Personalizing Care for Atrial Fibrillation: The Promise of Gene-Guided Strategies

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Objectives

- Genetics influence vulnerability for developing AF
- Genetics likely impact the efficacy of catheter ablation and anti-arrhythmic drugs for AF
- Gene-guided treatment strategies for AF may improve patient outcomes

Atrial Fibrillation (AF)

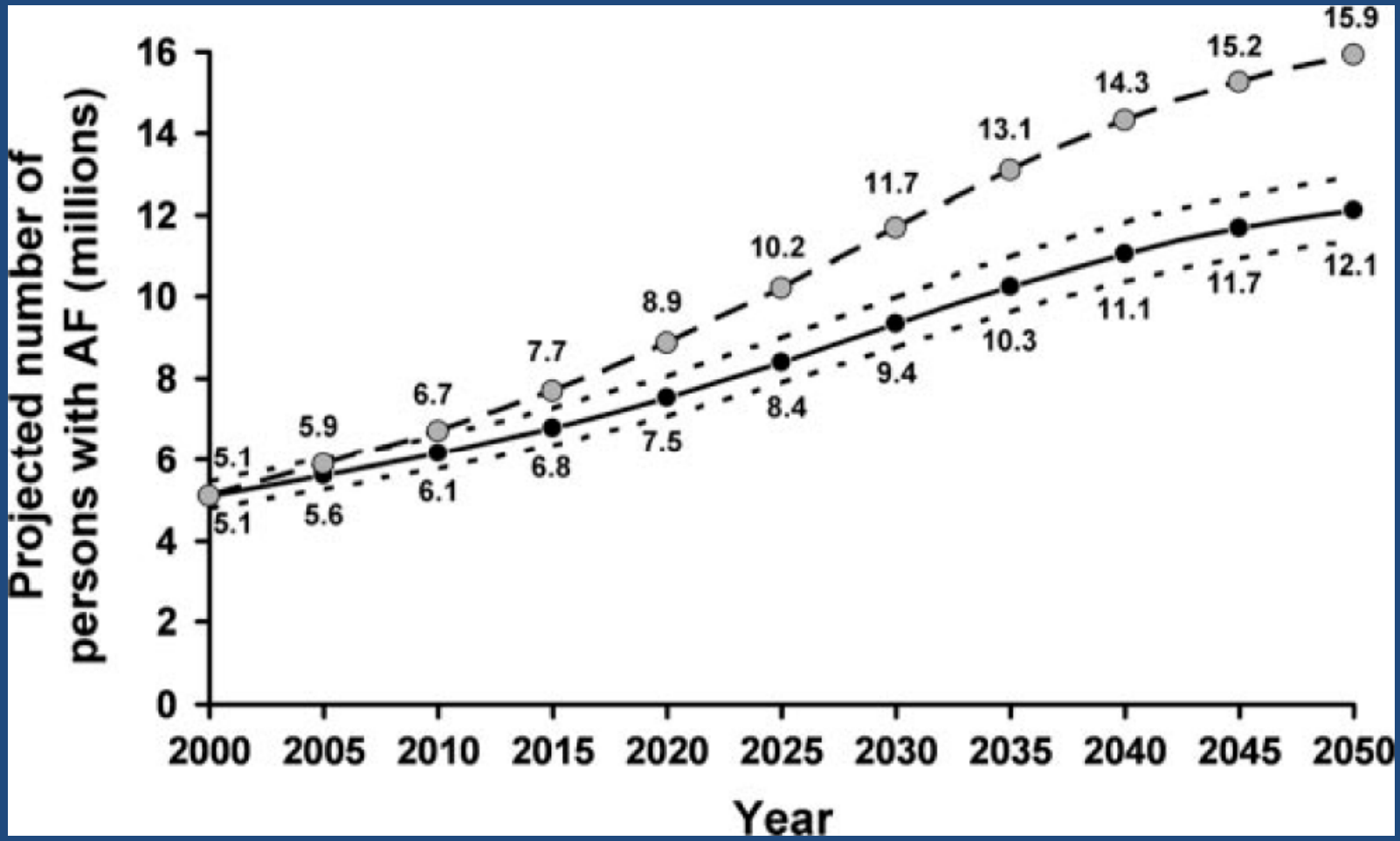
- Most common sustained cardiac arrhythmia
  - Lifetime risk of developing AF at 40 years of age is 1 in 4[1]
- Prevalence is increasing
  - 2.3 million affected in the US in 2000[2]
  - Estimates suggest this value may surge to close to 16 million by 2050[3]

1. Lloyd-Jones DM, *et al. Circulation* 2004

2. Go AS, *et al. JAMA* 2001

3. Miyasaka Y, *et al. Circulation* 2006

The Increasing Burden of AF



Miyasaka Y, *et al. Circulation* 2006

Clinical Impact

- Independent Risk Factor[1] for
  - Death
  - Stroke
  - Heart Failure
- Estimates suggest that AF and its sequelae cost the US health care system > $26 billion annually[2]

1. Benjamin EJ, *et al. Circulation* 1998

2. Kim MH, *et al. Circ Cardiovasc Qual Outcomes* 2011

Treatment

- A Rhythm Disorder
  - Anti-arrhythmic drugs
  - Ablation
  - Anti-coagulation
- How is AF most often treated?
  - Rate-control strategy
  - Anti-coagulation

The New England Journal of Medicine

VOLUME 347 DECEMBER 5, 2002 NUMBER 23

A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) INVESTIGATORS*

Conclusions Management of atrial fibrillation with the rhythm-control strategy offers no survival advantage over the rate-control strategy, and there are potential advantages, such as a lower risk of adverse drug effects, with the rate-control strategy. Anticoagulation should be continued in this group of high-risk patients. (N Engl J Med 2002;347:1825-33.)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 19, 2008 VOL. 358 NO. 25

Rhythm Control versus Rate Control for Atrial Fibrillation and Heart Failure

Denis Roy, M.D., Mario Talajic, M.D., Stanley Nattel, M.D., D. George Wyse, M.D., Ph.D., Paul Dorian, M.D., Kerry L. Lee, Ph.D., Martial G. Bourassa, M.D., J. Malcolm O. Arnold, M.D., Alfred E. Buxton, M.D., A. John Camm, M.D., Stuart J. Connolly, M.D., Marc Dubuc, M.D., Anique Ducharme, M.D., M.Sc., Peter G. Guerra, M.D., Stefan H. Hohnloser, M.D., Jean Lambert, Ph.D., Jean-Yves Le Heuzey, M.D., Gilles O'Hara, M.D., Ole Dyg Pedersen, M.D., Jean-Lucien Rouleau, M.D., Bramah N. Singh, M.D., D.Sc., Lynne Warner Stevenson, M.D., William G. Stevenson, M.D., Bernard Thibault, M.D., and Albert L. Waldo, M.D., for the Atrial Fibrillation and Congestive Heart Failure Investigators*

CONCLUSIONS

In patients with atrial fibrillation and congestive heart failure, a routine strategy of rhythm control does not reduce the rate of death from cardiovascular causes, as compared with a rate-control strategy. (ClinicalTrials.gov number, NCT00597077.)

Does rhythm control actually work?

