ONLINE-ONLY DATA SUPPLEMENT

Age-specific incidence, outcome, cost and projected future burden of atrial fibrillation-related embolic vascular events: a population-based study

Gabriel S.C. Yiin DPhil, Dominic P.J. Howard DPhil, Nicola L.M. Paul DPhil, Linxin Li DPhil, Ramon Luengo-Fernandez DPhil, Linda M. Bull RGN, Sarah J.V. Welch RGN, Sergei A. Gutnikov DPhil, Ziyah Mehta DPhil, Peter M. Rothwell FMedSci on behalf of the Oxford Vascular Study

Methods

OCSP and OXVASC Methodology

The OXVASC and OCSP primary care practices had the same hospital referral patterns, held accurate age-sex registers of their patients, and were willing to refer any patient with a suspected cerebrovascular event to the study and allow regular searches of their computerized diagnostic coding systems. In both studies, the population was 94% white.[1]

Definitions and diagnosis: Diagnosis was designed to be as similar as possible in OXVASC to OCSP. The same definitions of stroke and TIA were used.[2] However, since clinical opinion about which clinical syndromes represent TIA or stroke has evolved over the last 25 years, the Principal Investigator of the OCSP had input into the design of OXVASC and reviewed a subset of cases to ensure that the application of definitions of events was comparable. Diagnosis was based on clinical findings and CT brain imaging as in OCSP. In addition, all CT scans were reviewed by a study neuroradiologist who was also involved in the OCSP and used the same criteria for haemorrhagic infarction and primary intracerebral haemorrhage as in the OCSP.

All events were categorized as first-ever incident or recurrent – based on clinical history rather than findings on brain imaging. As in the OCSP, a first-ever stroke that occurred in a patient with a previous TIA was coded as incident, but a first-ever TIA in a patient with a previous stroke was coded as recurrent.[3] The other OCSP requirements for definition of an "incident" TIA were also adhered to.[3] As in the OCSP, patients who had an event whilst temporarily away from Oxford were included, but visitors to Oxford who were not registered with one of the study family physicians were excluded.

Case Ascertainment: The following sources of ascertainment were used in OXVASC and OCSP:
1) Collaborating primary care physicians reported cases to the study physicians by telephone, fax or pager as soon as they became aware of a possible TIA or stroke. Patients not requiring immediate hospital admission were seen in a daily clinic, or at home if transfer to hospital was not inappropriate.
2) The study team maintained frequent personal contact with the general practices by regular visits, a quarterly newsletter, and via a liaison family physician in each practice.
3) Computerized hospital diagnostic codes were reviewed regularly. In OCSP, the Oxford Record Linkage system[4] was used. In OXVASC, the coding department for the Oxford Hospitals Trust provided a monthly GP-practice specific list of all patients with ICD-10 codes for TIA and stroke and all deaths in hospital. A similar list was obtained from the Oxford Eye Hospital and local community hospitals.
4) Hospital admission and Emergency Department registers were reviewed daily.

5) Out of hospital deaths were identified via the Coroner's Office, by review of all death certificates in the study practices, and by ICD-10 vascular death codes from the local Department of Public Health.

Several methods of case-ascertainment that were not used in OCSP were employed in OXVASC:
1) Daily visits to the Acute Medical Admissions Unit, Acute Stroke Unit, Neurology wards and Stroke Rehabilitation wards, and daily contact with Hospital Bereavement Officers to identify all patients brought into hospital dead or who died soon after arrival.
2) A computer-generated list of all requests for brain and cerebral vascular imaging was reviewed on a monthly basis and all referrals for carotid Doppler ultrasound were reviewed on a weekly basis.
3) Patients with visual symptoms were referred directly to the study from the Eye Emergency Unit and Department of Ophthalmology and lead clinical staffs in the other departments (e.g. paediatrics, obstetrics etc) were contacted monthly to ascertain strokes in patients under their care.

Clinical assessment and investigation: A study clinician assessed patients as soon as possible after the event in hospital, in a daily dedicated clinic or at home. Informed consent was sought, where possible, or assent was obtained from a relative. A standard clinical history and examination were performed. As in the OCSP, pre-morbid handicap and disability was assessed with the Rankin[5] score. If a patient died prior to assessment, an eyewitness account of the clinical event and reviewed any relevant records were obtained. Event and baseline characteristics were recorded and all patients underwent standardized investigations including blood screen, 12-lead electrocardiogram, brain imaging (CT and/or MRI) and vascular imaging (carotid/peripheral duplex ultrasonography or CT/MR angiography). The treating physicians completed supplementary investigations such as echocardiography when indicated.

If death occurred outside hospital or prior to brain imaging, the autopsy result was reviewed. Given the high rate (98%) of imaging/autopsy in OXVASC, strokes of unknown type were coded as ischaemic for the purpose of analysis. In OCSP, strokes that did not have brain imaging or autopsy (12%) were classified as haemorrhages only if clinical scoring systems indicated a high degree of certainty.[6] Otherwise they are coded as ischaemic for the purpose of this analysis. Diagnosis of subarachnoid haemorrhage[6] and clinical subtyping of stroke[7] were the same as in OCSP.

Both OCSP and OXVASC recorded pre-morbid medication and vascular risk factors from the patient or relative, hospital records and primary care records. The most recent measurement of blood pressure was recorded in both studies from the general practice records. Total cholesterol concentration was measured at the time of assessment after the TIA or stroke. All surviving cases were followed-up by a research nurse or therapist at 1, 6, 12, 24, 60 and 120 months from the time of the stroke and the modified Rankin score was determined. If a recurrent vascular event was suspected, the patient was assessed by a study physician.

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Extended methods for ascertainment of systemic emboli in OXVASC

Ascertainment of patients with acute systemic (non-cerebral) embolic events was done using overlapping methods of hot and cold pursuit similar to those used for acute cerebral events. Hot pursuit was based on: 1) Daily searches of Emergency Department admission and symptom/diagnosis registers; 2) Daily listing from the central admissions department of all patients from our general practices admitted to hospital, and assessment of these patients in hospital; 3) Daily visits to the cardiac surgery and vascular surgery wards and review of daily lists of all patients referred to vascular surgery or for peripheral angiography; 4) Daily identification via Bereavement Officers of patients dead on arrival at hospital or who died soon after; 5) Daily assessment of all patients undergoing diagnostic angiographic, angioplasty/stenting or peripheral arterial surgical procedures in any territory.

The methods of cold pursuit were: 1) Weekly review of all listed surgical procedures undertaken by vascular and cardiovascular surgery; 2) Frequent contact with general practices and monthly searches of computerized practice diagnostic codes; 3) Monthly practice-specific list of all patients with relevant diagnostic codes from the coding departments covering all acute and community hospitals; 4) Monthly visits to the Coroner's Office to review out-of-hospital deaths; 5) Review of all death certificates and relevant clinical details in the study general practices; 6) Practice-specific listings of all ICD-10 death codes from the local Department of Public Health; 7) Review of vascular surgery outpatient clinic letters to identify all patients attending vascular clinics who were not admitted to hospital.

A study clinician assessed patients as soon as possible after the event. Informed consent was sought, where possible, or assent was obtained from a relative. Standardized clinical history and cardiovascular examination were recorded. We also recorded from the patient, their hospital records and their primary care records, details of the clinical event, medication, past medical history, all investigations relevant to their admission and all interventions subsequent to the event. Vascular assessment included clinical examination and measurement of the abdominal and peripheral pulses, Buerger's test and ankle Doppler pressure recordings. For cases in which clinical vascular assessment was not possible by the study clinician prior to urgent revascularisation or death, we used assessments made by the admitting clinician.

If a patient died prior to assessment, we obtained eyewitness accounts and reviewed any relevant records. If death occurred outside hospital or prior to investigation, the autopsy result was reviewed. Clinical details were sought from primary care physicians or other clinicians on all deaths of possible vascular aetiology. Initial clinical assessments were made by study clinical research fellows alongside the clinical teams. All diagnoses were subsequently reviewed by a vascular surgeon.

Acute peripheral arterial events were defined as any acute vascular event in any part of the arterial system that affected the aorta and its major branches, a limb or an organ other than the heart or the brain/eye and led to hospital admission or caused death in the community. All patients were followed-up by a research nurse or via their family doctor, with recurrent events also identified by the on-going study surveillance. If a recurrent vascular event was suspected, the patient was assessed by a study physician. All events were categorized as first-ever incident or recurrent and specific to territory. An incident acute systemic embolic event implied the first ever acute embolic arterial event in any vascular territory apart from the brain. Only incident events were included in the analysis for this manuscript. Patients who had an event whilst temporarily away from Oxfordshire were included, but visitors to Oxfordshire who were not registered with one of the study practices were excluded.

Recording and coding of deaths in the OXVASC population

Out of hospital death accounts for a small proportion of ischaemic strokes and systemic emboli, but in view of previous data on the inaccuracy of death certification of vascular disease[1-2], all deaths in the OXVASC population were recorded and coded as follows:

i. *All certified deaths due to vascular disease*: All deaths with the underlying cause coded for the purposes of national statistics as being due to "ischaemic heart disease" (ICD I210-I229, I251, I259), "cerebrovascular disease" (ICD I600-I619, I630-I669, I670, I678, I679, I694, I698), "peripheral vascular disease" (ICD I700, I710-I729, I739-I749, I790), or "visceral vascular disease" (ICD D735, K763, N280, K550, K551, K558, K559).

ii. *All certified acute vascular deaths*: All deaths where the underlying cause of death was coded for the purposes of national statistics as being due to "acute ischaemic heart disease" (ICD I210-I229), "acute cerebrovascular disease" (ICD I600-I619, I630-I669), "acute peripheral vascular disease" (ICD I710, I711, I713, I715, I718, I720-I729, I739-I749, I790), or "acute visceral vascular disease" (ICD D735, K763, N280, K550, K558, K559).

iii. *Probable or definite acute vascular deaths*: All deaths in (ii) excluding unclassifiable sudden deaths (as defined below) and other deaths that after evaluation of the clinical and/or post-mortem data were considered to have been incorrectly attributed (i.e. there was definite evidence of another cause), and with the addition of any deaths not in (ii) that were considered by the OXVASC researchers to have been due to an acute vascular event.

iv. Possible acute vascular deaths: All deaths in (iii) excluding sudden deaths for which the only supporting evidence was a previous history of symptomatic vascular disease in the relevant arterial territory (unless there was a documented acute myocardial infarction, acute stroke or acute peripheral arterial event within the previous 30 days).

Unclassifiable deaths, which were mainly out-of-hospital deaths, were certified as having a vascular cause, but had no witness description of the event or of preceding symptoms to suggest acute vascular disease in a specific territory, no post-mortem evidence of an acute vascular event or other cause of death, no post-mortem evidence of clinically significant coronary atherosclerosis, and no past history of symptomatic vascular disease in a relevant arterial territory.

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Appendix I

Additional details on under-treatment of patients with incident embolic event and known prior AF in relation to risk scores and outcomes in OXVASC

Of the 280 patients with incident embolic event and not anticoagulated, 217 (77.5%) had a $CHADS_2$ score ≥2 (Table 3, Tables IX-XI), of whom 51 (23.5%) had a documented absolute or relative contraindication (Table XII) and 181 (83.4%) had a HAS-BLED score <3 (Table XI). 194 (57.7%) were on antiplatelet drugs, but 86 (25.6%) were on no antithrombotic (Table 3, Figure I). In patients with ischaemic stroke, anticoagulation was associated with reduced severity (NIHSS: anticoagulated = 5.5 ± 5.7; antiplatelet/none = 8.3 ± 7.5, p=0.006).

