Epidemiology and Pathophysiology of AF

Tae-Joon Cha, MD, PhD, FHRS

Division of cardiology

University of Kosin, Busan, South Korea.

Prevalence of Diagnosed Atrial Fibrillation in Adults

National Implications for Rhythm Management and Stroke Prevention: the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study

Alan S. Go, MD
Elaine M. Hylek, MD, MPH
Kathleen A. Phillips, BA
YuChiao Chang, PhD
Lori E. Henault, MPH
Joe V. Selby, MD, MPH
Daniel E. Singer, MD

Context Atrial fibrillation is the most common arrhythmia in elderly persons and a potent risk factor for stroke. However, recent prevalence and projected future numbers of persons with atrial fibrillation are not well described.

Objective To estimate prevalence of atrial fibrillation and US national projections of the numbers of persons with atrial fibrillation through the year 2050.

Design, Setting, and Patients Cross-sectional study of adults aged 20 years or older who were enrolled in a large health maintenance organization in California and who had atrial fibrillation diagnosed between July 1, 1996, and December 31, 1997.

Main Outcome Measures Prevalence of atrial fibrillation in the study population of 1.89 million; projected number of persons in the United States with atrial fibrillation between 1995-2050.

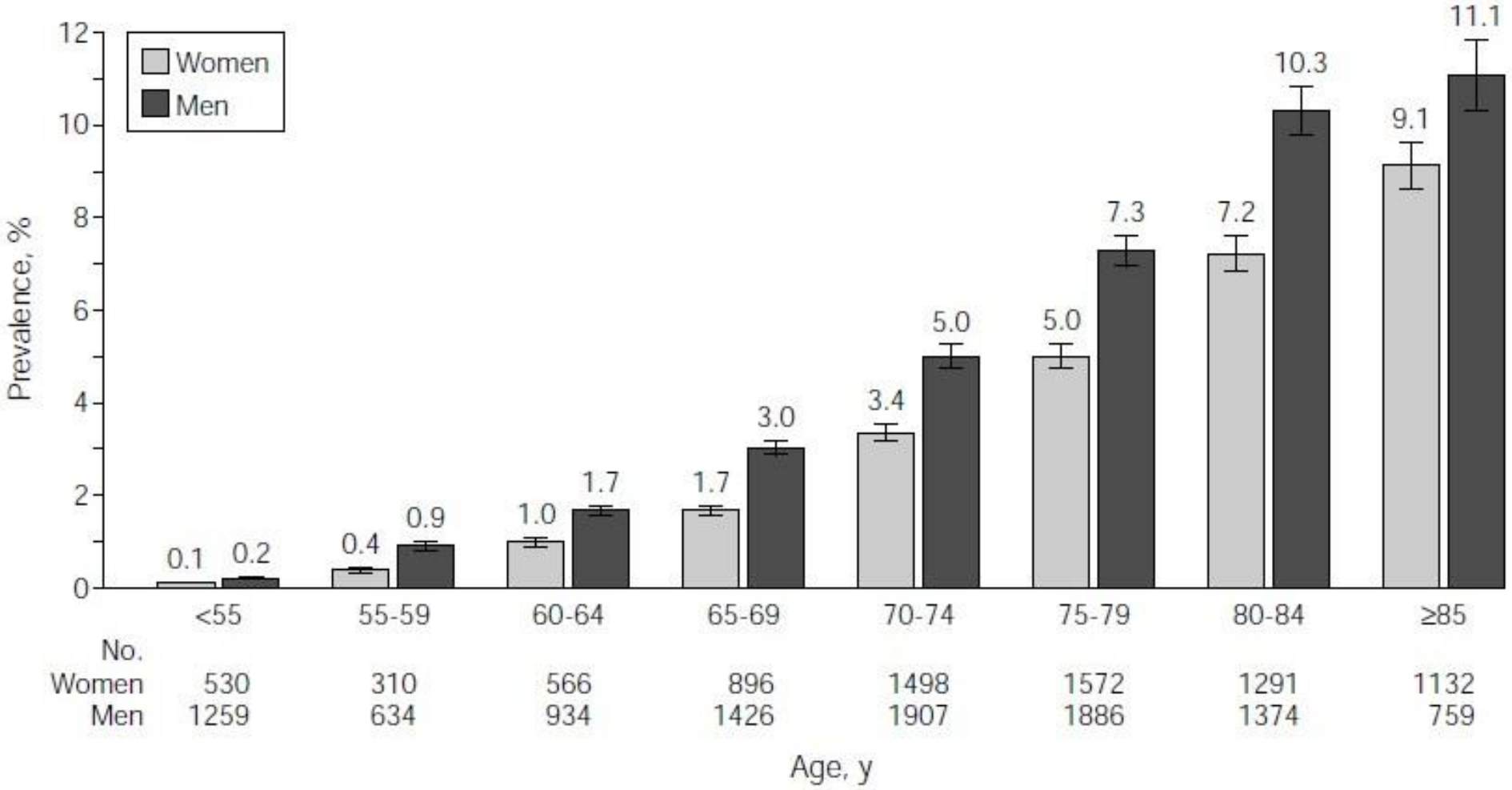
Results A total of 17974 adults with diagnosed atrial fibrillation were identified during the study period; 45% were aged 75 years or older. The prevalence of atrial fibrillation was 0.95% (95% confidence interval, 0.94%-0.96%). Atrial fibrillation was more common in men than in women (1.1% vs 0.8%; $P<.001$). Prevalence increased from 0.1% among adults younger than 55 years to 9.0% in persons aged 80 years or older. Among persons aged 50 years or older, prevalence of atrial fibrillation was higher in whites than in blacks (2.2% vs 1.5%; $P<.001$). We estimate approximately 2.3 million US adults currently have atrial fibrillation. We project that this will increase to more than 5.6 million (lower bound, 5.0; upper bound, 6.3) by the year 2050, with more than 50% of affected individuals aged 80 years or older.

Conclusions Our study confirms that atrial fibrillation is common among older adults and provides a contemporary basis for estimates of prevalence in the United States. The number of patients with atrial fibrillation is likely to increase 2.5-fold during the next 50 years, reflecting the growing proportion of elderly individuals. Coordinated efforts are needed to face the increasing challenge of optimal stroke prevention and rhythm management in patients with atrial fibrillation.

JAMA. 2001;285:2370-2375 www.jama.com

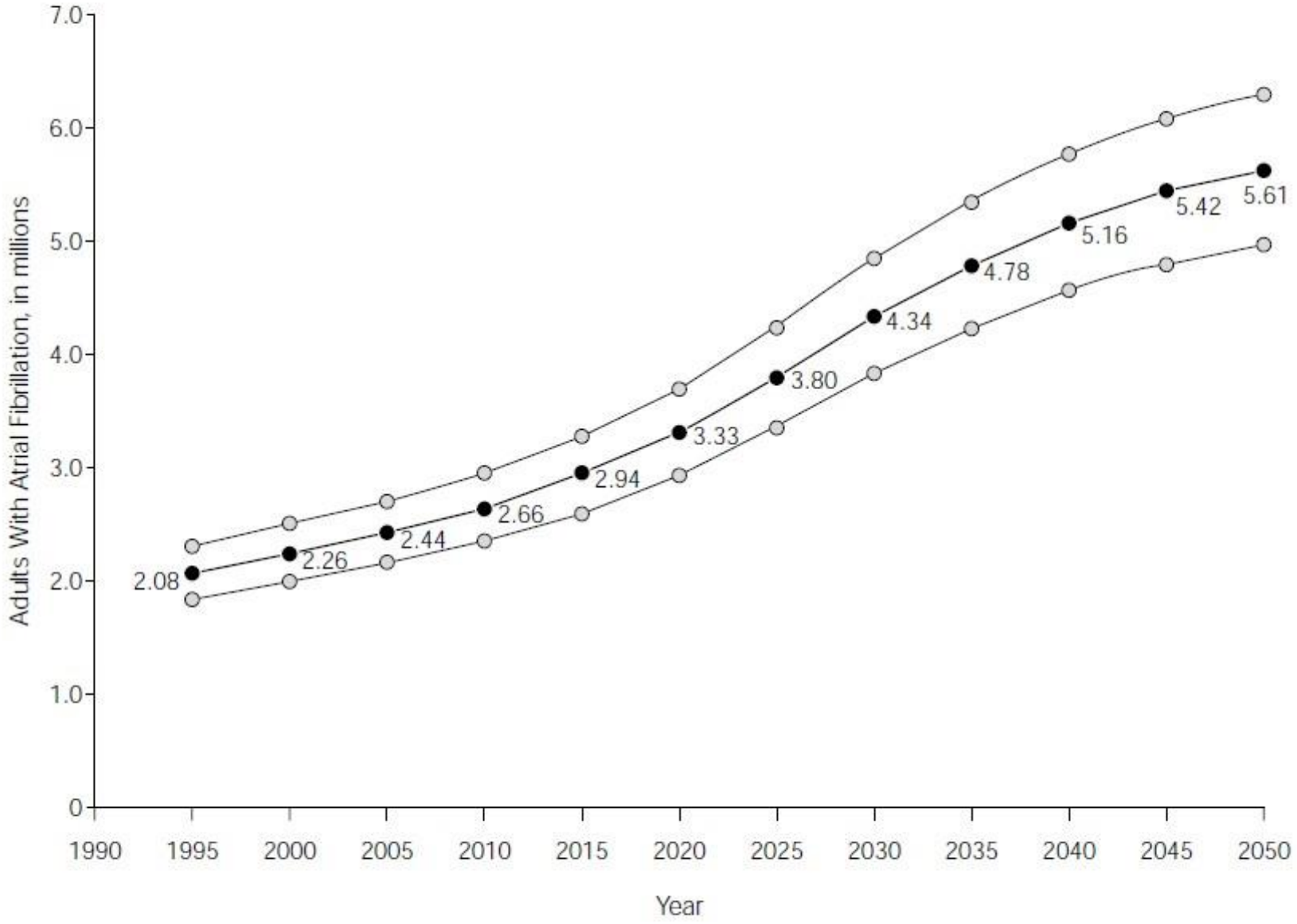
ATRIAL FIBRILLATION IS THE most common clinically significant cardiac arrhythmia. It is also a potent risk factor for ischemic stroke, increasing the risk of stroke 5-fold and accounting for approximately 15% of all strokes nationally.[1] Symptomatic atrial fibrillation may also reduce quality of life, functional status, and cardiac performance.[2] It is associated with higher medical costs as well as an increased risk of death.[3] Specifying the prevalence of atrial fibrillation in the United States has important implications for understanding the population burden of disability and medical costs associated with this arrhythmia.

Figure 2. Prevalence of Diagnosed Atrial Fibrillation Stratified by Age and Sex



Errors bars represent 95% confidence intervals. Numbers represent the number of men and women with atrial fibrillation in each age category.

Figure 3. Projected Number of Adults With Atrial Fibrillation in the United States Between 1995 and 2050



Upper and lower curves represent the upper and lower scenarios based on sensitivity analyses.

Worldwide Epidemiology of Atrial Fibrillation

A Global Burden of Disease 2010 Study

Sumeet S. Chugh, MD; Rasmus Havmoeller, MD, PhD; Kumar Narayanan, MD; David Singh, MD; Michiel Rienstra, MD, PhD; Emelia J. Benjamin, MD, ScM; Richard F. Gillum, MD; Young-Hoon Kim, MD; John H. McAnulty, Jr, MD; Zhi-Jie Zheng, MD, PhD; Mohammad H. Forouzanfar, MD; Mohsen Naghavi, MD; George A. Mensah, MD; Majid Ezzati, PhD; Christopher J.L. Murray, MD

Background—The global burden of atrial fibrillation (AF) is unknown.

Methods and Results—We systematically reviewed population-based studies of AF published from 1980 to 2010 from the 21 Global Burden of Disease regions to estimate global/regional prevalence, incidence, and morbidity and mortality related to AF (DisModMR software). Of 377 potential studies identified, 184 met prespecified eligibility criteria. The estimated number of individuals with AF globally in 2010 was 33.5 million (20.9 million men [95% uncertainty interval (UI), 19.5–22.2 million] and 12.6 million women [95% UI, 12.0–13.7 million]). Burden associated with AF, measured as disability-adjusted life-years, increased by 18.8% (95% UI, 15.8–19.3) in men and 18.9% (95% UI, 15.8–23.5) in women from 1990 to 2010. In 1990, the estimated age-adjusted prevalence rates of AF (per 100 000 population) were 569.5 in men (95% UI, 532.8–612.7) and 359.9 in women (95% UI, 334.7–392.6); the estimated age-adjusted incidence rates were 60.7 per 100 000 person-years in men (95% UI, 49.2–78.5) and 43.8 in women (95% UI, 35.9–55.0). In 2010, the prevalence rates increased to 596.2 (95% UI, 558.4–636.7) in men and 373.1 (95% UI, 347.9–402.2) in women; the incidence rates increased to 77.5 (95% UI, 65.2–95.4) in men and 59.5 (95% UI, 49.9–74.9) in women. Mortality associated with AF was higher in women and increased by 2-fold (95% UI, 2.0–2.2) and 1.9-fold (95% UI, 1.8–2.0) in men and women, respectively, from 1990 to 2010. There was evidence of significant regional heterogeneity in AF estimations and availability of population-based data.

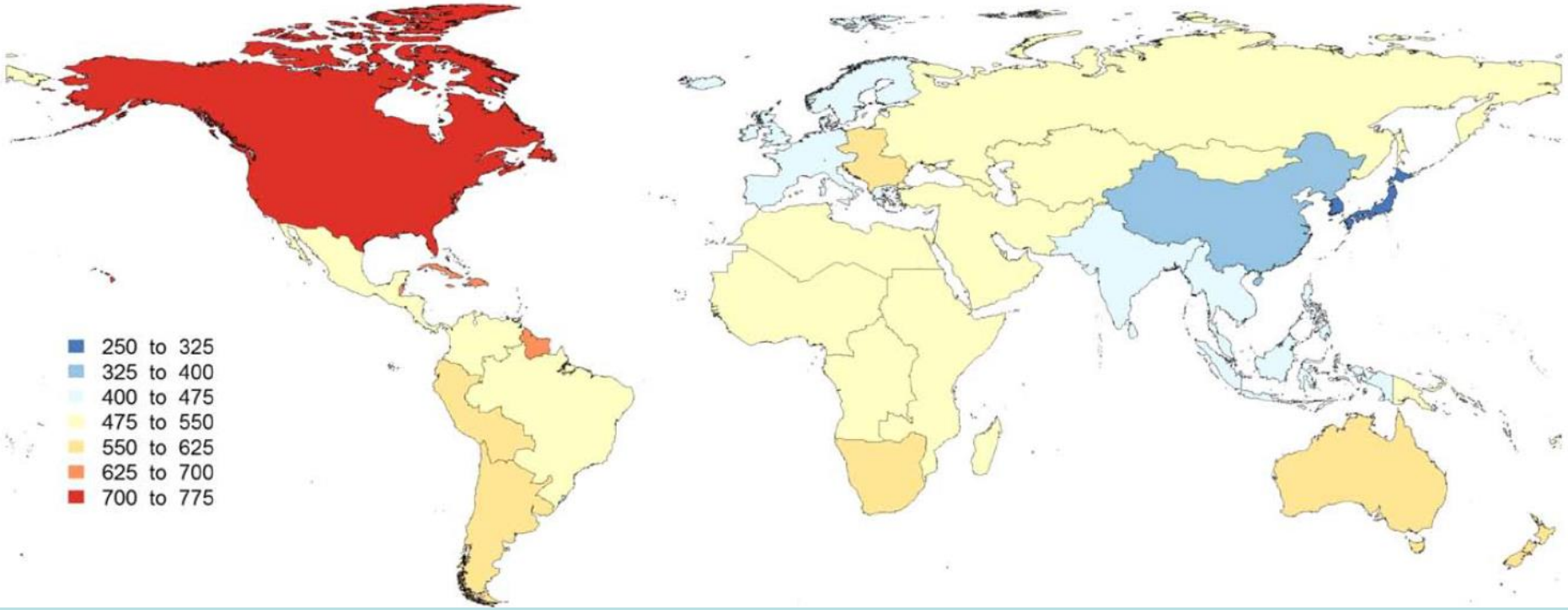
Conclusions—These findings provide evidence of progressive increases in overall burden, incidence, prevalence, and AF-associated mortality between 1990 and 2010, with significant public health implications. Systematic, regional surveillance of AF is required to better direct prevention and treatment strategies. **(*Circulation*. 2014;129:837-847.)**

Key Words: atrial fibrillation ■ epidemiology ■ incidence ■ prevalence ■ risk factors, prevention

Table 1. Estimated Age-Adjusted Prevalence Rates With 95% Uncertainty Intervals of Atrial Fibrillation (per 100 000 Population) for Men and Women

	1990	1995	2000	2005	2010
Men					
Global, all ages	569.5 (532.8–612.7)	578.1 (541.2–620.9)	586.8 (549.8–629.5)	595.1 (557.3–639.0)	596.2 (558.4–636.7)
Age ≥35 y	1307.4 (1222.5–1407.3)	1327.3 (1243.2–1425.7)	1347.6 (1263.4–1445.8)	1366.6 (1281.0–1467.1)	1368.5 (1280.8–1462.7)
Developed countries	608.2 (547·0–693.5)	625.6 (564.0–712.5)	643.1 (580.3–730.2)	660.0 (594.5–740.8)	660.9 (597.1–738.2)
Developing countries	546.6 (503.0–599.6)	551.1 (506.6–604.8)	555.8 (511.0–610.1)	561.3 (517.5–618.4)	565.7 (522.9–617.6)
Women					
Global, all ages	359.9 (334.7–392.6)	363.4 (338.5–395.3)	366.7 (342.0–397.8)	369.6 (345.5–399.9)	373.1 (347.9–402.2)
Age ≥35 y	826.5 (768.4–902.3)	834.7 (776.6–909.2)	842.3 (784.7–915.5)	849.0 (792.4–919.6)	856.8 (797.7–923.5)
Developed countries	362.5 (319.3–422.3)	370.1 (326.7–429.5)	377.5 (334.0–436.8)	385.1 (340.1–446.8)	387.7 (343.8–450.0)
Developing countries	358.2 (329.8–393.0)	359.0 (330.8–394.0)	359·8 (331.5–395.0)	360.9 (331.6–396.0)	366.1 (337.4–400.8)

Prevalence of atrial fibrilation and flutter (per 100,000) by region, 2010



AF prevalence rate

- The low prevalence rates (2010) were estimated in the Asia-Pacific region for both men and women (0.3402% and 0.196%, respectively).
- The highest rates were estimated in North America (0.9257% for men and 0.5208% for women)