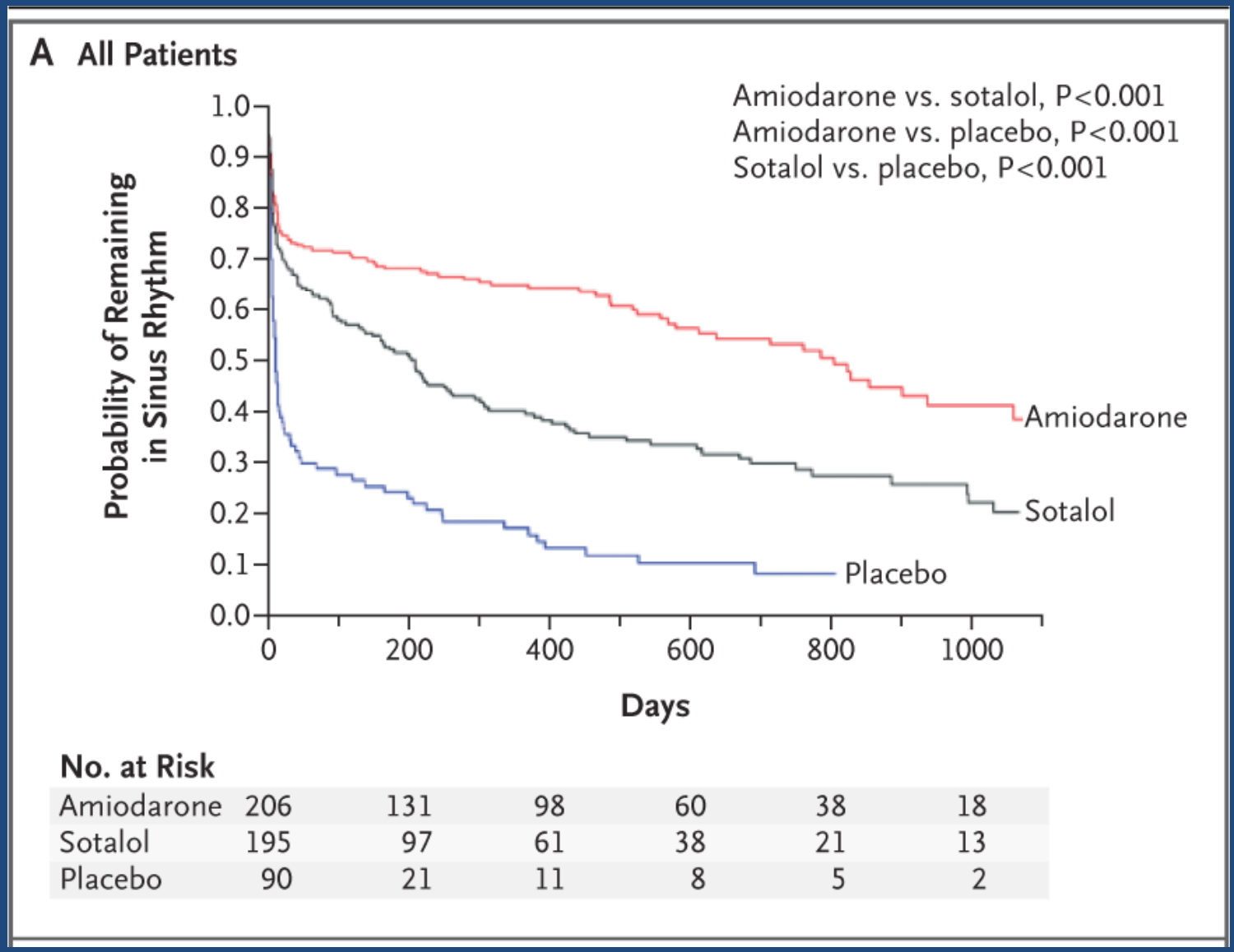
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Amiodarone versus Sotalol for Atrial Fibrillation

Bramah N. Singh, M.D., D.Sc., Steven N. Singh, M.D., Domenic J. Reda, Ph.D., X. Charlene Tang, M.D., Ph.D., Becky Lopez, R.N., Crystal L. Harris, Pharm.D., Ross D. Fletcher, M.D., Satish C. Sharma, M.D., J. Edwin Atwood, M.D., Alan K. Jacobson, M.D., H. Daniel Lewis, Jr., M.D., Dennis W. Raisch, Ph.D., and Michael D. Ezekowitz, M.B., Ch.B., Ph.D., for the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) Investigators*

