Appendix 3: Characteristics of 23 included randomised trials in stroke prevention in AF (references below)

Study **(Centre type)** **[Countries]**	**Study type** **Sponsor (sponsor's role)**	**Age eligibility (Mean age)** **[% Male]**	**AF type**	**No. rand.**	**Interventions compared**	**Tmt duration (months)**	**Mean time in therapeutic range (INR)**	**Outcomes**	**Time of outcome assessment (months)**
ACTIVE W(1) (Multicentre) [North & South America, Europe, Russia, Israel, Australia, Asia, South Africa]	Phase III Sanofi -Aventis and Bristol-Myers Squibb (The sponsor contributed to the study design "but had no role in data collection, data analysis, data Interpretation, or writing of the report")	≥18 yrs. (70.2 yrs.) [66.1%]	Non-valvular ECG diagnosed	6706	**Antiplatelet** 1. Clopidogrel 75mg + (aspirin 75-100mg) od **Warfarin** 2. INR 2-3 (some patients may have received other vitamin K antagonists in use in their country)	Not given	63.8%	Efficacy-All stroke, ischemic stroke, haemorrhagic stroke, MI Safety-All bleeding, major bleeding, minor bleeding, fatal bleeding, death (all causes)	15.4
AFASAK(2) (Two centres) [Denmark]	Phase III NycoMed AS, Oslo, Norway; Henrik Henriksen's Foundation; Kathrine and Vigo Skovgaard's Foundation; and Danish Medical Research Foundation (Not stated)	≥18 yrs. (74.2 yrs.) [53.6%]	Chronic non-valvular ECG diagnosed	1007	**Warfarin** 1. INR 2-3 **Antiplatelet (aspirin)** 2. 75mg od 3. Placebo od	24	73%	Efficacy-All stroke, fatal stroke, minor ischemic stroke, TIA Safety-Bleeding, death (all causes)	24

AFASAK II(3) (Single centre) [Denmark]	Phase III The Danish Heart Foundation, Copenhagen; Nycomed DAK A/S Roskilde, Denmark; Du Pont Pharma, Wilmington, Del; The Danish Foundation for Medical Research for the Region of Copenhagen; and many other non-industry funders (Not stated)	≥18 yrs. (74.2 yrs.) [60%]	Chronic non-valvular ECG diagnosed	677	**Warfarin** 1. 1.25mg/day fixed dose 2. 1.25mg/day fixed dose plus aspirin 300mg/day od 3. INR 2-3 **Aspirin** 4. 300mg od	42	73%	Efficacy-All stroke, ischemic stroke, haemorrhagic stroke, fatal stroke, stroke or systemic embolism, TIA, MI Safety-Major bleeding, minor bleeding, intracranial bleeding, death (all causes)	42
AF-ASA-VKA-CHINA(4) (Two centres) [China]	Phase III Grant from talent pool subject of Shanghai Shi Dong Hospital (Not applicable)	≥80 yrs. (NR) [NR]	Persistent & Permanent non-valvular Confirmed by the case history & ECG	110	**Warfarin** 1. INR 1.6-2.5 **Antiplatelet (aspirin)** 2. 100mg od	24	NR	Efficacy-Stroke or systemic embolism, ischemic stroke, MI Safety-All bleeding, major bleeding, minor bleeding, fatal bleeding, death (all causes)	1, 6, 12, 18, and 24