Rates of premorbid anticoagulation for known prior AF in patients with AF-related ischaemic events were highest at younger ages (Table 3), falling to 12.9% (19/147) at 80-89 and 0% (0/61) at ≥90. Prior anticoagulation was less frequent in women than in men (23/186 vs 33/150, p=0.02), but this was due to the over-representation of women in older age groups. Of the 208 patients aged ≥80, 189 (90.9%) were not anticoagulated. Of these 189, 167 (88·4%) had a premorbid $CHADS_2$ score ≥2, 139 (83.2%) had a HAS-BLED score <3 (Table XI), and only 10 (5.3%) had previously had a trial of anticoagulation and had discontinued treatment (Table XIII). Of the 167 with a $CHADS_2$ score ≥2, only 43 (25.7%) had any documented relative or absolute contraindication (Table XII).

Of the 189 patients who were aged ≥80 and not anticoagulated (Table XIVA-B), 166 (87.8%) had no major disability (i.e. were still independently mobile - mRS≤3) prior to the event and 99 (52.4%) were previously completely independent (mRS≤2). Of the 167 (88·4%) who had an embolism risk score favouring treatment ($CHADS_2$ score ≥2), 125 (74.9%) were dead or institutionalized after the event. Indeed, of all disabling or fatal events at age ≥80 in the study population, 230/449 (51.2%) were AF-related and 181 (40.3%) occurred in patients with known prior AF. Of 136 patients aged ≥80 with known prior AF and $CHADS_2$ ≥2 who had an incident event resulting in death or institutionalization at six months follow-up, only 11 (8·1%) were anticoagulated prior to the event (Figures IIA-F).

Table and Figure legends

Table IA: Anticoagulation rate by age (UK studies)

Studies	Anticoagulation rate (%) by age
Bromley Hospital NHS Trust, UK (study period not specified)[1] Chronic AF only	Age 75-89: 6.4%
Northumberland, UK[2] Study period not specified	Age ≥75: 16.9%
General Practice Research Database (GPRD), England & Wales[3] Prevalence 1998: 1.2%	1994 Age ≥75: 10.9% Age ≥85: 4.5% 1998 Age ≥75: 21.2% Age ≥85: 11.0%
ECHOES study, UK[4] Prevalence 1999: 2%	Age ≥75: 17.9%
Southwest Scotland[5] No prevalence given 27 practices, 1999	Age ≥75: 29.0%
South Wales[6,7] Prevalence 2000: 1.4% (6,108/424,000)	Age >75: 27.3% Age >80: 20.8%
DIN-Link database, UK[8] "Active" AF Prevalence 2003:1.2% (12,353/1,003,372)	Age ≥75: 44.2% Age ≥85: 27.1%
South London (2004), UK[9] Prevalence: 1.2% (944/81,811)	Age ≥75: 35.5% Age ≥85: 26.4%

Table 1B: Anticoagulation rate by age (other countries)

Studies	Anticoagulation rate (%) by age
Connecticut Hospitals, USA[10] (1994)	Age 75-84: 34% Age ≥85: 23%
Long term care facilities, USA[11] (1993-5)	Age 75-84: 34.6% Age ≥85: 53.1%
Cardiovascular Health Study, USA (1995)[12]	Age 80-89: 24.2% Age ≥90: 15.4%
Missouri Medicare beneficiaries, USA (1993-6)[13] Without contraindications*	All AF patients Age >75: 29% Age >75: 41%*
Kaiser Permanente North California[14,15] Prevalence 1996-97: 0.95% (17,955/1,890,000); without contraindications*	Age 75-84: 57.3%* Age ≥85: 35.4%*
Åkersberga Community Health Centre, Sweden[16] Prevalence (1992-8): 0.45%	1992-3 Age ≥75: 26.0% 1997-8 Age ≥75: 25.0%
Italian teaching hospital (1999)[17] Prevalence:7.2% Chronic AF only	Age ≥75: 11.3%
National Ambulatory National Medical Care survey, USA[18] Prevalence (1991-2000): 0.57%	1991-1992 Age ≥80: 14.3% 1999-2000 Age ≥80: 47.5%
Stockholm South General Hospital (2002), Sweden[19] *Warfarin in AF patients without Contraindication	Age ≥80: 30% Age ≥80: 46%*
FALSTAF Study group, France (2002)[20] Permanent AF only	Age ≥80: 63.5%

National Anticoagulation Benchmark and Outcomes Report (NABOR) program, USA (2002)[21]	Age ≥80: 46%
Hospital study, USA (2001-2)[22]	Age 80-89: 45% Age ≥90: 24%

Table 1C: Anticoagulation rate by age and risk scores in the UK

Studies	Anticoagulation rate (%) by $CHADS_2$ or $CHA_2DS_2VASc \geq 2$	Anticoagulation rate (%) by age
Oxfordshire, UK (unpublished) Prevalence on 31/08/2012: 1.4% (9,449/676,395)	58.3% (31/03/2011-31/08/2012)	--
Continuous Recording Scheme, Scotland[23] Prevalence 2002: 0.87% (3,135/362,155)	42%	Age ≥75: 37.1% Age >85: 23.0%
GPRD, UK[24] No prevalence given Unclear study period Chronic AF only	22.6%	Age ≥75: 32.9% Age ≥80: 25.0% Age >85: 15.9%
GPRD, UK[25] No prevalence given 2000-9	$CHADS_2 \geq 2$ + age ≥80: 33% $CHA_2DS_2VASc \geq 2$ + age ≥80: 32%	Age ≥80: 31.9%
GRASP-AF, UK[26] Prevalence 2009-12: 1.76% (231,833/13,100,000)	$CHADS_2 \geq 2$ + age ≥80: 47.4%	Age ≥80:46.0%

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Table II: Distribution of AF/flutter types with timing of incident ischaemic stroke presentation in OXVASC

	Paroxysmal (%)	Persistent* (%)	Permanent (%)	Total (%)
Premorbid				
<80 years	36 (32.4)	20 (17.5)	54 (34.2)	110 (28.7)
≥80 years	46 (41.4)	28 (24.5)	90 (57.0)	164 (42.8)
Only at presentation	12 (10.8)	53 (46.5)	10 (6.3)	75 (19.6)
Within first month	17 (15.3)	13 (11.4)	4 (2.5)	34 (8.9)
Total	111 (100)	114 (100)	158 (100)	383 (100)

*AF was defined as persistent rather than permanent if it had been present apparently continuously but for less than one year.

Table III: The Oxford and TOAST-classification of AF-related incident ischaemic strokes in OXVASC

Oxford-classification

Category	Number (%)
Total anterior circulation infarct	86 (22·5)
Partial anterior circulation infarct	158 (41.3)
Lacunar infarct	39 (10.2)
Posterior circulation infarct	92 (24.0)
Anterior and posterior circulation	4 (1.0)
Uncertain	4 (1.0)
Total	383 (100)

TOAST-classification

Category	Paroxysmal AF Known (%)	New (%)	Persistent/ Permanent AF (%)	Total (%)
Cardioembolic	74 (90.2)	23 (79.3)	248 (91.1)	345 (90.1)
Large vessel	0 (0)	0 (0)	3 (1.1)	3 (0.8)
Small vessel	1 (1.2)	1 (3.4)	0 (0)	2 (0.5)
Undetermined	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)
Multiple	7 (8.5)	5 (17.2)	21 (7.7)	33 (8.6)
Other	0 (0)	0 (0)	0 (0)	0 (0)
Total	82 (100)	29 (100)	272 (100)	383 (100)

Table IV: Age-specific rate per 1000 population per year of incident AF-related ischaemic stroke in OCSP and OXVASC

OCSP (1981-86)	Men	Rate per 1000 per year (95% CI)	Women	Rate per 1000 per year (95% CI)	Total	Rate per 1000 per year (95% CI)
<35	0/25034	--	0/22587	--	0/47621	--
35-44	0/5959	--	0/5777	--	0/11736	--
45-54	0/4577	--	1/4467	**0.06 (0.00,0.31)**	1/9044	**0.03 (0.00,0.15)**
55-64	4/3986	**0.25 (0.07,0.64)**	3/4058	**0.18 (0.04,0.54)**	7/8044	**0.22 (0.09,0.45)**
65-74	13/2766	**1.17 (0.63,2.01)**	12/3108	**0.97 (0.5,1.69)**	25/5874	**1.06 (0.69,1.57)**
75-84	17/1223	**3.48 (2.02,5.56)**	18/2006	**2.24 (1.33,3.55)**	35/3229	**2.71 (1.89,3.77)**
≥85	5/234	**5.34 (1.73,12.47)**	12/735	**4.08 (2.11,7.13)**	17/969	**4.39 (2.55,7.02)**
Total	39/43779	**0.22 (0.16,0.3)**	46/42738	**0.27 (0.2,0.36)**	85/86517	**0.25 (0.2,0.3)**
						0.38 (0.21,0.54)*
				Premorbid AF	56/86517	**0.16 (0.12,0.21)**
				New AF	29/86517	**0.08 (0.06,0.12)**
OXVASC (2002-12)						
<35	0/22496	--	0/20821	--	0/43317	--
35-44	1/7219	**0.01 (0,0.08)**	0/6343	--	1/13562	**0.01 (0.00,0.04)**
45-54	3/6205	**0.05 (0.01,0.14)**	1/5836	**0.02 (0.00,0.10)**	4/12041	**0.03 (0.01,0.09)**
55-64	18/5221	**0.35 (0.20,0.54)**	6/5015	**0.12 (0.04,0.26)**	24/10236	**0.23 (0.15,0.35)**
65-74	40/3496	**1.14 (0.82,1.56)**	34/3685	**0.92 (0.64,1.29)**	74/7181	**1.03 (0.81,1.29)**
75-84	73/2077	**3.52 (2.76,4.42)**	72/2660	**2.71 (2.12,3.41)**	145/4737	**3.06 (2.58,3.60)**
≥85	36/532	**6.77 (4.74,9.37)**	99/1123	**8.82 (7.17,10.74)**	135/1654	**8.16 (6.84,9.66)**
Total	171/47246	**0.36 (0.31,0.42)**	212/45482	**0.47 (0.41,0.53)**	383/92728	**0.41 (0.37,0.46)**
						0.48 (0.33,0.63)*
				Premorbid AF	274/92728	**0.30 (0.26,0.33)**
				New AF	109/92728	**0.12 (0.10,0.14)**

*Standardized to 2010 UK population

Table V: Proportion of patients with incident ischaemic stroke and paroxysmal AF according to age <80 or ≥80

Paroxysmal AF	OCSP (%)	OXVASC (%)	P value
All AF			
Age <80	12 (52.2)	52 (46.8)	
Age ≥80	11 (47.8)	59 (53.2)	0.64
Total	23 (100)	111 (100)	
Premorbid AF			
Age <80	9 (56.2)	36 (43.9)	
Age ≥80	7 (43.8)	46 (56.1)	0.37
Total	16 (100)	82 (100)	
New AF			
Age <80	3 (42.9)	16 (55.2)	
Age ≥80	4 (57.1)	13 (44.8)	0.68
Total	7 (100)	29 (100)	

Table VI: Proportion of patients with non-disabling (1-month mRS <3) incident ischaemic stroke and any AF type or paroxysmal AF according to age <80 or ≥80

Non-disabling incident ischaemic stroke	OCSP (%)	OXVASC (%)	P value
Any AF type			
Age <80	27 (79.4)	77 (69.4)	
Age ≥80	7 (20.6)	34 (30.6)	0.26
Total	34 (100)	111 (100)	
Paroxysmal AF			
Age <80	5 (71.4)	31 (83.8)	
Age ≥80	2 (28.6)	6 (16.2)	0.59
Total	7 (100)	37 (100)	

Tables VIIA-D: Baseline characteristics of patients with AF-related events

Table VIIA: Baseline characteristics of patients with incident ischaemic stroke and known premorbid AF