Singh BN, *et al. N Engl J Med* 2004



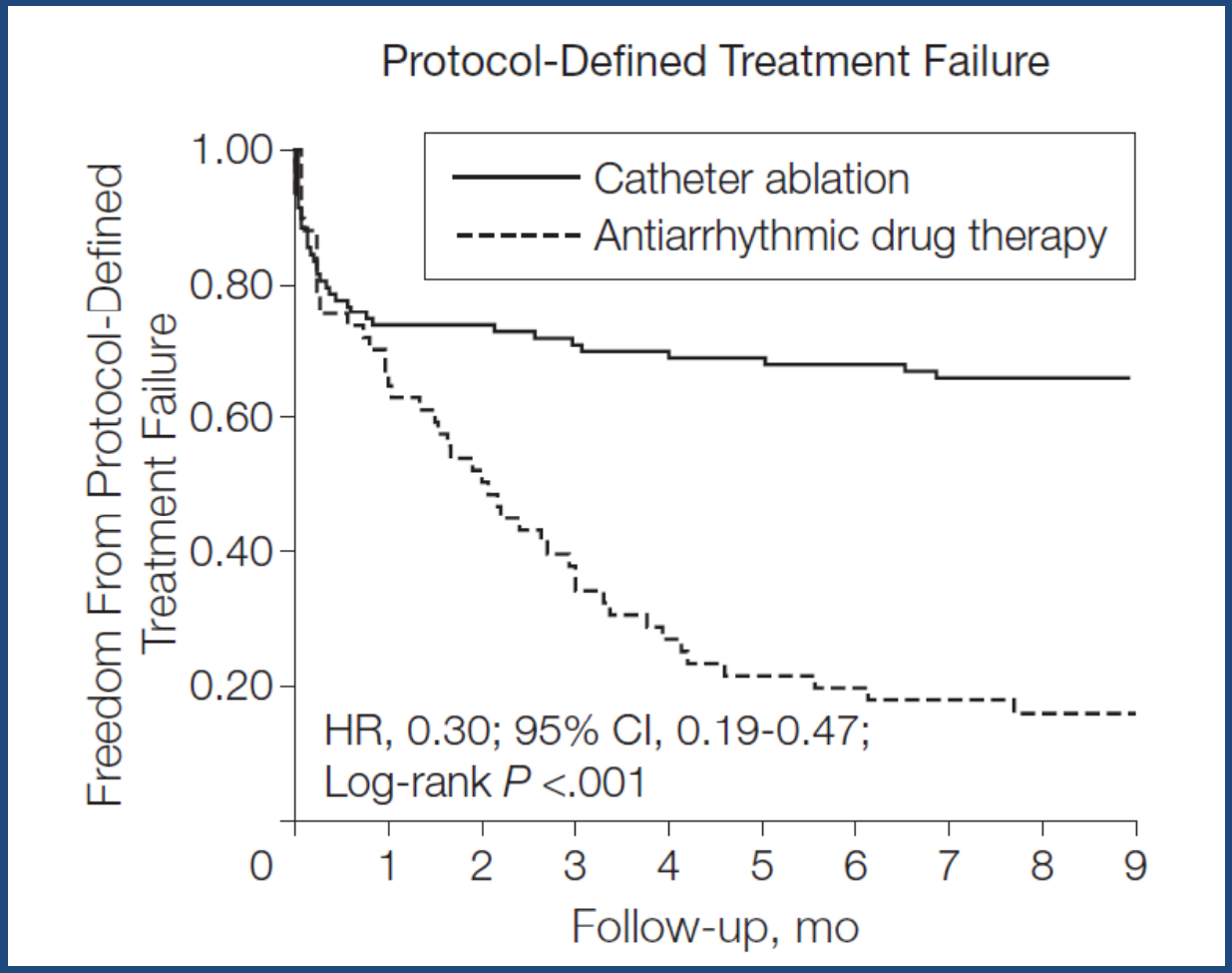
Singh BN, *et al. N Engl J Med* 2004

Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation

A Randomized Controlled Trial

Wilber DJ, *et al. JAMA* 2010

AF Ablation

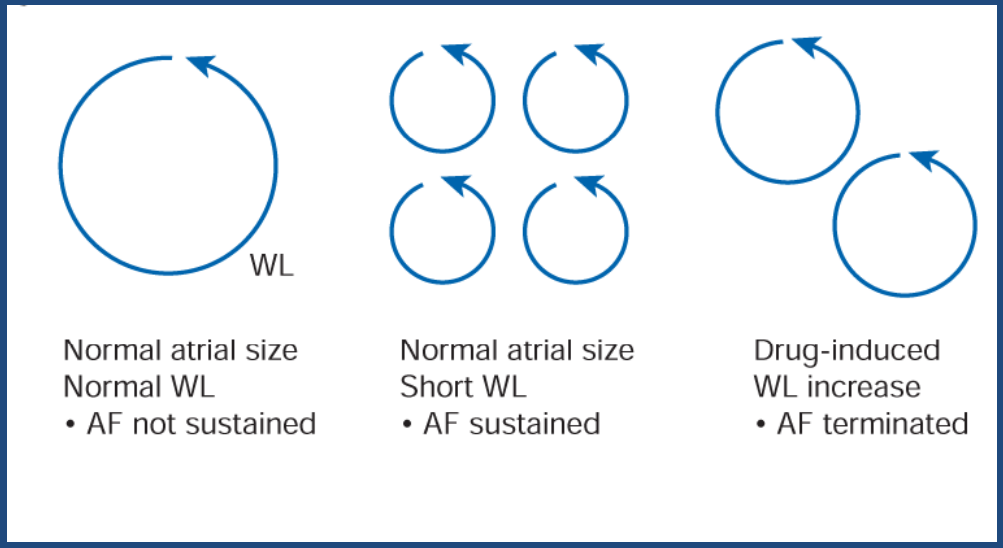


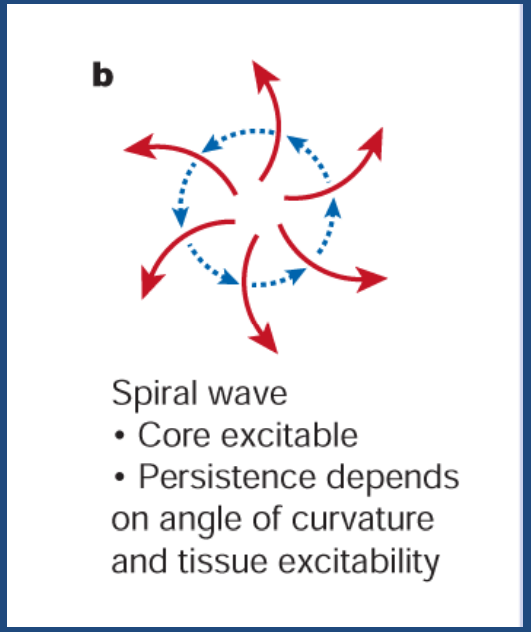
Wilber DJ, *et al. JAMA* 2010

Why the variable response to the SAME arrhythmia?

Competing Mechanisms

Multiple Wavelet Hypothesis





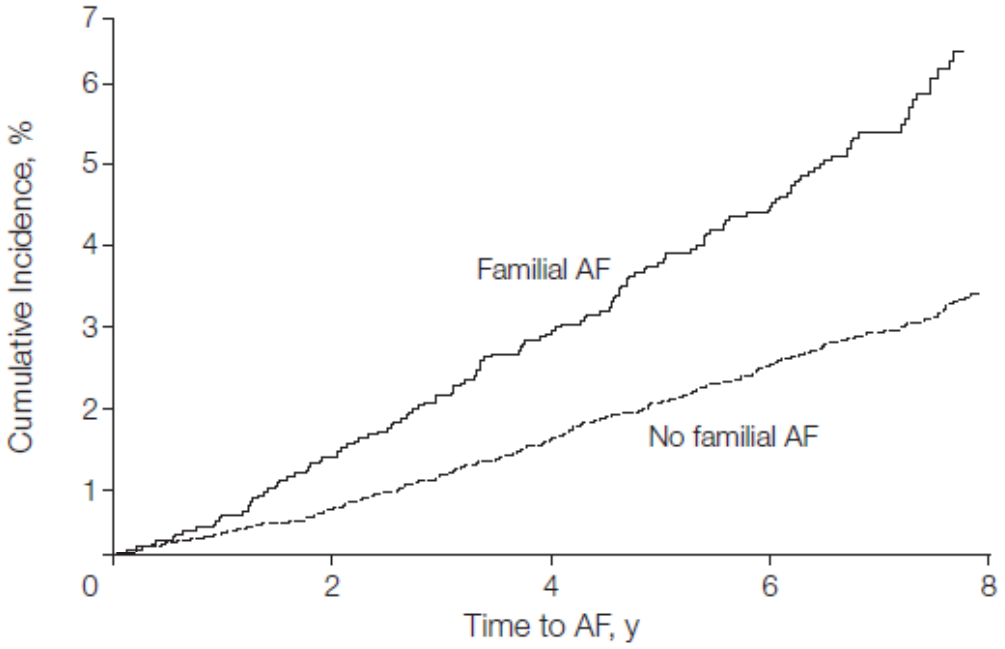
Focal AF

Nattel S. *Nature* 2002

Unravelling AF Pathophysiology: The Role of Genetics

AF & Genetics

Figure 1. Cumulative AF Incidence by Presence or Absence of Antecedent AF in a First-Degree Relative Accounting for Competing Risk of Death



Person-examinations at risk				
Familial AF	2393	2334	2256	2063
No familial AF	9578	9383	9121	8498

Lubitz SA, *et al. JAMA* 2010

The Search for Genetic Culprits

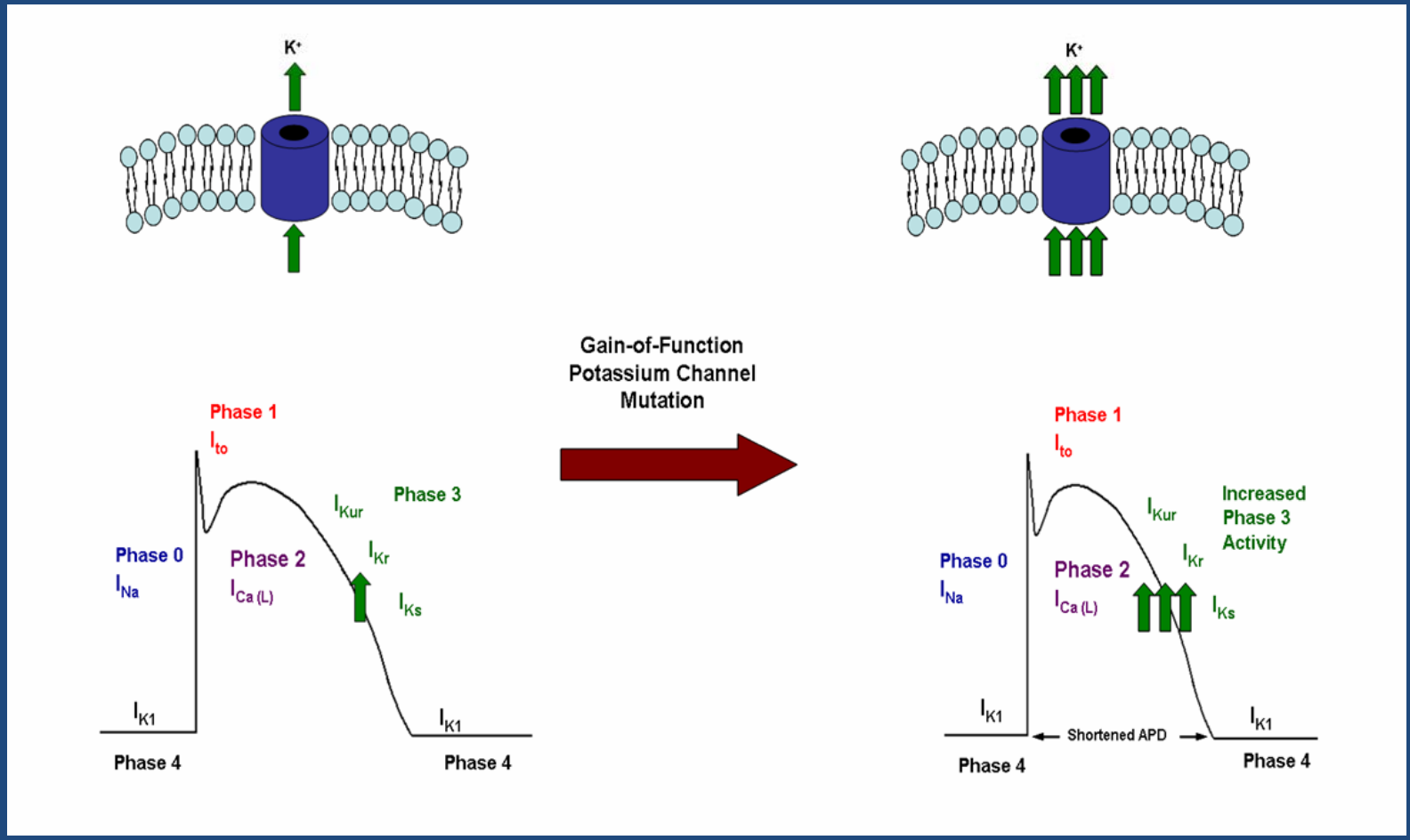
The First Gene

KCNQ1 Gain-of-Function Mutation in Familial Atrial Fibrillation

Yi-Han Chen,[1*†] Shi-Jie Xu,[2,3*†] Saïd Bendahhou,[4] Xiao-Liang Wang,[5] Ying Wang,[2] Wen-Yuan Xu,[1] Hong-Wei Jin,[5] Hao Sun,[2] Xiao-Yan Su,[1] Qi-Nan Zhuang,[2] Yi-Qing Yang,[1] Yue-Bin Li,[2] Yi Liu,[1] Hong-Ju Xu,[1] Xiao-Fei Li,[1] Ning Ma,[1] Chun-Ping Mou,[1] Zhu Chen,[2,6] Jacques Barhanin,[4] Wei Huang[2,3,6]