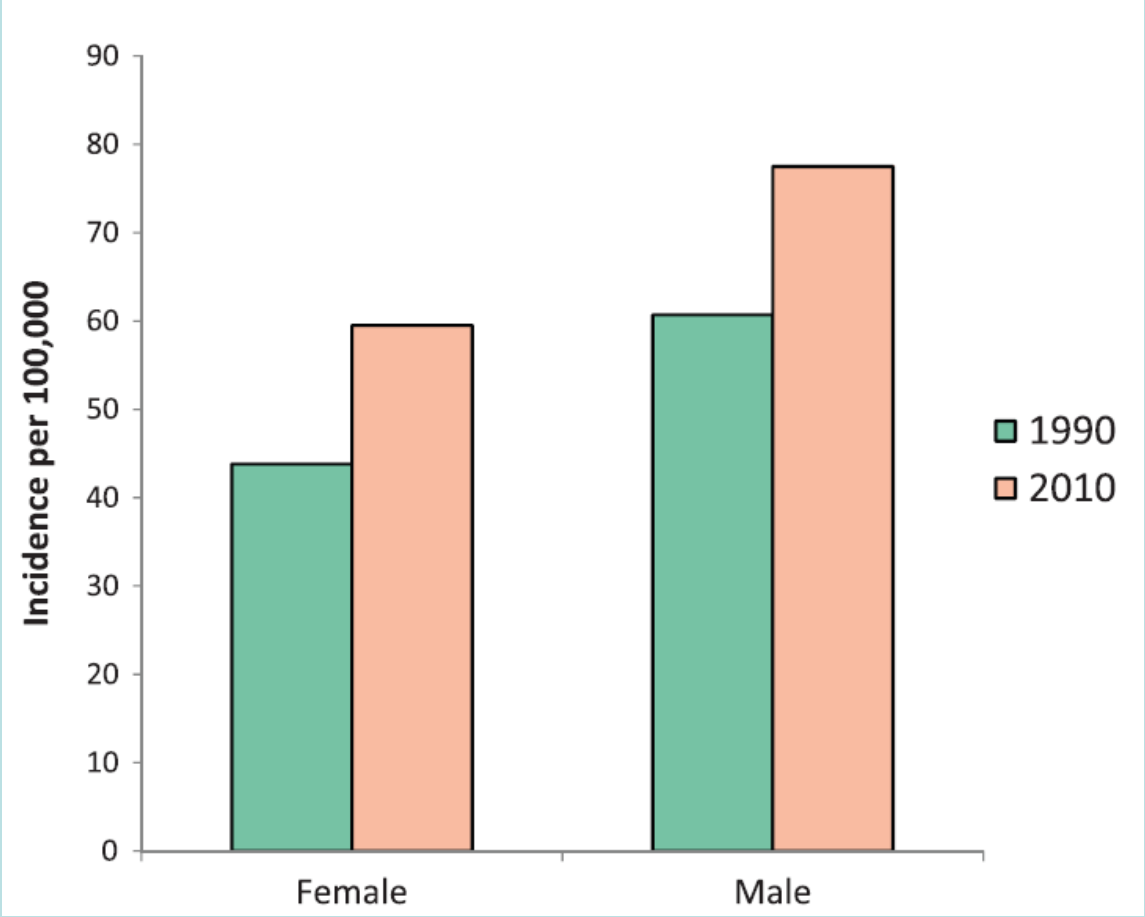
Table 2. Estimated Age-Adjusted Incidence Rates with 95% Uncertainty Intervals of Atrial Fibrillation (per 100 000 Person-years) for Men and Women

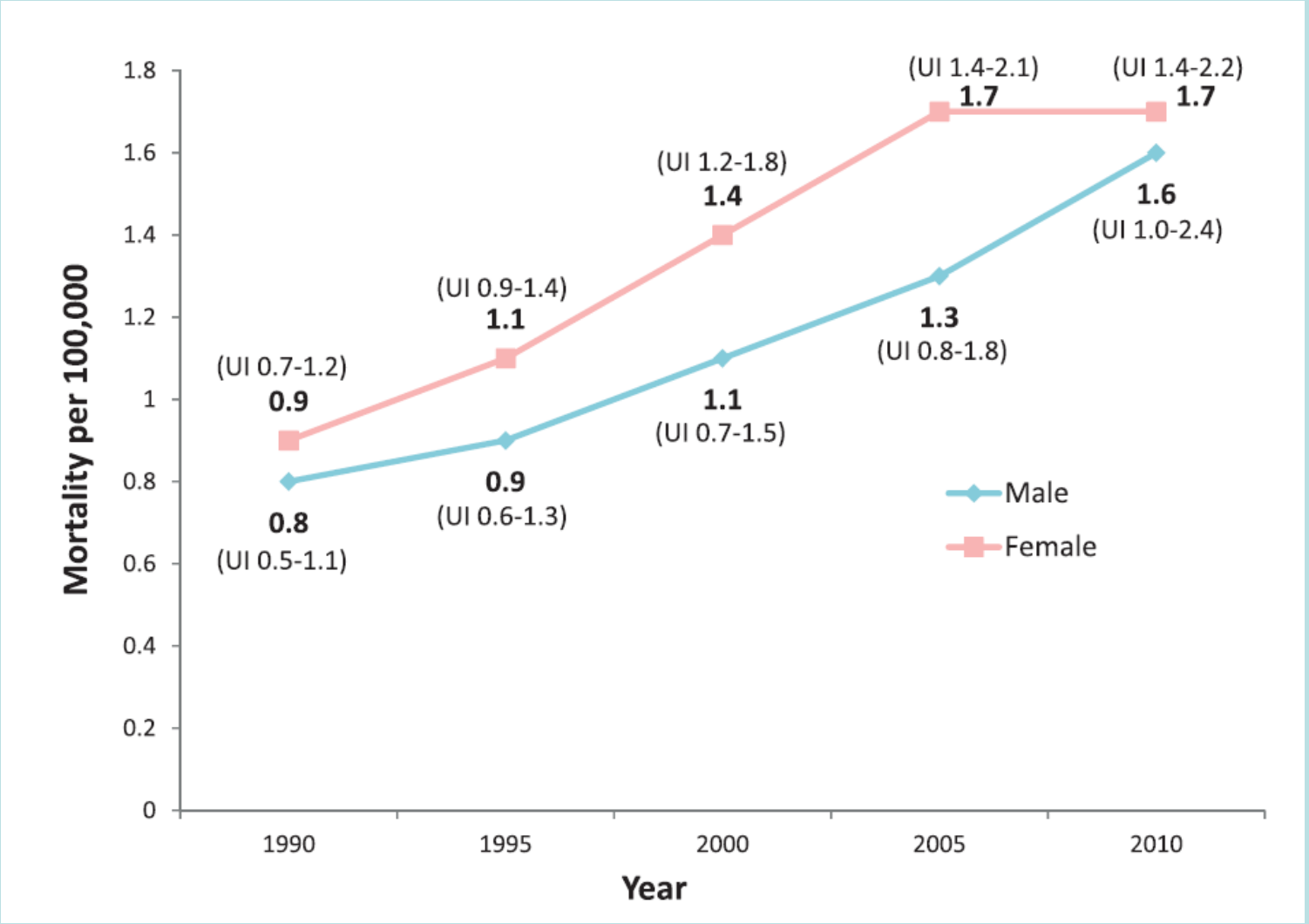
	1990	2010
Men		
Global, all ages	60.7 (49.2–78.5)	77.5 (65.2–95.4)
Age ≥35 y	141.0 (114.6–182.6)	181.2 (152.6–222.8)
Developed countries	78.4 (67.5–91.9)	123.4 (107.6–141.5)
Developing countries	50.0 (33.8–76.8)	53.8 (38.7–79.8)
Women		
Global, all ages	43.8 (35.9–55.0)	59.5 (49.9–74.9)
Age ≥35 y	102.0 (83.9–127.9)	139.7 (117.1–175.3)
Developed countries	52.8 (45.0–62.9)	90.4 (77.8–104.5)
Developing countries	36.0 (24.5–54.7)	40.0 (27.2–62.6)

AF incidence rates

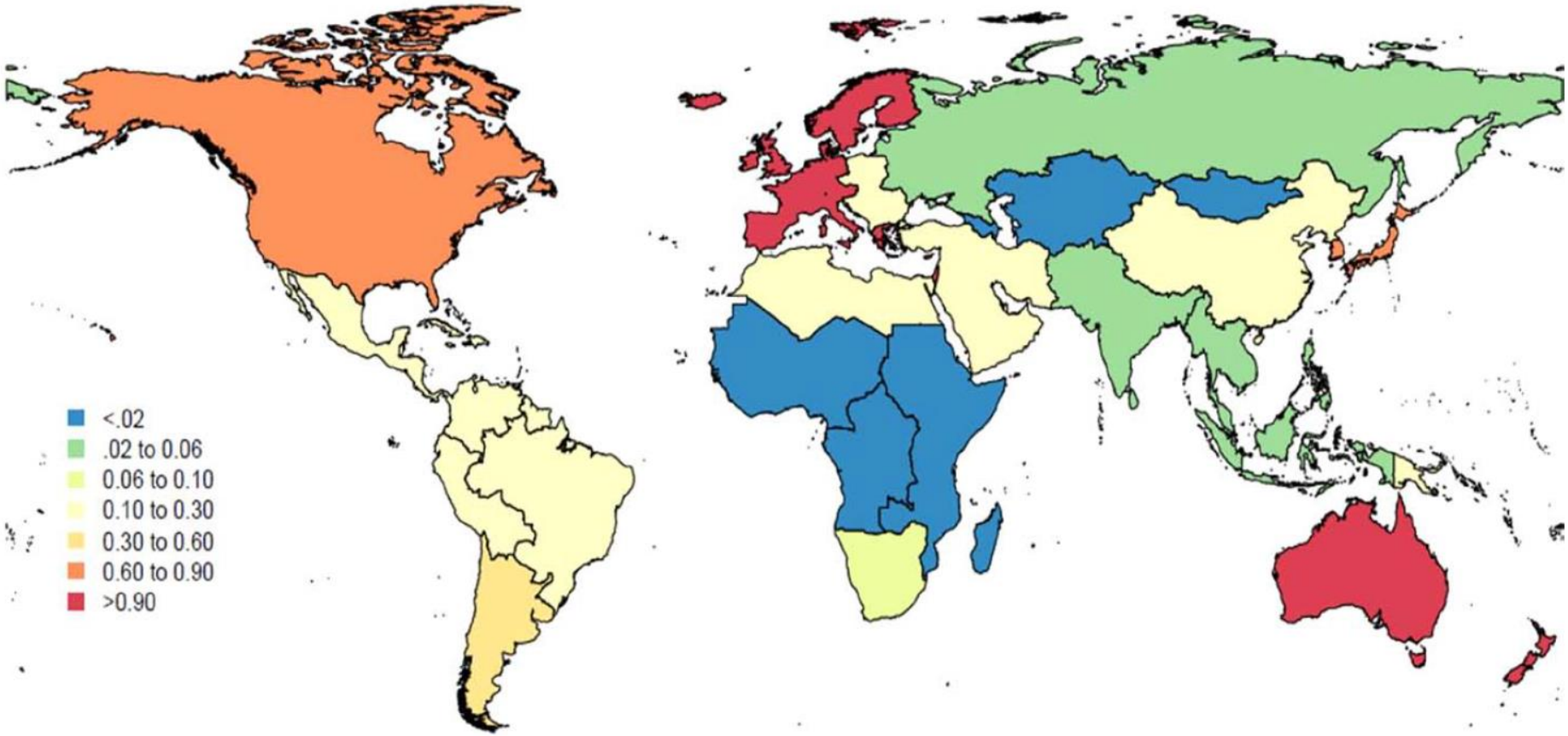
AF incidence rates were lowest in Asia-Pacific region for both men and women (0.038% and 0.0198%, respectively).

The highest rates were estimated in North America (0.2645% for men and 0.1963% for women).


Incidence per 100,000
90
80
70
60
50
40
30
20
10
0
Female
Male
1990
2010


Mortality per 100,000
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1990
1995
2000
2005
2010
Year
(UI 0.7-1.2)
0.9
(UI 0.9-1.4)
1.1
(UI 1.2-1.8)
1.4
(UI 1.4-2.1)
1.7
(UI 1.4-2.2)
1.7
0.8
(UI 0.5-1.1)
0.9
(UI 0.6-1.3)
1.1
(UI 0.7-1.5)
1.3
(UI 0.8-1.8)
1.6
(UI 1.0-2.4)
Male
Female

Percent deaths attributable to atrial fibrillation and flutter by region, 2010



European Heart Journal (2013) **34**, 2746–2751
doi:10.1093/eurheartj/eht280

Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060

Bouwe P. Krijthe[1,2], Anton Kunst[3], Emelia J. Benjamin[4,5,6], Gregory Y.H. Lip[7], Oscar H. Franco[1], Albert Hofman[1], Jacqueline C.M. Witteman[1,2], Bruno H. Stricker[1,2,8]*, and Jan Heeringa[1]

[1]Department of Epidemiology, Erasmus Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands; [2]Netherlands Consortium for Healthy Aging (NCHA), The Netherlands; [3]Department of Public Health, Amsterdam Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [4]National Heart, Lung, and Blood Institute's and Boston University's Framingham Heart Study, Framingham, MA, USA; [5]Department of Epidemiology, School of Public Health, Boston University, Boston, MA, USA; [6]Cardiology and Preventive Medicine Sections, Evans Department of Medicine, Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, MA, USA; [7]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; and [8]Inspectorate of Health Care, The Hague, The Netherlands

Received 26 February 2013; revised 17 May 2013; accepted 26 June 2013; online publish-ahead-of-print 30 July 2013

Aims Since atrial fibrillation (AF) is associated with increased risks of cardiovascular and cerebrovascular complications, estimations on the number of individuals with AF are relevant to healthcare planning. We aimed to project the number of individuals with AF in the Netherlands and in the European Union from 2000 to 2060.

Methods and results Age- and sex-specific AF prevalence estimates were obtained from the prospective community-based Rotterdam Study. Population projections for the Netherlands and the European Union were obtained from the European Union's statistics office. In the age stratum of 55–59 years, the prevalence of AF was 1.3% in men (95% CI: 0.4–3.6%) and 1.7% in women (95% CI: 0.7–4.0%). The prevalence of AF increased to 24.2% in men (95% CI: 18.5–30.7%), and 16.1% in women (95% CI: 13.1–19.4%), for those >85 years of age. This age- and sex-specific prevalence remained stable during the years of follow-up. Furthermore, we estimate that in the European Union, 8.8 million adults over 55 years had AF in 2010 (95% CI: 6.5–12.3 million). We project that this number will double by 2060 to 17.9 million (95% CI: 13.6–23.7 million) if the age- and sex-specific prevalence remains stable.

Conclusion We estimate that from 2010 to 2060, the number of adults 55 years and over with AF in the European Union will more than double. As AF is associated with significant morbidities and mortality, this increasing number of individuals with AF may have major public health implications.

Table 3 Projected number of adults with atrial fibrillation in The Netherlands and the European Union between 2000 and 2060

Year	The Netherlands (in thousands)			Age >75	Total	%[a]	European Union (in millions)			Age >75	Total	%[a]
	Men	Women	Age <75				Men	Women	Age <75			
2000	98.2	112.9	83.9	127.3	211.1	1.3	3.4	3.9	2.9	4.3	7.2	1.5
2005	110.2	121.1	92.7	138.6	231.3	1.4	3.7	4.2	3.1	4.9	7.9	1.6
2010	128.1	131.5	103.1	156.5	259.6	1.6	4.2	4.6	3.2	5.6	8.8	1.8
2015	151.2	145.0	119.8	176.3	296.1	1.7	4.8	5.0	3.4	6.3	9.8	1.9
2020	175.9	162.2	135.6	202.5	338.0	2.0	5.3	5.4	3.8	6.9	10.7	2.1
2025	203.9	183.5	139.0	248.4	387.5	2.2	5.9	5.8	4.0	7.7	11.7	2.3
2030	231.3	205.7	145.5	291.5	436.9	2.5	6.6	6.3	4.2	8.6	12.9	2.5
2035	255.8	226.9	147.1	335.7	482.8	2.7	7.2	6.9	4.4	9.7	14.1	2.7
2040	272.9	244.3	140.8	376.3	517.1	2.9	7.9	7.4	4.4	10.9	15.3	2.9
2045	284.1	256.5	129.4	411.3	540.7	3.1	8.4	7.9	4.3	12.0	16.3	3.1
2050	291.0	262.7	122.3	431.4	553.7	3.2	8.9	8.2	4.2	12.9	17.1	3.3
2055	291.7	261.9	125.4	428.1	553.6	3.2	9.2	8.4	4.2	13.4	17.6	3.4
2060	289.7	258.0	129.6	418.1	547.7	3.2	9.4	8.5	4.1	13.8	17.9	3.5

[a]Percentage of total population.

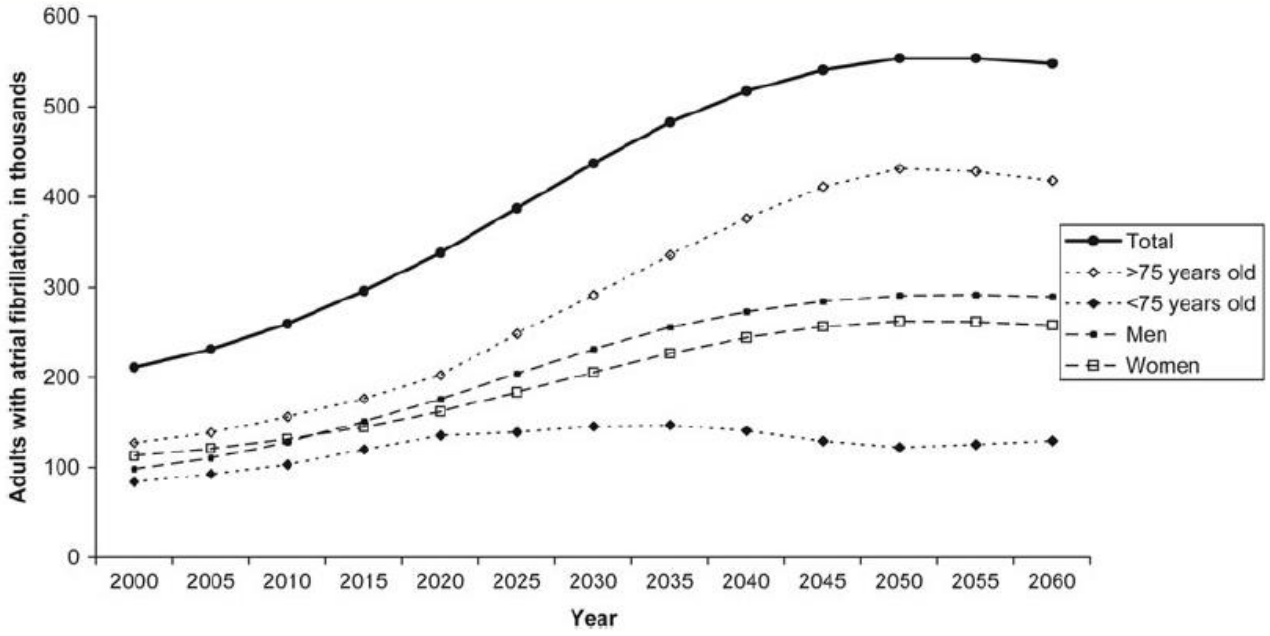


Figure 1 Projected number of adults with atrial fibrillation in the Netherlands between 2000 and 2060.

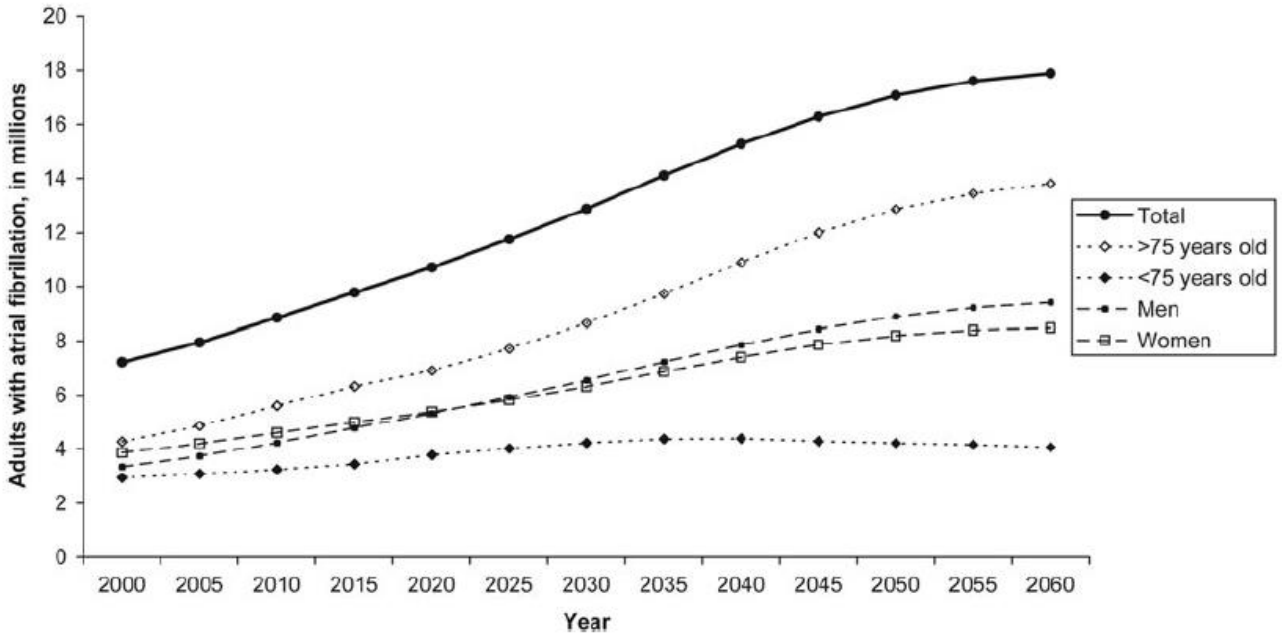


Figure 2 Projected number of adults with atrial fibrillation in the European Union between 2000 and 2060.

