Recent use of investigational drug or device	EC	EC
Prior randomization into NOAC trial	EC	EC
Short life expectancy	EC	EC
Psychosocial reasons that make study participation impractical	EC	EC
Prisoner	EC	
Compulsorily detained for treatment of illness	EC	
Haemorrhagic disorder or bleeding diathesis		EC
Recent fibrinolytic agents use		EC <sup>17</sup>
Patients considered unreliable		EC
Known intracranial neoplasm, arteriovenous malformation, or aneurysm		EC
Known HIV history at baseline		EC
Known allergy to VKA or investigational drug		EC
Employees of the investigator or study centre		EC

Shown are the inclusion and inclusion criteria across the two landmark NOAC trials.

Highlights: green, in trial protocol and present in the registry as defined by the trial protocol; yellow, in trial protocol and can be operationalised with sufficient validity from the registry although not recorded in the registry precisely as defined by the trial protocol (see comments below for operational definition applied in the registry); red, in trial protocol but absent and cannot be operationalised with sufficient validity in the registry; grey, not part of a trial's inclusion and exclusion criteria.

AF, atrial fibrillation; ALT, alanine transaminase; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AST, aspartate transaminase; EC, in the study as exclusion criterion; GARFIELD-AF, Global Anticoagulant Registry in the FIELD; IC, in the study as inclusion criterion; LVEF, left ventricular ejection fraction; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TIA, transient ischaemic attack.

<sup>1</sup> Defined in ARISTOTLE as symptomatic congestive heart failure within three months, operationalised in GARFIELD-AF as history of congestive heart failure;

<sup>2</sup> Defined in ROCKET AF as use of antihypertensive medications within six months before the screening visit or persistent systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg, operationalised in GARFIELD-AF as hypertension history or use of  $\geq 2$  antihypertensive drugs at baseline;

<sup>3</sup> Defined in GARFIELD-AF as the use of  $\geq 2$  antihypertensive drugs at baseline;

<sup>4</sup> Defined in ROCKET AF as use of antihypertensive medications within six months before the screening visit, operationalised in GARFIELD-AF as use of  $\geq 2$  antihypertensive drugs at baseline;

- <sup>5</sup> Defined in ROCKET AF as use of antidiabetic medications within six months before screening visit, operationalised in GARFIELD-AF as use of antidiabetic drugs at baseline;
- <sup>6</sup> Patients with reversible cause for AF were excluded from GARFIELD-AF;
- <sup>7</sup> Defined in ARISTOTLE as persistent, uncontrolled hypertension (systolic blood pressure (SBP) >180 mm Hg, or diastolic blood pressure (DBP) >100 mmHg), operationalised in GARFIELD-AF as baseline SBP>180 or DBP>100 mmHg;
- <sup>8</sup> Defined in ROCKET AF as SBP  $\geq$ 180 mmHg or DBP  $\geq$ 100 mmHg;
- <sup>9</sup> Defined in ARISTOTLE as serum creatinine >2.5 mg/dL or a calculated creatinine clearance <25 mL/min, operationalised in GARFIELD-AF as chronic kidney disease (CKD) class IV or V;
- <sup>10</sup> Defined in ROCKET AF as calculated creatinine clearance <30 mL/min as per Cockcroft and Gault formulas at the screening visit, operationalised in GARFIELD-AF as chronic kidney disease (CKD) class IV or V;
- <sup>11</sup> Operationalised in GARFIELD-AF as history of bleeding, dementia, compliance concern of dementia or baseline GARFIELD-AF bleeding score >4% at two years;
- <sup>12</sup> Medical history element recorded in GARFIELD-AF, without date of diagnosis;
- <sup>13</sup> Defined in ROCKET AF as modified Rankin score of 4 to 5;
- <sup>14</sup> In ARISTOTLE as part of the high bleeding risk criterion, defined as increased bleeding risk that is believed to be a contraindication to oral anticoagulation (e.g. previous intracranial haemorrhage);
- <sup>15</sup> Defined in ROCKET AF as aspirin in combination with thienopyridines within five days before randomization, operationalised in GARFIELD-AF as concomitant aspirin and thienopyridine use at baseline;
- <sup>16</sup> Use of this medication was scored in GARFIELD-AF, without dosage information
- <sup>17</sup> Medication use recorded in the registry, without date of (last) usage;