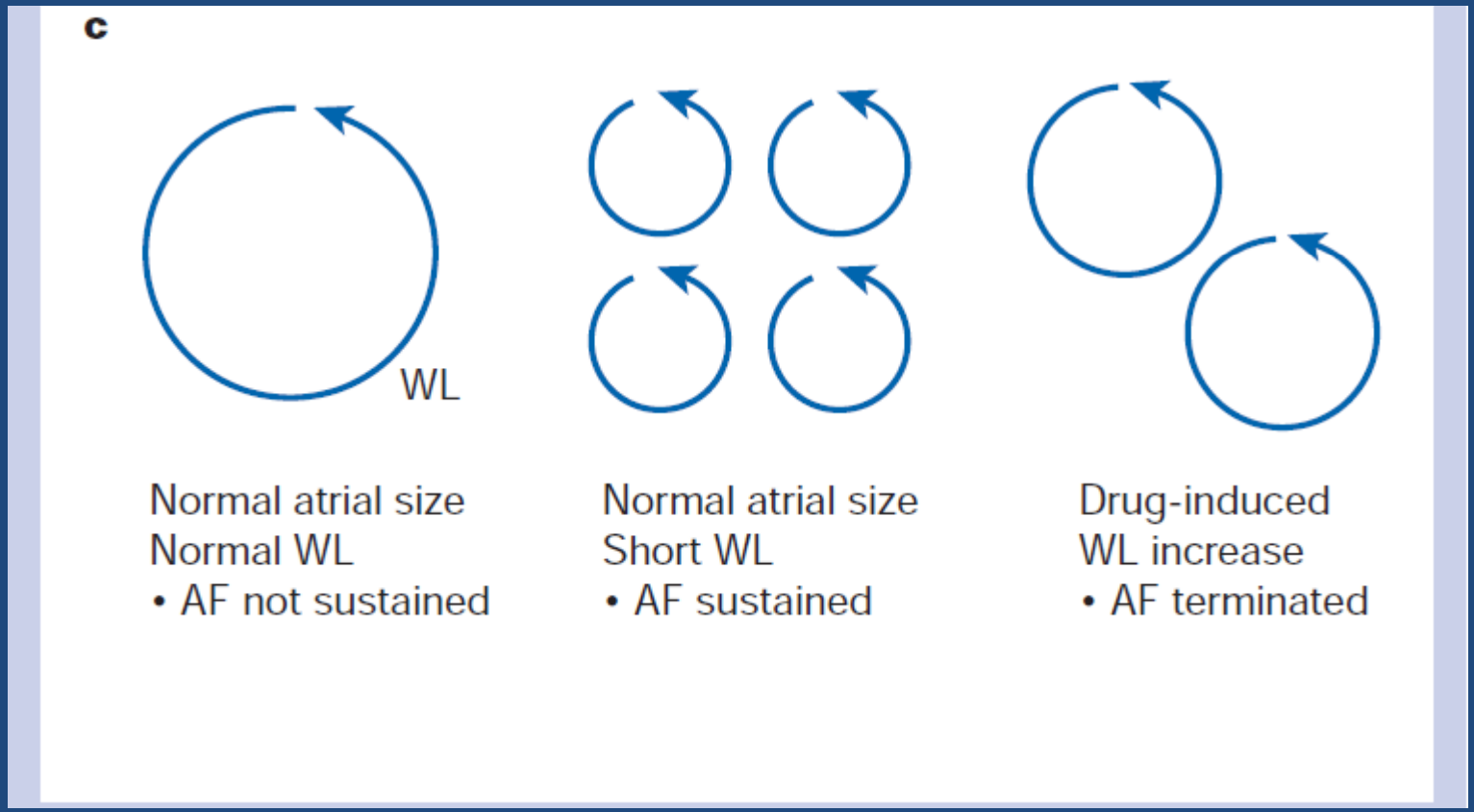
Science 2003

Gain-of-Function Potassium Channel Mutation



Roberts JD & Gollob MH. *Clinical Cardiogenetics* 2011

Multiple Wavelet Hypothesis



Nattel, S. *Nature* 2002

Other Gain-of-Function Potassium Channel Mutations & AF

- *KCNQ1*
- *KCNE2*
- *KCNJ2*
- *KCNE5*
  - *KCNE5* encodes an inhibitory β-subunit of I_{Ks}. A loss-of-function mutation in *KCNE5* leads to an increased I_{Ks}
- *KCNH2*
  - In the context of Short-QT syndrome

Prevalence of AF in SQTS = 20%

Table 6 SQTS Diagnostic Criteria

	Points
QT_c, ms	
<370	1
<350	2
<330	3
Jpoint-Tpeak interval <120 ms	1
Clinical history*	
History of sudden cardiac arrest	2
Documented polymorphic VT or VF	2
Unexplained syncope	1
Atrial fibrillation	1
Family history*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

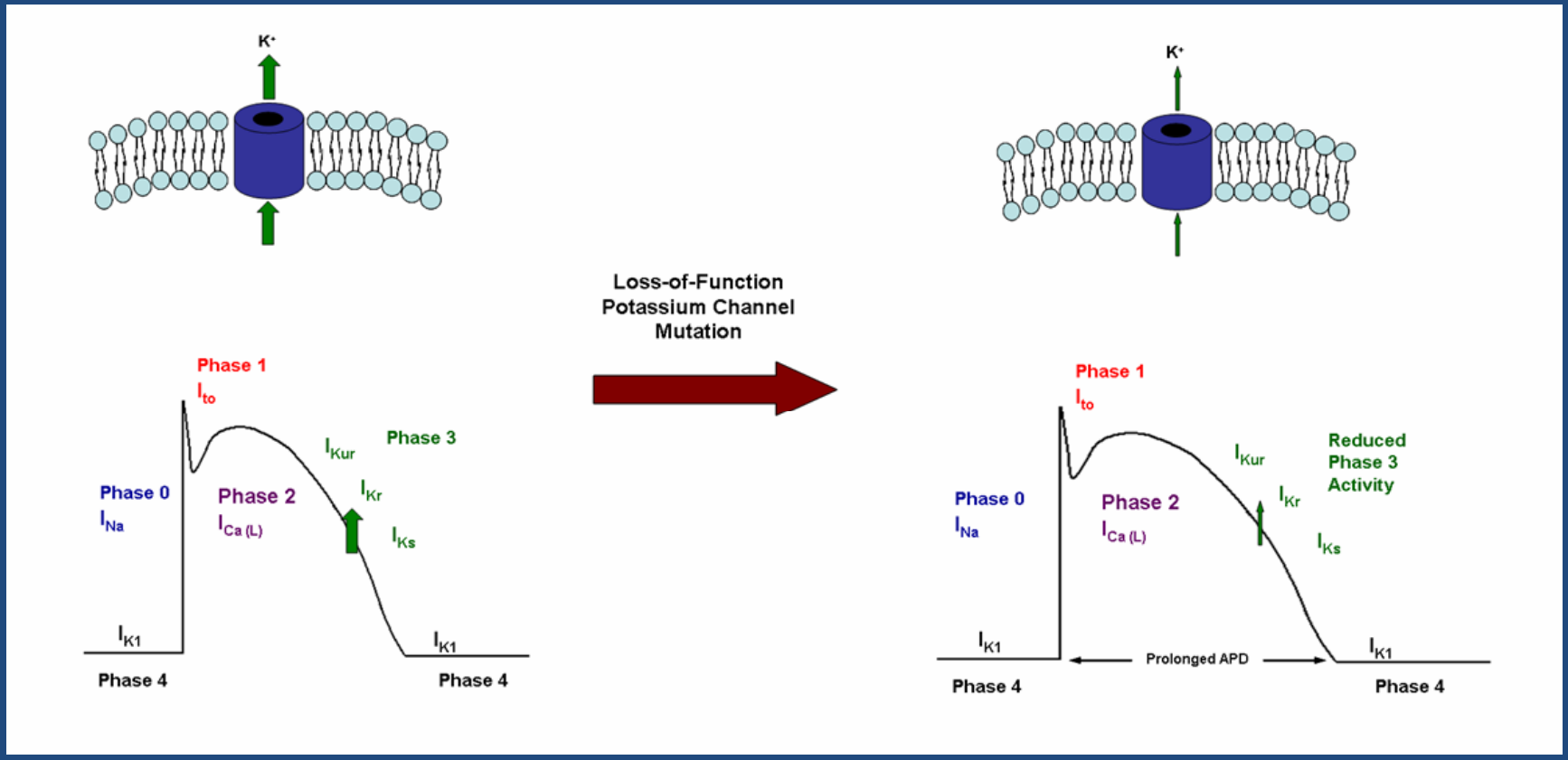
Gollob MH, Redpath CJ, & Roberts JD *J Am Coll Cardiol* 2011

