ATRIAL FIBRILLATION
NETWORK

Flec-SL – AFNET 3

Hauptergebnis

The Flec-SL – AFNET 3 trial

Professor Paulus Kirchhof

Professor of Cardiovascular Medicine

University of Birmingham Centre for Cardiovascular Sciences and SWBH NHS Trust, Birmingham, UK

Department of Cardiology and Angiology, University Hospital Münster, Germany

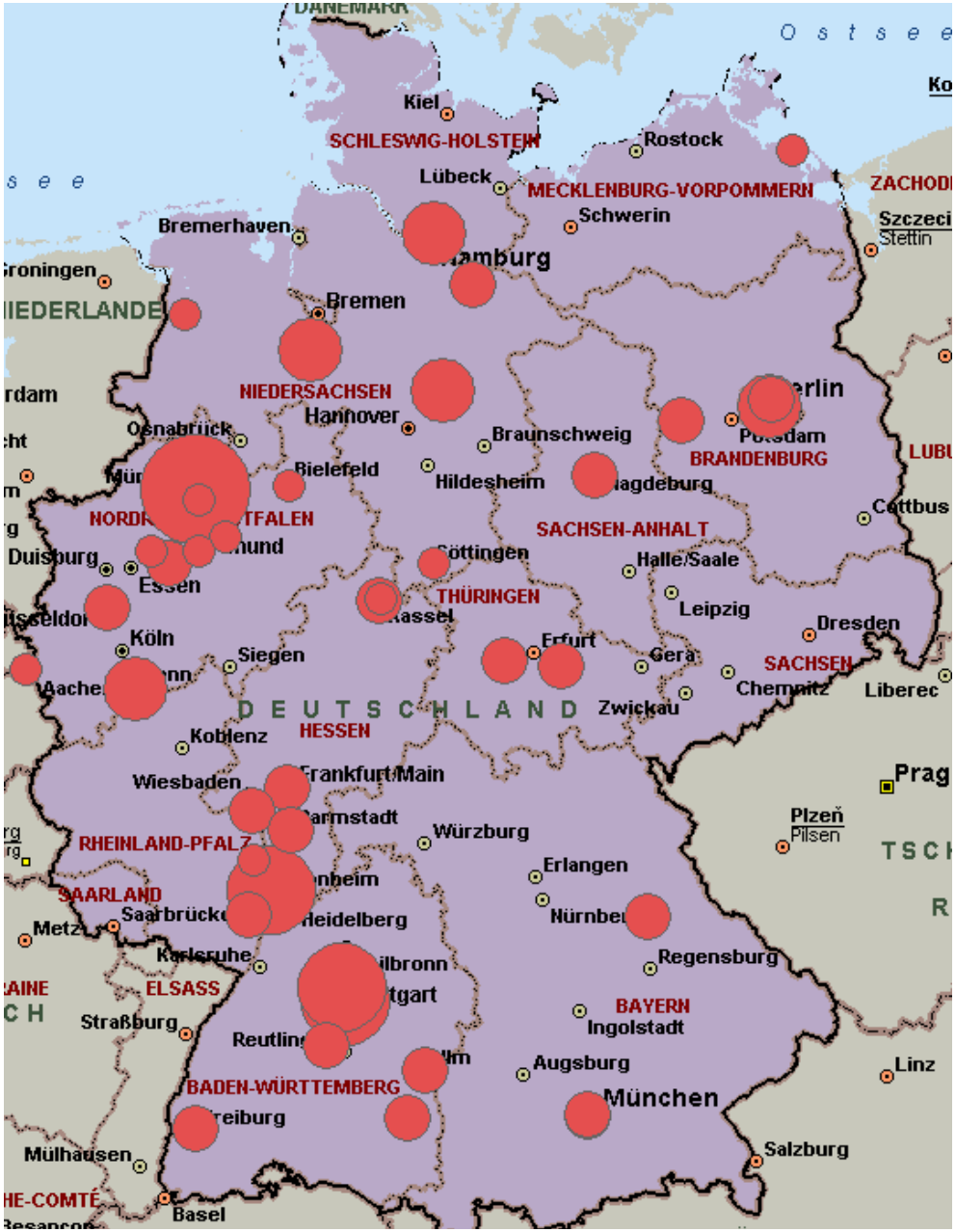
Flec-SL AFNET 3 is registered at ISRCTN62728742

Flec SL Hypothesis

Targeted, short-term pharmacological reversal of electrical remodeling is not inferior to prevent recurrent AF after cardioversion when compared to standard long-term antiarrhythmic medication.