- <sup>18</sup> Defined in ARISTOTLE as haemoglobin <10 g/dL, baseline laboratory test results or anaemia history were not included in the GARFIELD-AF CRF;
- <sup>19</sup> Defined in ROCKET AF as haemoglobin <10 g/dL, baseline laboratory test results or anaemia history were not included in the GARFIELD-AF CRF;
- <sup>20</sup> Defined in ARISTOTLE as platelet count  $\leq 100,000/\text{mm}^3$ , baseline laboratory test results or thrombocytopenia history were not included in the GARFIELD-AF CRF;
- <sup>21</sup> Defined in ROCKET AF as platelet count <90,000/ $\mu\text{L}$ , baseline laboratory test results or thrombocytopenia history were not included in the GARFIELD-AF CRF;
- <sup>22</sup> Operationalised in GARFIELD-AF as compliance concern of limited access to INR monitoring;
- <sup>23</sup> Defined in ARISTOTLE as mitral valve stenosis, which is not specifically recorded in GARFIELD-AF;
- <sup>24</sup> Defined in ROCKET AF as haemodynamically significant mitral valve stenosis or prosthetic heart valve (annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty are permitted), neither of which were specifically recorded in GARFIELD-AF;
- <sup>25</sup> Operationalised in GARFIELD-AF as presence of intracardiac thrombus;
- <sup>26</sup> Defined in GARFIELD-AF as dementia history, dementia as compliance concern, or bleeding risk, fall risk or previous bleeding event as reason not to start oral anticoagulation;
- <sup>27</sup> Operationalised in GARFIELD-AF as cardioversion at baseline or  $\leq 48$  days of registry enrolment;
- <sup>28</sup> Operationalised in GARFIELD-AF as cirrhosis history;
- <sup>29</sup> Defined in GARFIELD-AF as any prior use of vitamin K anticoagulants

**Supplementary Table S2.** Variables included in the propensity score weighting scheme. All variables were recorded at baseline

<b>General</b>	<b>Demographics</b>	<b>Vital signs</b>	<b>Medical history</b>	<b>Medication</b>
Country of enrolment	Sex	BMI		Antiplatelet use
Cohort of enrolment	Age	Heart rate	Congestive heart failure	
Care setting speciality	Ethnicity	Systolic blood pressure	Acute coronary syndromes	
Care setting location		Diastolic blood pressure	Vascular disease	
Current smoking			Carotid occlusive disease	
Heavy alcohol consumption			Prior stroke/TIA/SE	
Type of AF			Prior bleeding	
			VTE	
			Hypertension	
			Hypercholesterolemia	
			Diabetes	
			Moderate to severe CKD	
			Hyperthyroidism	
			Hypothyroidism	

All variables were assessed at baseline.

AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; SE, systemic embolism; TIA, transient ischaemic attack; VTE, venous thromboembolism.

**Supplementary Table S3.** Missingness proportion (%) for selected variables by study

population and baseline treatment

Variable	ROCKET AF trial eligible patients		ARISTOTLE trial eligible patients	
	Rivaroxaban	VKA	Apixaban	VKA
	(N = 2005)	(N = 4368)	(N = 2570)	(N = 8005)
Country	0.0	0.0	0.0	0.0
Cohort	0.0	0.0	0.0	0.0
Sex	0.0	0.0	0.0	0.0
Race/ethnicity	1.7	1.8	3.2	1.7
Type of AF	0.0	0.0	0.0	0.0
Care setting location	0.0	0.0	0.0	0.0
Care setting specialty	0.0	0.0	0.0	0.0
Heart failure	0.0	0.0	0.0	0.0
Vascular disease	1.1	1.0	1.1	1.0
ACS	0.6	0.7	0.7	0.6
Carotid occlusive disease	2.2	2.4	1.6	2.1
Prior stroke/TIA/SE	0.7	1.0	1.1	0.9
Prior bleeding	0.3	0.5	0.5	0.4
VTE	0.7	0.8	0.7	0.7
Hypertension	0.1	0.3	0.2	0.2
Hypercholesterolaemia	3.6	4.5	2.1	4.9
Diabetes	0.0	0.0	0.0	0.0
Cirrhosis	2.0	2.2	1.6	2.2
CKD	3.9	6.7	3.3	6.9
Dementia	0.8	0.5	0.8	0.6
Hyperthyroidism	2.7	3.0	2.3	3.1
Hypothyroidism	2.7	3.1	2.1	3.2
Alcohol consumption	16.1	15.1	18.9	15.0
Smoking status	9.6	8.2	11.0	7.9
Antiplatelet therapy	1.9	0.0	1.7	0.0
Age	0.0	0.0	0.0	0.0

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SBP	5.1	7.3	5.5	6.4
DBP	5.1	7.3	5.5	6.4
Pulse	7.3	8.4	6.0	7.3
BMI	19.7	24.0	20.6	23.0

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AF, atrial fibrillation; ACS, acute coronary syndromes; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; SE, systemic embolism; SBP, systolic blood pressure; TIA, transient ischemic attack; VTE, venous thromboembolism.

AF, atrial fibrillation; ACS, acute coronary syndromes; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; SE, systemic embolism; SBP, systolic blood pressure; TIA, transient ischemic attack; VTE, venous thromboembolism.

## APPENDIX: Complete list of GARFIELD-AF Principle Investigators

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