Kv1.5 channelopathy due to *KCNA5* loss-of-function mutation causes human atrial fibrillation

Timothy M. Olson[1,2,3], Alexey E. Alekseev[1,3], Xiaoke K. Liu[1,3], Sungjo Park[1,3], Leonid V. Zingman[1,3], Martin Bienengraeber[1,3], Srinivasan Sattiraju[1,3], Jeffrey D. Ballew[1], Arshad Jahangir[1,3] and Andre Terzic[1,3,*]

Hum Mol Genet 2006

Loss-of-Function Potassium Channel Mutation



Roberts JD & Gollob MH. *Clinical Cardiogenetics* 2011

Atrial Torsade?

Cesium-Induced Atrial Tachycardia Degenerating into Atrial Fibrillation in Dogs: Atrial Torsades de Pointes?

TADASHI SATOH, M.D., and DOUGLAS P. ZIPES, M.D.

From the Krannert Institute of Cardiology, Indiana University School of Medicine and Roudebush Veterans Affairs Medical Center, Indianapolis, Indiana

Prolonged Atrial Action Potential Durations and Polymorphic Atrial Tachyarrhythmias in Patients with Long QT Syndrome

PAULUS KIRCHHOF, M.D., LARS ECKARDT, M.D., MICHAEL R. FRANZ, M.D., PH.D.,*
GEROLD MÖNNIG, M.D., PETER LOH, M.D., HORST WEDEKIND, M.D.,
ERIC SCHULZE-BAHR, M.D., GÜNTER BREITHARDT, M.D.,
and WILHELM HAVERKAMP, M.D.

From the Department of Cardiology and Angiology, Hospital of the University of Münster, and Institute for Arteriosclerosis Research at the University of Münster, Münster, Germany; and *Departments of Pharmacology and Cardiology, Georgetown University and VA Medical Center, Washington, DC, USA

AF (or Atrial Torsade) & LQTS

Prevalence of early-onset atrial fibrillation in congenital long QT syndrome

Jonathan N. Johnson, MD,* David J. Tester, BS,*† James Perry, MD, FHRS,‡
Benjamin A. Salisbury, PhD,§ Carol R. Reed, MD,§ Michael J. Ackerman, MD, PhD*†¶

CONCLUSION Compared to the background prevalence of 0.1%, early-onset AF was observed in almost 2% of patients with genetically proven LQTS and should be viewed as an uncommon but possible LQT-related dysrhythmia. Clinical complaints of palpitations warrant thorough assessment in patients with LQTS.

Heart Rhythm 2008

Other Mechanisms?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Somatic Mutations in the Connexin 40 Gene (*GJA5*) in Atrial Fibrillation

Michael H. Gollob, M.D., Douglas L. Jones, Ph.D., Andrew D. Krahn, M.D., Lynne Danis, M.L.T., Xiang-Qun Gong, Ph.D., Qing Shao, Ph.D., Xiaoqin Liu, M.D., John P. Veinot, M.D., Anthony S.L. Tang, M.D., Alexandre F.R. Stewart, Ph.D., Frederique Tesson, Ph.D., George J. Klein, M.D., Raymond Yee, M.D., Allan C. Skanes, M.D., Gerard M. Guiraudon, M.D., Lisa Ebihara, M.D., Ph.D., and Donglin Bai, Ph.D.

N Engl J Med 2006

Heart Rhythm Disorders

A Novel *SCN5A* Gain-of-Function Mutation M1875T Associated With Familial Atrial Fibrillation

Takeru Makiyama, MD, PHD,* Masaharu Akao, MD, PHD,* Satoshi Shizuta, MD,* Takahiro Doi, MD,* Kei Nishiyama, MD,* Yuko Oka, MD,† Seiko Ohno, MD, PHD,* Yukiko Nishio, MD,* Keiko Tsuji, MS,† Hideki Itoh, MD, PHD,† Takeshi Kimura, MD, PHD,* Toru Kita, MD, PHD,* Minoru Horie, MD, PHD†

Kyoto and Otsu, Japan

J Am Coll Cardiol 2008

Cardiac sodium channel mutation in atrial fibrillation

Patrick T. Ellinor, MD, PhD,*† Edwin G. Nam, BA,† Marisa A. Shea, RN,* David J. Milan, MD,*†
Jeremy N. Ruskin, MD,* Calum A. MacRae, MB, ChB, PhD†

- A loss-of-function Asn1986Lys *SCN5A* mutation was suggested to prolong atrial action potential duration
- The resultant AF is presumably reflective of atrial torsade
- Treatment?

Heart Rhythm 2008

AF more than just ion channels?

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Atrial Natriuretic Peptide Frameshift Mutation in Familial Atrial Fibrillation

Denice M. Hodgson-Zingman, M.D., Margaret L. Karst, B.A., Leonid V. Zingman, M.D., Denise M. Heublein, C.L.T., Dawood Darbar, M.D., Kathleen J. Herron, B.A., Jeffrey D. Ballew, M.S., Mariza de Andrade, Ph.D., John C. Burnett, Jr., M.D., and Timothy M. Olson, M.D.

N Engl J Med 2008

AF is heterogeneous

Table 1 Mechanistic Subclassification of Lone AF

AF Subclassification	Culprit Gene(s)	Functional Effect
1. Enhanced atrial action potential repolarization	*KCNQ1* (11,15,16)	Enhanced slow component of the delayed rectifier potassium current (I_{Ks})
	KCNE2 (17)	Enhanced *KCNQ1-KCNE2* potassium current
	KCNJ2 (18)	Enhanced inward rectifier current (I_{K1})
	KCNE5 (19)	Enhanced I_{Ks}
2. Delayed atrial action potential repolarization	*KCNA5* (28)	Decreased ultrarapid component of the delayed rectifier potassium current (I_{Kur})
	SCN5A (35)	Hyperpolarizing shift in $Na_v1.5$ inactivation
3. Conduction velocity heterogeneity	*GJA5* (40)	Decreased gap junction conduction
4. Cellular hyperexcitability	*SCN5A* (44,45)	Depolarizing shift in $Na_v1.5$ inactivation
5. Hormonal modulation of atrial electrophysiology	*NPPA* (12)	Increased circulating levels of mutant atrial natriuretic peptide
6. Cholinergic	Unknown	Enhanced cholinergic sensitivity

Roberts JD & Gollob MH. *J Am Coll Cardiol* 2010

Original Article

Selective Targeting of Gain-of-Function KCNQ1 Mutations Predisposing to Atrial Fibrillation

Courtney M. Campbell, PhD; Jonathan D. Campbell, BS; Christopher H. Thompson, PhD; Eleonora Savio Galimberti, MD, PhD; Dawood Darbar, MD; Carlos G. Vanoye, PhD; Alfred L. George Jr, MD

Conclusions—The enhanced sensitivity of KCNQ1 gain-of-function mutations for HMR-1556 suggests the possibility of selective therapeutic targeting, and, therefore, our data illustrate a potential proof of principle for genotype-specific treatment of this heritable arrhythmia. (***Circ Arrhythm Electrophysiol*. 2013;6:960-966.**)

Are There Common Genetic Variants that predispose to AF?

Can they guide pharmacogenomic treatment strategies?