50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study

Renate B Schnabel, Xiaoyan Yin, Philimon Gona, Martin G Larson, Alexa S Beiser, David D McManus, Christopher Newton-Cheh, Steven A Lubitz, Jared W Magnani, Patrick T Ellinor, Sudha Seshadri, Philip A Wolf, Ramachandran S Vasan, Emelia J Benjamin, Daniel Levy**

Lancet 2015; 386: 154–62
Published Online May 8, 2015
http://dx.doi.org/10.1016/S0140-6736(14)61774-8

See Comment page 113

*Contributed equally

National Heart, Lung, and Blood Institute's Framingham Study, Framingham, MA, USA (R B Schnabel MD, X Yin PhD, P Gona Phd, M G Larson ScD, A S Beiser PhD, C Newton-Cheh MD, S Seshadri MD, P A Wolf MD, Prof R S Vasan MD, Prof E J Benjamin MD, Prof D Levy MD); **Department of Epidemiology** (Prof E J Benjamin) **and Department of Biostatistics** (X Yin, M G Larson, A S Beiser), **Boston University School of Public Health, Boston, MA, USA; Department of Mathematics and Statistics, Boston University, Boston, MA, USA** (M G Larson); **Whitaker Cardiovascular Institute,** (Prof R S Vasan, Prof E J Benjamin), **Evans Memorial Medicine**

Summary

Background Comprehensive long-term data on atrial fibrillation trends in men and women are scant. We aimed to provide such data through analysis of the Framingham cohort over 50 years.

Methods We investigated trends in incidence, prevalence, and risk factors for atrial fibrillation and its association with stroke and mortality after onset in 9511 participants enrolled in the Framingham Heart Study between 1958 and 2007. We analysed trends within 10 year groups (1958–67, 1968–77, 1978–87, 1988–97, and 1998–2007), stratified by sex.

Findings During 50 years of observation (202 417 person-years), 1544 cases of new-onset atrial fibrillation occurred (of whom 723 [47%] were women). Between 1958–67 and 1998–2007, age-adjusted prevalence of atrial fibrillation quadrupled from 20·4 to 96·2 cases per 1000 person-years in men and from 13·7 to 49·4 cases per 1000 person-years in women; age-adjusted incidence increased from 3·7 to 13·4 new cases per 1000 person-years in men and from 2·5 to 8·6 new cases per 1000 person-years in women ($p_{trend}<0·0001$ for all comparisons). For atrial fibrillation diagnosed by electrocardiograph (ECG) during routine Framingham examinations, age-adjusted prevalence per 1000 person-years increased (12·6 in 1958–67 to 25·7 in 1998–2007 in men, $p_{trend}=0·0007$; 8·1 to 11·8 in women, $p_{trend}=0·009$). However, age-adjusted incidence of atrial fibrillation by Framingham Heart Study ECGs did not change significantly with time. Although the prevalence of most risk factors changed over time, their associated hazards for atrial fibrillation changed little. Multivariable-adjusted proportional hazards models revealed a 74% (95% CI 50–86%) decrease in stroke (hazards ratio [HR] 3·77, 95% CI 1·98–7·20 in 1958–1967 compared with 1998–2007; $p_{trend}=0·0001$) and a 25% (95% CI –3–46%) decrease in mortality (HR 1·34, 95% CI 0·97–1·86 in 1958–1967 compared with 1998–2007; $p_{trend}=0·003$) in 20 years following atrial fibrillation onset.

Interpretation Trends of increased incidence and prevalence of atrial fibrillation in the community were probably partly due to enhanced surveillance. Measures are needed to enhance early detection of atrial fibrillation, through increased awareness coupled with targeted screening programmes and risk factor-specific prevention.

Funding NIH, NHLBI, NINDS, Deutsche Forschungsgemeinschaft.

	1958–67	1968–77	1978–87	1988–97	1998–2007	p_{trend}*
Men						
Number at risk	1925	2399	2569	2595	2128	..
Person-years at risk	14044	17448	19223	19196	17270	..
Age, years†	55·0 (5·8)	58·6 (8·1)	60·4 (9·9)	60·8 (10·6)	63·1 (10·5)	..
Atrial fibrillation based on all sources						
Number of atrial fibrillation cases	40	101	166	266	248	..
Crude incidence rate	2·85	5·79	8·64	13·86	14·36	<0·0001
Age-adjusted incidence rate	3·70	7·31	9·07	14·32	13·37	<0·0001
Age-adjusted period prevalence	20·4	37·7	52·3	81·8	96·2	<0·0001
Atrial fibrillation based on Framingham Heart Study Clinic ECGs						
Number of atrial fibrillation cases	23	38	56	70	81	..
Crude incidence rate	1·61	2·12	2·81	3·43	4·30	<0·0001
Age-adjusted incidence rate	1·83	2·55	2·86	3·35	3·75	0·06
Age-adjusted period prevalence	12·6	19·1	24·0	25·7	25·7	0·0007
Women						
Number at risk	2401	2924	3174	3315	2857	..
Person-years at risk	18356	23360	25254	25046	23220	..
Age, years†	55·0 (5·8)	59·6 (8·4)	62·7 (10·7)	62·9 (11·8)	64·7 (11·9)	..
Atrial fibrillation based on all sources						
Number of atrial fibrillation cases	35	90	161	194	243	..
Crude incidence rate	1·91	3·85	6·38	7·75	10·47	<0·0001
Age-adjusted incidence rate	2·52	4·69	5·47	6·14	8·55	<0·0001
Age-adjusted period prevalence	13·7	25·1	29·5	34·3	49·4	<0·0001
Atrial fibrillation based on Framingham Heart Study clinic ECGs						
Number of atrial fibrillation cases	21	46	51	50	52	..
Crude incidence rate	1·10	1·88	1·93	1·91	2·13	0·03
Age-adjusted incidence rate	1·31	2·11	1·64	1·40	1·58	0·13
Age-adjusted period prevalence	8·1	14·8	13·9	12·6	11·8	0·009

Data are n or mean (SD). All participants were 50–89 years of age and free of atrial fibrillation at enrolment. Atrial fibrillation incidence rates are per 1000 person-years of follow up. Adjusted incidence rates were calculated using direct standardisation of sex-pooled and time-pooled 10-year age groups. Atrial fibrillation prevalence rates are person-years lived by atrial fibrillation individuals per 1000 total person-years lived during each period, ie, by all person-years contributed by survivors (including those developed atrial fibrillation before the period) at the beginning of the period. Atrial fibrillation cases include all those participants who developed atrial fibrillation in or before the corresponding period. For the first period, during which there was no participant in the 80–89 year age group, the incidence rates were standardised to the overall distribution among the remaining age groups only. *p_{trend} was obtained with Poisson regression. †Mean age is for the population at risk for development of atrial fibrillation; age is the earliest eligible age within a decade.

Table 1: **Atrial fibrillation incidence rates and age-adjusted period prevalence, by sex and decade**

	1958–67	1968–77	1978–87	1988–97	1998–2007	p_{trend}*	Trend direction
Number of new-onset atrial fibrillation cases	70	178	284	399	434	..	
Smoking	27 (40·9%)	35 (22·3%)	60 (21·7%)	62 (15·6%)	55 (12·7%)	0·0002	Decrease
Alcohol consumption							
None	25 (42·4%)	53 (31·7%)	127 (46·7%)	168 (42·7%)	186 (44·0%)	0·64	No trend†
Mild	28 (47·5%)	92 (55·1%)	122 (44·9%)	200 (50·9%)	214 (50·6%)	0·28	No trend†
Moderate or heavy	6 (10·2%)	22 (13·2%)	23 (8·5%)	25 (6·4%)	23 (5·4%)	0·005	Decrease
Body-mass index							
Normal (<25 kg/m²)	20 (30·3%)	56 (35·7%)	107 (39·9%)	115 (30·4%)	105 (27·7%)	0·0009	Decrease
Overweight (25–30 kg/m²)	28 (42·4%)	68 (43·3%)	101 (37·7%)	173 (45·8%)	140 (36·9%)	0·42	No trend†
Obese (≥31 kg/m²)	18 (27·3%)	33 (21·0%)	60 (22·4%)	90 (23·8%)	134 (35·4%)	<0·0001	Increase
Systolic blood pressure							
Optimal (<120 mm Hg)	5 (7·1%)	19 (10·7%)	36 (12·7%)	53 (13·3%)	88 (20·3%)	<0·0001	Increase
Normal (120–129 mm Hg)	9 (12·9%)	13 (7·3%)	32 (11·3%)	57 (14·3%)	73 (16·9%)	0·001	Increase
High-normal (130–139 mm Hg)	8 (11·4%)	23 (12·9%)	51 (18·0%)	75 (18·8%)	91 (21·0%)	0·009	Increase
Stage I hypertension (140–159 mm Hg)	21 (30·0%)	64 (36·0%)	99 (35·0%)	134 (33·6%)	108 (24·9%)	0·001	Decrease
Stage II–IV hypertension (≥160 mm Hg)	27 (38·6%)	59 (33·1%)	65 (23·0%)	80 (20·1%)	73 (16·9%)	<0·0001	Decrease
Hypertension treatment	15 (22·1%)	55 (32·9%)	135 (47·7%)	219 (55·4%)	257 (59·8%)	<0·0001	Increase
Diabetes	4 (5·7%)	25 (14·0%)	44 (15·7%)	66 (16·7%)	80 (19·6%)	0·004	Increase
Electrocardiographic left ventricular hypertrophy	9 (12·9%)	21 (11·8%)	19 (6·9%)	23 (6·2%)	12 (2·9%)	<0·0001	Decrease
Significant heart murmur	14 (20·0%)	32 (18·9%)	52 (19·2%)	42 (10·7%)	31 (8·1%)	<0·0001	Decrease
Prevalent heart failure	4 (5·7%)	15 (8·4%)	17 (6·0%)	23 (5·8%)	15 (3·5%)	0·009	Decrease
Prevalent myocardial infarction	6 (8·6%)	16 (9·0%)	27 (9·5%)	45 (11·3%)	47 (10·8%)	0·27	No trend†

Data are n (%). In total 1365 (88·4%) atrial fibrillation cases were identified with index examinations. The remaining 179 patients were excluded from this analysis for missing eligible index examinations. This table presents the age-adjusted and sex-adjusted prevalence of baseline characteristics for atrial fibrillation cases with index examination. For each characteristic, prevalence in different decades are predicted values from a logistic model where the characteristic is the outcome variable, decade as main predictor if the trend test is significant, with age and sex as covariates. The observed prevalence by sex is presented in the appendix. The prevalence might not add up to exactly 1 for multiple categorical variables because of rounding. *p values are obtained from logistic models adjusting for age and sex fitted on observed data. †trend was not statistically significant.

Table 2: **Baseline characteristics in individuals with new-onset atrial fibrillation, by decade**

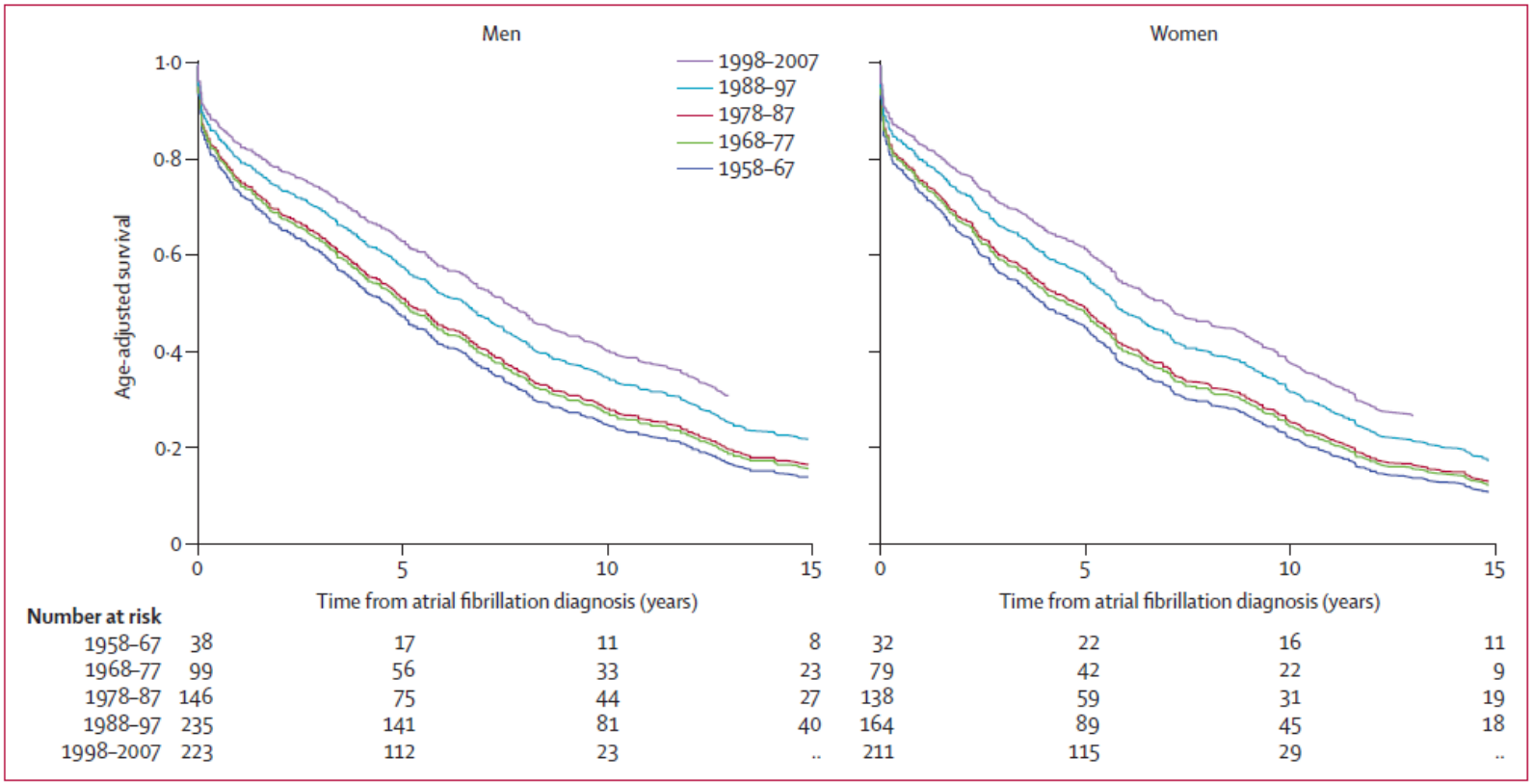


Figure: **Age-adjusted survival after new onset of atrial fibrillation, by sex and decade, in men and women**

Europace (2015) **17**, 1018–1022
doi:10.1093/europace/euv036

The risk of atrial fibrillation in the general male population: a lifetime follow-up of 50-year-old men

Zacharias Mandalenakis[1]*, Lotta Von Koch[1], Henry Eriksson[1], Mikael Dellborg[1], Kenneth Caidahl[1,2], Lennart Welin[1], Annika Rosengren[1], and Per-Olof Hansson[1]

[1]Department of Molecular and Clinical Medicine/Cardiology, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; and
[2]Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden

Received 1 October 2014; accepted after revision 2 February 2015; online publish-ahead-of-print 4 April 2015

Aim This study aimed to estimate the prevalence, incidence rate, and lifetime risk of developing atrial fibrillation (AF) in a population-based study of Swedish men.

Methods and results The study is a part of 'The Study of Men Born in 1913', which is a longitudinal prospective cohort study of 855 men born in 1913 and living in the city of Gothenburg in Sweden. They were followed from the age of 50 years until 98 years with repeated examinations and data from the Swedish National Hospital Discharge Register. A total of 185 (21.6%) men developed AF. The prevalence of AF increased from 0.4% at 50 years old, to 1.9% by 60 years old, to 4.6% by 70 years old, to 12.5% by 80 years old, and to 15.7% by 90 years old. The lifetime risk of developing AF was 22.5%.

Conclusion Atrial fibrillation is rare at the age of 50 in Swedish men, but it increases exponentially with age, markedly accelerating after 70 years old. In nonagenarians, one of five men has or has had AF.

Keywords Atrial fibrillation • Epidemiology • Incidence • Prevalence • Population-based studies • Lifetime risk

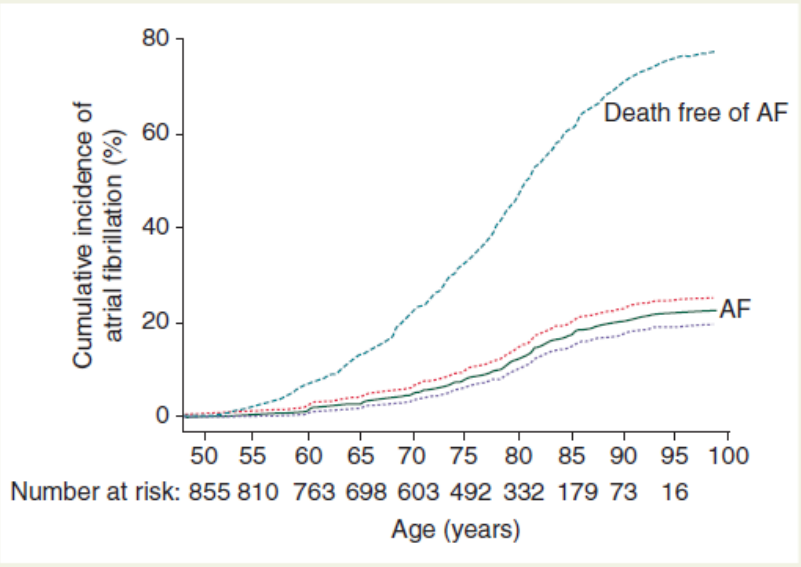


Figure 1 Cumulative incidence of AF.

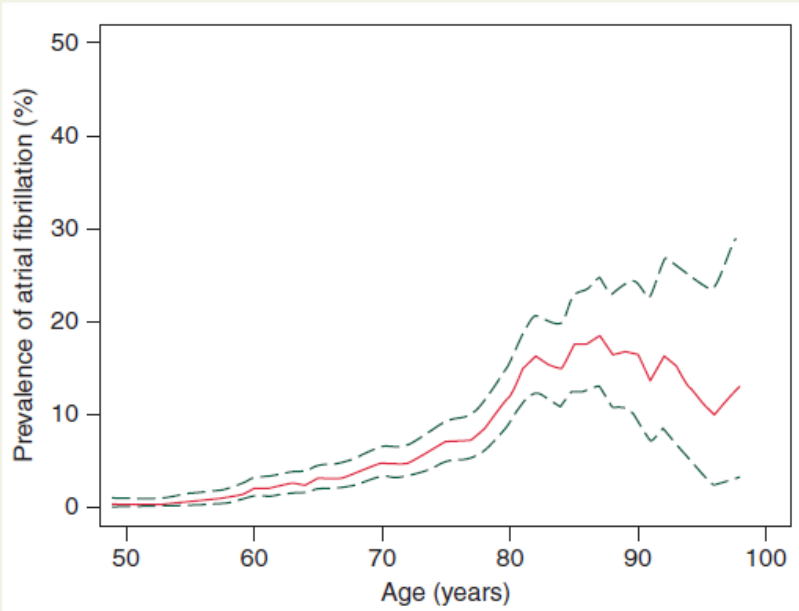


Figure 2 Prevalence of AF during 48 years of follow-up.