	OCSP (1981-86; n=56)	OXVASC (2002-2012; n=274)	P value
Baseline characteristics			
Male sex (%)	26 (46.4)	126 (46.0)	0.952
Mean age (SD)	77.5 (8.8)	80·4 (9.4)	**0.038**
Premorbid risk factor			
Congestive cardiac failure	13 (23.2)	85 (31.0)	0.244
Hypertension	40 (71.4)	208 (75.9)	0.479
Age≥75	34 (60.7)	204 (74.5)	**0.037**
Diabetes	11 (19.6)	49 (17.9)	0.756
Previous TIA	16 (28.6)	46 (16.8)	**0.040**
Previous MI	12 (21.4)	59 (21.5)	0.986
Angina	10 (17.9)	87 (31.8)	**0.038**
Current smoking	13 (23.2)	17 (6.2)	**<0.0001**
Hypercholesterolaemia[#]	25 (44.6)	88 (32.1)	0.072
Peripheral vascular disease	5 (44.6)	40 (14.6)	0.260
Valvular heart disease	17 (30.4)	73 (26.6)	0.570
Premorbid medications			
Antiplatelet agent(s)	5 (8.9)	167 (60.9)	**<0.0001**
Lipid lowering agent	0	82 (29.9)	**<0.0001**
Antihypertensive(s)	16 (28.6)	212 (77.4)	**<0.0001**
Anticoagulant	3 (5.4)	46 (16.8)	**0.028**

[#]defined as ≥6.0 mmol/l

Table VIIB: Baseline characteristics, medication use, outcome and case fatality in AF-related incident systemic emboli in OXVASC

	Total AF (n=71)	Premorbid AF (n=62)
Baseline characteristics		
Male sex (%)	27 (38.0)	24 (38.7)
Mean age (SD)	82·5 (9.8)	83.4 (8.2)
Premorbid risk factor		
Congestive cardiac failure	25 (35.2)	23 (37.1)
Hypertension	55 (77.5)	47 (75.8)
Age≥75	57 (80.3)	51 (82.3)
Diabetes	10 (14.1)	9 (14.5)
Previous TIA	11 (15.5)	10 (16.1)
Previous MI	20 (28.2)	19 (30.6)
Current smoking	11 (15.5)	7 (11.3)
Hypercholesterolaemia[#]	30 (42.3)	24 (38.7)
Peripheral vascular disease	16 (22.5)	16 (25.8)
Valvular heart disease	12 (16.9)	10 (16.1)
Premorbid medications		
Antiplatelet agent(s)	36 (50.7)	32 (51.6)
Lipid lowering agent	27 (38.0)	21 (33.9)
Antihypertensive(s)	54 (76.1)	47 (75.8)
Anticoagulant	10 (14.1)	10 (16.1)
Modified Rankin scale		
30 day [Mean (SD)]	4.72 (1.7)	4·81 (1.7)
6 months [Mean (SD)]	4.85 (1.7)	4·94 (1.7)
Case fatality		
30 day (%)	42 (59.2)	38 (61.3)
6 months (%)	46 (64.8)	42 (67.7)

[#]defined as ≥6.0 mmol/l

Table VIIC: Patients with incident ischaemic stroke at age ≥80 and any AF in OCSP versus OXVASC

	OCSP (1981-86; n=34)	OXVASC (2002-2012; n=224)	P value
Baseline characteristics			
Male sex (%)	12 (35.3)	83 (37.1)	0.843
Mean age (SD)	86.0 (4.4)	86.6 (4.3)	0.472
Premorbid risk factor			
Congestive cardiac failure	12 (35.3)	60 (26.8)	0.303
Hypertension	25 (73.5)	177 (79.0)	0.469
Diabetes	5 (14.7)	28 (12.5)	0.782
Previous TIA	6 (17.6)	39 (17.4)	0.973
Previous MI	6 (17.6)	46 (20.5)	0.696
Angina	6 (17.6)	68 (30.4)	0.127
Current smoking	4 (11.8)	5 (2.2)	**0.020**
Hypercholesterolaemia[#]	11 (32.4)	59 (26.3)	0.462
Peripheral vascular disease	2 (5.9)	36 (16.1)	0.190
Valvular heart disease	8 (23.5)	48 (21.4)	0.782
Premorbid medications			
Antiplatelet agent(s)	1 (2.9)	127 (56.7)	**<0.0001**
Lipid lowering agent	0	54 (24.1)	**0.0004**
Antihypertensive(s)	5 (14.7)	173 (77.2)	**<0.0001**
Anticoagulant	0	15 (6.7)	0.231

[#]defined as ≥6.0 mmol/l

Table VIID: Patients with ischaemic stroke at aged ≥80 and known prior AF in OCSP versus OXVASC

	OCSP (1981-86; n=23)	OXVASC (2002-2012; n=164)	P value
Baseline characteristics			
Male sex (%)	10 (43.5)	61 (37.2)	0.561
Mean age (SD)	85.8 (4.7)	86.6 (4.3)	0.424
Premorbid risk factor			
Congestive cardiac failure	8 (34.8)	52 (31.7)	0.767
Hypertension	17 (73.9)	135 (82.3)	0.390
Diabetes	4 (17.4)	27 (16.5)	1.000
Previous TIA	5 (21.7)	30 (18.3)	0.775
Previous MI	6 (26.1)	37 (22.6)	0.707
Angina	3 (13.0)	58 (35.4)	**0.034**
Current smoking	3 (13.0)	1 (0.6)	**0.006**
Hypercholesterolaemia[#]	6 (26.1)	46 (28.0)	0.844
Peripheral vascular disease	1 (4.3)	25 (15.2)	0.209
Valvular heart disease	5 (21.7)	41 (25.0)	0.734
Premorbid medications			
Antiplatelet agent(s)	0	108 (65.9)	**<0.0001**
Lipid lowering agent	0	46 (28.0)	**0.001**
Antihypertensive(s)	4 (2.9)	134 (81.7)	**<0.0001**
Anticoagulant	0	14 (8.5)	0.224

[#]defined as ≥6.0 mmol/l

Table VIII: Comparison of functional outcome and case fatality at 1-month and 6-month follow up in first-ever ischaemic stroke with any and premorbid AF in OXVASC and OCSP; mRS= modified Rankin scale; *missing data in 4-6%

Total AF	**OCSP (n=85)**	**OXVASC (n=383)**	**P value**
30 days			
mRS			
Mean (SD)	3.48 (1.9)	3.66 (1.9)*	0.428
Median	3	4	
Case fatality (%)	21 (24.7)	88 (23.0)	0.733
6 months			
mRS			
Mean (SD)	3.72 (2.1)	3.80 (2.1)*	0.760
Median	4	4	
Case fatality (%)	32 (37.6)	143 (37.3)	0.957
Premorbid AF	**OCSP (n=56)**	**OXVASC (n=274)**	**P value**
30 days			
mRS			
Mean (SD)	3.71 (1.9)	3.80 (1.8)*	0.748
Median	3	4	
Case fatality (%)	17 (30.4)	71 (25.9)	0.493
6 months			
mRS			
Mean (SD)	3.73 (2.1)	3.91 (2.1)*	0.557
Median	4	4	
Case fatality (%)	21 (37.5)	109 (39.8)	0.750

Table IX: Relationship between premorbid antithrombotic therapy, pre-morbid risk scores and age in patients with incident ischaemic stroke and systemic embolism with known prior AF in OXVASC

	$CHADS_2$ Mean (Median)	CHA_2DS_2VASc Mean (Median)	HAS-BLED* Mean (Median)	Warfarin [n (%)]	No anti-thrombotics [n (%)]	Mono-antiplatelet [n (%)]	Dual-antiplatelet [n (%)]
Ischaemic stroke							
Age group							
<60 (n=8)	1.38 (1.5)	1·88 (1.5)	0.75 (1)	5 (62.5)	1 (12.5)	2 (25.0)	0
60-69 (n=27)	1.41 (1)	2.67 (2)	1.33 (1)	7 (25.9)	7 (25.9)	13 (48.1)	0
70-79 (n=75)	2.01 (2)	3.76 (4)	1.77 (2)	20 (26.7)	15 (20.0)	38 (50.7)	2 (2.7)
80-89 (n=118)	2.64 (2.5)	4.57 (4)	1.47 (1)	14 (11.9)	32 (27.1)	69 (58.5)	3 (2.5)
≥90 (n=46)	2.74 (2.5)	4.80 (5)	1.65 (2)	0	11 (23.9)	33 (71.7)	2 (4.3)
Total	2.32 (2)	4.12 (4)	1.55 (1)	46 (16.8)	66 (24.1)	155 (56.6)	7 (2.6)
Systemic embolism							
Age group							
<60 (n=1)	0	0	1 (1)	0	0	1 (100)	0
60-69 (n=1)	1.00 (1.00)	3.00 (3.0)	1 (1)	1 (100)	0	0	0
70-79 (n=16)	2.31 (2.5)	4.56 (4.5)	2.19 (2)	4 (25.0)	4 (25.0)	6 (37.5)	2 (12.5)
80-89 (n=29)	3.21 (3)	5.48 (6)	2.34 (2)	5 (17.2)	10 (34.5)	14 (48.3)	0
≥90 (n=15)	2.40 (2)	4.67 (5)	2.20 (2)	0	6 (40.0)	6 (40.0)	3 (20.0)
Total	2.69 (3)	4.92 (5)	2.23 (2)	10 (16.1)	20 (32.3)	27 (43.5)	5 (8.1)

*We did not have information on labile INR in those patients on pre-morbid warfarin and hence the maximum HAS-BLED score was out of eight instead of nine.

Tables XA-B: Premorbid warfarin use according to premorbid $CHADS_2$, CHA_2DS_2VASc and HAS-BLED scores in patients with incident ischaemic stroke (XA) and systemic embolism (XB) and known prior AF in OXVASC

XA) Ischaemic stroke with known prior AF

	Premorbid $CHADS_2$ (%)							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**Total**
Premorbid Warfarin use: Yes	3 (16.7)	10 (21.3)	12 (12.6)	14 (20.3)	5 (14.7)	1 (11.1)	1 (50)	46 (16.8)
No	15 (83.3)	37 (78.7)	83 (87.4)	55 (79.7)	29 (85.3)	8 (88.9)	1 (50)	228 (83.2)
Total	18 (100)	47 (100)	95 (100)	69 (100)	34 (100)	9 (100)	2 (100)	274 (100)

	Premorbid CHA_2DS_2VASc score (%)										
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Total**
Premorbid Warfarin use: Yes	1 (20)	2 (16.7)	5 (27.8)	9 (17.0)	12 (15)	9 (16.1)	5 (15.2)	2 (15.4)	0 (0)	1 (100)	46 (16.8)
No	4 (80)	10 (83.3)	13 (72.2)	44 (83.0)	68 (85)	47 (83.9)	28 (84.8)	11 (84.6)	3 (100)	0 (0)	228 (83.2)
Total	5 (100)	12 (100)	18 (100)	53 (100)	80 (100)	56 (100)	33 (100)	13 (100)	3 (100)	1 (100)	274 (100)

	Premorbid HAS-BLED score (%)					
	0	**1**	**2**	**3**	**4**	**Total**
Premorbid Warfarin use: Yes	3 (50)	25 (17.4)	14 (14.6)	3 (13.0)	1 (20)	46 (16.8)
No	3 (50)	119 (82.6)	82 (85.4)	20 (87.0)	4 (80)	228 (83.2)
Total	6 (100)	144 (100)	96 (100)	23 (100)	5 (100)	274 (100)

XB) Systemic embolism with known prior AF

		Premorbid $CHADS_2$ (%)							
		0	**1**	**2**	**3**	**4**	**5**	**6**	**Total**
Premorbid Warfarin use:	**Yes**	1 (50)	2 (16.7)	3 (21.4)	3 (18.8)	0 (0)	1 (20)	0 (0)	10 (16.1)
	No	1 (50)	10 (83.3)	11 (78.6)	13 (81.3)	12 (100)	4 (80)	1 (100)	52 (83.9)
	Total	2 (100)	12 (100)	14 (100)	16 (100)	12 (100)	5 (100)	1 (100)	62 (100)