Meta-analysis identifies six new susceptibility loci for atrial fibrillation

Patrick T Ellinor[1–4,75], Kathryn L Lunetta[5,6,75], Christine M Albert[4,7,8,75], Nicole L Glazer[9,75], Marylyn D Ritchie[10,11,75], Albert V Smith[12,13,75], Dan E Arking[14,75], Martina Müller-Nurasyid[15–17,75], Bouwe P Krijthe[18,19,75], Steven A Lubitz[1,7,75], Joshua C Bis[9,75], Mina K Chung[20,21,75], Marcus Dörr[22,75], Kouichi Ozaki[23,75], Jason D Roberts[24], J Gustav Smith[25,26], Arne Pfeufer[27,28], Moritz F Sinner[1,6,15], Kurt Lohman[29], Jingzhong Ding[30], Nicholas L Smith[9,31–33], Jonathan D Smith[20,34], Michiel Rienstra[1,35], Kenneth M Rice[36], David R Van Wagoner[20,21], Jared W Magnani[6,37], Reza Wakili[15], Sebastian Clauss[15], Jerome I Rotter[38], Gerhard Steinbeck[15], Lenore J Launer[39], Robert W Davies[40], Matthew Borkovich[24], Tamara B Harris[39], Honghuang Lin[37], Uwe Völker[41], Henry Völzke[42], David J Milan[1,2], Albert Hofman[18,19], Eric Boerwinkle[43], Lin Y Chen[44], Elsayed Z Soliman[45], Benjamin F Voight[26], Guo Li[9], Aravinda Chakravarti[14], Michiaki Kubo[46], Usha B Tedrow[4,7,8], Lynda M Rose[7], Paul M Ridker[4,7,8], David Conen[47], Tatsuhiko Tsunoda[48], Tetsushi Furukawa[49], Nona Sotoodehnia[9,50], Siyan Xu[5,51], Naoyuki Kamatani[52], Daniel Levy[6], Yusuke Nakamura[53], Babar Parvez[54], Saagar Mahida[1], Karen L Furie[4,55], Jonathan Rosand[3,4,55], Raafia Muhammad[54], Bruce M Psaty[9,32,33,56], Thomas Meitinger[27,28], Siegfried Perz[57], H-Erich Wichmann[58–60], Jacqueline C M Witteman[18,19], W H Linda Kao[61,62], Sekar Kathiresan[26,63], Dan M Roden[54,64], Andre G Uitterlinden[18,19,65], Fernando Rivadeneira[18,19,65], Barbara McKnight[36], Marketa Sjögren[66], Anne B Newman[67], Yongmei Liu[68], Michael H Gollob[24], Olle Melander[66], Toshihiro Tanaka[23,76], Bruno H Ch Stricker[17,19,65,69,70,76], Stephan B Felix[22,76], Alvaro Alonso[71,76], Dawood Darbar[54,76], John Barnard[72,76], Daniel I Chasman[4,7,76], Susan R Heckbert[9,32,33,76], Emelia J Benjamin[6,37,51,73,76], Vilmundur Gudnason[12,13,76] & Stefan Kääb[15,74,76]

Nat Genet 2012

9 Common Variants Associated with AF

Table 2 Summary of GWAS meta-analysis results with $P < 5 \times 10^{-8}$

						Discovery			Replication		Overall	
SNP	Locus	Closest gene	SNP location relative to closest gene	Minor/ major allele	MAF (%)	RR (95% CI)	Meta *P* value	I^2 (%), *P* value	RR (95% CI)	Meta *P* value	RR (95% CI)	Meta *P* value
rs6666258	1q21	*KCNN3-PMVK*	Intronic	C/G	29.9	1.18 (1.13–1.23)	2.0×10^{-14}	42.3, 0.04	–	–	–	–
rs3903239	1q24	*PRRX1*	46 kb upstream	G/A	44.7	1.14 (1.10–1.18)	9.1×10^{-11}	53.2, 6.3×10^{-3}	1.13 (1.06–1.20)	2.0×10^{-4}	**1.14 (1.10–1.17)**	**8.4×10^{-14}**
rs6817105	4q25	*PITX2*	150 kb upstream	C/T	13.1	1.64 (1.55–1.73)	1.8×10^{-74}	80.8, 1.4×10^{-10}	–	–	–	–
rs2040862	5q31	*WNT8A*	Intronic	T/C	17.8	1.15 (1.09–1.21)	3.2×10^{-8}	10, 0.34	1.04 (0.96–1.12)	3.6×10^{-1}	1.12 (1.07–1.17)	2.5×10^{-7}
rs3807989	7q31	*CAV1*	Intronic	A/G	40.4	0.88 (0.84–0.91)	9.6×10^{-11}	10, 0.34	0.93 (0.88–0.97)	2.7×10^{-3}	**0.90 (0.87–0.92)**	**3.6×10^{-12}**
rs10821415	9q22	*C9orf3*	Intronic	A/C	42.4	1.13 (1.08–1.18)	7.9×10^{-9}	49.5, 0.015	1.09 (1.04–1.15)	7.2×10^{-4}	**1.11 (1.08–1.15)**	**4.2×10^{-11}**
rs10824026	10q22	*SYNPO2L*	5 kb upstream	G/A	15.8	0.85 (0.81–0.90)	1.7×10^{-8}	37.9, 0.06	0.91 (0.83–0.99)	3.5×10^{-2}	**0.87 (0.83–0.91)**	**4.0×10^{-9}**
rs1152591	14q23	*SYNE2*	Intronic	A/G	47.6	1.13 (1.09–1.18)	6.2×10^{-10}	25.7, 0.16	1.12 (1.06–1.19)	1.9×10^{-4}	**1.13 (1.09–1.17)**	**5.8×10^{-13}**
rs7164883	15q24	*HCN4*	Intronic	G/A	16.0	1.16 (1.10–1.22)	1.3×10^{-8}	0, 0.85	1.24 (1.16–1.32)	1.3×10^{-10}	**1.19 (1.14–1.24)**	**2.8×10^{-17}**
rs2106261	16q22	*ZFHX3*	Intronic	T/C	17.6	1.24 (1.17–1.30)	3.2×10^{-16}	58.8, 1.6×10^{-3}	–	–	–	–

MAF, minor allele frequency; RR, relative risk. I^2 represents the proportion of variability in the effect size due to between-study variability. We did not attempt replication of the previously published genetic loci associated with atrial fibrillation on chromosomes 1q21 (*KCNN3*)[2], 4q25 (*PITX2*)[4] and 16q22 (*ZFHX3*)[3,5].

Ellinor PT, *et al. Nat Genet* 2012

Arrhythmia/Electrophysiology

Integrating Genetic, Transcriptional, and Functional Analyses to Identify 5 Novel Genes for Atrial Fibrillation

Moritz F. Sinner, MD, MPH*; Nathan R. Tucker, PhD*; Kathryn L. Lunetta, PhD*; Kouichi Ozaki, PhD*; J. Gustav Smith, MD, PhD*; Stella Trompet, PhD*; Joshua C. Bis, PhD*; Honghuang Lin, PhD*; Mina K. Chung, MD*; Jonas B. Nielsen, MD*; Steven A. Lubitz, MD, MPH*; Bouwe P. Krijthe, PhD*; Jared W. Magnani, MD, MSc*; Jiangchuan Ye, MD, PhD; Michael H. Gollob, MD; Tatsuhiko Tsunoda, PhD; Martina Müller-Nurasyid, PhD; Peter Lichtner, PhD; Annette Peters, PhD; Elena Dolmatova, MD; Michiaki Kubo, MD, PhD; Jonathan D. Smith, PhD; Bruce M. Psaty, MD, PhD; Nicholas L. Smith, PhD; J. Wouter Jukema, MD, PhD; Daniel I. Chasman, PhD; Christine M. Albert, MD, MPH; Yusuke Ebana, MD, PhD; Tetsushi Furukawa, MD, PhD; Peter W. Macfarlane, DSc; Tamara B. Harris, MD, MS; Dawood Darbar, MD; Marcus Dörr, MD; Anders G. Holst, MD, PhD; Jesper H. Svendsen, MD, DMSc; Albert Hofman, MD, PhD; Andre G. Uitterlinden, MD, PhD; Vilmundur Gudnason, MD; Mitsuaki Isobe, MD, PhD; Rainer Malik, PhD; Martin Dichgans, MD; Jonathan Rosand, MD, MSc; David R. Van Wagoner, PhD; METASTROKE Consortium; AFGen Consortium; Emelia J. Benjamin, MD, ScM†; David J. Milan, MD†; Olle Melander, MD, PhD†; Susan R. Heckbert, MD, PhD†; Ian Ford, PhD†; Yongmei Liu, MD, PhD†; John Barnard, PhD†; Morten S. Olesen, MSc, PhD†; Bruno H.C. Stricker, MB, PhD†; Toshihiro Tanaka, MD, PhD†; Stefan Kääb, MD, PhD†; Patrick T. Ellinor, MD, PhD†