Kirchhof P, et al. Am Heart J.150: 899 (2005)

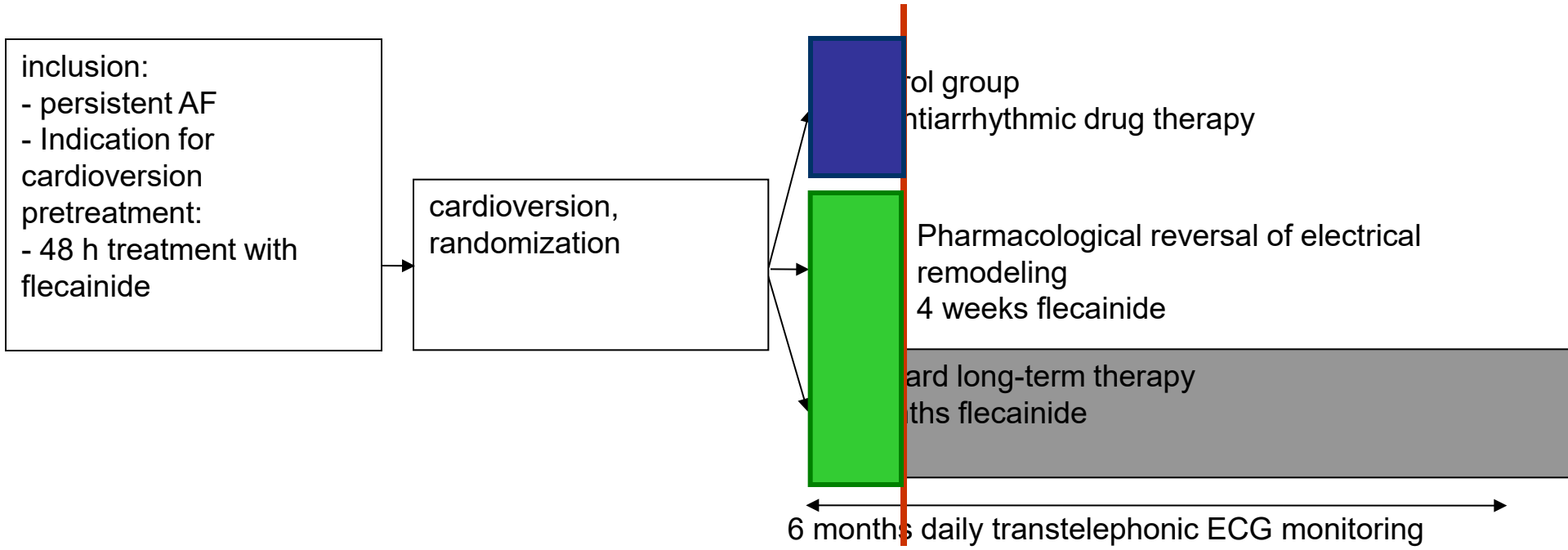
Flec-SL patient recruitment



635 patients, 44 centers

Top recruiting centers
(University Hospital Münster)
University Hospital Mannheim
Cardiology Office Ludwigsburg
Robert Bosch Hospital Stuttgart