		Premorbid CHA_2DS_2VASc score (%)									
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Total**
Premorbid Warfarin use:	**Yes**	0 (0)	0 (0)	1 (20)	2 (33.3)	2 (16.7)	3 (23.1)	1 (7.1)	1 (12.5)	0 (0)	10 (16.1)
	No	1 (100)	0 (0)	4 (80)	4 (66.7)	10 (83.3)	10 (76.9)	13 (92.9)	7 (87.5)	3 (100)	52 (83.9)
	Total	1 (100)	0 (0)	5 (100)	6 (100)	12 (100)	13 (100)	14 (100)	8 (100)	3 (100)	62 (100)

		Premorbid HAS-BLED score (%)					
		0	**1**	**2**	**3**	**4**	**Total**
Premorbid Warfarin use:	**Yes**	0 (0)	5 (38.5)	2 (7.1)	3 (20)	0 (0)	10 (16.1)
	No	0 (0)	8 (61.5)	26 (92.9)	12 (80)	6 (100)	52 (83.9)
	Total	0 (0)	13 (100)	28 (100)	15 (100)	6 (100)	62 (100)

Table XI: Comparison of premorbid $CHADS_2$ and HAS-BLED scores in patients with incident embolic events and known prior AF but not on anticoagulation in OXVASC

(A) All ages

		Premorbid HAS-BLED score (/9) (%)					Total
		0	1	2	3	4	
Premorbid $CHADS_2$ (/6)	0	2 (66.7)	7 (5.5)	6 (5.6)	1 (3.1)	0 (0)	16 (5.7)
	1	1 (33.3)	28 (22.0)	13 (12.0)	5 (15.6)	0 (0)	47 (16.8)
	2	0 (0)	43 (33.9)	40 (37.0)	9 (28.1)	2 (20)	94 (33.6)
	3	0 (0)	31 (24.4)	24 (22.2)	8 (25)	5 (50)	68 (24.3)
	4	0 (0)	15 (11.8)	16 (14.8)	8 (25)	2 (20)	41 (14.6)
	5	0 (0)	3 (2.4)	7 (6.5)	1 (3.1)	1 (10)	12 (4.3)
	6	0 (0)	0 (0)	2 (1.9)	0 (0)	0 (0)	2 (0.7)
	Total	3 (100)	127 (100)	108 (100)	32 (100)	10 (100)	280 (100)

(B) Age ≥80

		Premorbid HAS-BLED score (/9) (%)				Total
		1	2	3	4	
Premorbid $CHADS_2$ (/6)	1	16 (17.8)	6 (8.5)	0 (0)	0 (0)	22 (11.6)
	2	34 (37.8)	26 (36.6)	7 (31.8)	2 (33.3)	69 (36.5)
	3	25 (27.8)	17 (23.9)	7 (31.8)	2 (33.3)	51 (27.0)
	4	12 (13.3)	14 (19.7)	7 (31.8)	1 (16.7)	34 (18.0)
	5	3 (3.3)	6 (8.5)	1 (4.5)	1 (16.7)	11 (5.8)
	6	0 (0)	2 (2.8)	0 (0)	0 (0)	2 (1.1)
	Total	90 (100)	71 (100)	22 (100)	6 (100)	189 (100)

(C) All ages and excluding absolute or relative contraindication

		Premorbid HAS-BLED score (/9) (%)					Total
		0	1	2	3	4	
Premorbid $CHADS_2$ (/6)	0	1 (50)	4 (5.1)	4 (6.7)	1 (4.5)	0 (0)	10 (5.9)
	1	1 (50)	18 (23.1)	5 (8.3)	3 (13.6)	0 (0)	27 (15.9)
	2	0 (0)	24 (30.8)	21 (35.0)	3 (13.6)	2 (25.0)	50 (29.4)
	3	0 (0)	21 (26.9)	15 (25.0)	8 (36.4)	3 (37.5)	47 (27.6)
	4	0 (0)	8 (10.3)	10 (16.7)	6 (27.3)	2 (25.0)	26 (15.3)
	5	0 (0)	3 (3.8)	5 (8.3)	1 (4.5)	1 (12.5)	10 (5.9)
	Total	2	78 (100)	60 (100)	22 (100)	8 (100)	170 (100)

(D) Age ≥80 and excluding absolute or relative contraindication

		Premorbid HAS-BLED score (/9) (%)				Total
		1	2	3	4	
Premorbid $CHADS_2$ (/6)	1	11 (20.0)	3 (7.7)	0 (0)	0 (0)	14 (12.2)
	2	20 (36.4)	11 (28.2)	3 (18.7)	2 (40)	36 (31.3)
	3	15 (27.3)	12 (30.8)	7 (43.7)	1 (20)	35 (30.4)
	4	6 (10.9)	9 (23.1)	5 (31.3)	1 (20)	21 (18.3)
	5	3 (5.5)	4 (10.3)	1 (6.3)	1 (20)	9 (7.8)
	Total	55 (100)	39 (100)	16 (100)	5 (100)	115 (100)

Table XII: Reasons for no premorbid warfarin use in patients at all ages and at age ≥80 years with incident embolic events, known prior AF and $CHADS_2$ score ≥2 in OXVASC

	Number (%)	
	All ages (n=217)	Age ≥80 (n=167)
No explanation	135 (62.2)	103 (61.7)
Patient refusal	21 (9.7)	15 (9.0)
Paroxysmal AF	7 (3.2)	5 (3.0)
In clinical trial	1 (0.5)	1 (0.6)
Previous cardioversion	1 (0.5)	0 (0)
Low $CHADS_2$ score	1 (0.5)	0 (0)
Absolute contraindication		
Multiple contraindications	4 (1.8)	3 (1.8)
Recent, active bleed	2 (0.9)	2 (1.2)
Non-compliant	1 (0.5)	1 (0.6)
Relative contraindication		
Previous bleed	14 (6.5)	12 (7.2)
Risk of falls	12 (5.5)	10 (6.0)
Dementia	7 (3.2)	7 (4.2)
Physician perception of unsuitability	4 (1.8)	2 (1.2)
Concurrent cancer	2 (0.9)	1 (0.6)
Anaemia	2 (0.9)	2 (1.2)
Renal or hepatic impairment	1 (0.5)	1 (0.6)
Old age	1 (0.5)	1 (0.6)
Frequent seizures	1 (0.5)	1 (0.6)

Table XIII: Reasons for stopping previous warfarin at any point prior to an embolic event in OXVASC; OAC=anticoagulation

All ages

	Frequency	Percent
1. OAC never started	258	92.1
2. Stopped due to absolute contraindication	3	1.1
3. Stopped due to relative contraindication	7	2.5
4. Stopped for minor illness but forgot to restart	1	0.4
5. Stopped OAC for no apparent reason	5	1.8
6. Stopped or changed to antiplatelets as in sinus rhythm	2	0.7
7. Stopped as patient later declined	1	0.4
8. Changed to antiplatelet for no obvious reason	3	1.1
Total	280	100.0

Age ≥80

	Frequency	Percent
1. OAC never started	179	94.7
2. Stopped due to absolute contraindication	3	1.6
3. Stopped due to relative contraindication	2	1.1
4. Stopped for minor illness but forgot to restart	1	0.5
5. Stopped OAC for no apparent reason	1	0.5
6. Stopped or changed to antiplatelets as in sinus rhythm	1	0.5
7. Stopped as patient later declined	0	0
8. Changed to antiplatelet for no obvious reason	2	1.1
Total	189	100.0

Tables XIVA-B: Changes in disability status (modified Ranking scale – mRS) in patients with an incident ischaemic stroke or systemic embolism but not on premorbid anticoagulants.

Table XIVA: Changes in disability status (modified Ranking scale – mRS) in patients with an incident ischaemic stroke or systemic embolism and <u>any</u> AF but not on premorbid anticoagulants.

All ages

All events		6 month mRS (%)				
		0-2	3	4-5	6	Total
Pre-morbid mRS	0-2	112 (97.4)	32 (60.4)	34 (61.8)	80 (46.0)	258 (65.0)
	3	3 (2.6)	21 (39.6)	11 (20.0)	67 (38.5)	102 (25.7)
	4-5	0 (0)	0 (0)	10 (18.2)	27 (15.5)	37 (9.3)
	Total	115 (100)	53 (100)	55 (100)	174 (100)	397 (100)

Ischaemic stroke		6 month mRS (%)				
		0-2	3	4-5	6	Total
Pre-morbid mRS	0-2	102 (97.1)	29 (58)	32 (65.3)	62 (47.0)	225 (67.0)
	3	3 (2.9)	21 (42)	7 (14.3)	49 (37.1)	80 (23.8)
	4-5	0 (0)	0 (0)	10 (20.4)	21 (15.9)	31 (9.2)
	Total	105 (100)	50 (100)	49 (100)	132 (100)	336 (100)

Age ≥80

All events		6 month mRS (%)				
		0-2	3	4-5	6	Total
Pre-morbid mRS	0-2	40 (95.2)	16 (50)	23 (57.5)	58 (42.0)	137 (54.4)
	3	2 (4.8)	16 (50)	9 (22.5)	56 (40.6)	83 (32.9)
	4-5	0 (0)	0 (0)	8 (20.0)	24 (17.4)	32 (12.7)
	Total	42 (100)	32 (100)	40 (100)	138 (100)	252 (100)

Ischaemic stroke		6 month mRS (%)				
		0-2	3	4-5	6	Total
Pre-morbid mRS	0-2	38 (95)	14 (46.7)	21 (61.8)	47 (44.8)	120 (57.4)
	3	2 (5)	16 (53.3)	5 (14.7)	40 (38.1)	63 (30.1)
	4-5	0 (0)	0 (0)	8 (23.5)	18 (17.1)	26 (12.4)
	Total	40 (100)	30 (100)	34 (100)	105 (100)	209 (100)

Table XIVB: Changes in disability status (modified Ranking scale – mRS) in patients with an incident ischaemic stroke or systemic embolism and <u>known prior</u> AF but not on premorbid anticoagulants.

All ages

All events		6 month mRS (%)				
		0-2	3	4-5	6	Total
Pre-morbid mRS	0-2	70 (97.2)	23 (65.7)	21 (58.3)	64 (46.7)	178 (63.6)
	3	2 (2.8)	12 (34.3)	8 (22.2)	54 (39.4)	76 (27.1)
	4-5	0 (0)	0 (0)	7 (19.4)	19 (13.9)	26 (9.3)
	Total	72 (100)	35 (100)	36 (100)	137 (100)	280 (100)

Ischaemic stroke		6 month mRS (%)				
		0-2	3	4-5	6	Total
Pre-morbid mRS	0-2	62 (96.9)	21 (63.6)	19 (59.4)	49 (49.5)	151 (66.2)
	3	2 (3.1)	12 (36.4)	6 (18.8)	37 (37.4)	57 (25.0)
	4-5	0 (0)	0 (0)	7 (21.8)	13 (13.1)	20 (8.8)
	Total	64 (100)	33 (100)	32 (100)	99 (100)	228 (100)

Age ≥80

All events		6 month mRS (%)				
		0-2	3	4-5	6	Total
Pre-morbid mRS	0-2	26 (92.9)	12 (54.5)	14 (53.8)	47 (41.6)	99 (52.4)
	3	2 (7.1)	10 (45.5)	7 (26.9)	48 (42.5)	67 (35.4)
	4-5	0 (0)	0 (0)	5 (19.3)	18 (15.9)	23 (12.2)
	Total	28 (100)	22 (100)	26 (100)	113 (100)	189 (100)

Ischaemic stroke		6 month mRS (%)				
		0-2	3	4-5	6	Total
Pre-morbid mRS	0-2	24 (92.3)	10 (50)	12 (54.6)	38 (46.4)	84 (56.0)
	3	2 (7.7)	10 (50)	5 (22.7)	32 (39.0)	49 (32.7)
	4-5	0 (0)	0 (0)	5 (22.7)	12 (14.6)	17 (11.3)
	Total	26 (100)	20 (100)	22 (100)	82 (100)	150 (100)

