ATRIAL FIBRILLATION
NETWORK

Flec-SL – AFNET 3

STUDIENDESIGN

The Flec-SL – AFNET 3 trial

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Flec-SL AFNET 3 is registered at ISRCTN62728742

Principles of Antiarrhythmic Drug Therapy to Maintain Sinus Rhythm

1. Treatment is motivated by attempts to reduce AF-related symptoms
2. Efficacy of antiarrhythmic drugs to maintain sinus rhythm is modest
3. Clinically successful antiarrhythmic drug therapy may reduce rather than eliminate recurrence of AF
4. If one antiarrhythmic drug 'fails', a clinically acceptable response may be achieved with another agent
5. Drug-induced proarrhythmia or extra-cardiac side-effects are frequent
6. Safety rather than efficacy considerations should primarily guide the choice of antiarrhythmic agent

ESC guidelines for the management of AF
Camm AJ, et al. Eur Heart J 31: 2369-2429. (2010)

Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label, blinded endpoint assessment trial

Paulus Kirchhof, Dietrich Andresen, Ralph Bosch, Martin Borggrefe, Thomas Meinertz, Ulli Parade, Ursula Ravens, Alexander Samol, Gerhard Steinbeck, Andras Treszl, Karl Wegscheider, Günter Breithardt

Appendix A: Participating AFNET centers and local investigators.

Prof. Dr. Block, Stiftsklinikum Augustinum, München; Prof. Dr. Böcker, St. Marienhospital Hamm; Prof. Dr. Borggrefe, Ms Göring-Sparn, Universitätsklinikum Mannheim; PD Dr. Bosch, Kard. Praxis Dres. Kruck / Bosch, Ludwigsburg; Dr. Boscher, Biberach; Dr. Dänschel, Ambulantes Herzzentrum Chemnitz; Dr. Dieckmann, Städt. Hellmig-Krankenhaus Kamen; Prof. Dr. Geller, Zentralklinikum Bad Berka GmbH; PD Dr. Nabauer, Dr. Gerth, Universitätsklinikum Großhadern, München; PD Dr. Götte, Universitätsklinikum Magdeburg; Dr. Gramley, Uniklinikum Mainz; Dr. Grönefeld, Asklepios Klinik Barmbek, Hamburg; Dr. Hanheide, Kath. Krankenhaus Dortmund West; Dr. Hayen, Klinikverbund Bassum / Sulingen; Dr. Henning, Universitätsklinikum Tübingen; Prof. Dr. Hindricks, Herzzentrum Leipzig; Dr. Jacobsohn, Helios Klinikum Gotha; Prof. Dr. Bode, Dr. Jacques, Univ. Klinikum Freiburg; Dr. Jäger, Praxis Dr. Jäger, Kassel; Dr. Jahnke, Praxis Dr. Jahnke, Ulm; Professor Dr. Jung, Klinikum Worms; Dr. Kilian, Krankenhaus Nord-West, Frankfurt; Dr. Killat, Praxis Dr. Killlat, Haßloch; Prof. Dr. Kirchhof, Dr Samol, Universitätsklinikum Münster; Dr. Lange, Praxis Dres. Lange-Richter, Hartmannsdorf; Prof. Dr. Willems, Dr. Drewitz, Universitäres Herzzentrum Hamburg gGmbH; Prof. Dr. Andresen, Dr. Mielke, Vivantes Klinikum, Berlin; Dr. Reinke, Herz-Jesu-Krankenhaus Münster; Dr. Remerie, Universitätsklinikum Bonn; Dr. Richter, Kreiskrankenhaus Wolgast; Dr. Rüdell, Praxis Dr. Rüdell, Kassel; Dr. Sack, Elisabeth Krankenhaus Recklinghausen; Dr. Sarnighausen, Praxis Dr. Sarnighausen, Lüneburg; Prof. Dr. Schauerte, Dr. Saygili, Universitätsklinikum Aachen; Prof. Dr. Sechtem, Dr. Parade, Robert-Bosch- Krankenhaus Stuttgart; Dr. Sprenger, Klinikum Brandenburg; Prof. Dr. Stellbrink, Klinikum Bielefeld; Dr. Taggeselle, Praxis Dr. Taggeselle, Markkleeberg; Dr. Ulrych, St. Barbara Krankenhaus, Schwandorf; Dr. Kim, Evangelisches Krankenhaus Düsseldorf; Prof. Dr. Werner, Klinikum Darmstadt; Dr. Wilke, Praxis Dr. Wilke, Papenburg; Prof. Dr. Zabel, Universitätsklinikum Göttingen, all in Germany