Results of 1st analysis step



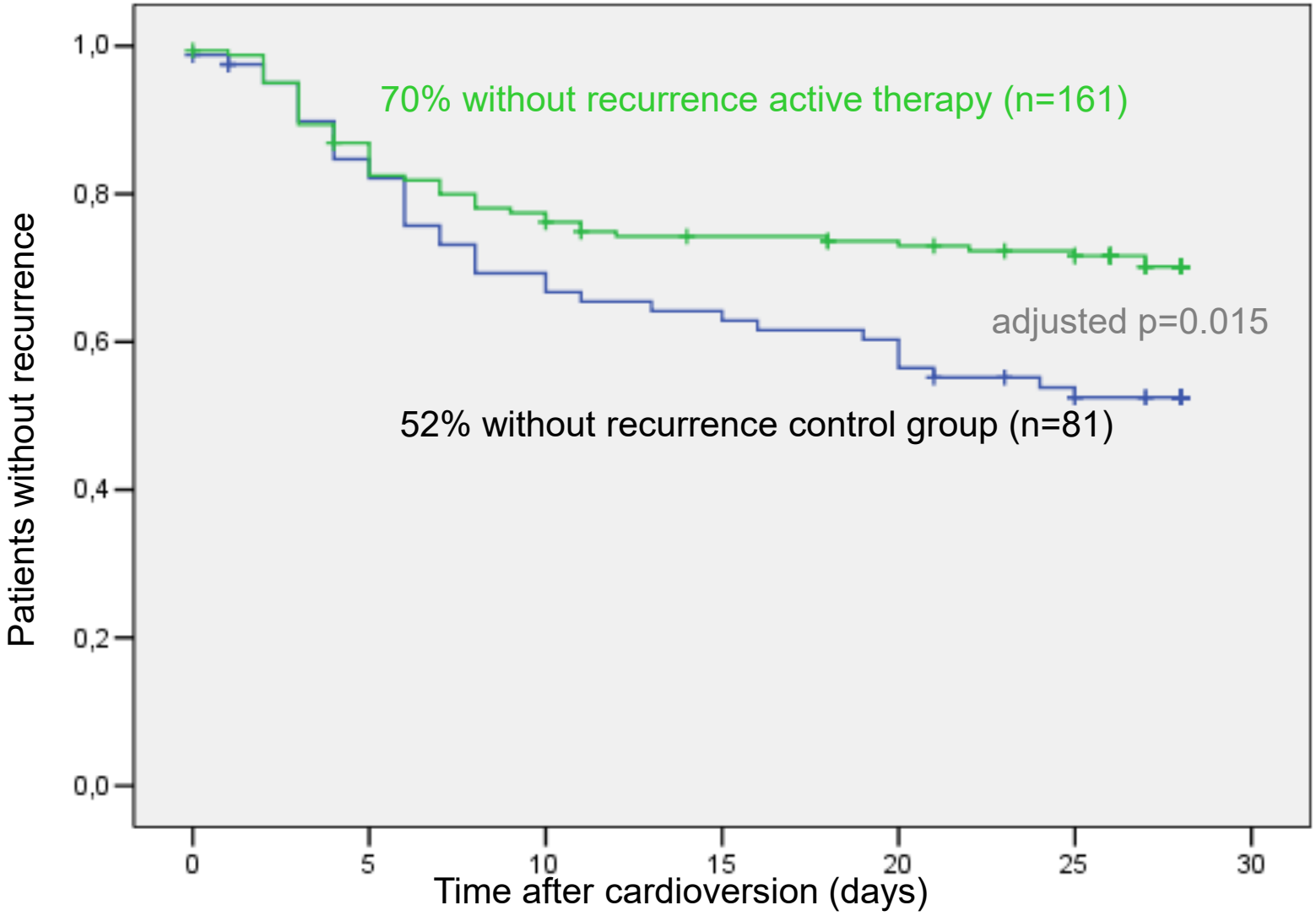
1st step: superiority of flecainide vs. control group after 1 month

- effectiveness analysis (flecainide effective vs. no therapy)
- done at 4 weeks follow-up in 81 control patients /161 flecainide (B+C) pts
- adjustment of patient numbers for 2nd analysis step
- blinded towards active therapy group assignment (short – long)

2nd step: noninferiority of short-term vs. long term therapy

Modified from Kirchhof P, et al. Am Heart J.150: 899 (2005)

1st step: AF recurrences



Kirchhof P, et al. Lancet 380: 238-246. (2012)