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Featured Review

Journal of Atrial Fibrillation

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Atrial Fibrillation In Athletes: Pathophysiology, Clinical Presentation, Evaluation and Management

Mohit K. Turagam, MD, Greg C. Flaker, MD, Poonam Velagapudi, MD, Sirisha Vadali, MD, Martin A. Alpert, MD

From the Division of Cardiovascular Medicine University of Missouri- School of Medicine, Columbia, Missouri, USA.

Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia in athletes, especially in middle-aged athletes. Studies have demonstrated that athletes who engage in endurance sports such as runners, cyclists and skiers are more prone to AF than other athletes. The effects of exercise on the onset and progression of AF is complex. Triggers of AF in athletes may include atrial ectopy and sports supplements. Substrates for AF in athletes include atrial remodeling, fibrosis, and inflammation. Modulators of AF in athletes include autonomic activation, electrolyte abnormalities, and possibly, gastroesophageal reflux. Management of AF in athletes with rate-controlling agents and antiarrhythmic drugs remains a challenge and can be associated with impaired athletic performance. The value of catheter ablation is emerging and should be considered in suitable athletes with AF.

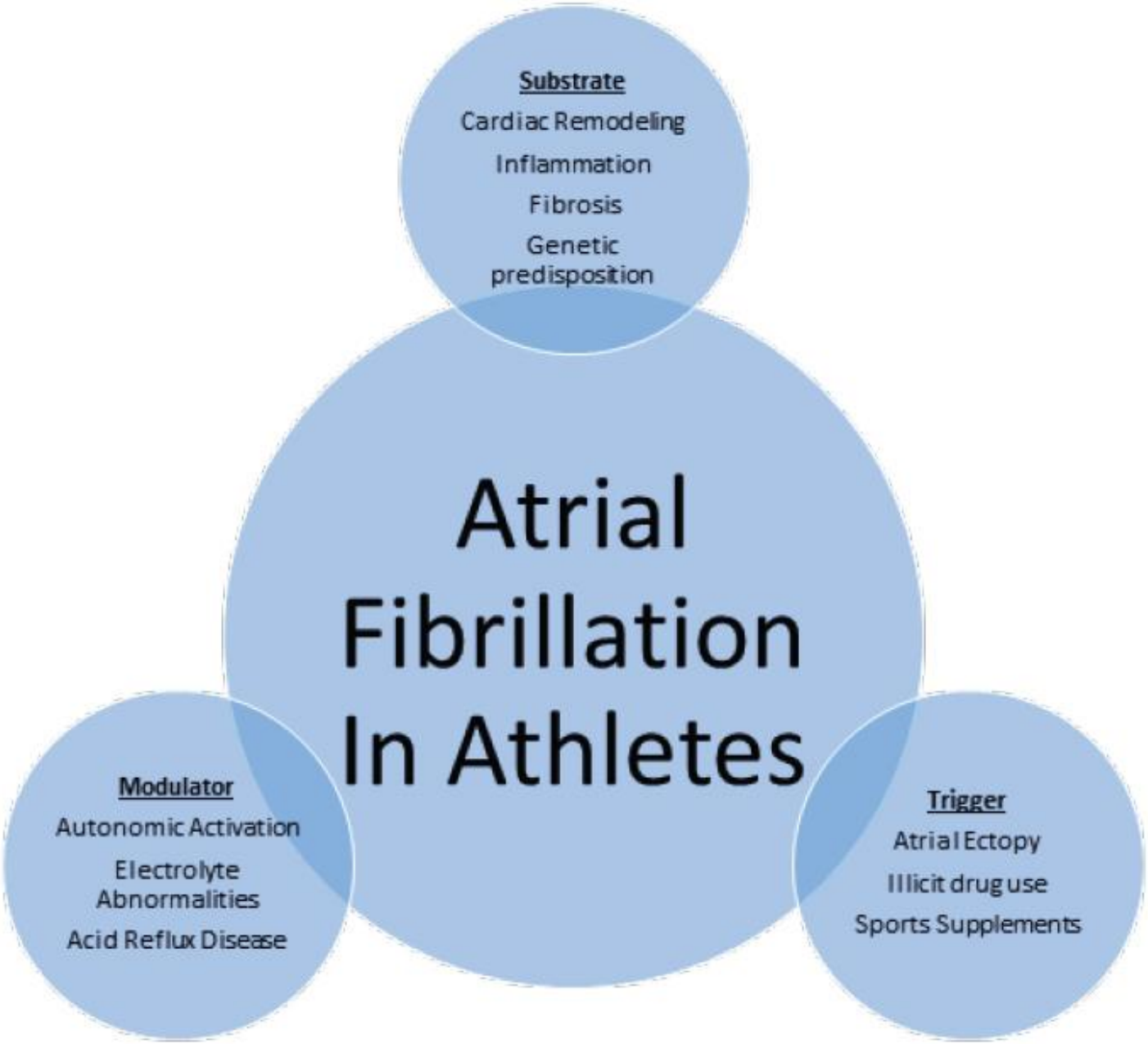


Figure:1 **Schematic representation of mechanism of atrial fibrillation in athletes**

Table 1: Selected Controlled Studies of the Prevalence of AF in Athletes

Study Type	Number of subjects	Age/Gender	Type of exercise	Prevalence of AF in athletes/ controls (%)
Karjalainen et al[15]	795	35-39 years/ Male	Cross country Running	5.3/0.9
Baldesberger et al[17]	196	~66 years/ Male	Cyclists vs. golfers	10/0
Mont et al[8]	216	<65 years/ Male + Female	Endurance athletes	63/15
Elosua et al[16]	109	41-55 years/ Male	Endurance athletes	32/14
Heidbuchel et al[22]		60 years/83% Male, 17% Female	Cycling, running, or swimming	
Molina et al[18]	557	48 years	Marathon runners vs. sedentary	5/0.7
Grimsmo et al[11]	78	54-62 years- Group I 72-80 years- Group II 87-92 years- Group III	Cross-country runners, skiers	12.8

European Heart Journal - Cardiovascular Pharmacotherapy Advance Access published December 27, 2016

European Heart Journal - Cardiovascular Pharmacotherapy
doi:10.1093/ehjcvp/pvw036

ORIGINAL ARTICLE
Atrial fibrillation

Thiazolidinediones are associated with a decreased risk of atrial fibrillation compared with other antidiabetic treatment: a nationwide cohort study

Jannik Langtved Pallisgaard[1,2]*, Tommi Bo Lindhardt[1,2], Laila Staerk[1,2], Jonas Bjerring Olesen[1], Christian Torp-Pedersen[3], Morten Lock Hansen[4], and Gunnar Hilmar Gislason[1,2,5,6]

[1]University Hospital Gentofte and Herlev, Kildegaardsvej 28, 2900 Hellerup, Copenhagen, Denmark; [2]Faculty of Health and Medical Sciences Blegdamsvej 3B, 2200, Copenhagen, Denmark; [3]Institute of Health Science and Technology, Fredrik Bajers Vej 7D, 9220 Aalborg, Denmark; [4]Zealand University Hospital Roskilde, Sygehusvej 10, 4000 Roskilde, Denmark; [5]Danish Heart Foundation, Vognmagergade 7, 3. sal, 1120 Copenhagen, Denmark; and [6]National Institute of Public Health University of Southern Denmark, Oster Farimagsgade 5 A, 1353 Copenhagen, Denmark

Received 20 September 2016; revised 25 October 2016; editorial decision 28 October 2016; accepted 1 November 2016

Aim The aim of this study was to investigate the association between thiazolidinediones (TZDs) vs. other antidiabetic drugs and risk of atrial fibrillation (AF) in diabetic patients.

Method and results Diabetes mellitus (diabetes) increases the risk of AF by approximately 34%. TZD is an insulin sensitizer that also has anti-inflammatory effects, which might decrease the risk of AF compared with other antidiabetic drugs. We used data from the Danish nationwide registries to study 108 624 patients with diabetes and without prior AF who were treated with metformin or sulfonylurea as first-line drugs. The incidence of AF was significantly lower with TZD as the second-line antidiabetic treatment compared with other second-line antidiabetic drugs ($P < 0.001$). The 10 year cumulative incidence [95% confidence interval (95% CI)] of AF was 6.2% (3.1–9.3%) with TZD vs. 10.2% (9.8–10.6%) with other antidiabetic drugs. The decreased risk of AF remained significant after adjusting for age, sex, and comorbidities with a hazard ratio (95% CI) of 0.76 (0.57–1.00), $P = 0.047$ associated with TZD treatment compared with other antidiabetic drugs.

Conclusion Use of a TZD to treat diabetes was associated with reduced risk of developing AF compared with other antidiabetic drugs as second-line treatment.

Keywords Atrial fibrillation • Diabetes mellitus • Thiazolidinediones • Prevention • Complications • Glitazones

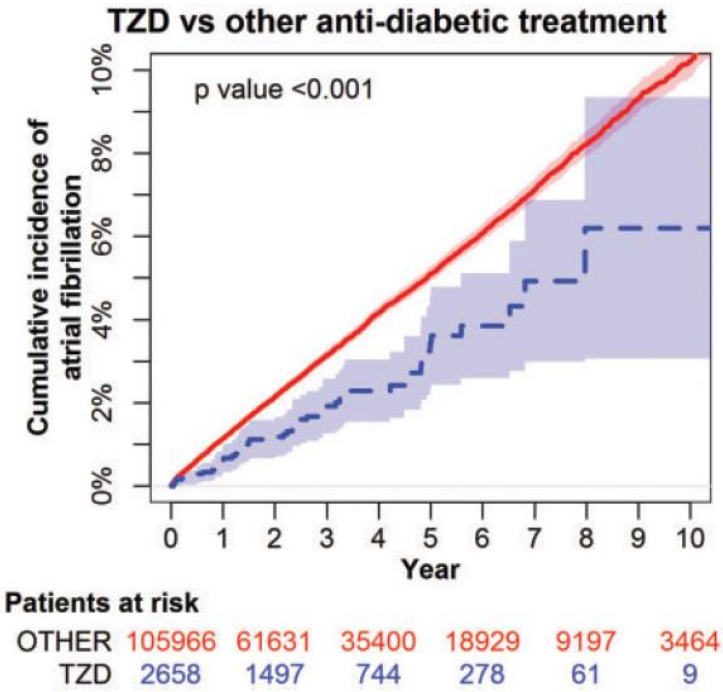


Figure 2 Cumulative incidence of atrial fibrillation with TZD and other antidiabetic treatment. Aalen–Johansen cumulative incidence of AF in the 'TZD group' and the 'other group'. The model takes into account competing risk of death. *P*-value from Fine and Gray competing risks regression model.

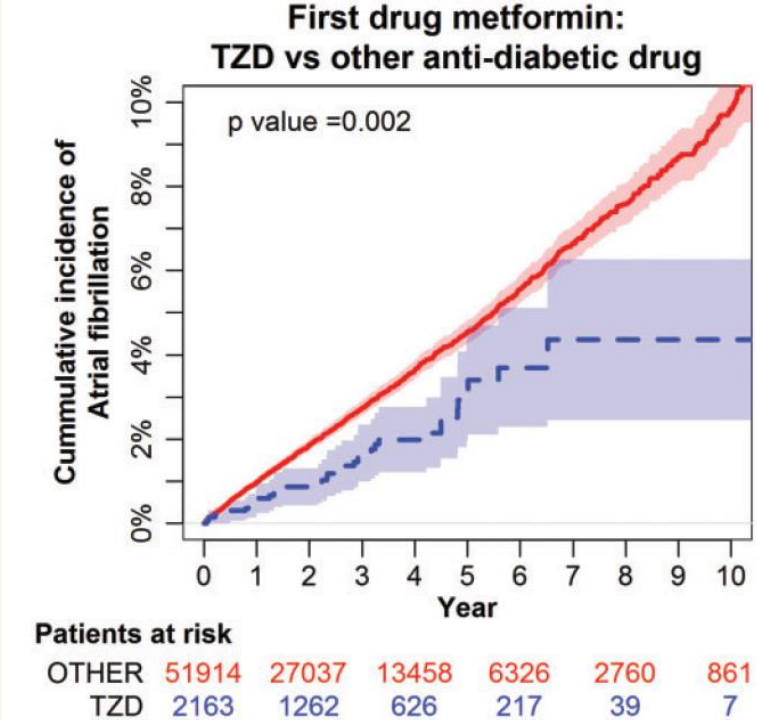


Figure 5 Aalen–Johansen cumulative incidence of AF in the 'TZD group' and the 'other group' in patients exclusively treated with metformin as first-line antidiabetic drug. The model takes into account competing risk of death. *P*-value from Fine and Gray competing risks regression model.

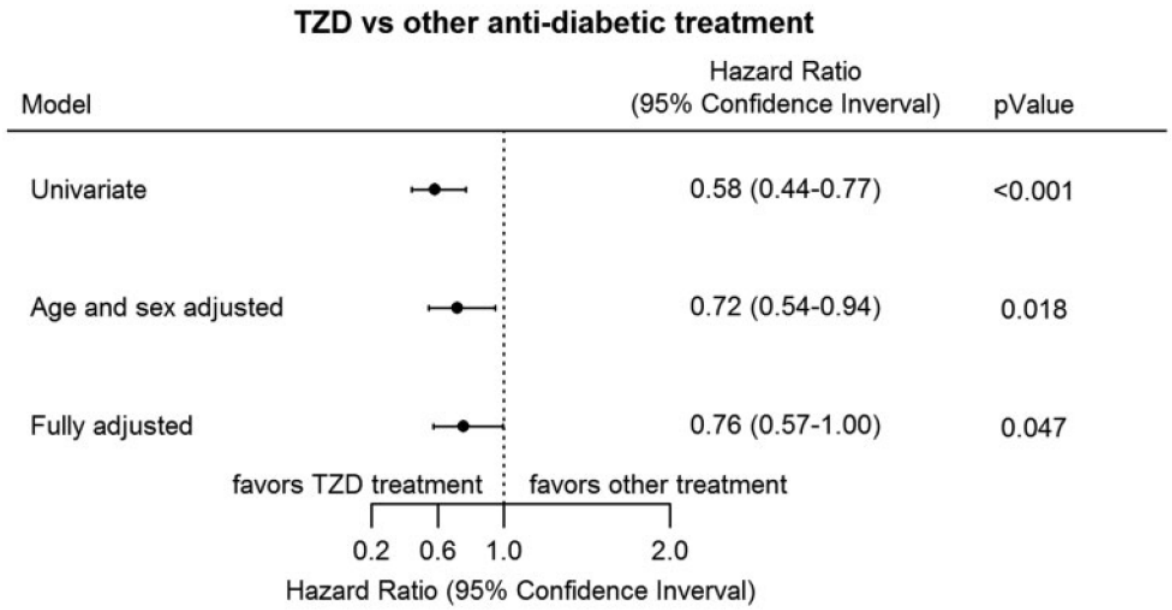


Figure 3 Cox hazard ratio of atrial fibrillation in the 'TZD group' with 'other group' as reference. The 'fully adjusted' model is adjusted for age, sex, stroke, heart failure, all cancer, hyperthyroidism, ischaemic heart disease, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, vascular disease, hypertension, statin use, prior CABG, and prior PCI.

EXTENDED REPORT

Allopurinol and the risk of atrial fibrillation in the elderly: a study using Medicare data

Jasvinder A Singh,[1,2,3] Shaohua Yu[2]

Handling editor Tore K Kvien

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2015-209008).

[1]Medicine Service, Birmingham VA Medical Center, Birmingham, Alabama, USA
[2]Department of Medicine at School of Medicine, and Division of Epidemiology at School of Public Health, University of Alabama at Birmingham (UAB), Birmingham, Alabama, USA
[3]Department of Orthopedic Surgery, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Correspondence to
Dr Jasvinder A Singh, University of Alabama, Faculty Office Tower 805B, 510 20th Street S, Birmingham, AL 35294, USA; Jasvinder.md@gmail.com

Received 10 December 2015
Revised 21 February 2016
Accepted 20 March 2016
Published Online First 10 May 2016

ABSTRACT

Objective To assess the effect of allopurinol use on the risk of incident atrial fibrillation (AF) in the elderly.

Methods We used the 5% random Medicare Claims data from 2006 to 2012 to examine the association of allopurinol use and incident AF in a cohort of patients with an absence of AF at baseline (at least 365 days). Multivariable-adjusted Cox regression analyses compared allopurinol exposed and non-exposed periods for the risk of AF, controlling for age, sex, race, Charlson–Romano comorbidity index and use of statins, diuretics, ACE inhibitors and β-blockers. HR with 95% CIs was calculated. Sensitivity analyses considered a longer baseline period (365 days vs 183 days) and individual comorbidities.

Results There were 9244 episodes of incident allopurinol use in 8569 beneficiaries, of which 1366 episodes (14.8%) had incident AF. In multivariable-adjusted analyses, allopurinol use was associated with an HR of 0.83 (95% CI 0.74 to 0.93) for incident AF. In a separate multivariable-adjusted model, compared with no allopurinol use, longer allopurinol use durations were associated with a lower HR of AF: 180 days–2 years, 0.85 (95% CI 0.73 to 0.99) and >2 years, 0.65 (95% CI 0.52 to 0.82). Other factors significantly associated with a higher hazard of AF were: age 75–<85 years and ≥85 years, higher Charlson index score and current β-blocker use. Sensitivity analyses confirmed these findings with minimal/no attenuation of HRs.

Conclusions Allopurinol use was associated with a reduced risk of incident AF in the elderly, especially its use for >6 months duration. Future studies should assess the mechanisms underlying this beneficial effect of allopurinol.

Allopurinol is the most commonly used urate-lowering therapy for the treatment of hyperuricaemia in patients with gout.[11 12] Allopurinol is a purine analogue. As a structural isomer of hypoxanthine (a naturally occurring purine in humans), allopurinol competes with the substrate for the enzyme xanthine oxidase, which then leads to reduced uric acid production. In addition to blocking uric acid production, inhibition of xanthine oxidase causes an increase in hypoxanthine and xanthine. Allopurinol reduces oxidative stress,[13–15] improves endothelial function,[16–20] reduces left ventricular mass[21 22] and has an anti-ischaemic action.[23] Emerging research supports a potential cardioprotective effect of allopurinol including improved outcomes for myocardial infarction (MI), heart failure[24–26] and mortality,[27–29] although two recent studies failed to find this association.[30 31] On the other hand, with the exception of one abstract that suggested the association of allopurinol and AF in a single-centre study,[32] there are no published studies assessing this association. This is an important area for study, given the prevalence of AF and the availability of allopurinol as a low-cost, generic drug that is well tolerated.

Our study objective was to explore the association of allopurinol with the incidence of AF in the elderly. Specifically, using the Medicare claims data, we assessed whether (1) allopurinol use (vs non-use) and (2) allopurinol use duration, were associated with the risk of incident AF, in the US elderly, 65 years and older.