Circulation 2014

5 Additional Common Variants Associated with AF

Table 1. Meta-analyses of SNP Associations With AF by Origin of Study

SNP	Chromosome	AF Risk Allele	Closest Gene	Relative Location	Original GWAS Data Set[4] RAF	Original GWAS Data Set[4] RR (95% CI)	Original GWAS Data Set[4] *P*	Replication RAF	Replication RR (95% CI)	Replication *P*	Overall Meta-Analysis RAF	Overall Meta-Analysis RR (95% CI)	Overall Meta-Analysis *P*
Europeans													
rs12415501	10q24	T	*NEURL*	Intronic	0.16	1.15 (1.10–1.22)	9.0×10^{-8}	0.16	1.22 (1.14–1.29)	6.0×10^{-10}*	0.16	1.18 (1.13–1.23)	6.5×10^{-16}*
rs10507248	12q24	T	*TBX5*	Intronic	0.73	1.13 (1.08–1.18)	8.5×10^{-8}	0.73	1.11 (1.05–1.17)	0.0001*	0.73	1.12 (1.08–1.16)	5.7×10^{-11}*
rs4642101	3p25	G	*CAND2*	Intronic	0.65	1.11 (1.06–1.15)	4.2×10^{-6}	0.65	1.09 (1.04–1.15)	0.0006*	0.65	1.10 (1.06–1.14)	9.8×10^{-9}*
rs13216675	6q22	T	*GJA1*	Intergenic	0.69	1.10 (1.05–1.15)	5.0×10^{-5}	0.68	1.10 (1.05–1.16)	0.0001*	0.69	1.10 (1.06–1.14)	2.2×10^{-8}*
Japanese													
rs6584555	10q24	C	*NEURL*	Intronic	0.12	1.33 (1.14–1.55)	2.8×10^{-4}	0.12	1.32 (1.25–1.39)	1.6×10^{-22}*	0.12	1.32 (1.26–1.39)	2.0×10^{-25}*
rs6490029	12q24	A	*CUX2*	Intronic	0.65	1.22 (1.09–1.37)	6.3×10^{-4}	0.64	1.11 (1.07–1.16)	5.0×10^{-7}*	0.64	1.12 (1.08–1.16)	3.9×10^{-9}*

Sinner MF *Circulation* 2014

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 55, No. 8, 2010
ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2009.11.041

QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

Chromosome 4q25 Variants and Atrial Fibrillation Recurrence After Catheter Ablation

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Leipzig, Germany

J Am Coll Cardiol 2010

4q25 & AF ablation

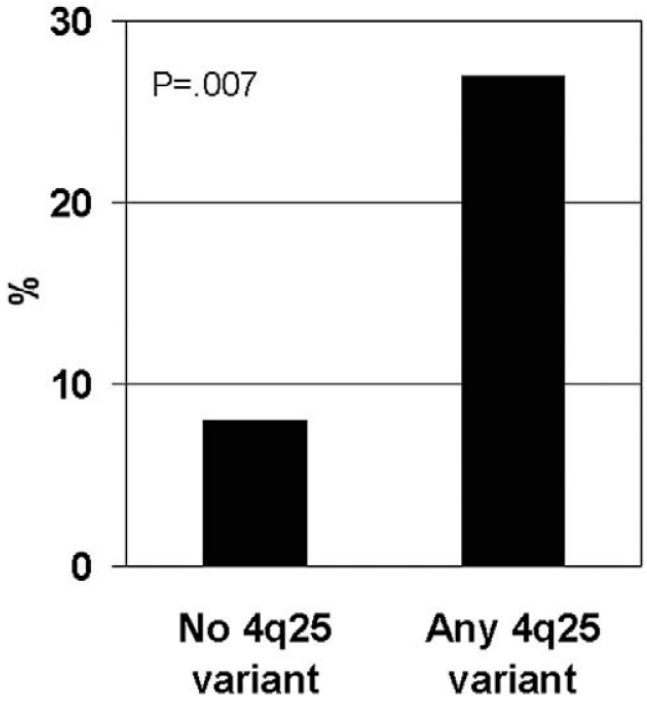


Figure 2 **AF Recurrence After 6 Months Stratified by the Presence of 4q25 Variants**

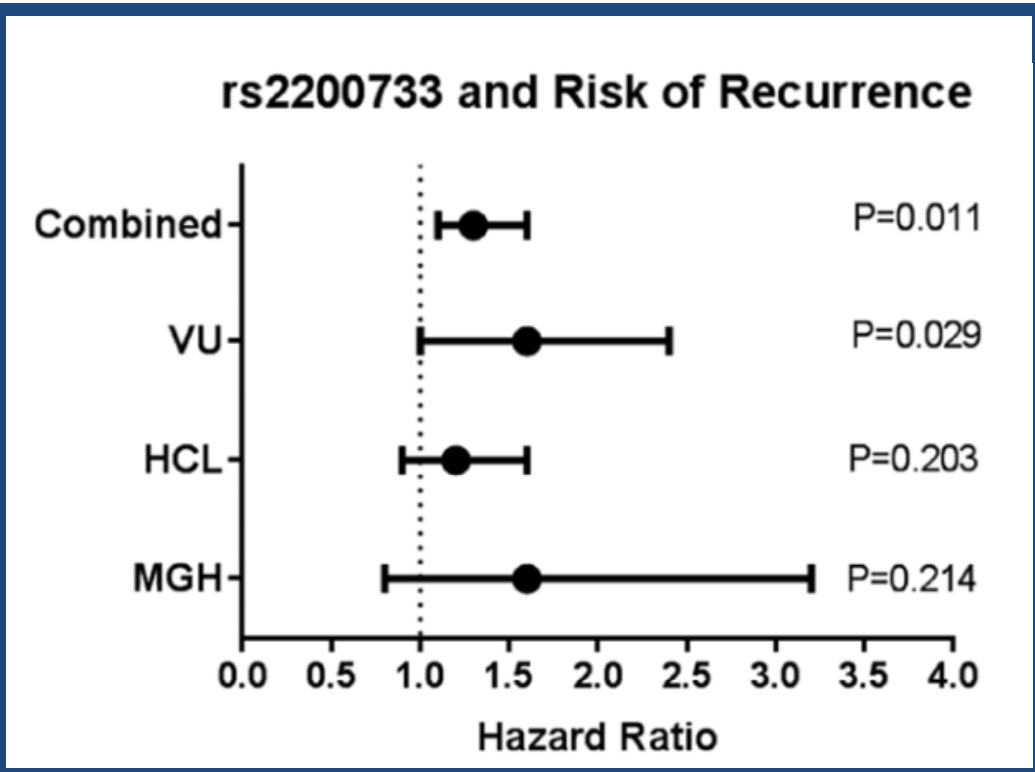
Note the increased risk for atrial fibrillation (AF) recurrence (odds ratio: 4.182, 95% confidence interval: 1.318 to 12.664, p = 0.011) if at least 1 4q25 variant was present compared with the wild type.