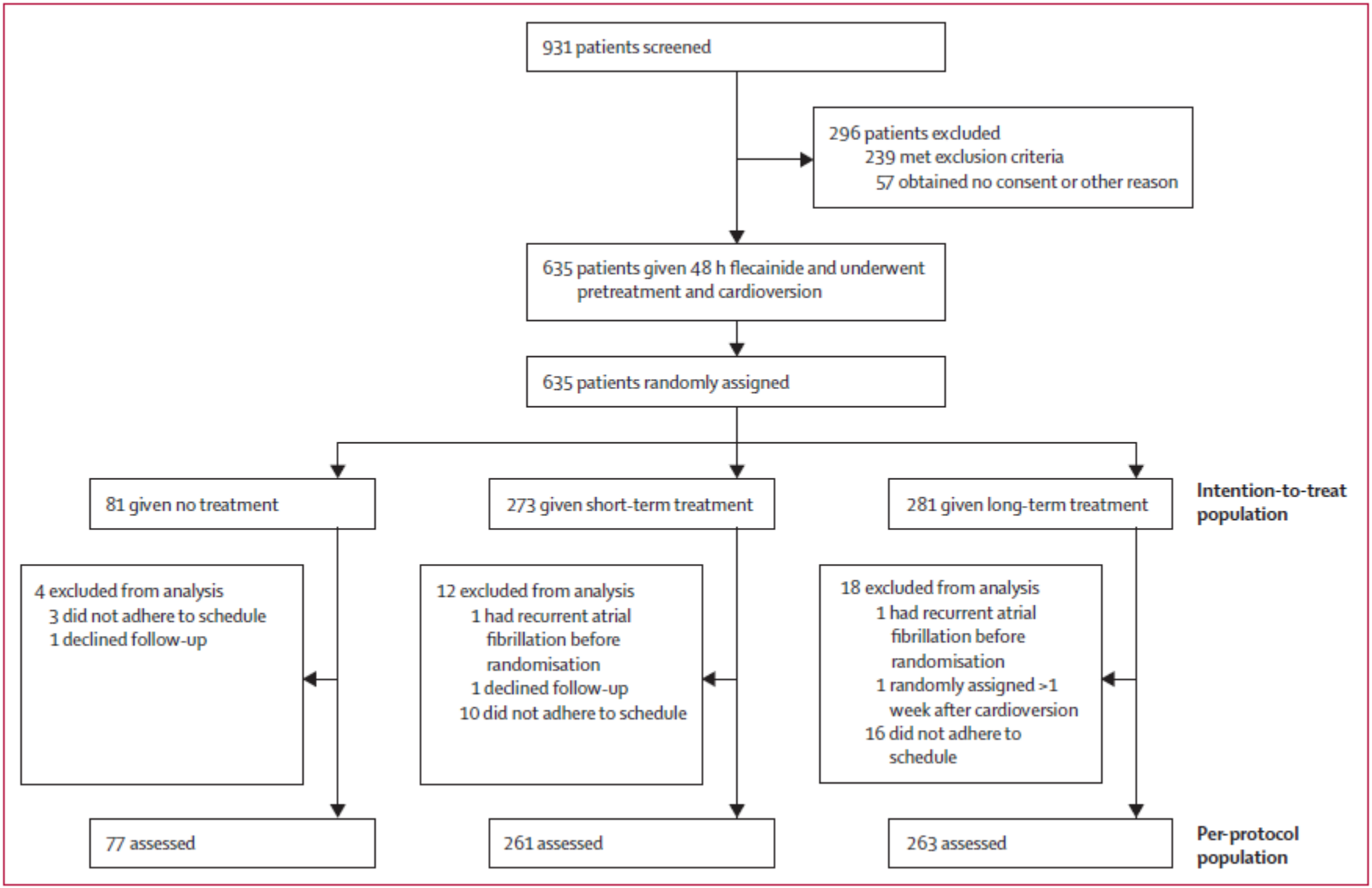
Patient characteristics

	Study population (n=635)	Control group (n=81)	Short-term treatment (n=273)	Long-term treatment (n=281)
Age (years)	63·7 (10·9)	64·1 (9·9)	63·5 (11·0)	63·8 (11·0)
Men	418 (65·8%)	57 (70·4%)	181 (66·3%)	180 (64·1%)
Blood pressure (mm Hg)				
Systolic	130·4 (17·9)	128·4 (18·7)	131·0 (17·3)	130·5 (18·3)
Diastolic	80·3 (10·6)	78·4 (11·9)	80·6 (10·7)	80·6 (10·1)
Diabetes mellitus	57 (9·0%)	5 (6·2%)	19 (7·0%)	33 (11·7%)
Coronary artery disease	37 (6·0%); n=620	5 (6·3%); n=79	13 (4·9%); n=264	19 (6·9%); n=277
Arterial hypertension	427 (67·2%)	48 (59·3%)	189 (69·2%)	190 (67·6%)
Valvular heart disease as detected by echocardiography	86 (13·5%)	13 (16·1%)	40 (14·7%)	33 (11·7%)
Weight (kg)	86·9 (16·5)	85·8 (14·5)	87·2 (18·1)	86·9 (15·4)
Body-mass index (kg/m^2)	28·3 (4·8)	27·9 (4·7)	28·6 (5·2)	28·2 (4·3)
Heart rate during atrial fibrillation (beats per min)	88·4 (21·7)	86·7 (20·1)	90·0 (21·4)	87·4 (22·3)
PQ interval after cardioversion (ms)	201·9 (40·6)	200·2 (42·0)	203·5 (41·0)	200·8 (39·9)
QRS duration at baseline (ms)	95·8 (17·0)	93·5 (14·3)	97·0 (17·3)	95·2 (17·5)
NYHA class*	n=625	n=80	n=267	n=278
0	443 (70·9%)	54 (67·5%)	186 (69·7%)	203 (73·0%)
I	73 (11·7%)	13 (16·3%)	32 (12·0%)	28 (10·1%)
II	98 (15·7%)	10 (12·5%)	45 (16·9%)	43 (15·5%)
III	11 (1·8%)	3 (3·8%)	4 (1·5%)	4 (1·4%)