Table XVA: Care costs for incident embolic vascular events in non-anticoagulated patients with known prior AF, extrapolated from OXVASC across the UK

	Rate/1,000/year (95% CI)			% of patients not treated with warfarin			UK Population Projections 2010 (in 1000s)			Number of events in patients with untreated known-AF			Cost of event (patients with untreated known-AF)	Total cost of events in patients with untreated known-AF, £ (in 000s)		
Age	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	£, per patient	Men	Women	Total
Ischaemic stroke in patients with known AF (i.e. premorbid AF)																
<80	0.14	0.10	0.12	68%	76%	71%	29,576	29,782	59,359	2,836	2,345	5,181	£17,442	£49,460	£40,907	£90,367
80-84	4.50	2.28	3.19	86%	89%	88%	607	886	1,493	2,364	1,795	4,159	£26,454	£62,547	£47,474	£110,021
85-89	4.16	5.21	4.84	94%	87%	89%	326	608	935	1,270	2,751	4,021	£26,454	£33,608	£72,773	£106,381
≥90	5.45	9.68	8.53	100%	100%	100%	134	342	476	730	3,312	4,042	£26,454	£19,305	£87,613	£106,918
Total	0.27	0.33	0.30	79%	87%	83%	30,643	31,619	62,262	7,200	10,203	17,403		£164,919	£248,767	£413,686
<80									59,359			5,181				£90,367
≥80									2,904			12,222				£323,319
Systemic emboli in patients with known AF (i.e. premorbid AF)																
<80	0.02	0.02	0.02	68%	76%	71%	29,576	29,782	59,359	393	469	862	£3,651	£1,434	£1,713	£3,146
80-84	0.61	0.59	0.60	86%	89%	88%	607	886	1,493	319	465	785	£14,842	£4,740	£6,907	£11,647
85-89	1.30	1.51	1.43	94%	87%	89%	326	608	935	397	796	1,193	£14,842	£5,892	£11,818	£17,710
≥90	3.40	2.80	2.97	100%	100%	100%	134	342	476	455	958	1,413	£14,842	£6,758	£14,216	£20,973
Total	0.05	0.08	0.07	79%	87%	83%	30,643	31,619	62,262	1,564	2,688	4,253		£18,824	£34,653	£53,477
<80	0.02	0.02	0.02	68%	76%	71%			59,359			862				£3,146
≥80	0.61	0.59	0.60	86%	89%	88%			2,904			3,391				£50,331

Table XVB: Care costs for AF-related incident embolic vascular events extrapolated from OXVASC across the UK, projections for 2050

	Rate/1,000/year (95% CI)			UK Population Projections 2050 (in 1000s)			Number of AF-related events			Cost of AF-related events	Total cost of AF-related events £ (in 000s)		
Age	Men	Women	Total	Men	Women	Total	Men	Women	Total	£, per patient	Men	Women	Total
AF-related IS													
<80	0.19	0.16	0.18	35,703	34,728	70,431	6,846	5,711	12,557	£19,603	£134,205	£111,951	£246,157
80-84	5.72	3.55	4.44	1,450	1,722	3,172	8,295	6,108	14,403	£24,345	£201,954	£148,692	£350,646
85-89	6.49	6.71	6.64	1,124	1,428	2,552	7,299	9,589	16,888	£24,345	£177,704	£233,434	£411,138
≥90	7.50	12.73	11.31	1,065	1,519	2,584	7,987	19,343	27,330	£24,345	£194,436	£470,909	£665,346
Total	0.36	0.47	0.41	39,343	39,398	78,741	30,428	40,750	71,178		£708,299	£964,987	£1,673,286
<80						70,431			12,557				£246,157
≥80						8,309			58,621				£1,427,129
AF-related systemic emboli													
<80	0.02	0.03	0.03	35,703	34,728	70,431	856	965	1,821	£13,969	£11,954	£13,483	£25,438
80-84	0.73	0.59	0.65	1,450	1,722	3,172	1,059	1,018	2,077	£13,606	£14,403	£13,854	£28,256
85-89	1.30	1.78	1.61	1,124	1,428	2,552	1,460	2,544	4,004	£13,606	£19,863	£34,608	£54,472
≥90	3.40	3.05	3.15	1,065	1,519	2,584	3,630	4,642	8,273	£13,606	£49,390	£63,159	£112,549
Total	0.06	0.10	0.08	39,343	39,398	78,741	7,005	9,169	16,174		£95,610	£125,105	£220,715
<80						70,431			1,821				£25,438
≥80						8,309			14,353				£195,277

Tables XVIA-G: Numbers used in calculation of extrapolations from OXVASC to current and future event numbers in the UK population

XVIA: UK population projections (in 1000s) by Office for National Statistics (UK)* for 1981-86, 2010, 2030 and 2050 by mid-point 10-year age bands

	1981-1986 averaged			2010			2030			2050		
Age	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
<35	14399	13910	28309	13918	13316	27235	15114	14450	29565	16089	15379	31468
35-44	3637	3606	7242	4378	4456	8834	4960	4671	9631	5149	4908	10056
45-54	3099	3112	6211	4215	4332	8547	4164	4109	8273	4494	4346	8840
55-64	2963	3204	6168	3599	3743	7342	4100	4308	8408	4689	4542	9230
65-74	2235	2872	5107	2572	2827	5399	3579	3886	7465	3762	3849	7611
75-84	991	1833	2824	1501	1993	3494	2431	2860	5291	2971	3428	6399
≥85	154	506	660	460	951	1411	1131	1628	2759	2190	2947	5137
Total	27477	29044	56521	30643	31619	62262	35480	35912	71392	39343	39398	78741

*http://www.statistics.gov.uk/hub/population/index.html. Assessed 18th Nov 2012.

XVIB: UK population projections (in 1000s) by the Office for National Statistics (UK)* for 2010, 2030 and 2050 by 5-year age bands

	2010			2030			2050		
Age	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
0- 4	1977	1881	3858	2043	1945	3988	2251	2143	4394
5- 9	1762	1685	3446	2096	2001	4097	2226	2125	4352
10-14	1825	1742	3567	2144	2051	4195	2152	2058	4210
15-19	2013	1899	3912	2176	2084	4259	2108	2018	4126
20-24	2213	2097	4310	2196	2118	4314	2258	2177	4436
25-29	2169	2081	4250	2161	2074	4235	2484	2379	4863
30-34	1960	1932	3891	2299	2178	4477	2610	2478	5088
35-39	2085	2117	4202	2470	2325	4794	2644	2515	5159
40-44	2293	2339	4632	2490	2347	4837	2505	2392	4897
45-49	2250	2316	4566	2233	2163	4396	2261	2182	4443
50-54	1965	2016	3981	1930	1946	3877	2233	2164	4397
55-59	1759	1820	3578	1990	2076	4066	2335	2257	4592
60-64	1840	1924	3764	2110	2233	4343	2353	2285	4638
65-69	1412	1520	2932	1977	2126	4104	2069	2058	4126
70-74	1160	1307	2468	1601	1760	3361	1693	1791	3484
75-79	894	1108	2002	1286	1477	2763	1521	1706	3226
80-84	607	886	1493	1145	1383	2529	1450	1722	3172
85-89	326	608	935	660	883	1542	1124	1428	2552
90-94	110	255	365	333	502	835	648	890	1538
95-99	22	76	98	117	197	313	292	428	720
≥100	2	11	13	22	46	68	126	201	327
Total	30643	31619	62262	35480	35912	71392	39343	39398	78741

*http://www.statistics.gov.uk/hub/population/index.html. Assessed 3rd Nov 2012

XVIC: Estimated number of patients with AF-related incident ischaemic stroke based on extrapolation of age/sex-specific rates in OCSP to UK population in 1981-86

OCSP 1981-86	**Total number/ number at risk**	**Rate/100,000/year (95% CI)**			**UK Population Projections 1981-86 (in 1000s)**			**Estimated numbers (in 1000s)**		
Age		Men	Women	Total	Men	Women	Total	Men	Women	Total
<80	51/84361	15.65	14.56	15.11	26996	27812	54809	4224	4049	8272
80-84	17/1187	436.55	318.01	358.04	327	725	1052	1427	2307	3734
≥85	17/969	534.19	408.16	438.60	154	506	660	820	2066	2887
Total	85/86517	22.27	26.91	24.56	27477	29044	56521	6471	8422	14893
									Age ≥80:	6621
									% Age ≥80:	44.5

XVID: Estimated number of patients with AF-related events based on extrapolation of age/sex-specific rates in OXVASC to UK population in 2010

	Total number/ number at risk	Rate/100,000/year (95% CI)			UK Population Projections 2010 (in 1000s)			Numbers (in 1000s)		
Age		Men	Women	Total	Men	Women	Total	Men	Women	Total
Ischaemic stroke										
<80	159/89068	19.18	16.44	17.85	29576	29782	59359	5671	4898	10569
80-84	89/2006	572.02	354.64	443.68	607	886	1493	3473	3140	6613
85-89	74/1115	649.35	671.31	663.72	326	608	935	2117	4085	6202
≥90	61/539	749.59	1273.46	1130.93	134	342	476	1003	4358	5361
Total	383/92728	36.19	46.61	41.30	30643	31619	62262	12265	16481	28745
Systemic emboli										
<80	23/89068	2.40	2.78	2.58	29576	29782	59359	709	828	1537
80-84	13/2006	73.02	59.11	64.81	607	886	1493	443	523	967
85-89	18/1115	129.87	178.10	161.45	326	608	935	423	1084	1507
≥90	17/539	340.72	305.63	315.18	134	342	476	456	1046	1502
Total	71/92728	5.71	9.67	7.66	30643	31619	62262	2032	3481	5513
All events										
<80	182/89068	21.57	19.22	20.43	29576	29782	59359	6380	5725	12106
80-84	102/2006	645.04	413.75	508.49	607	886	1493	3916	3664	7580
85-89	92/1115	779.22	849.41	825.17	326	608	935	2541	5168	7709
≥90	78/539	1090.31	1579.09	1446.11	134	342	476	1459	5404	6863
Total	454/92728	41.91	56.29	48.96	30643	31619	62262	14297	19961	34258

XVIE: Increment in age-specific incidence rates between OXVASC and OCSP over 25 years

	Number in 10 years	**Number at risk per year**	**Rate/1000**	**Relative rate (OXVASC/OCSP)**			
Age (yr)				Increase over 25yr	% increase per 10yr	"Factor" for 20yr	"Factor" for 40yr
OXVASC							
<80	159	89068	0.178516	1.181158	7.246336	**1.144927**	**1.289853**
≥80	224	3660	6.119801	1.552275	22.09099	**1.44182**	**1.88364**
Total	383	92728	0.413036	1.68163			
OCSP							
<80	51	84361	0.151136				
≥80	34	2156	3.942473				
Total	85	86517	0.245616				

XVIF: Estimated number of patients with AF-related events based on extrapolation of age/sex-specific rates in OXVASC to UK population in 2030