Husser D, *et al. J Am Coll Cardiol* 2010

Original Article

Common Genetic Variants and Response to Atrial Fibrillation Ablation

M. Benjamin Shoemaker, MD, MSCI*; Andreas Bollmann, MD, PhD*; Steven A. Lubitz, MD, MPH*; Laura Ueberham; Harsimran Saini, MD; Jay Montgomery, MD; Todd Edwards, PhD; Zachary Yoneda, MD; Moritz F. Sinner, MD, MPH; Arash Arya, MD; Philipp Sommer, MD; Jessica Delaney, MD; Sandeep K. Goyal, MD; Pablo Saavedra, MD; Arvindh Kanagasundram, MD; S. Patrick Whalen, MD; Dan M. Roden, MD; Gerhard Hindricks, MD; Christopher R. Ellis, MD; Patrick T. Ellinor, MD, PhD*; Dawood Darbar, MD*; Daniela Husser, MD*



Circ Arrhythm Electrophysiol 2015

Editorial

The Burgeoning Field of Ablatogenomics

Jason D. Roberts, MD; Gregory M. Marcus, MD, MAS

Circ Arrhythm Electrophysiol 2015

4q25 & AADs

Symptomatic Response to Antiarrhythmic Drug Therapy Is Modulated by a Common Single Nucleotide Polymorphism in Atrial Fibrillation

Babar Parvez, MD, Joseph Vaglio, MD, Shane Rowan, MD, Raafia Muhammad, MD, Gayle Kucera, RN, Tanya Stubblefield, RN, Shannon Carter, RN, Dan Roden, MD, Dawood Darbar, MD

Nashville, Tennessee

J Am Coll Cardiol 2012

GENE-AF Registry

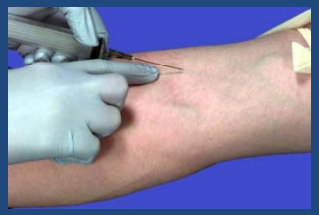
- Through combining data from randomized controlled trials and high volume Afib centers
  - Will establish large biobank with clinical outcomes
    - Anticipate approximately 3000 samples within 3 years
- Will provide the opportunity to systematically evaluate associations between genetic carrier status and clinical outcomes
  - Will do for:
    - Ablation
    - Anti-Arrhythmic Drugs
    - NOACs

Accessibility & Practicality of Genetic Testing

- Clinical genetic testing is presently limited to a limited number of centres in both the US & Canada
  - Otherwise it remains the domain of research laboratories
- This presents a major obstacle to incorporation of a pharmaco- or ablatogenomic approach to clinical care.

Current Central Lab Process

1. Collect Blood Sample



2. Ship to Central Lab

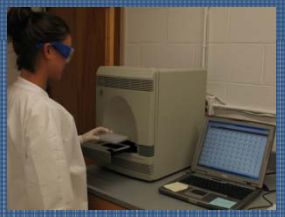
3. Pipet Blood into Tubes

DNA Collection

DNA Extraction

4. DNA Purification Robot

5. Mainframe DNA Analyzer



6. Follow-up appointment

DNA Amplification

DNA Analysis / Interpretation

Results in 2-7 days
(to be interpreted by a Cardiologist)

Point-of-Care Genetic Testing

SPARTAN RX CYPC19

- Operated by Nurses with no prior laboratory expertise
- Requires a 30 minute training session
- 4 step procedure:
  - Acquisition of a buccal swab
  - Insertion of the swab into an assay cartridge
  - Insertion of the reaction solution into the genetic testing device
  - Analysis of *CYP2C19*2* status triggered by pressing a button
- Result available within 45 minutes

Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial

Jason D Roberts, George A Wells, Michel R Le May, Marino Labinaz, Chris Glover, Michael Froeschl, Alexander Dick, Jean-Francois Marquis, Edward O'Brien, Sandro Goncalves, Irena Druce, Alexandre Stewart, Michael H Gollob, Derek Y F So

ClinicalTrials.gov, NCT01184300.

Lancet 2012

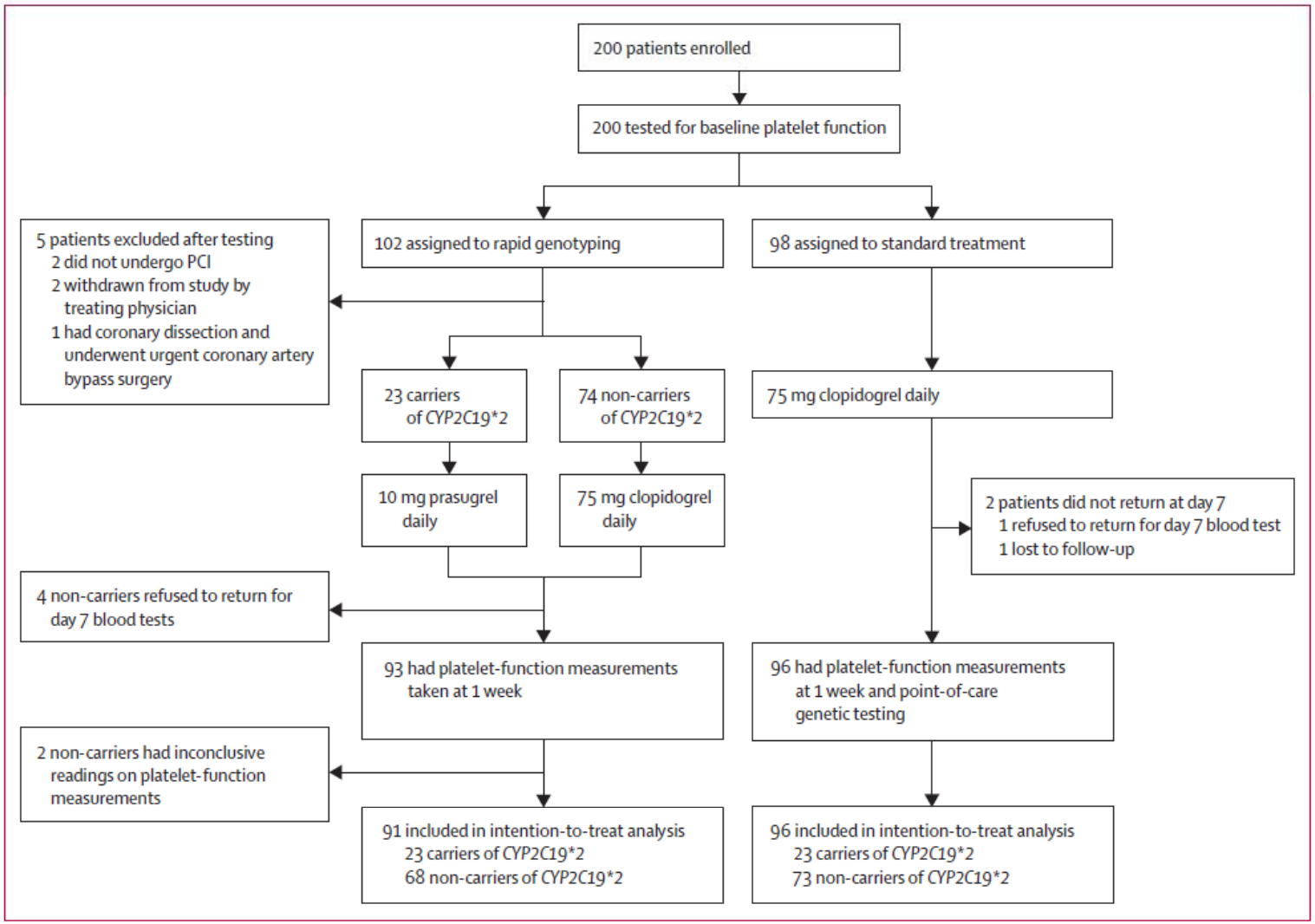


Figure 1: **Study design**
PCI=percutaneous coronary intervention.

Roberts JD *Lancet* 2012

The Point-of-Care Genetic Test

23 (25%) of 91 patients assigned to the rapid genotyping group carried at least one copy of the *CYP2C19*2* allele, compared with 23 (24%) of 96 in the standard therapy group. Of the individuals carrying a *CYP2C19*2* allele, four (4%) patients in the rapid genotyping group and three (3%) in the standard treatment group were homozygous. When compared with direct DNA sequencing, one case in the rapid genotyping group had been incorrectly identified as a *CYP2C19*2* carrier. The device had a sensitivity of 100% (95% CI 92·3–100), a specificity of 99·3% (96·3–100), and a conclusive rate of 93·6%.

Roberts JD *Lancet* 2012

theranos

Take Home Message

AF Pharmaco- & Ablatogenomics

- In its infancy
  - One common genetic variant (4q25) appears to have robust data for predicting ablation success
  - Roles of additional SNPs and rare variants remain to be clarified
- The “Promise”
  - Increased Efficacy
    - Our ultimate goal should be a Number Needed to Treat close to 1
  - Reduced Adverse Events
    - By targeting only the etiologic factor, and accounting for patient vulnerabilities, risks should be minimized

However

- Not going to happen overnight
  - And in the early days, there will be more losses than wins
- Like any other novel treatments, personalized treatment strategies will need to be rigorously evaluated and their efficacy proven through randomized controlled trials
  - Don’t believe the hype…

Thank you