Karnofsky score	8·3 (1·2)	8·5 (1·1)	8·2 (1·2)	8·4 (1·2)
SF-12 physical score	39·1 (10·8); n=422	39·0 (11·5); n=63	39·1 (11·2); n=180	39·2 (10·2); n=179
SF-12 mental score	48·3 (10·5); n=425	50·3 (9·8); n=63	48·4 (10·3); n=179	47·7 (10·8); n=183
CHADS-2 score†	1·1 (0·9); n=624	1·0 (0·8); n=80	1·1 (1·0); n=267	1·1 (0·9); n=277
0	163 (26·1%)	24 (30%)	68 (25·5%)	71 (25·6%)
1	282 (45·2%)	41 (51·3%)	122 (45·7%)	119 (43·0%)
2	128 (20·5%)	11 (13·8%)	53 (19·9%)	64 (23·1%)
3	39 (6·3%)	3 (3·8%)	17 (6·4%)	19 (6·9%)
4	12 (1·9%)	1 (1·3%)	7 (2·6%)	4 (1·4%)
Duration of atrial fibrillation (months)	27·5 (50·9); n=384	32·6 (58·1); n=48	24·7 (47·2); n=161	20·3 (35·0); n=175
Cardiovascular treatment at baseline	n=617	n=80	n=267	n=270
β blocker	478 (77·5%)	64 (80·0%)	206 (77·2%)	208 (77·0%)
Verapamil	13 (2·1%)	3 (3·8%)	4 (1·5%)	6 (2·2%)
Digitalis glycosides	77 (12·5%)	12 (15·0%)	37 (13·9%)	28 (10·4%)
Diuretics	196 (31·8%)	19 (23·8%)	94 (35·2%)	83 (30·7%)
ACE inhibitors or ARBs	285 (46·2%)	35 (43·9%)	122 (45·7%)	128 (47·4%)
Statins	91 (14·8%)	12 (15·0%)	38 (14·2%)	41 (15·2%)
Antiplatelet treatment (acetyl salicylic acid or clopidogrel)	44 (7·1%)	11 (13·8%)	18 (6·7%)	15 (5·6%)
Oral anticoagulation, heparin, or LMWH	465 (75·4%)	66 (82·5%)	198 (74·2%)	201 (74·4%)
Combination treatment (antiplatelet plus oral anticoagulation, heparin, or LMWH)	18 (2·9%)	4 (5·0%)	3 (1·1%)	11 (4·1%)