METHODS

Study cohort and population of interest

Table 5 Sensitivity analysis additionally adjusted for diabetes, hypertension, PVD and CVD: association of risk factors with hazard of atrial fibrillation in patients who received allopurinol with an absence of atrial fibrillation in the baseline period before the index date of allopurinol episode

	Univariate		Multivariable-adjusted (model 1)		Multivariable-adjusted (model 2)	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (in years)						
65–<75	Ref		Ref		Ref	
75–<85	**1.47 (1.31 to 1.66)**	**<0.0001**	**1.48 (1.31 to 1.67)**	**<0.0001**	**1.48 (1.31 to 1.67)**	**<0.0001**
≥85	**2.12 (1.83 to 2.46)**	**<0.0001**	**2.12 (1.85 to 2.51)**	**<0.0001**	**2.16 (1.85 to 2.51)**	**<0.0001**
Gender						
Male	Ref		Ref		Ref	
Female	1.04 (0.93 to 1.15)	0.50	0.94 (0.84 to 1.05)	0.24	0.93 (0.84 to 1.04)	0.23
Race						
White	Ref		Ref		Ref	
Black	**0.83 (0.70 to 0.97)**	**0.02**	**0.82 (0.69 to 0.96)**	**0.01**	**0.81 (0.69 to 0.95)**	**0.009**
Other	**0.69 (0.58 to 0.83)**	**<0.0001**	**0.64 (0.53 to 0.77)**	**<0.0001**	**0.64 (0.53 to 0.76)**	**<0.0001**
Diabetes	**1.24 (1.12 to 1.38)**	**<0.0001**	**1.28 (1.15 to 1.44)**	**<0.0001**	**1.28 (1.15 to 1.43)**	**<0.0001**
Hypertension	1.21 (0.97 to 1.51)	0.08	1.06 (0.85 to 1.33)	0.61	1.07 (0.85 to 1.33)	0.58
PVD	**1.44 (1.29 to 1.62)**	**<0.0001**	1.29 (1.14 to 1.46)	**<0.0001**	1.29 (1.14 to 1.46)	**<0.0001**
CVD	**1.24 (1.09 to 1.41)**	**0.001**	1.09 (0.95 to 1.25)	0.22	1.09 (0.95 to 1.24)	0.23
Statins	0.95 (0.72 to 1.24)	0.69	0.86 (0.64 to 1.14)	0.29	0.86 (0.64 to 1.14)	0.29
β-blockers	**1.58 (1.22 to 2.05)**	**0.0005**	**1.62 (1.24 to 2.13)**	**0.0005**	**1.62 (1.23 to 2.12)**	**0.0005**
Diuretics	1.09 (0.85 to 1.40)	0.51	0.99 (0.75 to 1.29)	0.92	0.99 (0.75 to 1.29)	0.91
ACE inhibitors	0.99 (0.72 to 1.36)	0.95	0.96 (0.69 to 1.33)	0.78	0.95 (0.69 to 1.33)	0.78
Allopurinol	**0.86 (0.77 to 0.97)**	**0.01**	**0.83 (0.74 to 0.93)**	**0.0015**	–	–
Allopurinol duration*						
0 days	Ref		–	–	Ref	
1–180 days	0.94 (0.80 to 1.11)	0.46	–	–	0.92 (0.78 to 1.08)	0.32
181 days–2 years	0.90 (0.77 to 1.04)	0.16	–	–	**0.85 (0.73 to 0.99)**	**0.04**
>2 years	**0.68 (0.54 to 0.65)**	**0.0009**	–	–	**0.65 (0.52 to 0.82)**	**0.0002**

Ref, referent category.
*Based on person day count.
Model 1=Allopurinol use+age+race+gender+diabetes+hypertension+PVD+CVD+β-blockers+diuretics+ACE inhibitors+statins.
Model 2=Allopurinol duration+age+race+gender+diabetes+hypertension+PVD+CVD+β-blockers+diuretics+ACE inhibitors+statins.
Bold indicates statistically significant associations with a p-value of <0.05.
CVD, cerebrovascular disease; PVD, peripheral vascular disease.

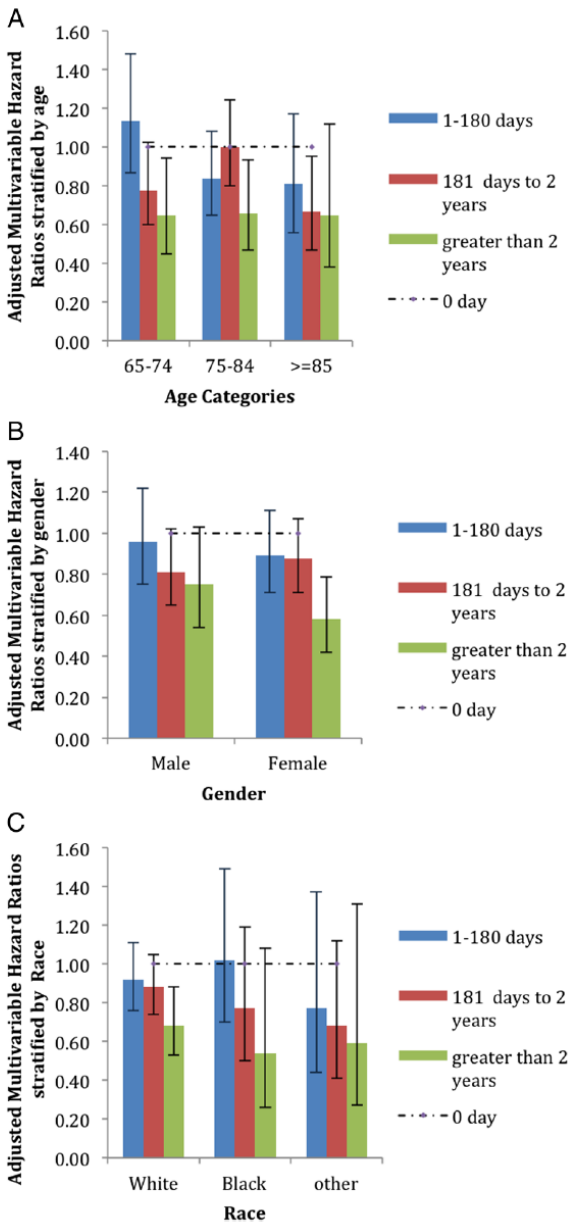
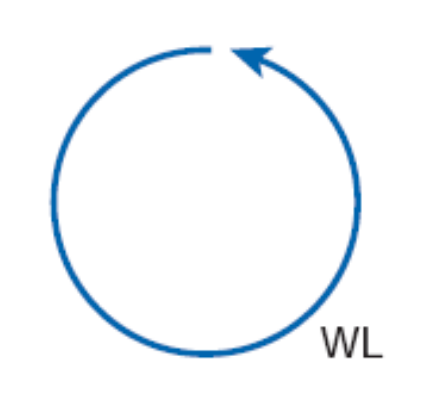
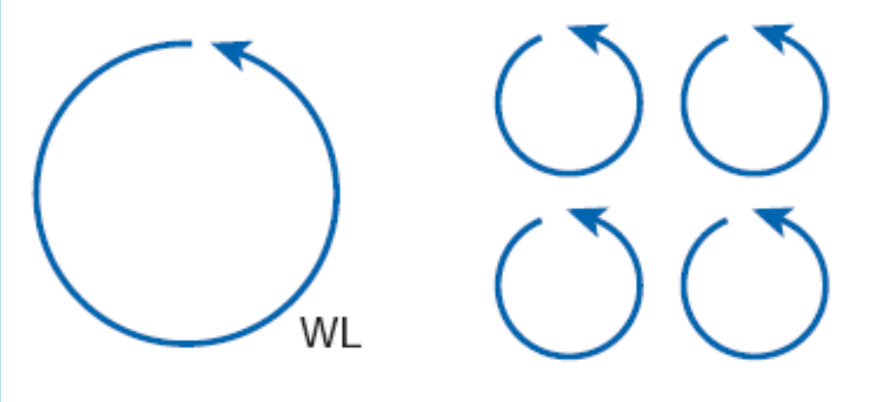


Figure 2 Figures represent multivariable-adjusted hazard ratios of atrial fibrillation with allopurinol exposure of 1–180 days, 181 days to 2 years and >2 years for each patient characteristic. Error bars represent the 95% confidence interval The horizontal hashed line represents a hazard ratio of 1, which represents the reference category of allopurinol use of 0 days (non-use). If the 95% error bar includes 1, the hazard ratio is statistically insignificant.

Reentry: Role of Refractory Periods, Conduction and Wavelength Changes



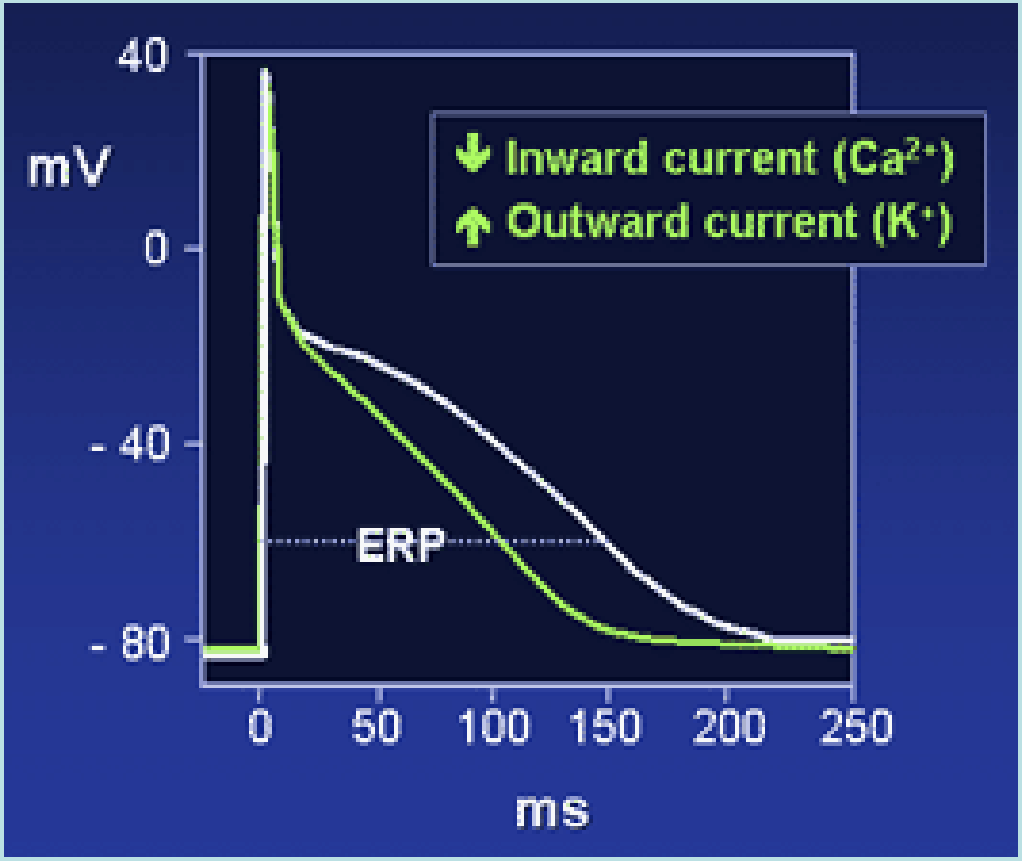
Wavelength (WL)=
Refractory period x conduction velocity
-minimal path length for reentry
-size of functional reentry circuits

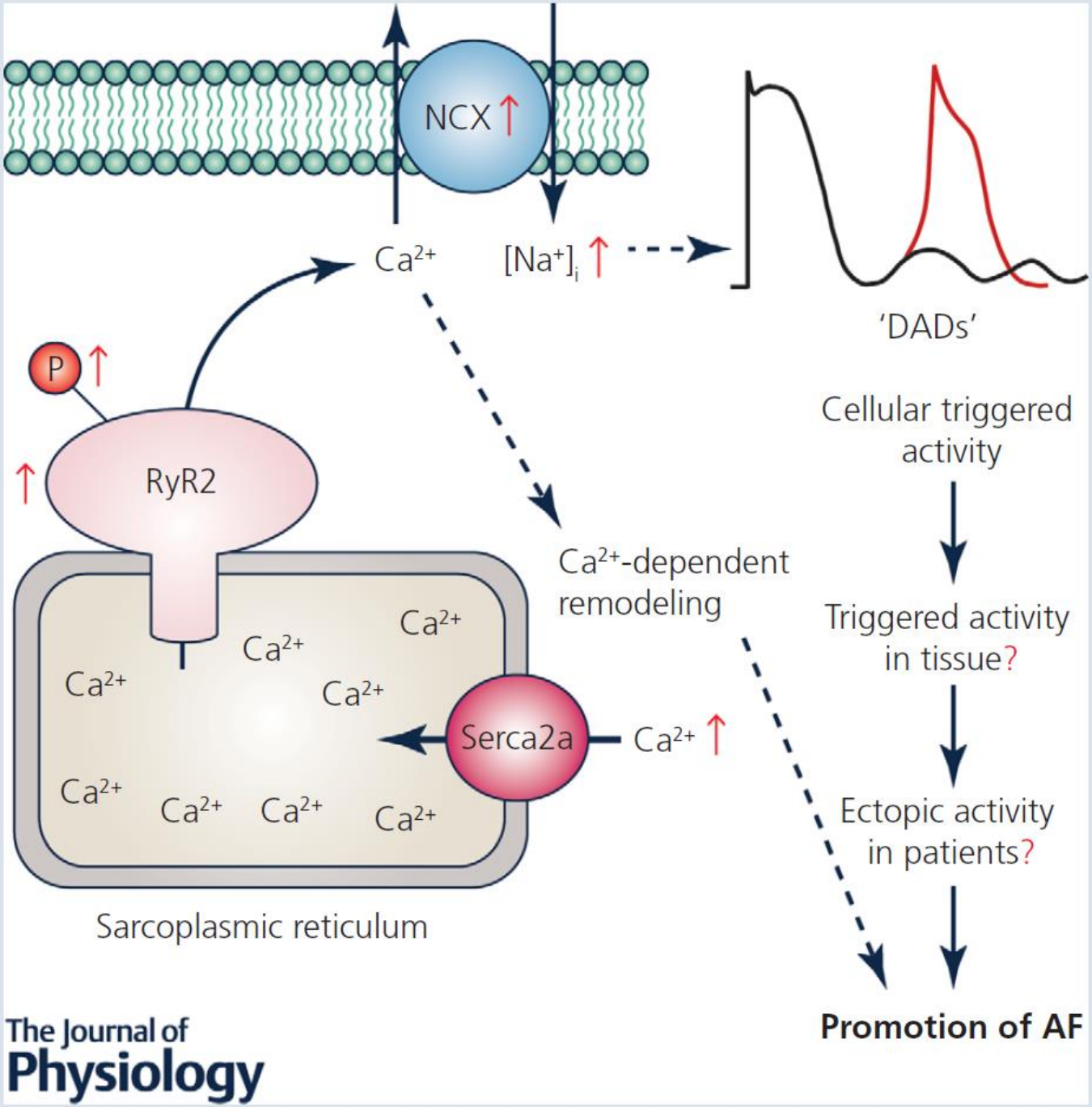


Normal atrial size
Normal WL
-reentry unstable
-AF not sustained

Normal atrial size
Short WL
(↓RP, ↓CV)
-AF sustained

How can wavelength be shortened enough to allow multiple-circuit reenty?



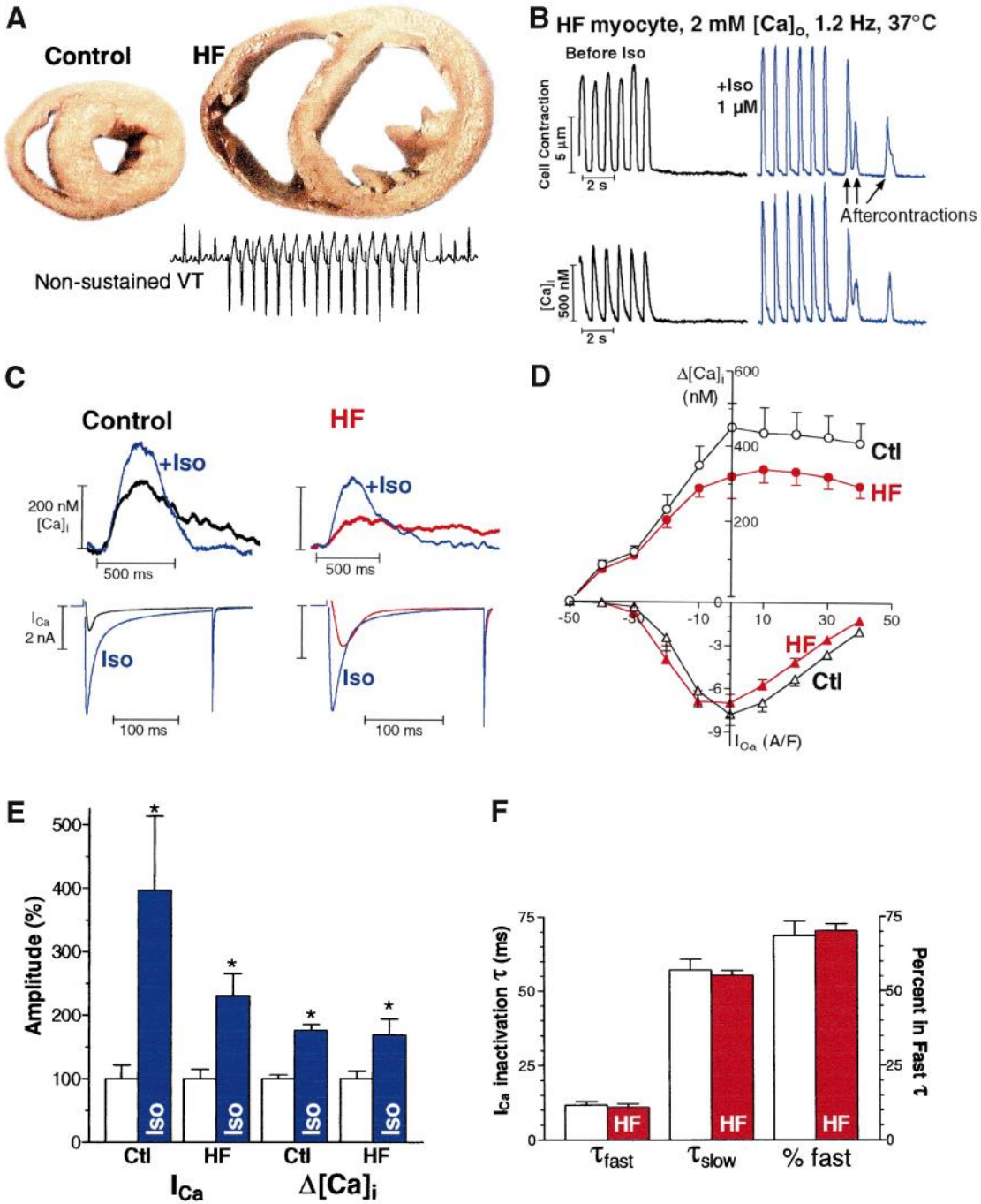

NCX ↑
Ca2+
[Na+]i ↑
'DADs'
P ↑
RyR2
↑
Cellular triggered activity
Ca2+-dependent remodeling
Triggered activity in tissue?
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Serca2a
Ca2+ ↑
Ectopic activity in patients?
Sarcoplasmic reticulum
Promotion of AF
The Journal of Physiology