Appendix B: Study committees

Data and safety monitoring board: Ernst G. Vester (chair); Achim Heinecke; Dieter Horstkotte

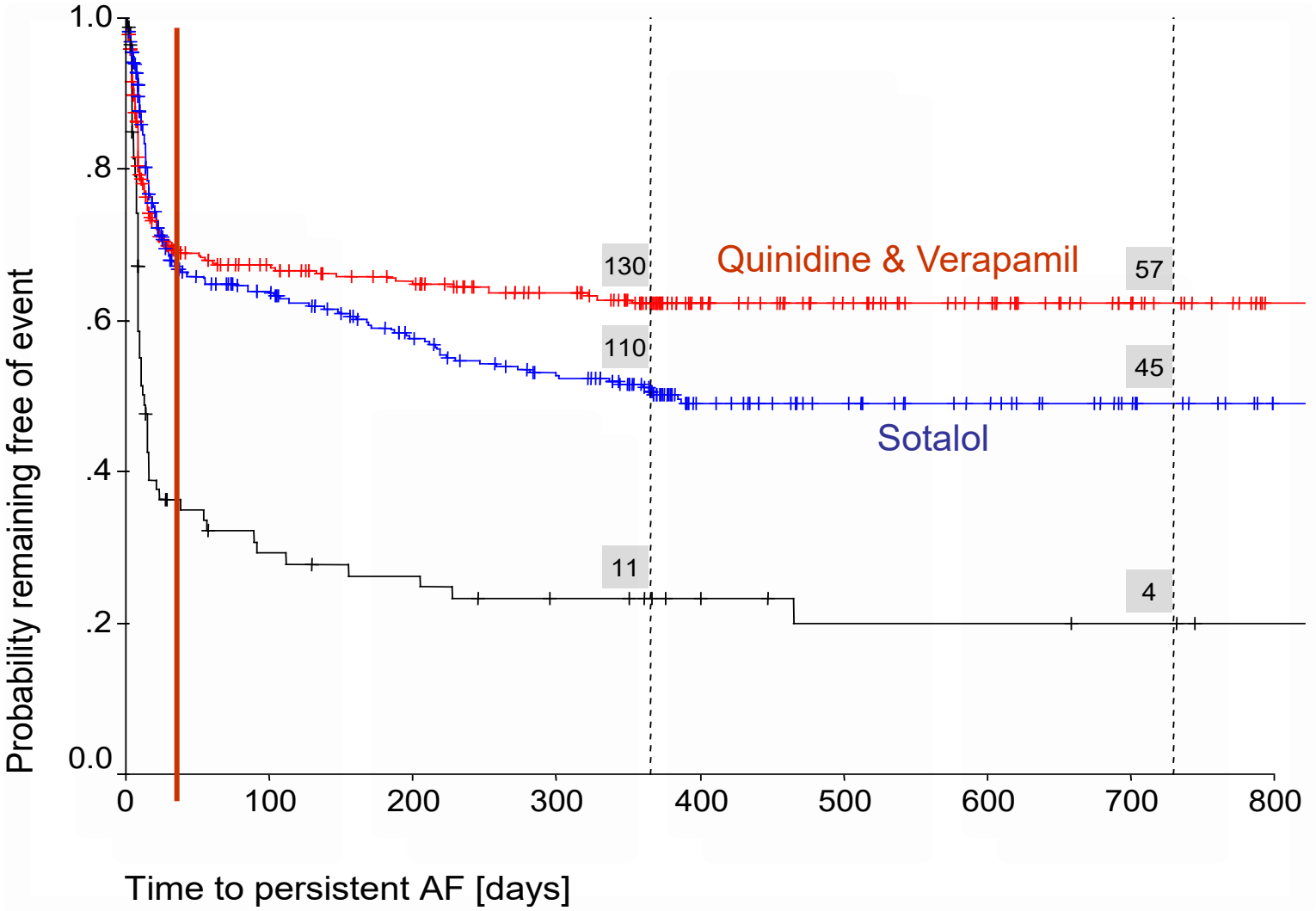
Steering committee: Paulus Kirchhof (chair); Dietrich Andresen; Günter Breithardt; Thomas Meinertz; Gerhard Steinbeck; Christina Waehling (MEDA Pharma representative); Thomas Fetsch (IKKF representative, non-voting); Karl Wegscheider (study statistician, non-voting)