Ischaemic stroke	**Rate/100,000/year (95% CI)**			**UK Population Projections 2030 (in 1000s)**			**Estimated numbers: no rate increase (in 1000s)**		
Age	Men	Women	Total	Men	Women	Total	Men	Women	Total
<80	19.18	16.44	17.85	33203	32901	66104	6367	5410	11777
80-84	572.02	354.64	443.68	1145	1383	2529	6552	4905	11457
85-89	649.35	671.31	663.72	660	883	1542	4283	5926	10209
≥90	749.59	1273.46	1130.93	472	745	1217	3538	9490	13028
Total	36.19	46.61	41.30	35480	35912	71392	20739	25732	46471
Systemic emboli									
<80	2.40	2.78	2.58	33203	32901	66104	796	914	1710
80-84	73.02	59.11	64.81	1145	1383	2529	836	818	1654
85-89	129.87	178.10	161.45	660	883	1542	857	1572	2429
≥90	340.72	305.63	315.18	472	745	1217	1608	2278	3886
Total	5.71	9.67	7.66	35480	35912	71392	4097	5582	9679
All events									
<80	21.57	19.22	20.43	33203	32901	66104	7163	6325	13487
80-84	645.04	413.75	508.49	1145	1383	2529	7388	5723	13111
85-89	779.22	849.41	825.17	660	883	1542	5139	7498	12637
≥90	1090.31	1579.09	1446.11	472	745	1217	5146	11768	16914
Total	41.91	56.29	48.96	35480	35912	71392	24836	31314	56150

XVIG: Estimated number of patients with incident AF-related events based on extrapolation of rates in OXVASC to UK population in 2050

Ischaemic stroke	**Rate/100,000/year (95% CI)**			**UK Population Projections 2050 (in 1000s)**			**Estimated numbers: no rate increase (in 1000s)**		
Age	Men	Women	Total	Men	Women	Total	Men	Women	Total
<80	19.18	16.44	17.85	35703	34728	70431	6846	5711	12557
80-84	572.02	354.64	443.68	1450	1722	3172	8295	6108	14403
85-89	649.35	671.31	663.72	1124	1428	2552	7299	9589	16888
≥90	749.59	1273.46	1130.93	1065	1519	2584	7987	19343	27330
Total	36.19	46.61	41.30	39343	39398	78741	30428	40750	71178
Systemic emboli									
<80	2.40	2.78	2.58	35703	34728	70431	856	965	1821
80-84	73.02	59.11	64.81	1450	1722	3172	1059	1018	2077
85-89	129.87	178.10	161.45	1124	1428	2552	1460	2544	4004
≥90	340.72	305.63	315.18	1065	1519	2584	3630	4642	8273
Total	5.71	9.67	7.66	39343	39398	78741	7005	9169	16174
All events									
<80	21.57	19.22	20.43	35703	34728	70431	7702	6676	14378
80-84	645.04	413.75	508.49	1450	1722	3172	9354	7126	16480
85-89	779.22	849.41	825.17	1124	1428	2552	8759	12132	20892
≥90	1090.31	1579.09	1446.11	1065	1519	2584	11617	23986	35603
Total	41.91	56.29	48.96	39343	39398	78741	37433	49920	87353

Table XVII: Quality and Outcomes framework guidance on AF management from 2006-2013[§]

Indicator	Points	2006-7	2007-8	2008-9	2009-10*	2010-11*	2011-12*	2012-13*	Payment stages
AF register (2006-2013)	5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
AF diagnosis (2006-12)	10	Yes	Yes	Yes	Yes	Yes	Yes	--	40-90%
OAC or antiplatelet agents (2006-12)	15	Yes	Yes	Yes	**points ↓from 15 to 12**	**points ↓from 15 to 12**	**points ↓from 15 to 12**	see below	40-90%
Use of $CHADS_2$ in preceding 15 months (2012-13)	10	--	--	--	--	--	--	Yes	40-90%
$CHADS_2$ score =1 in preceding 15 months + use of OAC or antiplatelet (2012-13)	6	--	--	--	--	--	--	Yes	50-90%
$CHADS_2$ ≥2 and treated with OAC (2012-13)	6	--	--	--	--	--	--	Yes	40-70%

[§]http://www.qof.ic.nhs.uk. Accessed December 10th 2012.
*Maximum QOF points for AF reduced from 30 in 2006-2009 to 27 in 2009-2013.

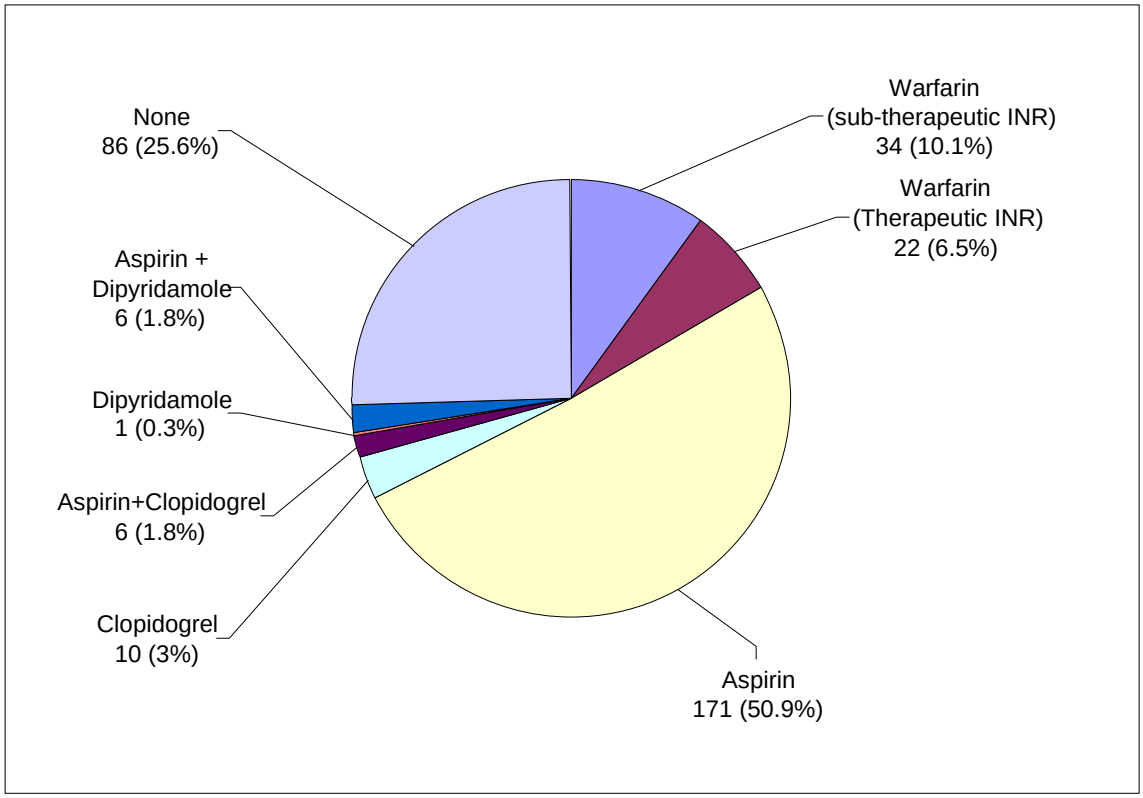
Table XVIII: Mean institutional costs incurred by patients with ischaemic event and known prior AF according to premorbid anticoagulation in first 5 years of OXVASC

	Mean cost (SD)
Patients with ischaemic stroke and known prior AF	
On warfarin (n=17)	£26,734 (S.D. 48,202)
Not on warfarin (n=109)	£22,816 (S.D. 44,058)
Patients with systemic emboli and known prior AF	
On warfarin (n=7)	£17,486 (S.D. 23,011)
Not on warfarin (n=24)	£12,511 (S.D. 22,003)

Table XIX: 6-month functional outcome in patients with ischaemic event and known prior AF according to premorbid anticoagulation in OXVASC

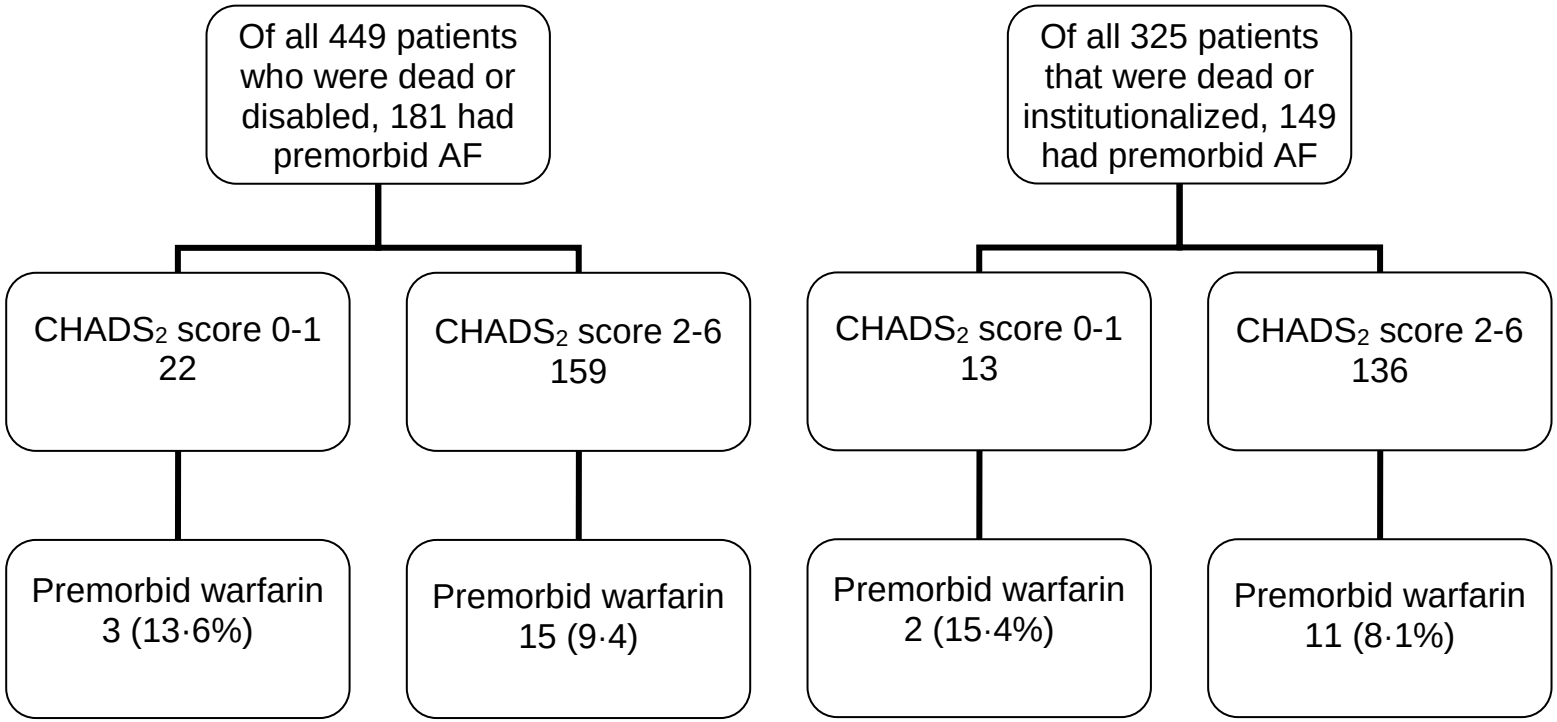
	No warfarin (%)	Warfarin (%)	P value
Ischaemic stroke and known prior AF			
mRS 0-2	63 (27.6)	17 (37.0)	
mRS 3-6	165 (72.4)	29 (63.0)	0.20
Total	228 (100)	46 (100)	
Systemic emboli and known prior AF			
mRS 0-2	8 (15.4)	1 (10)	
mRS 3-6	44 (84.6)	9 (90)	1.00
Total	52 (100)	10 (100)	

Figure I: Premorbid antithrombotic therapy in the 336 OXVASC patients with incident AF-related ischaemic stroke or systemic embolism and known prior AF