(Continues on next page)

Kirchhof P, et al. Lancet 380: 238-246. (2012)

Study flow chart



Kirchhof P, et al. Lancet 380: 238-246. (2012)

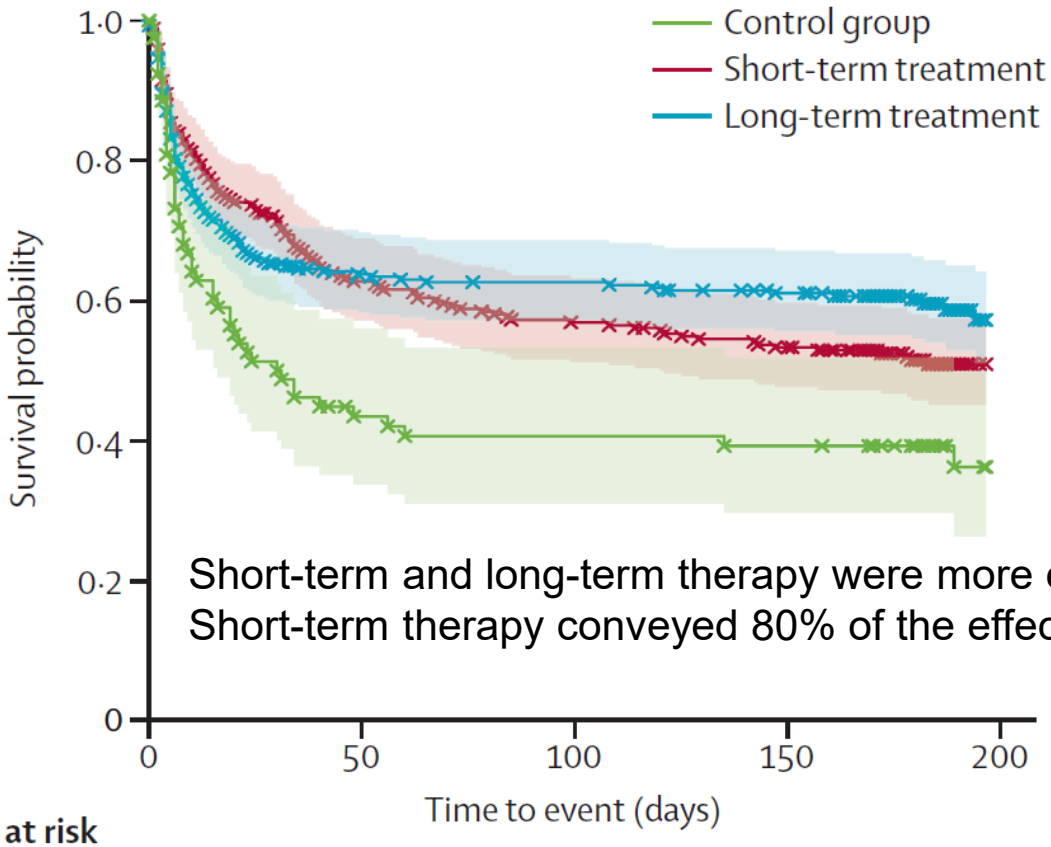
Main patient characteristics

- 635 patients
- mean age 64 (11) years
- 37 (6%) coronary artery disease
- 67% hypertension, 9% diabetes mellitus, BMI 28 (5)
- 2.5% reduced LV systolic function
- Left atrial diameter 47 (4) mm
- Heart rate during AF 89 (22) bpm
- PR after cardioversion 0.2 (0.04) s
- CHADS2 score (0-4): 26% - 46% - 21% - 6% - 2%
- 20% cardioversion during flecainide pre-treatment
  - cumulative flecainide prior to cardioversion 452 (157) mg
  - mean flecainide serum level at baseline 267 (142) ng/ml

Kirchhof P, et al. Lancet 380: 238-246. (2012)

Primary outcome (ITT)

635 patients, mean age 64 years, flecainide 4 weeks vs long-term therapy
Primary outcome: time to persistent atrial fibrillation or death, monitored by telemetric ECG



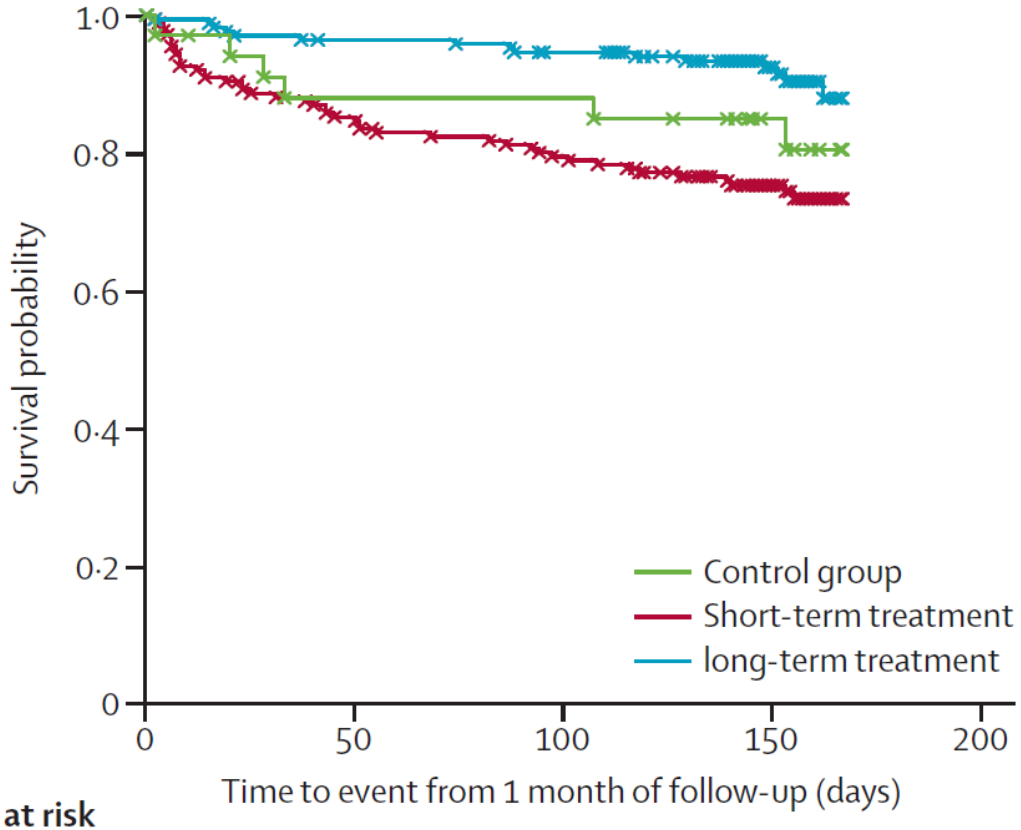
Short-term and long-term therapy were more effective than no therapy
Short-term therapy conveyed 80% of the effect of long-term therapy

Number at risk				
Control group	81	31	29	28
Short-term treatment group	273	161	145	135
Long-term treatment group	281	166	162	152

Kirchhof P, et al. Lancet 380: 238-246. (2012)

Residual recurrences

635 patients, mean age 64 years, flecainide 4 weeks vs long-term therapy
Shown: Recurrences in patients who remained in sinus rhythm 4 weeks after CV