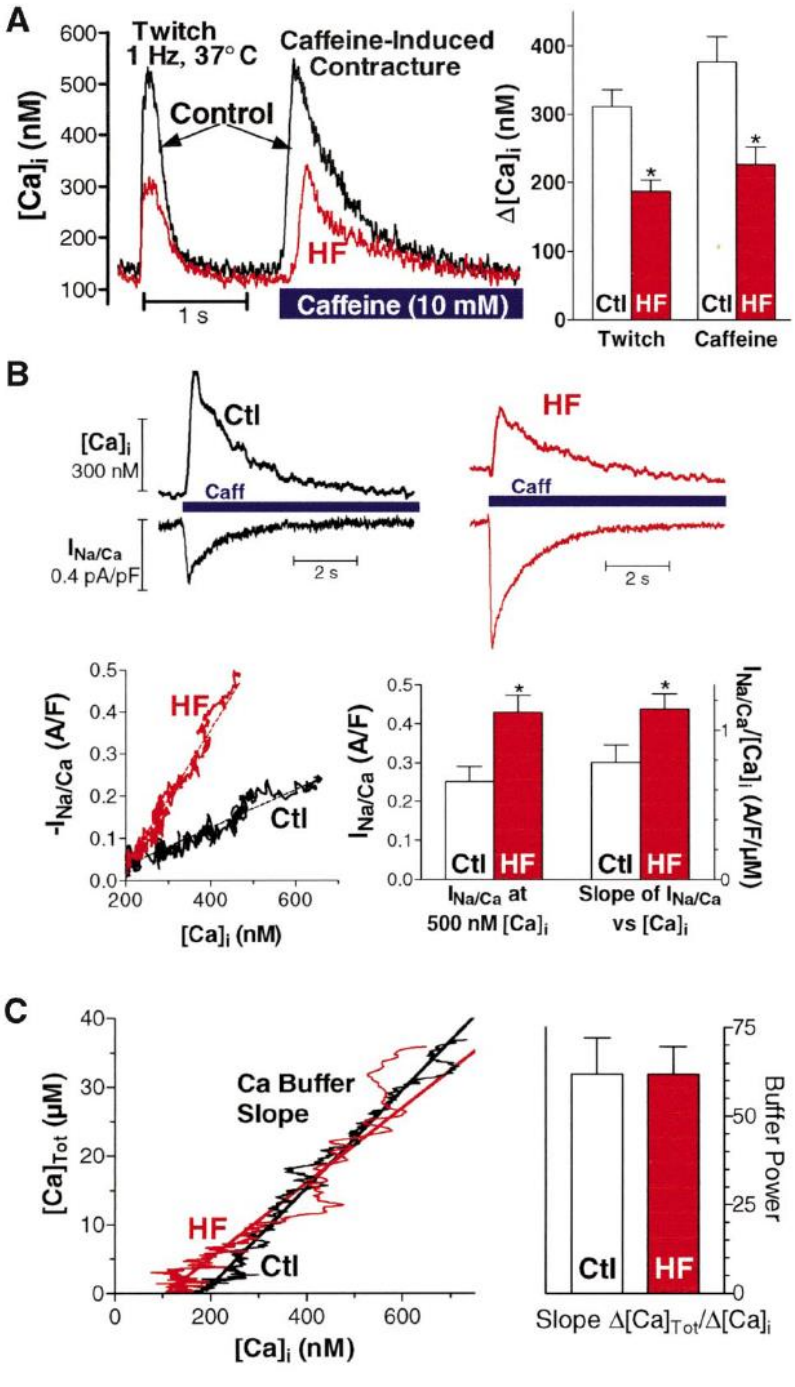
Arrhythmogenesis and Contractile Dysfunction in Heart Failure

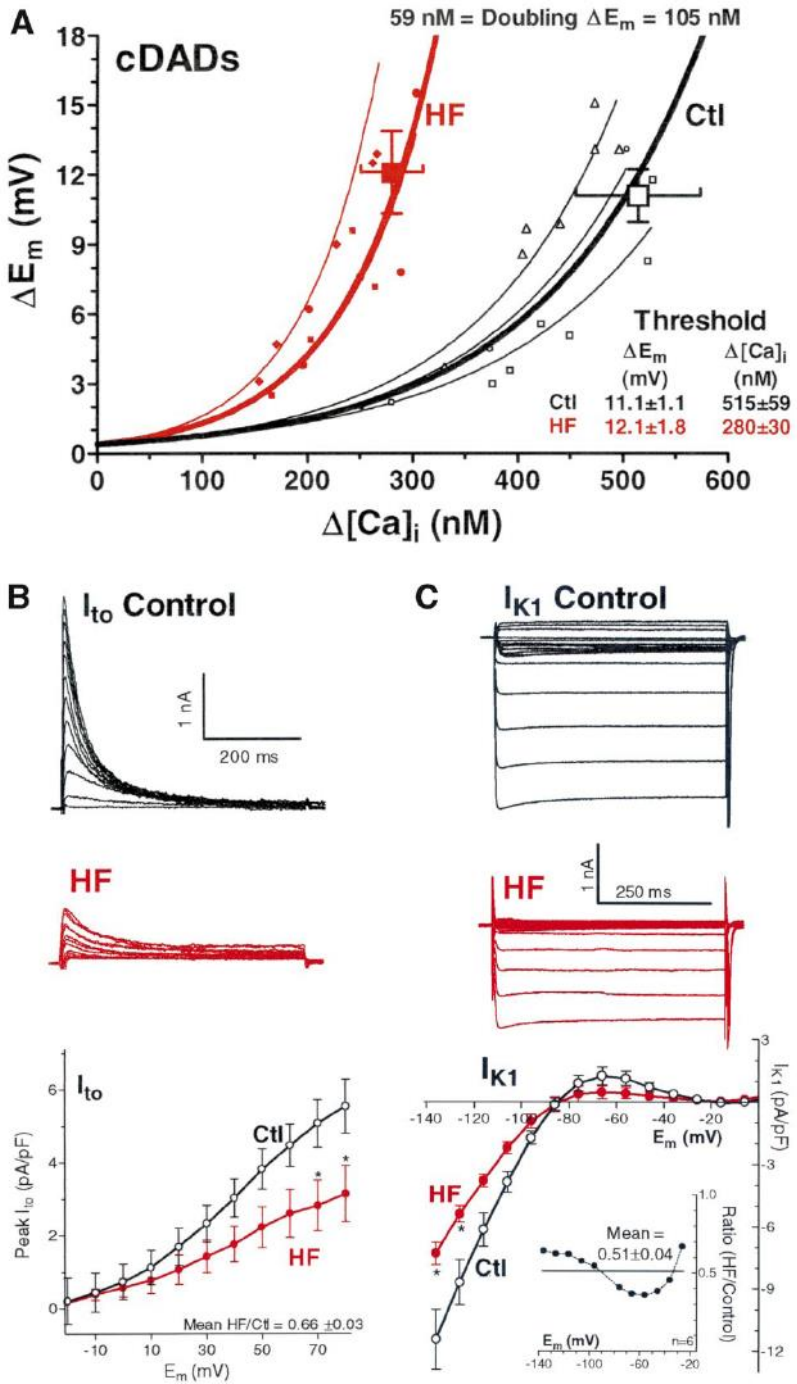
Roles of Sodium-Calcium Exchange, Inward Rectifier Potassium Current, and Residual β-Adrenergic Responsiveness

Steven M. Pogwizd,* Klaus Schlotthauer,* Li Li, Weilong Yuan, Donald M. Bers

Abstract—Ventricular arrhythmias and contractile dysfunction are the main causes of death in human heart failure (HF). In a rabbit HF model reproducing these same aspects of human HF, we demonstrate that a 2-fold functional upregulation of Na^+-Ca^{2+} exchange (NaCaX) unloads sarcoplasmic reticulum (SR) Ca^{2+} stores, reducing Ca^{2+} transients and contractile function. Whereas β-adrenergic receptors (β-ARs) are progressively downregulated in HF, residual β-AR responsiveness at this critical HF stage allows SR Ca^{2+} load to increase, causing spontaneous SR Ca^{2+} release and transient inward current carried by NaCaX. A given Ca^{2+} release produces greater arrhythmogenic inward current in HF (as a result of NaCaX upregulation), and ≈50% less Ca^{2+} release is required to trigger an action potential in HF. The inward rectifier potassium current (I_{K1}) is reduced by 49% in HF, and this allows greater depolarization for a given NaCaX current. Partially blocking I_{K1} in control cells with barium mimics the greater depolarization for a given current injection seen in HF. Thus, we present data to support a novel paradigm in which changes in NaCaX and I_{K1}, and residual β-AR responsiveness, conspire to greatly increase the propensity for triggered arrhythmias in HF. In addition, NaCaX upregulation appears to be a critical link between contractile dysfunction and arrhythmogenesis. **(*Circ Res*. 2001;88: 1159-1167.)**


A
Control
HF
Non-sustained VT
B
HF myocyte, 2 mM [Ca]o, 1.2 Hz, 37°C
Before Iso
+Iso
1 μM
Cell Contraction
5 μm
2 s
Aftercontractions
[Ca]i
500 nM
2 s
C
Control
HF
+Iso
200 nM
[Ca]i
500 ms
ICa
2 nA
Iso
100 ms
D
Δ[Ca]i
(nM)
600
400
200
0
Ctl
HF
-50
-30
-10
10
30
50
-3
-6
-9
ICa (A/F)
E
Amplitude (%)
500
400
300
200
100
0
Iso
Ctl
HF
ICa
Δ[Ca]i
F
ICa inactivation τ (ms)
75
50
25
0
Percent in Fast τ
τfast
τslow
% fast


A
Twitch
1 Hz, 37° C
Caffeine-Induced
Contracture
Control
HF
Caffeine (10 mM)
1 s
[Ca]i (nM)
Δ[Ca]i (nM)
Ctl
HF
Twitch
Caffeine
B
Ctl
HF
Caff
[Ca]i
300 nM
INa/Ca
0.4 pA/pF
2 s
-INa/Ca (A/F)
[Ca]i (nM)
INa/Ca (A/F)
INa/Ca/[Ca]i (A/F/μM)
INa/Ca at
500 nM [Ca]i
Slope of INa/Ca
vs [Ca]i
C
Ca Buffer
Slope
[Ca]Tot (μM)
[Ca]i (nM)
Buffer Power
Slope Δ[Ca]Tot/Δ[Ca]i


A
59 nM = Doubling ΔEm = 105 nM
cDADs
HF
Ctl
ΔEm (mV)
Δ[Ca]i (nM)
Threshold
ΔEm (mV)
Δ[Ca]i (nM)
Ctl 11.1±1.1 515±59
HF 12.1±1.8 280±30
B
Ito Control
1 nA
200 ms
HF
Ito
Peak Ito (pA/pF)
Ctl
HF
Mean HF/Ctl = 0.66 ±0.03
Em (mV)
C
IK1 Control
HF
1 nA
250 ms
IK1
IK1 (pA/pF)
Em (mV)
HF
Ctl
Mean = 0.51±0.04
Ratio (HF/Control)
n=6

Dissociation Between Ionic Remodeling and Ability to Sustain Atrial Fibrillation During Recovery From Experimental Congestive Heart Failure

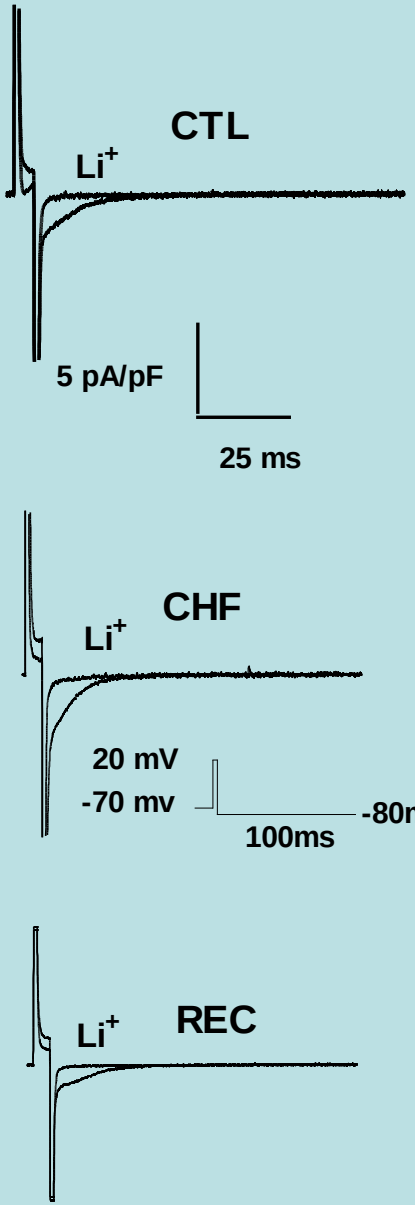
Tae-Joon Cha, MD; Joachim R. Ehrlich, MD; Liming Zhang, MSc; Yan-Fen Shi, MD; Jean-Claude Tardif, MD; Tack Ki Leung, MD; Stanley Nattel, MD

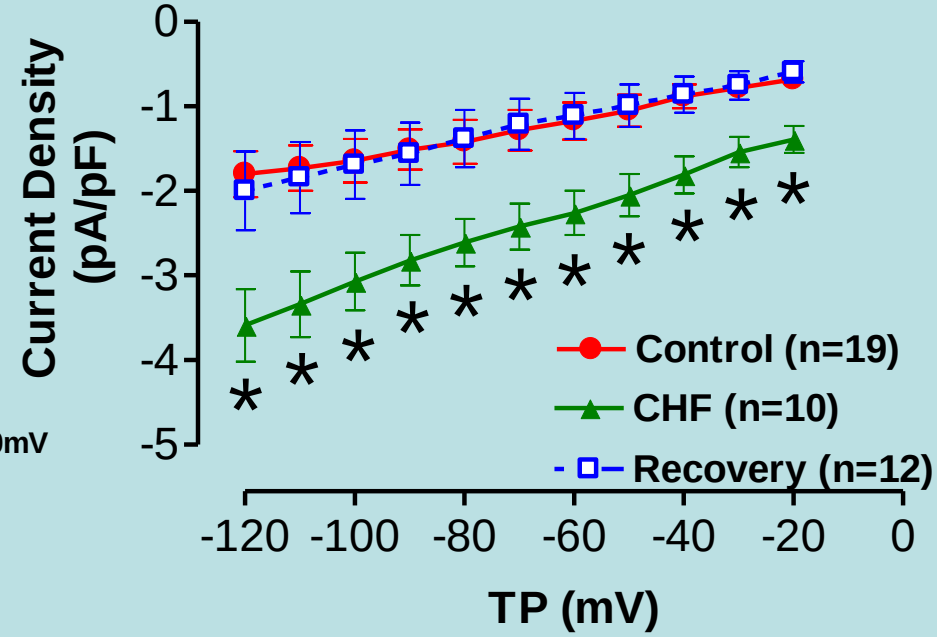
Background—Congestive heart failure (CHF) downregulates atrial transient outward (I_{to}), slow delayed rectifier (I_{Ks}), and L-type Ca^{2+} ($I_{Ca,L}$) currents and upregulates Na^{+}-Ca^{2+} exchange current (I_{NCX}) (ionic remodeling) and causes atrial fibrosis (structural remodeling). The relative importance of ionic versus structural remodeling in CHF-related atrial fibrillation (AF) is controversial.

Methods and Results—We measured hemodynamic and echocardiographic parameters, mean duration of burst pacing–induced AF (DAF), and atrial-myocyte ionic currents in dogs with CHF induced by 2-week ventricular tachypacing (240 bpm), CHF dogs allowed to recover without pacing for 4 weeks (REC), and unpaced controls. Left ventricular ejection fraction averaged 58.6±1.2% (control), 36.2±2.3% (CHF, $P<0.01$), and 57.9±1.6% (REC), indicating full hemodynamic recovery. Similarly, left atrial pressures were 2.2±0.3 (control), 13.1±1.5 (CHF), and 2.4±0.4 (REC) mm Hg. CHF reduced I_{to} density by ≈65% ($P<0.01$), decreased $I_{Ca,L}$ density by ≈50% ($P<0.01$), and diminished I_{Ks} density by ≈40% ($P<0.01$) while increasing I_{NCX} density by ≈110% ($P<0.05$). In REC, all ionic current densities returned to control values. DAF increased in CHF (1132±207 versus 14.3±8.8 seconds, control) and remained increased with REC (1014±252 seconds). Atrial fibrous tissue content also increased in CHF (2.1±0.2% for control versus 10.2±0.7% for CHF, $P<0.01$), with no recovery observed in REC (9.4±0.8%, $P<0.01$ versus control, P=NS versus CHF).

Conclusions—With reversal of CHF, there is complete recovery of ionic remodeling, but the prolonged-AF substrate and structural remodeling remain. This suggests that structural, not ionic, remodeling is the primary contributor to AF maintenance in experimental CHF. **(*Circulation*. 2004;109:412-418.)**

Changes of Na^+-Ca^{++} Exchanger





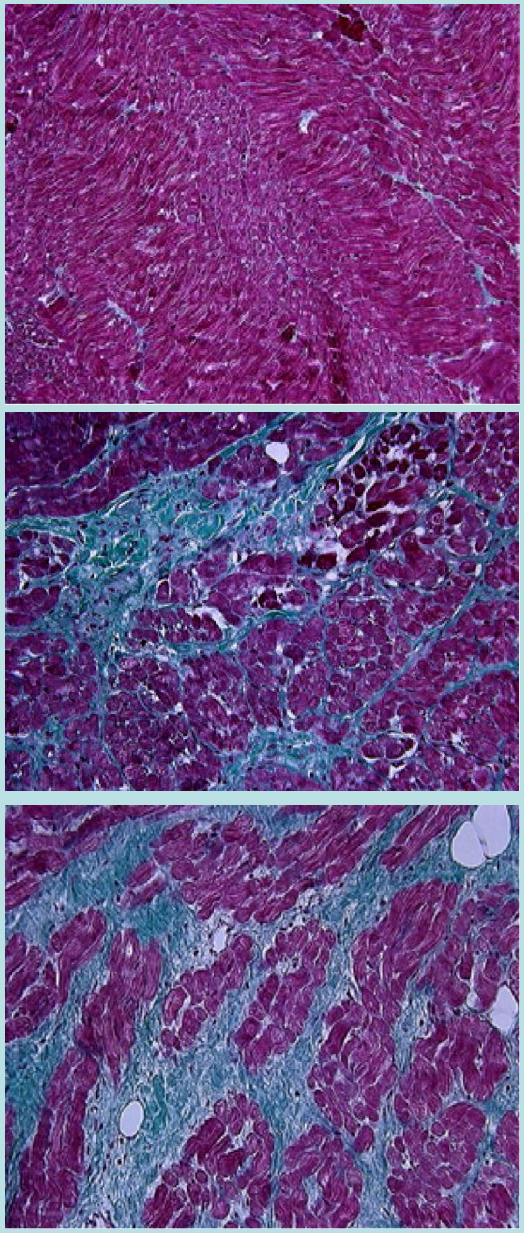
In summary, I_{NCX} was significantly increased by CHF and completely recovered by REC.