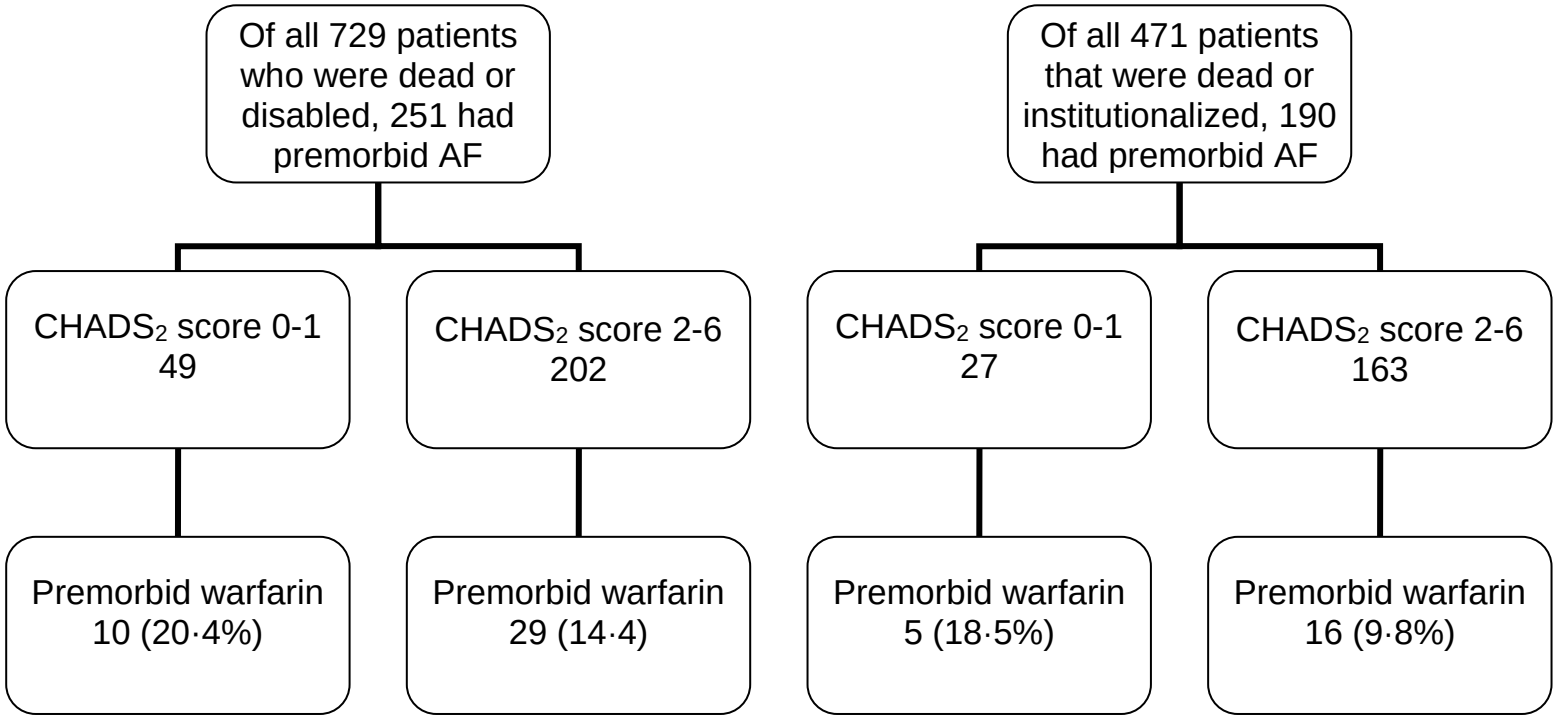


Figures IIA-F: Premorbid warfarin use in OXVASC patients with known prior AF who had a fatal/disabling embolic event or were institutionalized at 6 months follow-up

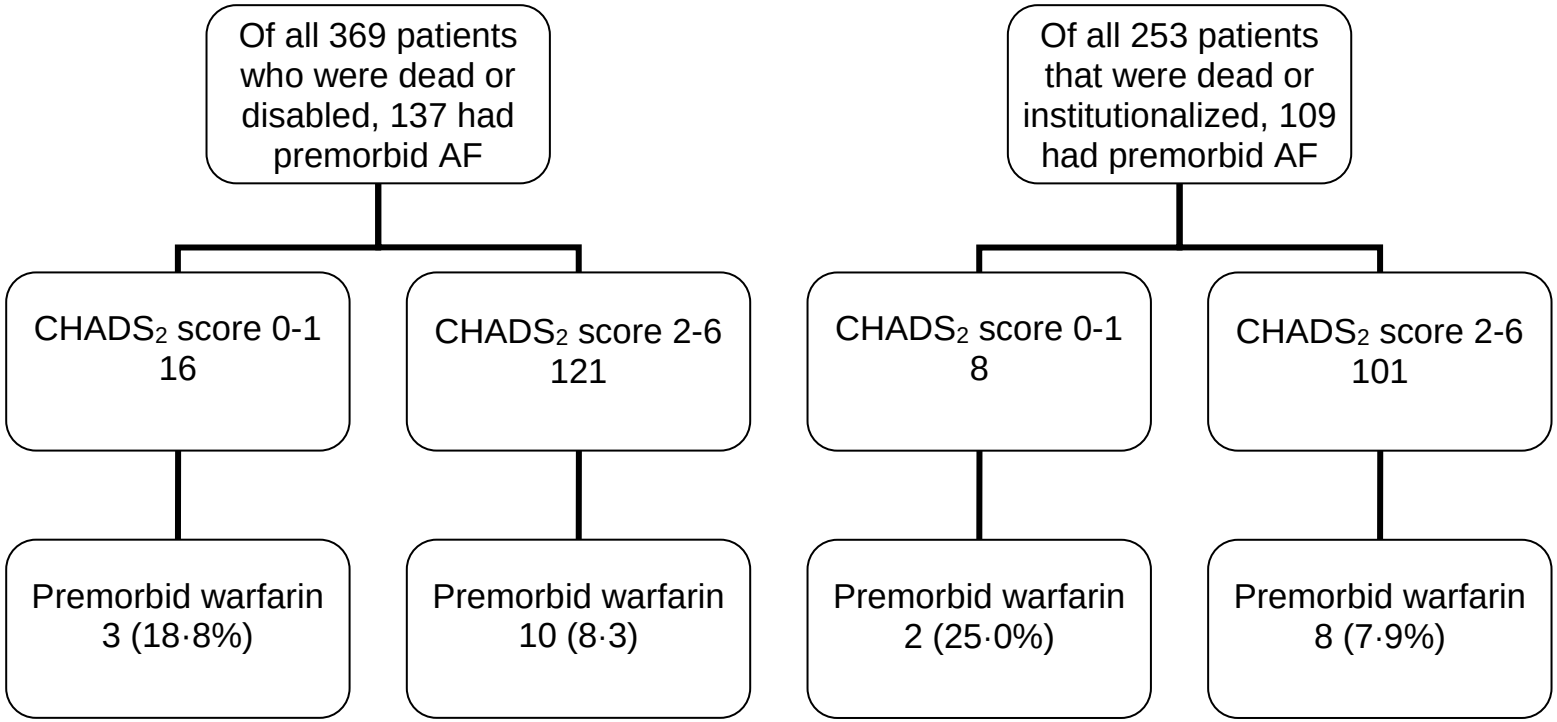
IIA: Premorbid warfarin use in OXVASC patients at age ≥80 with known prior AF who had a fatal/disabling embolic event or were institutionalized at 6 months follow-up. Total AF embolic events disabled/dead=230/449; Total AF embolic events institutionalized/dead=185/325



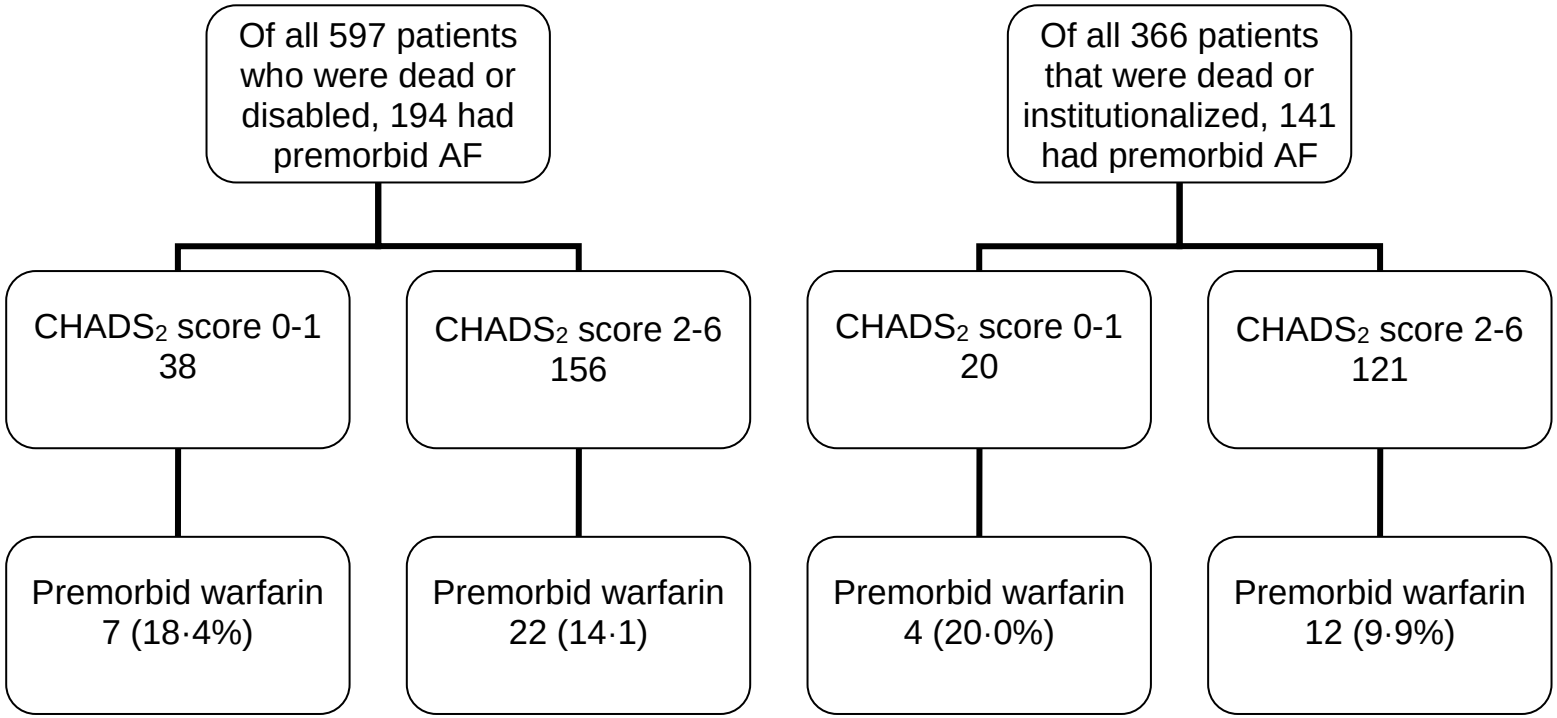
IIB: Premorbid warfarin use in OXVASC patients with known prior AF who had a fatal/disabling embolic event or were institutionalized at 6 months follow-up. Total AF embolic events disabled/dead=325/729; Total AF embolic events institutionalized/dead=240/471