Central blinded Holter ECG analysis: Elena Aleynichenko, Julia Köbe

Central study management: Sabine Jürgensmeyer

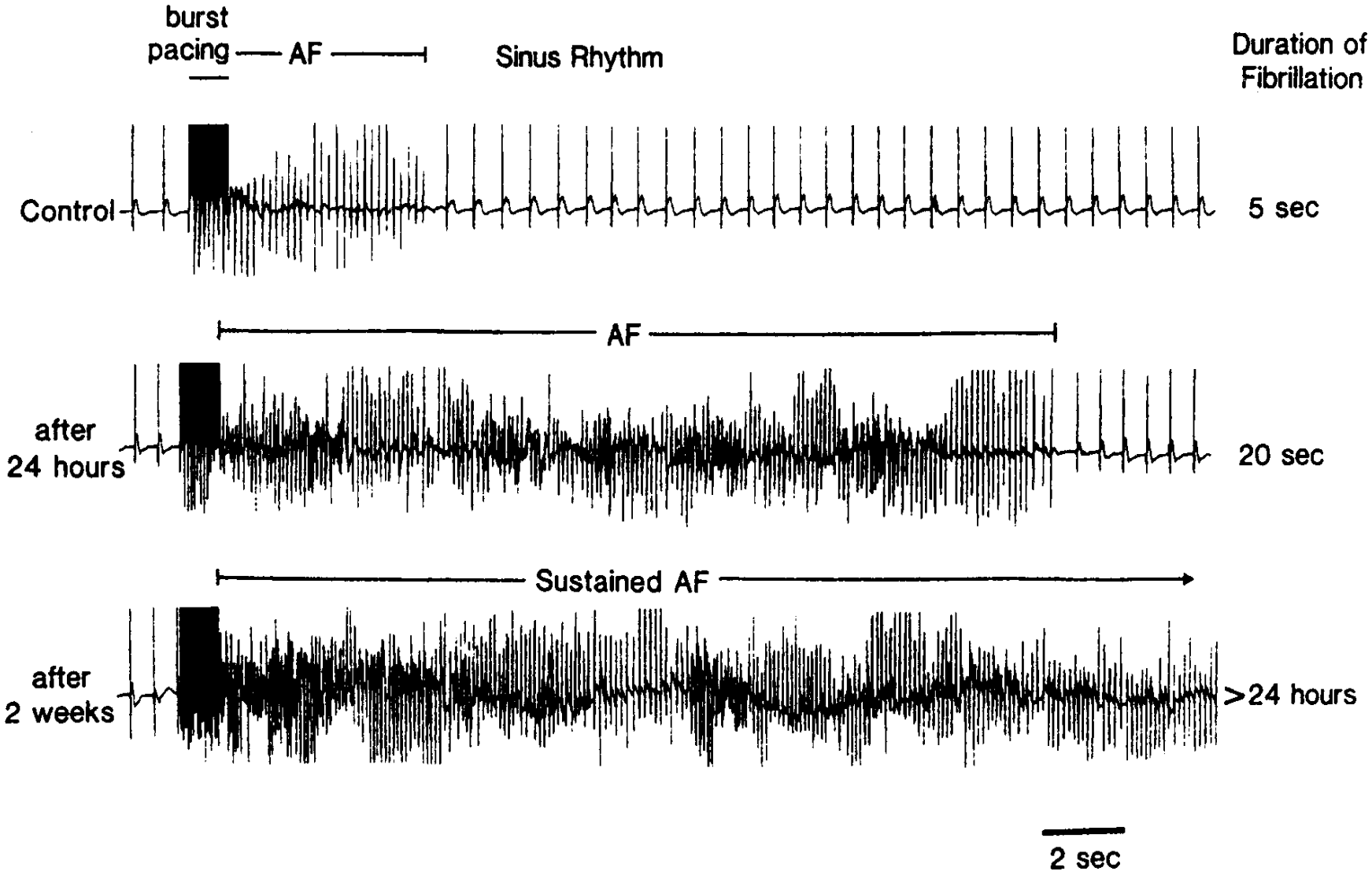
Kirchhof P, et al. Lancet published on line 18.6 2012, DOI:10.1016/S0140-6736(12)60570-4. (2012)