(x200)

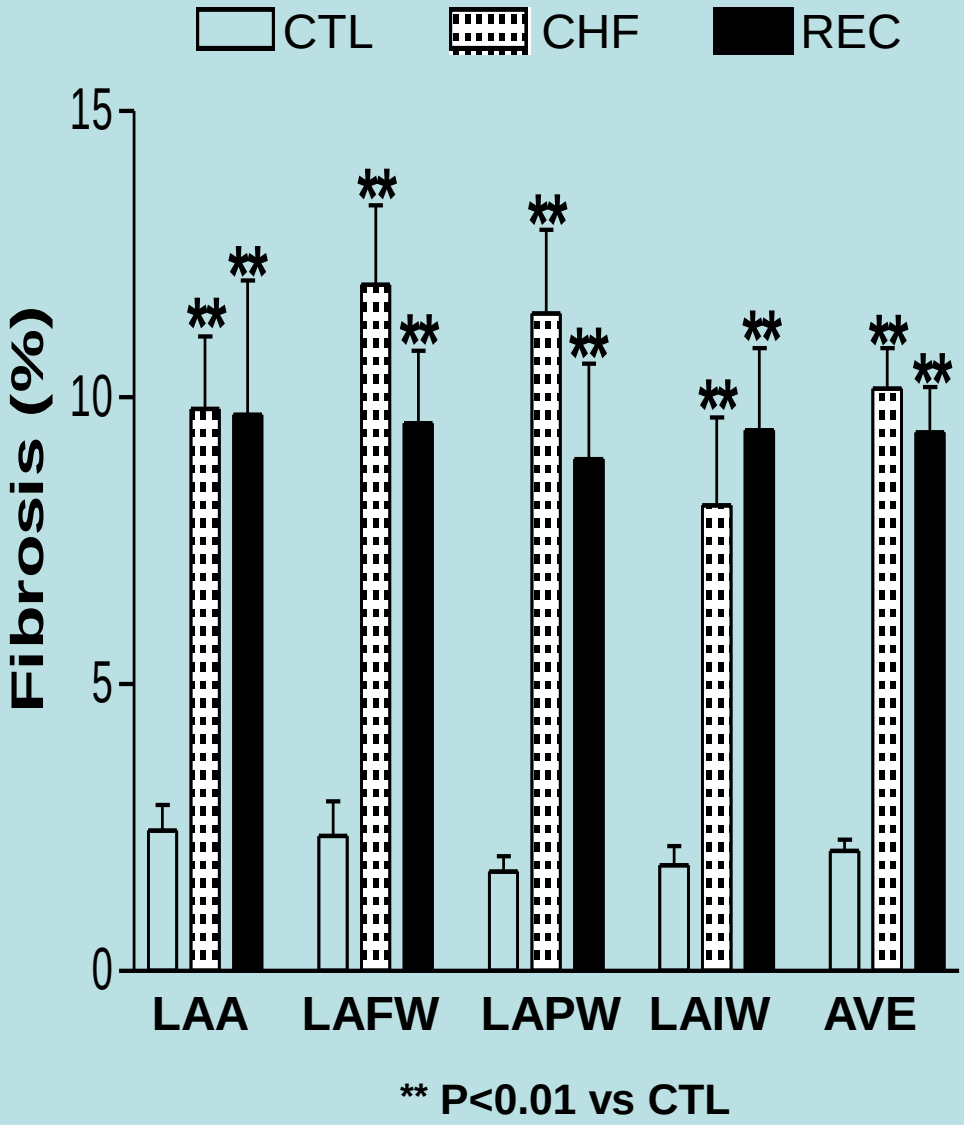
CTL

CHF

REC

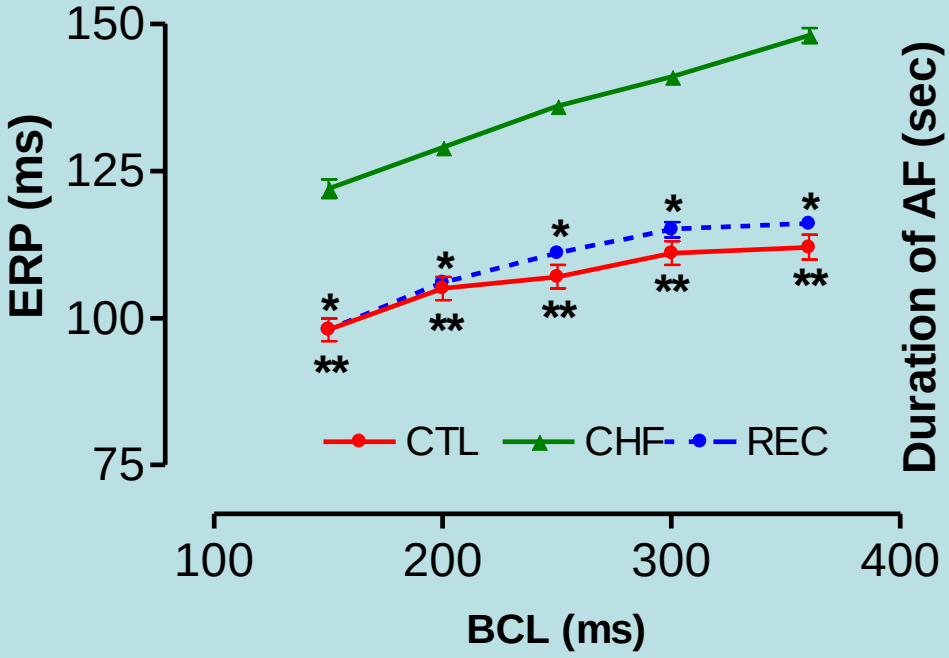


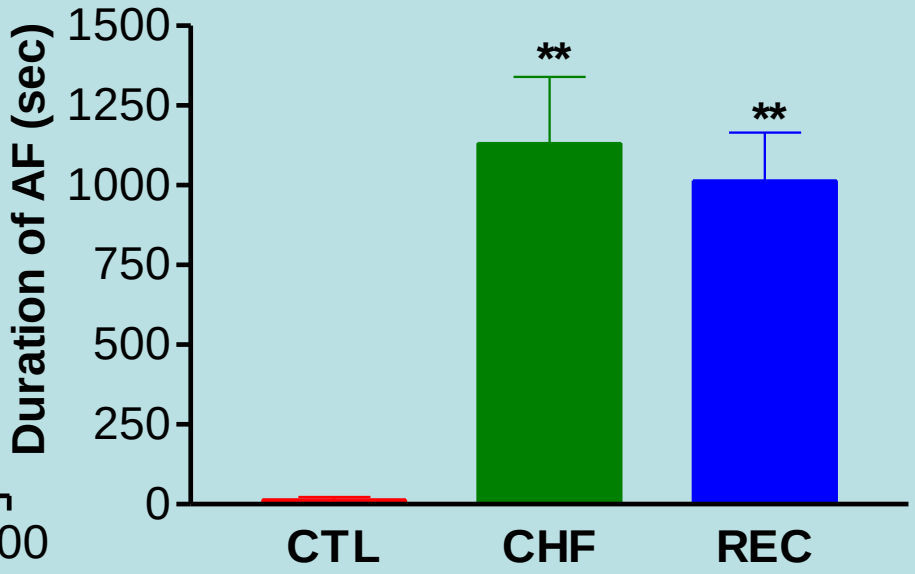
Changes of Fibrosis



Thus, fibrosis induced by 2-week tachypacing showed no recovery with REC.

Changes of ERP and Duration of AF



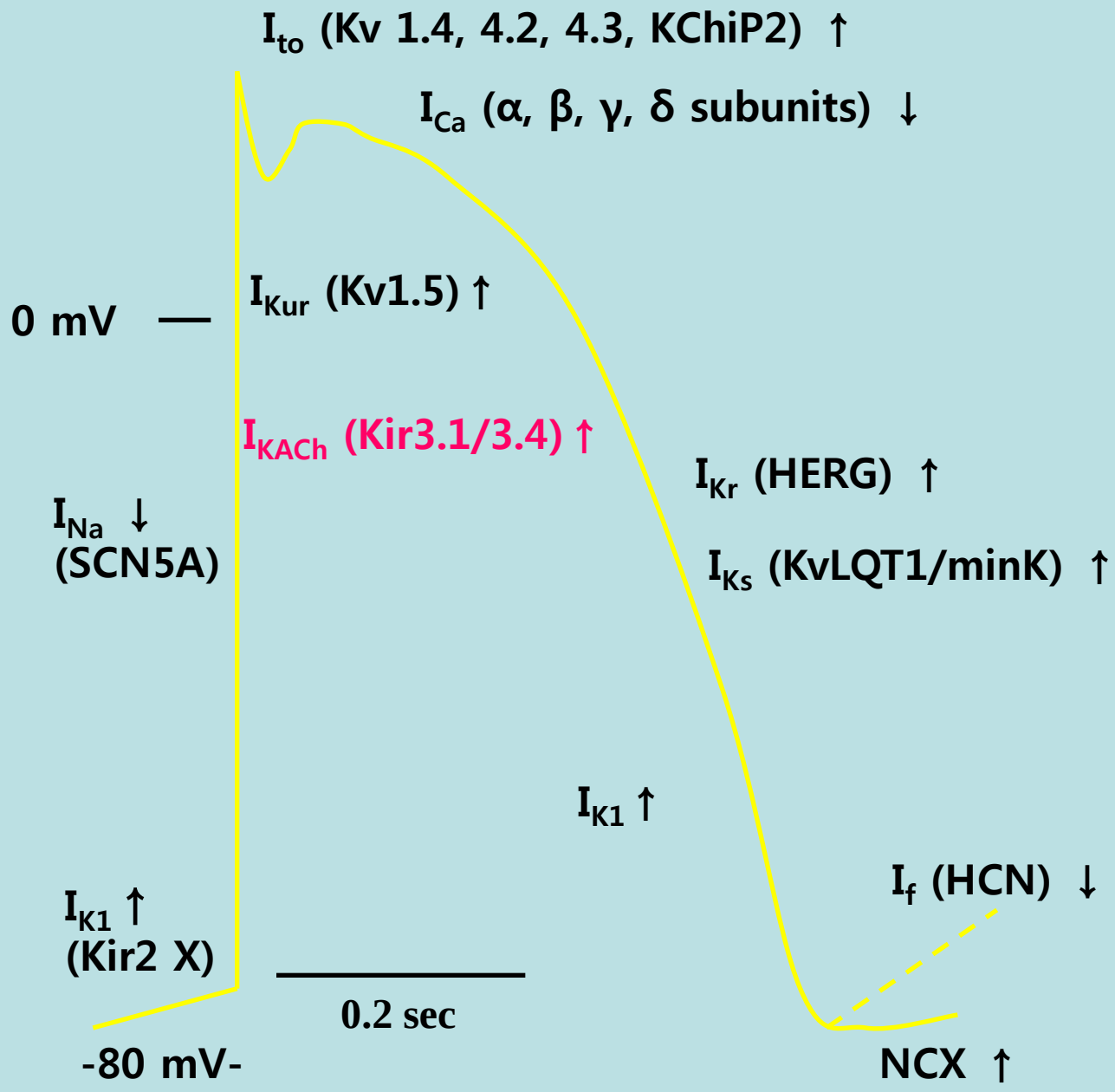


** P<0.01 vs control group.

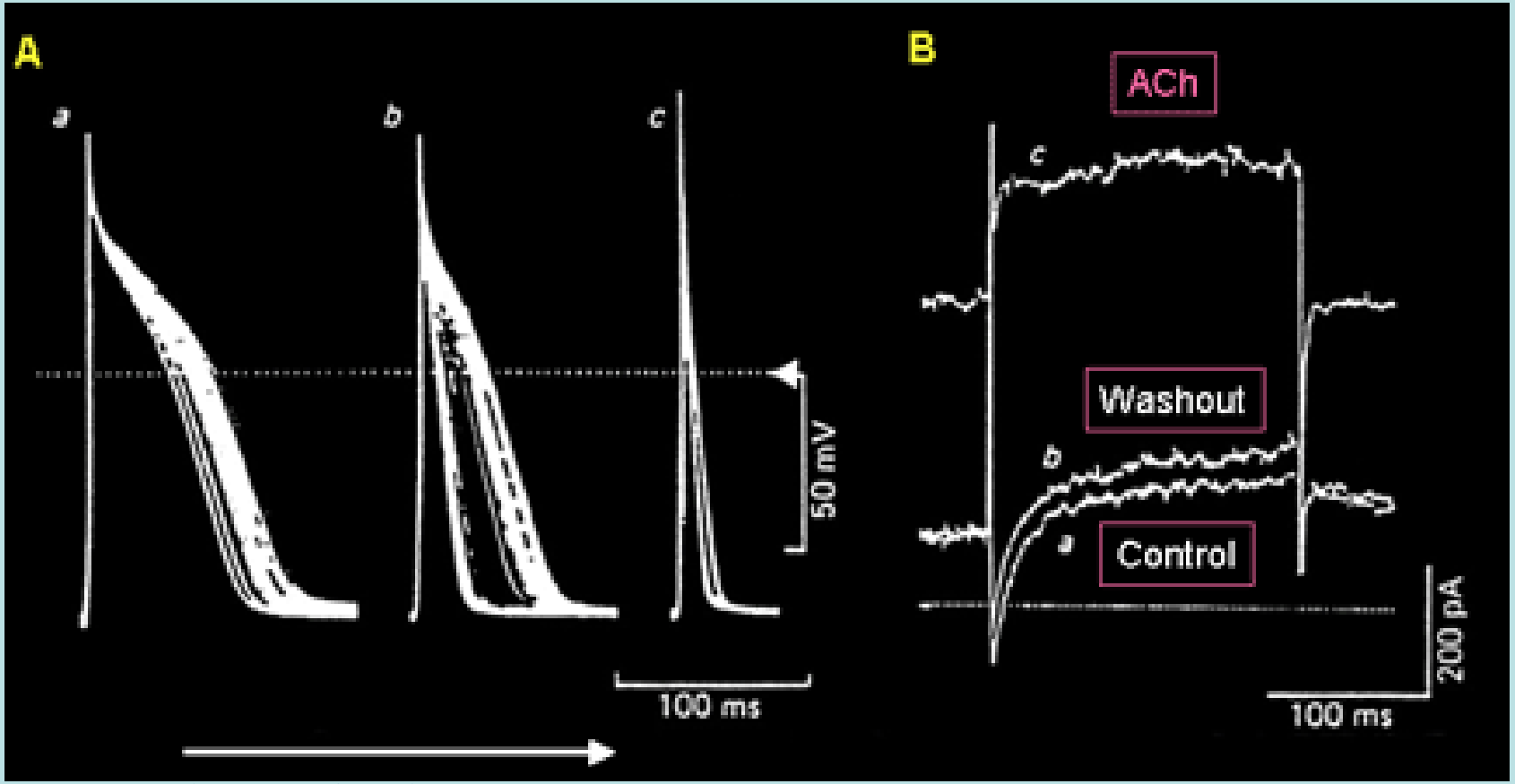
* P<0.05 CTL vs REC, ** P<0.05 CTL vs CHF

Electrical remodeling indicated by ERP recovered with REC, consistent with ionic changes. The CHF-related AF substrate, indicated by AF duration, remained in REC.

Ionic Determinants of the Action Potential



Vagal Effects of Atrial Repolarization



Increasing I_{KACh}

Kir3-based Inward Rectifier Potassium Current: Potential Role in Atrial Tachycardia Remodeling Effects on Atrial Repolarization and Arrhythmias

Tae-Joon Cha,* Joachim R. Ehrlich, Denis Chartier,**

Xiaon-Yan Qi, Ling Xiao, Stanley Nattel,

***Kosin universtiy, Busan, South Korea**
**** J. W. Goethe-University, Frankfurt, Germany**
Montreal heart institute, Montreal, Canada

Circulation 2006, 113: 1730-1737

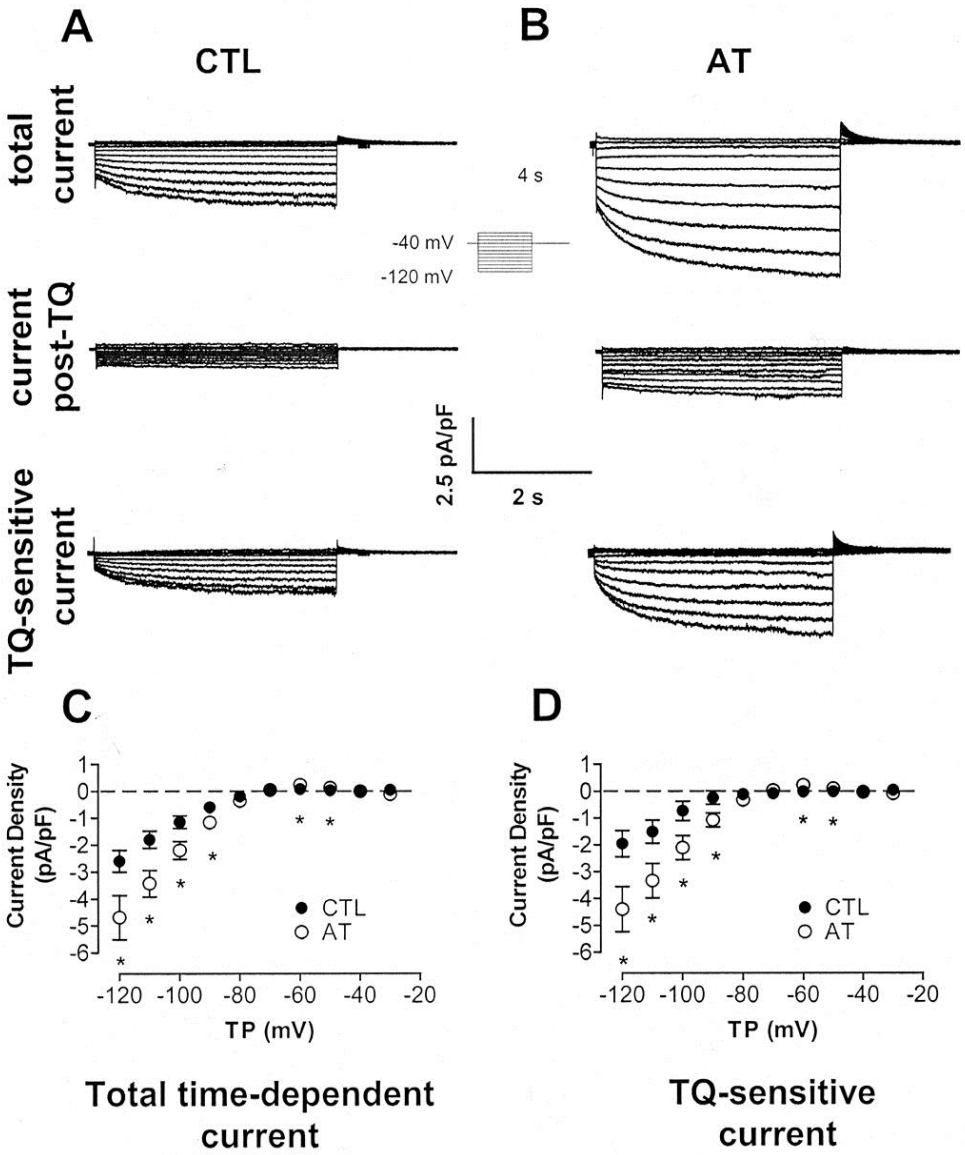
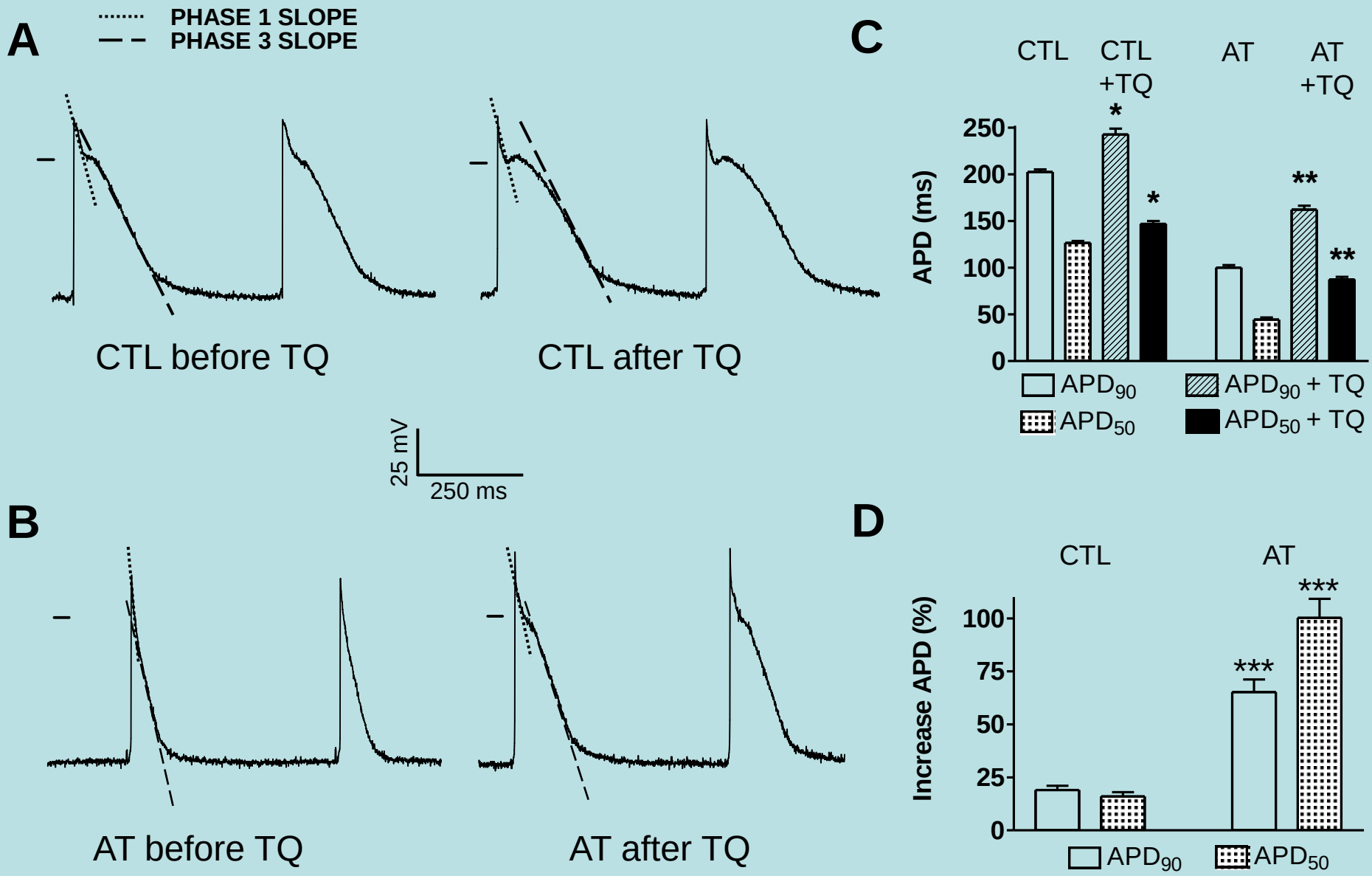
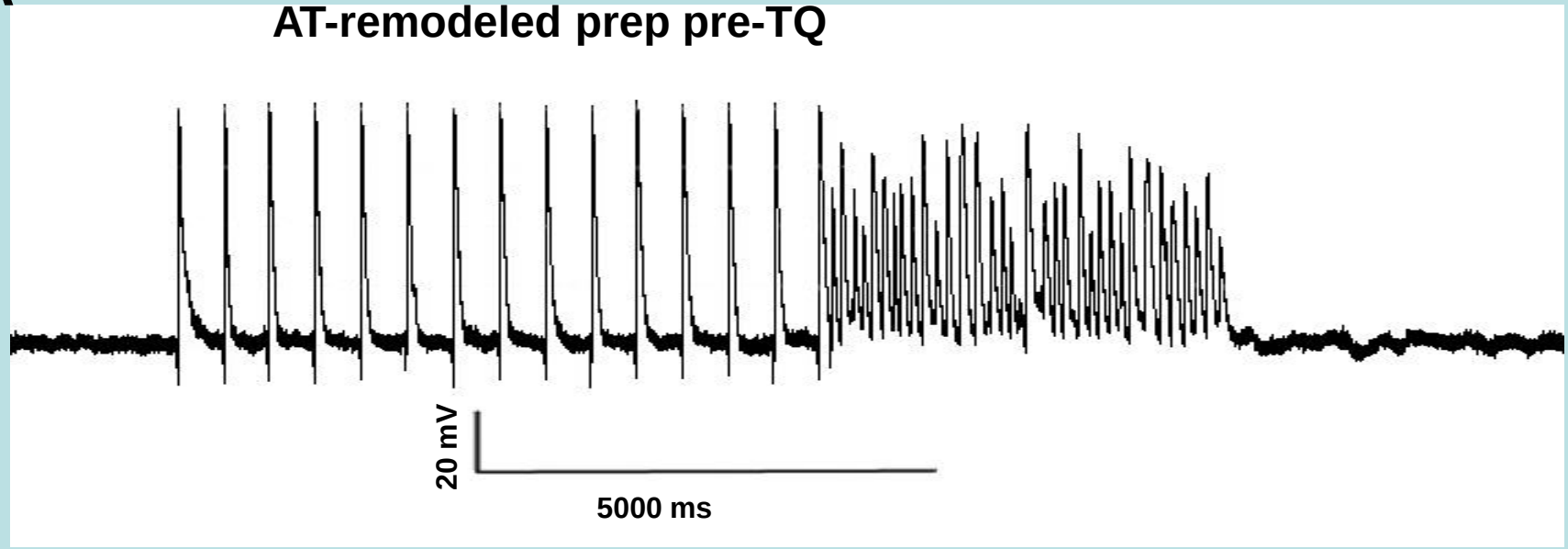