AF-DABIG-VKA-JAPAN(5) (Multicentre) [Japan]	Phase II Boehringer Ingelheim (The sponsor was involved in the trial)	≥20 yrs. (NR) [NR]	Paroxysmal, persistent or permanent non-valvular ECG diagnosed	174	**Dabigatran** 1. 110mg bd 2. 150mg bd **Warfarin** 3. INR 2-3 (INR ≥1.6 to ≤2.6 in ≥70 yrs.)	3 NR		Efficacy-Stroke or systemic embolism Safety-All bleeding, major bleeding, composite clinically relevant bleeding	3
AF-EDOX-VKA-ASIA(6) (Multicentre) [Taiwan, South Korea, Hong Kong & Singapore]	Phase II Daiichi Sankyo Co., Ltd., Tokyo, Japan (The sponsor had influence on the study design, data management & analysis, and key decisions)	18-80 yrs. (65.1 yrs.) [65.4%]	Non-valvular ECG diagnosed $CHADS_2$≥ 1	235	**Edoxaban** 1. 30mg od 2. 60mg od **Warfarin** 3. INR 2-3	3 (Edoxaban) 6 (Warfarin)	45.1%	Efficacy-Stroke or systemic embolism Safety-All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding	3
AF-EDOX-VKA-JAPAN(7) (Multicentre) [Japan]	Phase II Daiichi Sankyo Co., Ltd., Tokyo, Japan (The funder "had input on the study design and data analysis & interpretation of results and wrote the clinical study report")	≥20 yrs. (NR) [NR]	Non-valvular ECG diagnosed $CHADS_2$≥ 1	536	**Edoxaban** 1. 30mg od 2. 45mg od 3. 60mg od **Warfarin** 4. INR 2-3 (INR 1.6-2.6 in ≥70 yrs.)	3	83% (≥70 yrs.) 73% (<70 yrs.)	Efficacy-Stroke or systemic embolism Safety-All bleeding, major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding	3

AF-EDOX-VKA-MULTI(8) (Multicentre) [North America, Chile, Europe & Russia]	Phase II Daiichi Sankyo Co., Ltd., Tokyo, Japan (Not clear)	18-85 yrs. (65.1 yrs.) [62.1%]	Persistent non-valvular ECG diagnosed $CHADS_2$ ≤2	1146	**Edoxaban** 1. 30mg od 2. 60mg od 3. 30mg bd 4. 60mg bd **Warfarin** 5. INR 2-3	3	49.7%	Efficacy-Stroke or systemic embolism, MI, hospital admission Safety-All bleeding, major bleeding, minor bleeding, clinically relevant non-major Bleed, composite clinically relevant bleeding, death (cardiovascular)	3
AF-VKA-ASA-CHINA(9) (Multicentre) [China]	Phase III 10th National Five-year Project of China (Not applicable)	50-80 yrs. (NR) [NR]	Non-valvular Diagnosis based on medical history, ECG and/or Holter recordings	690	**Warfarin** 1. INR 2.1-2.5 2. INR 1.6-2 **Antiplatelet (aspirin)** 3. 200mg od	24 (mean 15)	NR	Efficacy-All stroke, ischemic stroke, haemorrhagic stroke, TIA Safety-Major bleeding, minor bleeding, death (all causes)	24

ARISTOTLE(10-20) (Multicentre) [North & South America, Europe, Russia, Israel, Australia, Asia, South Africa]	Phase III Bristol-Myers Squibb and Pfizer (The trial was designed in conjunction with the sponsors & "The primary analyses were performed both at Bristol-Myers Squibb and at the Duke Clinical Research Institute")	≥18 yrs. (Median 70 yrs.) [64.7%]	Non-valvular or flutter ECG diagnosed	18201	**Apixaban** 1. 5mg bd **Warfarin** 2. INR 2-3	21.6 (median)	62.2%	Efficacy-All stroke, ischemic stroke, haemorrhagic stroke, stroke or systemic embolism, MI Safety-All bleeding, major bleeding, composite clinically relevant bleeding, intracranial bleeding, death (all causes)	21.6 (median for Intracranial bleeding)
ARISTOTLE-J(21) (Multicentre) [Japan]	Phase II Pfizer Inc. and Bristol-Myers Squibb (Not clear)	≥20 yrs. (70.3 yrs.) [82.9%]	Non-valvular Diagnosis based on ECG, Holter recording or intracardiac electrogram	222	**Apixaban** 1. 2.5mg bd 2. 5mg bd **Warfarin** 3. INR 2-3 (INR 2-2.6 in ≥70 yrs.)	3	60%	Efficacy-Stroke or systemic embolism, ischaemic stroke, TIA Safety-All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, death (all causes)	3