Clustered AF recurrences after CV



Fetsch T et al. Eur Heart J 25:1385-94 (2004)

Electrical remodeling begets AF



Wijffels et al., Circulation 92: 1954-1968 (1995)

„Targeted reversal“ of electrical remodeling

AF-induced action potential shortening predisposes to AF.

Antiarrhythmic drugs „reverse“ atrial action potential shortening.

The atrial action potential „normalises“ after 4 weeks of sinus rhythm.

Thereafter, AF recurrences are rare.

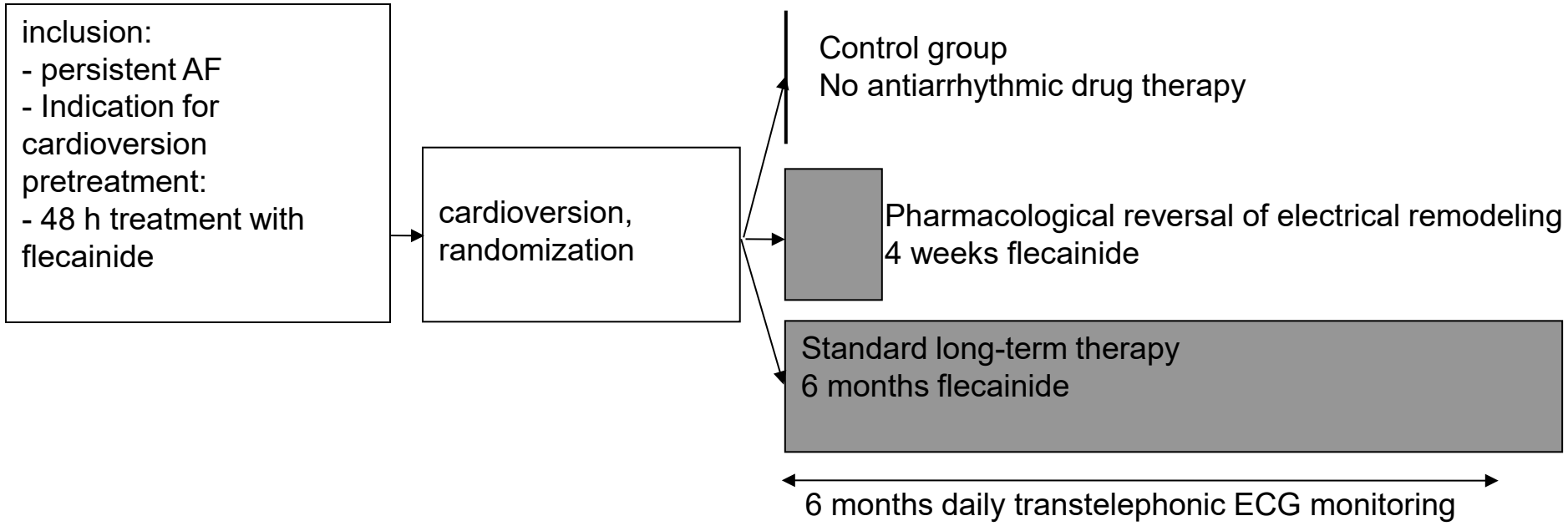
Wijffels et al., Circulation 92: 1954-1968 (1995)
Nattel S. Nature 415:219-26 (2002)
Hobbs WJ et al. Circulation 101:1145-51 (2000)
Kirchhof et al, Bas Res Cardiol 100: 112-20 (2005)

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 Design



Prospective, randomised, open, blinded outcome design (PROBE)

Primary outcome: time to persistent AF or death

Two hierarchichal analysis steps:

1. superiority of flecainide vs. no therapy (4 weeks FU, initial patients)
2. noninferiority of short-term vs. long-term therapy (all patients)

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