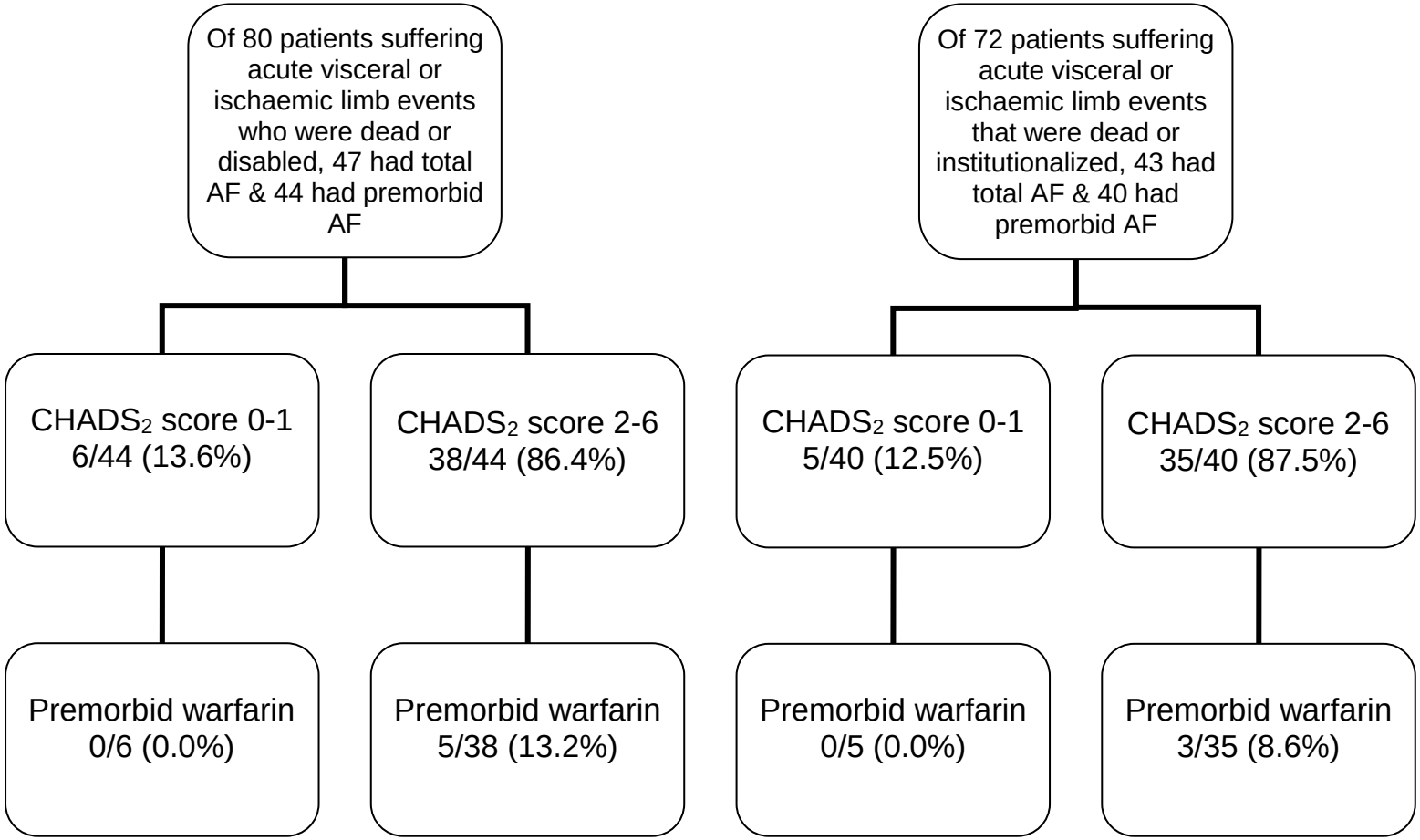
IIC: Premorbid warfarin use in OXVASC patients at age ≥80 with known prior AF who had a fatal/disabling ischaemic stroke or were institutionalized at 6 months follow-up. Total AFIIS (AF-related incident ischaemic stroke) disabled/dead =183/369;
Total AFIIS institutionalized/dead =142/253



IID: Premorbid warfarin use in OXVASC patients with known prior AF who had a fatal/disabling stroke or were institutionalized at 6 months follow-up. Total AFIIS disabled/death=262; Total AFIIS institutionalized/dead=186



IIE: Premorbid warfarin use in OXVASC patients at age ≥80 with known prior AF who had a fatal/disabling (6M mRS=3-6) systemic embolism or were institutionalized at 6 months follow-up.



IIF: Premorbid warfarin use in OXVASC patients with known prior AF who had a fatal/disabling (6M mRS=3-6) systemic embolism or were institutionalized at 6 months follow-up.

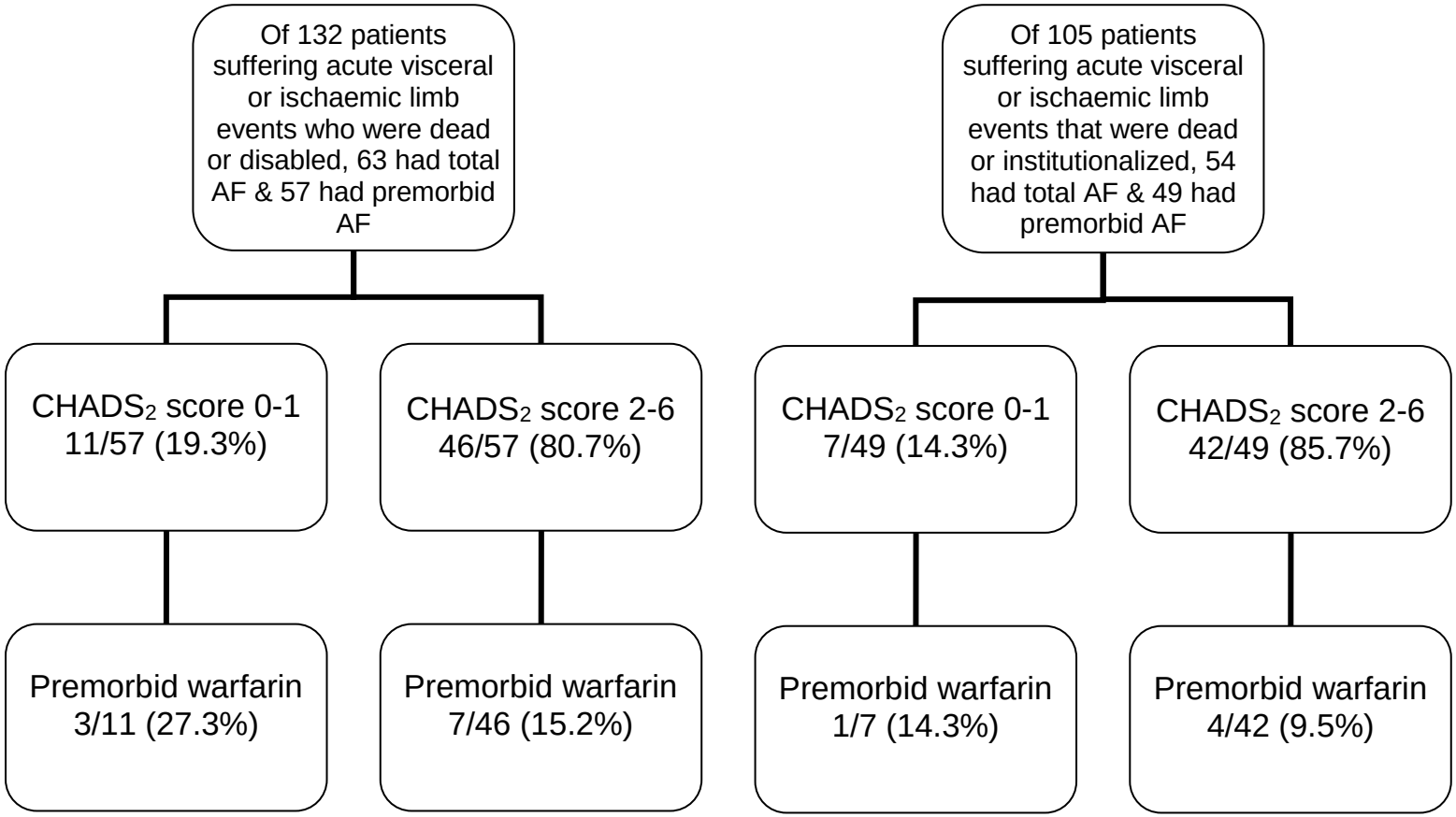


Figure III: Premorbid antithrombotic agent use according to $CHADS_2$ score (n=336); white bar=anticoagulation, gray bar=antiplatelet(s), black bar=no antithrombotic agent

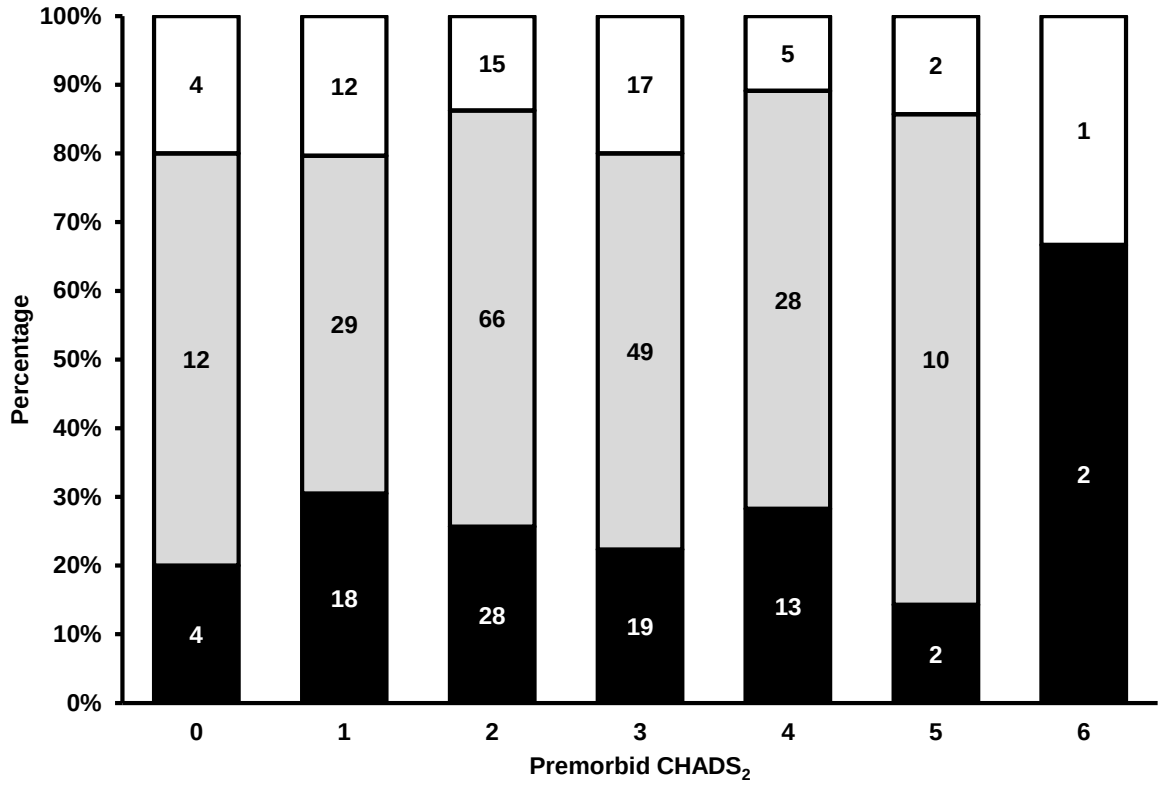


Figure IV: 5-year risk of institutionalization in a nursing or residential home care after AF-related incident stroke

For our analysis, only the costs for patients institutionalized within 6 months of incident stroke were included in the analysis.

Figure V: Rates of prior anticoagulation in patients with incident stroke or ischaemic stroke and known prior AF in OXVASC and other recent stroke incidence studies; OAC=oral anticoagulation; *incident ischaemic stroke

Studies	OAC / Premorbid AF	% OAC	95% CI
2001-5 Barbados	19 / 64	29.7	18.5-40.9
2002-3 Auckland, NZ	71 / 289	24.6	19.6-29.5
2000-6 Dijon, France*	30 / 139	21.6	14.7-28.4
2005-6 North Dublin*	16 / 62	25.8	14.9-36.7
2006-7 Ludwigshafen, Germany*	42 / 121	34.7	26.2-43.2
2002-12 OXVASC, UK*	46 / 274	16.8	12.4-21.2
TOTAL	224 / 949	23.6	18.6-28.6
Heterogeneity	**p= 0.004476**