AVERROES(22-25) (Multicentre) [North & South America, Europe, Russia, Israel, Australia, Asia, South Africa]	Phase III Bristol-Myers Squibb and Pfizer (The sponsor was involved in the design, data collection, and analysis)	≥50 yrs. (70 yrs.) [58.5%]	Non-valvular ECG diagnosed	5599	**Apixaban** 1. 5mg bd (2.5mg if >80 yrs./≤60 kg/renal status) **Antiplatelet (aspirin)** 2. 81-324mg od	13.1 (mean)		Efficacy-All stroke, stroke or systemic embolism, ischaemic stroke, haemorrhagic stroke, MI Safety-Major bleeding, minor bleeding, clinically relevant non-major bleeding, intracranial bleeding, fatal bleeding, death (cardiovascular), death (all causes)	13.1 (mean)
BAFTA(26) (Multicentre) [UK]	Phase III The Medical Research Council UK and supported by MidReC and the Primary Care Research trust (The sponsor had no direct role in study design, in data collection, analysis or interpretation, in writing the report, or in the decision to submit for publication)	≥75 yrs. (81.5 yrs.) [54.6%]	Non-valvular or atrial flutter ECG diagnosed	973	**Antiplatelet (aspirin)** 1. 75mg od **Warfarin** 2. INR 2-3	32.4 (mean)	67%	Efficacy-All stroke, MI Safety-Major bleeding, death (all causes)	32.4 (mean)

Chinese ATAFS(27) (Multicentre) [China]	Phase III Not disclosed	40-80 yrs. (63.3 yrs.) [59.7%]	Non-valvular	704	**Antiplatelet (aspirin)** 1. 150-160mg od **Warfarin** 2. INR 2-3 (INR 1.6-2.5 in >75 yrs.)	Not reported	 NR	Efficacy-All stroke Safety-Death (all causes)	2-24 (median=19)
ENGAGE AF-TIMI 48(28, 29) (Multicentre) [North & South America, Europe, Russia, Israel, Australia, Asia, South Africa]	Phase III Daiichi Sankyo Pharma Development (Not clear)	≥21 yrs. (NR) [61.9%]	Non-valvular ECG diagnosed $CHADS_2$ ≥2	21105	**Edoxaban** 1. 30mg od 2. 60mg od **Warfarin** 3. INR 2-3	29.8 (median)	 64.9%	Efficacy-All stroke, ischemic stroke, haemorrhagic stroke, fatal stroke, stroke or systemic embolism, MI Safety-Major bleeding, minor bleeding, fatal bleeding, intracranial bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, death (cardiovascular), death (all causes)	29.8 (median)

EXPLORE-Xa(30) (Multicentre) [USA, Canada & Germany]	Phase II Portola Pharmaceuticals, South San Francisco, CA, USA (Not stated)	≥18 yrs. (73 yrs.) [66.5%]	New or existing non-valvular or atrial flutter Diagnosed by Holter, ECG, rhythm strip, pacemaker, or other intracardiac recording	508	**Betrixaban** 1. 40mg od 2. 60mg od 3. 80mg od **Warfarin** 4. INR 2-3	4.9 (mean)	 63.4%	Efficacy-All stroke Safety-All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, death (all causes)	4.9 (mean)
J-ROCKET AF(31) (Multicentre) [Japan]	Phase III Bayer Yakuhin Ltd (The funder was "responsible for trial design and study data collection")	≥20 yrs. (71.1 yrs.) [80.6%]	Non-valvular ECG diagnosed	1280	**Rivaroxaban** 1. 15mg od **Warfarin** 2. INR 2-3 (INR 1.6-2.6 in ≥70 yrs.)	30	 65%	Efficacy-All stroke, ischemic stroke, haemorrhagic stroke, stroke or systemic embolism, MI Safety-Composite clinically relevant bleeding, death (cardiovascular), death (all causes)	30