Number at risk				
Control group	35	29	29	19
Short-term treatment group	177	149	137	97
long-term treatment group	169	160	155	97

Kirchhof P, et al. Lancet 380: 238-246. (2012)

Secondary outcomes part 1

	Control	Short-term treatment	Long-term treatment	Short-term treatment vs control		Long-term treatment vs control		Short-treatment vs long-term treatment	
				Difference	p value	Difference	p value	Difference	p value
Documented atrial fibrillation episodes before reaching the primary endpoint	9·0 (2 to 14); n=48	14 (5·5 to 23·5); n=120	13 (6 to 23); n=106	4 (1 to 8)*	0·0106†	4 (0 to 8)*	0·0319†	1 (−3 to 4)*	0·6979†
Days with documented atrial fibrillation before reaching the primary endpoint	8·0 (2 to 12); n=48	12 (5 to 20); n=120	11 (5 to 22); n=106	3 (1 to 7)*	0·0147†	3 (0 to 7)*	0·0455†	0 (−3 to 3)*	0·7739†
Admissions to hospital because of atrial fibrillation	0 (0 to 0); n=76	0 (0 to 0); n=260	0 (0 to 0); n=269	0 (0–0)*	0·7101†	0 (0–0)*	0·9776†	0 (0–0)*	0·5484†
Visits without admission	1 (0 to 3); n=76	1 (0 to 3); n=260	1 (0 to 3); n=269	0 (0 to 1)*	0·1399†	0 (0–0)*	0·7667†	0 (0–0)*	0·0615†
Serious adverse events of special interest‡	1 (1·2%)	9 (3·3%)	10 (3·6%)	..	0·3252§	..	0·2830§	..	0·8655§
Major adverse cardiovascular or cerebrovascular events	1	5	4	..	..	..	..	..	..
Resuscitation	0	0	1	..	..	..	..	..	..
Syncope	0	2	4	..	..	..	..	..	..
Sustained ventricular tachycardia	0	2	0	..	..	..	..	..	..
Transient cerebral ischemic event	0	0	1	..	..	..	..	..	..
Major adverse cardiovascular and cerebrovascular events during follow-up	1 (1·2%)	5 (1·8%)	4 (1·4%)	..	0·7147§	..	0·8979§	..	0·7041§
Stroke	0	3	2	..	..	..	..	..	..
Myocardial infarction	0	0	0	..	..	..	..	..	..
Death	0	0	0	..	..	..	..	..	..
Major bleed	1	2	2	..	..	..	..	..	..
Left ventricular ejection fraction at 6 months¶	62·1% (59·6 to 64·5); n=45‖	62·3% (61·0 to 63·5); n=172‖	63·0% (61·9 to 64·2); n=190‖	0·2 (−2·6 to 3·0)	0·8206**	0·9 (−1·8 to 3·6)	0·5381**	−0·7 (−2·4 to 1·0)	0·4588**
Total number of telemetric ECGs	5183	24275	24315	..	..	..	..	..	..
Mean number of telemetric ECGs adjusted for the time to primary endpoint (mean [95% CI])††	80·3 (67·4 to 93·3)	87·6 (80·6 to 94·6)	86·5 (77·6 to 95·5)	7·3 (−7·5 to 22·0)	0·3335	2·8 (−11·9 to 17·5)	0·7131	4·5 (−5·3 to 14·3)	0·3704
Mean number of telemetric ECGs per patient and per week	5·9	5·9	5·5	..	..	..	..	..	..
Flecainide serum trough concentrations at 1 month follow-up (ng/mL)	..	410·8, (378·4 to 443·1); n=180	449·8 (417·9 to 481·8); n=184	..	..	..	..	−39 (−84·4 to 6·4)	0·0921
QRS duration at 1 month (ms)	95·3 (89·5 to 101·1); n=69	104·8 (101·4 to 108·2); n=221	105·4 (101·6 to 109·2); n=239	9·5 (2·7 to 16·4)	0·0065	10·1 (2·4 to 17·8)	0·0140	−0·6 (−5·7 to 4·5)	0·8201
p value vs baseline‡‡	0·4987	<0·0001	<0·0001	..	..	..	..	..	..