PATAF(32) (Multicentre) [Netherlands]	Phase III Prevention fund (grant 002817010), Zorg Onder-zoek Nederland; Roche Nicholas BV, Bladel, Holland, donated aspirin (Not stated)	≥60 yrs. (74.8 yrs.) [44.9%]	Chronic or intermitten t ECG diagnosed	729	**Warfarin** 1. INR <2 2. INR 2.5-3.5 (some patients received other coumarins – phenprocoumon or acenocoumarol) **Antiplatelet (aspirin)** 3. 150mg od	32.4 (mean)	NR	Efficacy-All stroke, ischaemic stroke, arterial event Safety-Death (cardiovascular), death (all causes)	32.4 (mean)
PETRO(33) (Multicentre) [USA, Denmark, Netherlands & Sweden]	Phase II Boehringer Ingelheim Pharmaceuticals, Biberach, Germany (The funder was responsible for the statistical analysis conducted according to a prospectively designed plan approved by the steering committee)	≥18 yrs. (69.5 yrs.) [81.9%]	Permanent, persistent, & paroxysma l non-valvular with coronary artery disease Diagnosis not explained	502*	**Dabigatran** 1. 50mg bd 2. 50mg + (aspirin 81mg) bd 3. 50mg + (aspirin 325mg) bd 4. 150mg bd 5. 150mg + (aspirin 81mg) bd 6. 150mg + (aspirin 325mg) bd 7. 300mg bd 8. 300mg + (aspirin 81mg) bd 9. 300mg + (aspirin 325mg) bd **Warfarin** 10. INR 2-3	3	57.2%	Efficacy-Stroke or Systemic embolism Safety-All bleeding, major bleeding, composite clinically relevant bleeding	3

RE-LY(34, 35) (Multicentre) [North & South America, Europe, Russia, Israel, Australia, Asia, South Africa]	Phase III Boehringer Ingelheim (The sponsor contributed in the design, conduct, and reporting of the study)	≥18 yrs. (71 yrs.) [63.6%]	Non-valvular ECG diagnosed Mean $CHADS_2$ 2.1	18113	**Dabigatran** 1. 110mg bd 2. 150mg bd **Warfarin** 3. INR 2-3	24 (mean)	64%	Efficacy-Stroke or systemic embolism, ischaemic stroke, haemorrhagic stroke, MI, PE, Hospital admission Safety-Major bleeding, minor bleeding, intracranial bleeding, extra-cranial minor bleeding, death (cardiovascular), death (all causes)	24 (mean)
ROCKET AF(36-39) (Multicentre) [North & South America, Europe, Russia, Israel, Australia, New Zealand, Asia, South Africa]	Phase III Johnson & Johnson and Bayer (The sponsor was not involved in the coordination of the trial, data management, and analyses)	≥18 yrs. (Median 73 yrs.) [60.3%]	Non-valvular ECG diagnosed $CHADS_2$ ≥2	14264	**Rivaroxaban** 1. 20mg od **Warfarin** 2. INR 2-3	19.4 (median)	55%	Efficacy-All stroke, stroke or systemic embolism, MI Safety-Major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, fatal bleeding, intracranial bleeding, death (all causes)	19.4 (median)

SPAF II(40) (Multicentre) [USA]	Phase III The Division of Stroke and Trauma, National Institute of Neurological Disorders and Stroke (Not clear)	Not clear (NR) [NR]	Non-valvular ECG diagnosed	1100	**Warfarin** 1. INR 2-4.5 in <75 yrs. 2. INR 2.0-4.5 in >75 yrs. **Antiplatelet (aspirin)** 3. 325mg (in <75 yrs.) od 4. 325mg (in >75 yrs.) od	37.2 (mean for age <75 years) 24 (mean for age >75 years)	NR	Efficacy-Stroke or systemic embolism, ischaemic stroke, MI, TIA Safety-Intracranial bleeding, death (all causes)	27.6 (mean)
WASPO(41) (Multicentre) [UK]	Phase III Not declared	>80 & <90 yrs. (Median 83 yrs.) [47%]	Permanent non-valvular ECG diagnosed	75	**Warfarin** 1. INR 2-3 **Antiplatelet (aspirin)** 2. 300mg od	12	69.2%	Efficacy-All stroke, TIA Safety-Death (all causes)	12

AF = atrial fibrillation; NVAF = non-valvular atrial fibrillation; MI = myocardial infarction; TIA = transient ischaemic attack; PE = pulmonary embolism; INR = international normalized ratio; ECG = electrocardiogram; rand = randomised; od = once daily; bd = twice daily; Tmt = treatment; NR = not reported.

*Our results are based on 515 patients as reported in the results tables; the trial report is inconsistent in this regard.

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