(Continues on next page)

Kirchhof P, et al. Lancet 380: 238-246. (2012)

Secondary outcomes cont‘ d

	Control	Short-term treatment	Long-term treatment	Short-term treatment vs control		Long-term treatment vs control		Short-treatment vs long-term treatment	
				Difference	p value	Difference	p value	Difference	p value
(Continued from previous page)									
SF-12 physical scores	45·3 (42·1 to 48·42); n=29‖	44·0 (42·4 to 45·6); n=111‖	43·8 (42·2 to 45·4); n=115‖	−1·2 (−4·8 to 2·4)	0·5010**	−1·5 (−5·0 to 2·1)	0·4196**	0·2 (−2·0 to 2·5)	0·8375**
p value vs baseline‡‡	0·0011	<0·0001	<0·0001	..	..	..	..	..	..
SF-12 mental scores	49·4 (46·6 to 52·1); n=29‖	51·1 (49·7 to 52·5); n=115‖	50·3 (48·9 to 51·7); n=116‖	1·7 (−1·3 to 4·6)	0·2594**	0·9 (−2·4 to 4·2)	0·6061**	0·8 (−1·8 to 2·7)	0·4350**
p value vs baseline‡‡	0·822	0·004	0·027	..	..	..	..	..	..
Karnofsky score at 1 month	8·8 (8·7 to 9·0); n=76‖	8·8 (8·7 to 9·0); n=253‖	8·9 (8·7 to 9·0); n=260‖	0·15 (−0·12 to 0·43)	0·274**	0·20 (−0·06 to 0·46)	0·131**	−0·04 (−0·22 to 0·14)	0·639**
p value vs baseline‡‡	0·2635	<0·0001	<0·0001	..	..	..	..	..	..
Karnofsky score at 6 months	8·8 (8·5 to 9·1); n=71‖	8·9 (8·7 to 9·0); n=246‖	9·0 (8·8 to 9·1); n=247‖	0·08 (−0·22 to 0·38)	0·5832**	0·18 (−0·12 to 0·47)	0·2439**	−0·11 (−0·31 to 0·09)	0·2629**
p value vs baseline‡‡	0·1001	<0·0001	<0·0001	..	..	..	..	..	..

Data are median (IQR) or n (%), unless otherwise stated. All numbers from the intention-to-treat population. *Hodges-Lehmann estimate with 95% CI. †Mann-Whitney test. ‡Serious adverse events of special interest include death, resuscitation, syncope, sustained ventricular tachycardia, myocardial infarction, stroke, transient cerebral ischaemic event, prolonged cerebral neurological insufficiency, and major bleed. §χ^2 test. ¶p=0·669 (ANCOVA adjusted for baseline). ‖Baseline-adjusted means of follow-up 6-month values (95% CIs). **ANCOVA adjusted for baseline. ††p=0·521 (ANCOVA adjusted for the time to primary endpoint). ‡‡Non-randomised comparison.

Table 2: **Secondary outcomes**

Kirchhof P, et al. Lancet 380: 238-246. (2012)

Main secondary outcomes

- number of recurrent AF episodes prior to persistent AF not different between groups: 9 (2-13) – 14 (6-23) – 13 (6-23)
- no difference in major adverse outcomes

  (control 1 (1.2%), short-term 9 (3.3%), long-term 10 (3.6%))

death	0 – 0 – 0
resuscitation / VT:	0 – 2 – 1
syncope:	0 – 2 – 4
stroke/TIA:	0 – 3 – 3
major bleed:	1 – 2 – 2

- improved quality of life at the end of FU:

Karnowsky (base 8.3 (1.2)):	8.8 (8.5-9.1)* – 8.9 (8.7-9.0)* – 9 (8.9-9.1)*
SF 12 physical (base 39 (11)):	45 (42-48)* – 44 (42-46)* – 44 (42-45)*
SF 12 mental (base 48 (10)):	49 (47-52) – 51 (50-53)* – 50 (49-52)*

* indicate $p<0.05$ versus baseline

Kirchhof P, et al. Lancet 380: 238-246. (2012)

Flec-SL interpretation

We have shown that short-term antiarrhythmic drug treatment after cardioversion is not as effective as long-term treatment, but can prevent about 80% of recurrences of atrial fibrillation at 6 months, and has similar effects on quality of life to long-term treatment. The findings have important clinical implications. First, long-term antiarrhythmic drug treatment with ion-channel blockers prevents recurrent atrial fibrillation after cardioversion in most patients. Second, short-term treatment should be considered for patients with atrial fibrillation who are at increased risk for complications or have infrequent recurrences, or both. Factors other than electrical remodelling contribute to recurrent atrial fibrillation after cardioversion, and other treatments should be developed to improve prevention of recurrent problems, ideally to be used in conjunction with ion-channel blockers.

Kirchhof P, et al. Lancet 380: 238-246. (2012)

ESC recommendation on short-term therapy

Short-term (4 weeks) antiarrhythmic therapy after cardioversion may be considered in selected patients e.g. those at risk for therapy-associated complications.	IIb	B	145

145 Kirchhof P, et al. Lancet 380: 238-246. (2012)
ESC AF guidelines update. Camm, AJ, et al. Eur Heart J 33: 2719-2747. (2012)