A
CTL
B
AT
total current
current post-TQ
TQ-sensitive current
4 s
-40 mV
-120 mV
2.5 pA/pF
2 s
C
D
Current Density (pA/pF)
CTL
AT
TP (mV)
Total time-dependent current
TQ-sensitive current

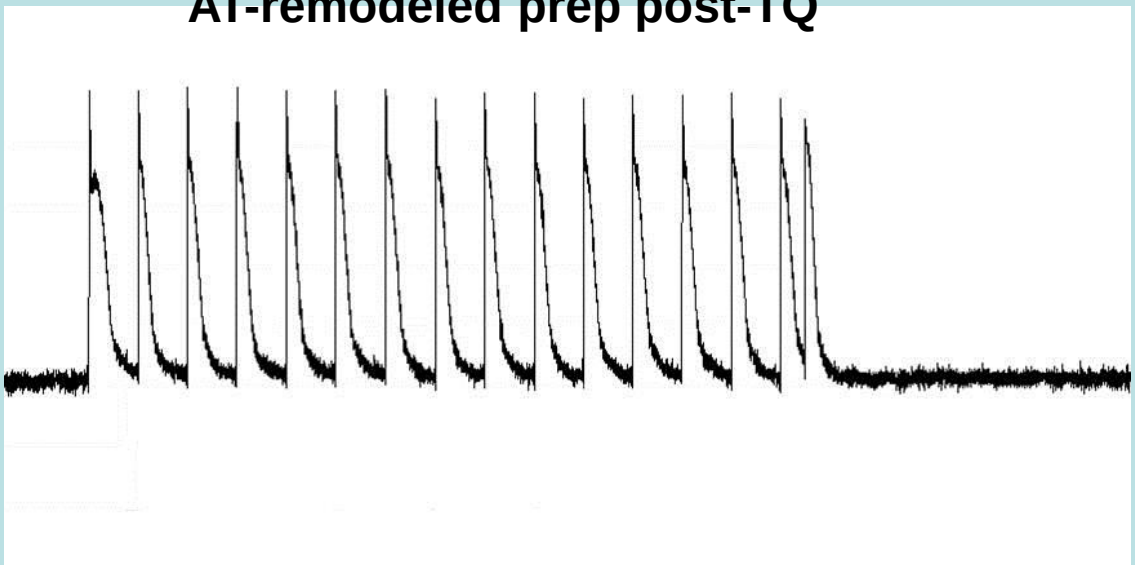
Fig. 1


A
PHASE 1 SLOPE
PHASE 3 SLOPE
CTL before TQ
CTL after TQ
25 mV
250 ms
B
AT before TQ
AT after TQ
C
CTL
CTL +TQ
AT
AT +TQ
APD (ms)
250
200
150
100
50
0
APD90
APD90 + TQ
APD50
APD50 + TQ
D
CTL
AT
Increase APD (%)
100
75
50
25
0
APD90
APD50

A


AT-remodeled prep pre-TQ
20 mV
5000 ms

B


AT-remodeled prep post-TQ

EUROPEAN SOCIETY OF CARDIOLOGY®

Europace (2010) **12**, 1490–1497
doi:10.1093/europace/euq280

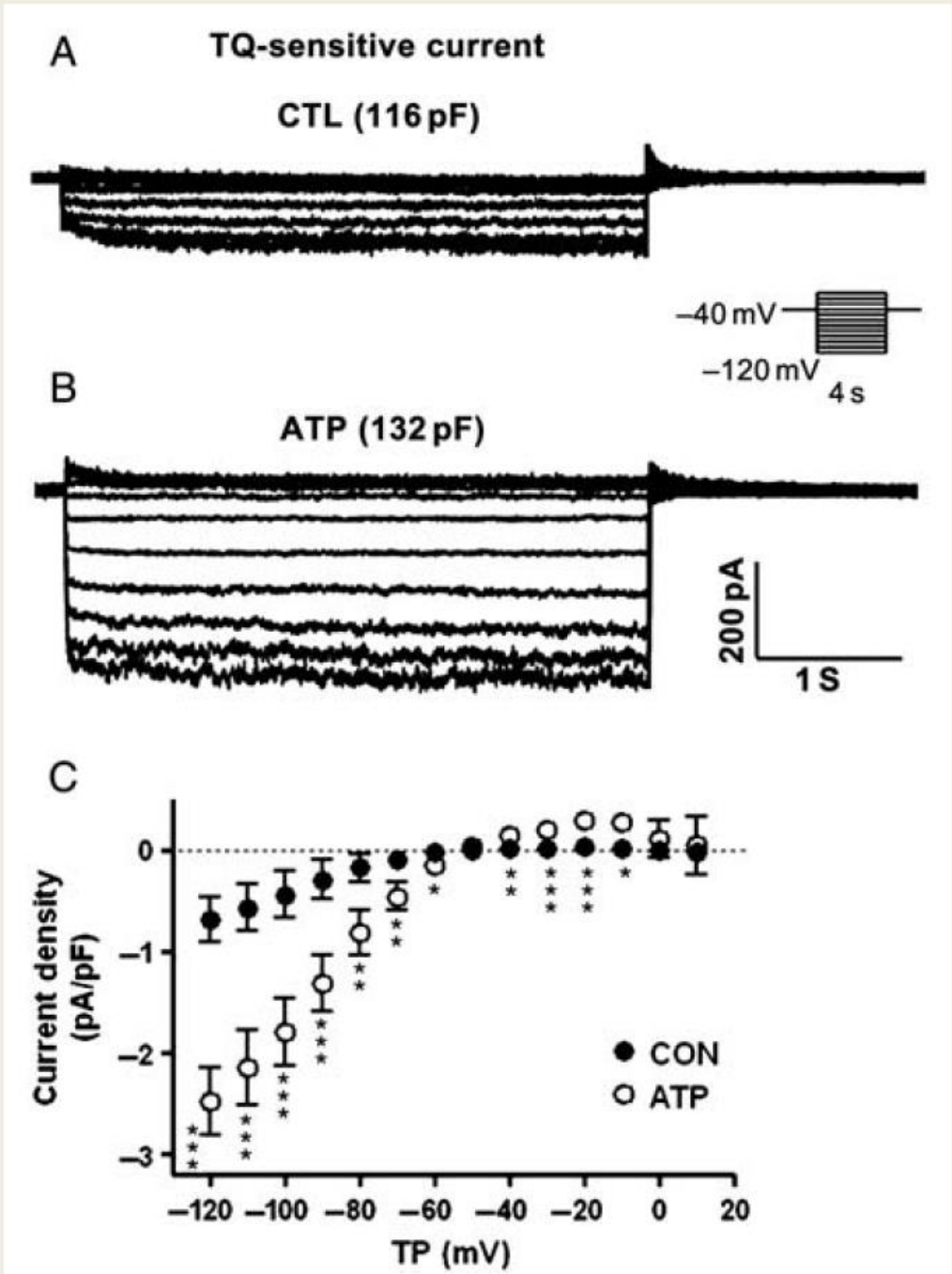
BASIC SCIENCE

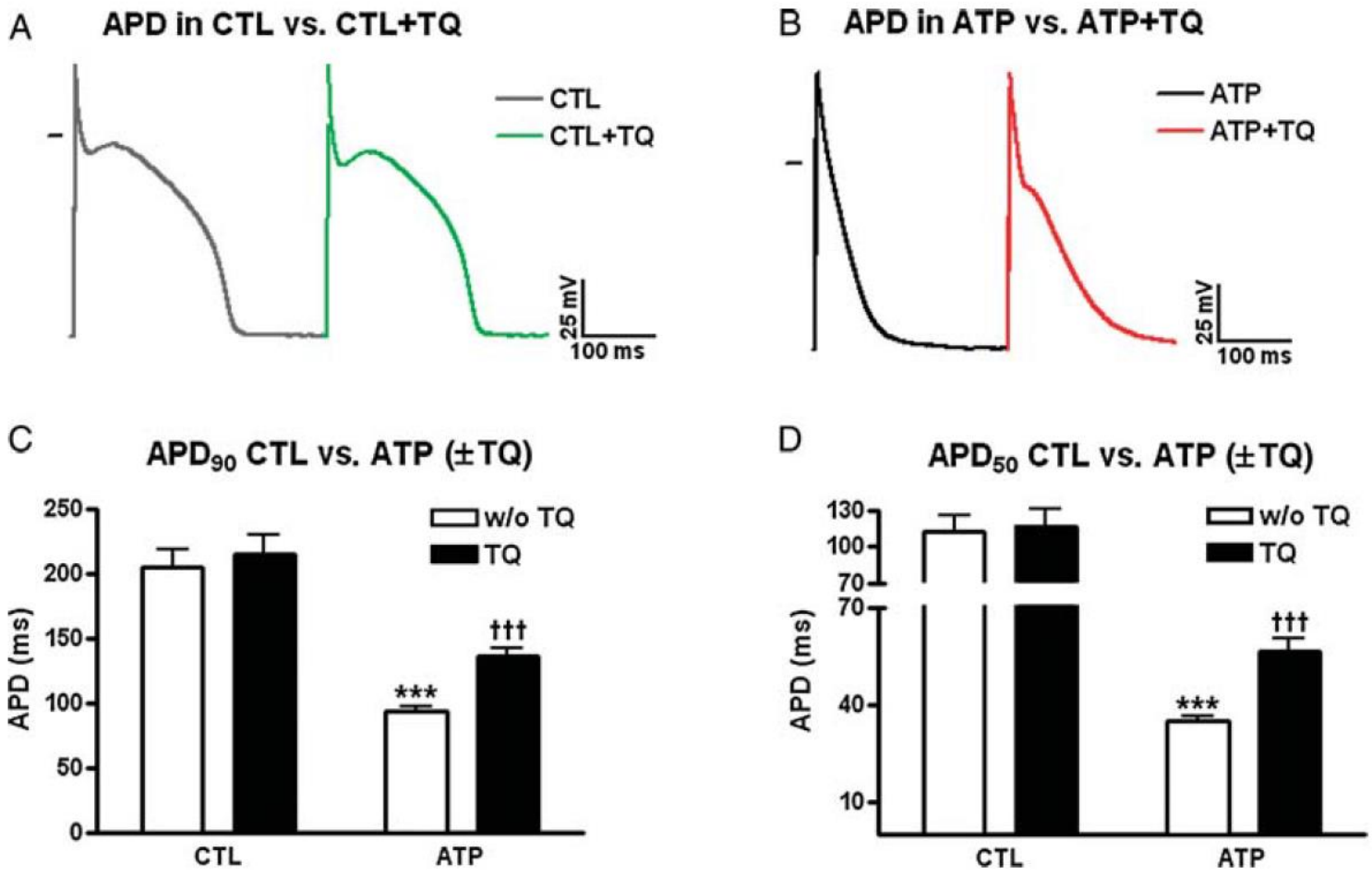
Role of constitutively active acetylcholine-mediated potassium current in atrial contractile dysfunction caused by atrial tachycardia remodelling

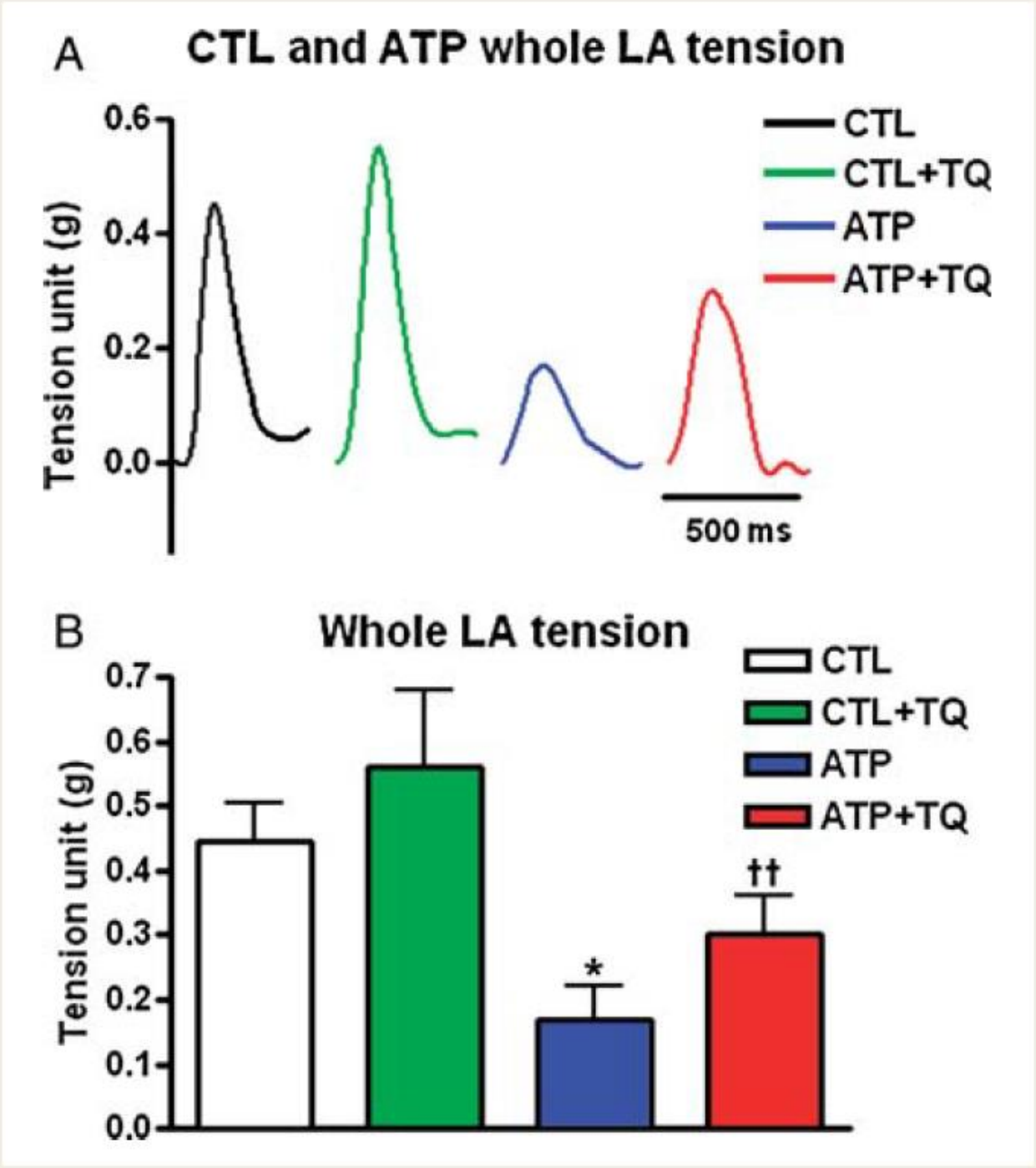
Sang-Ho Koo[1], Reza Wakili[2], Jung-Ho Heo[1], Denis Chartier[2], Hyun-Su Kim[1], Sun-Jung Kim[1], Jae-Woo Lee[1], Xiao Yan Qi[2], Stanley Nattel[2†], and Tae-Joon Cha[1*†]

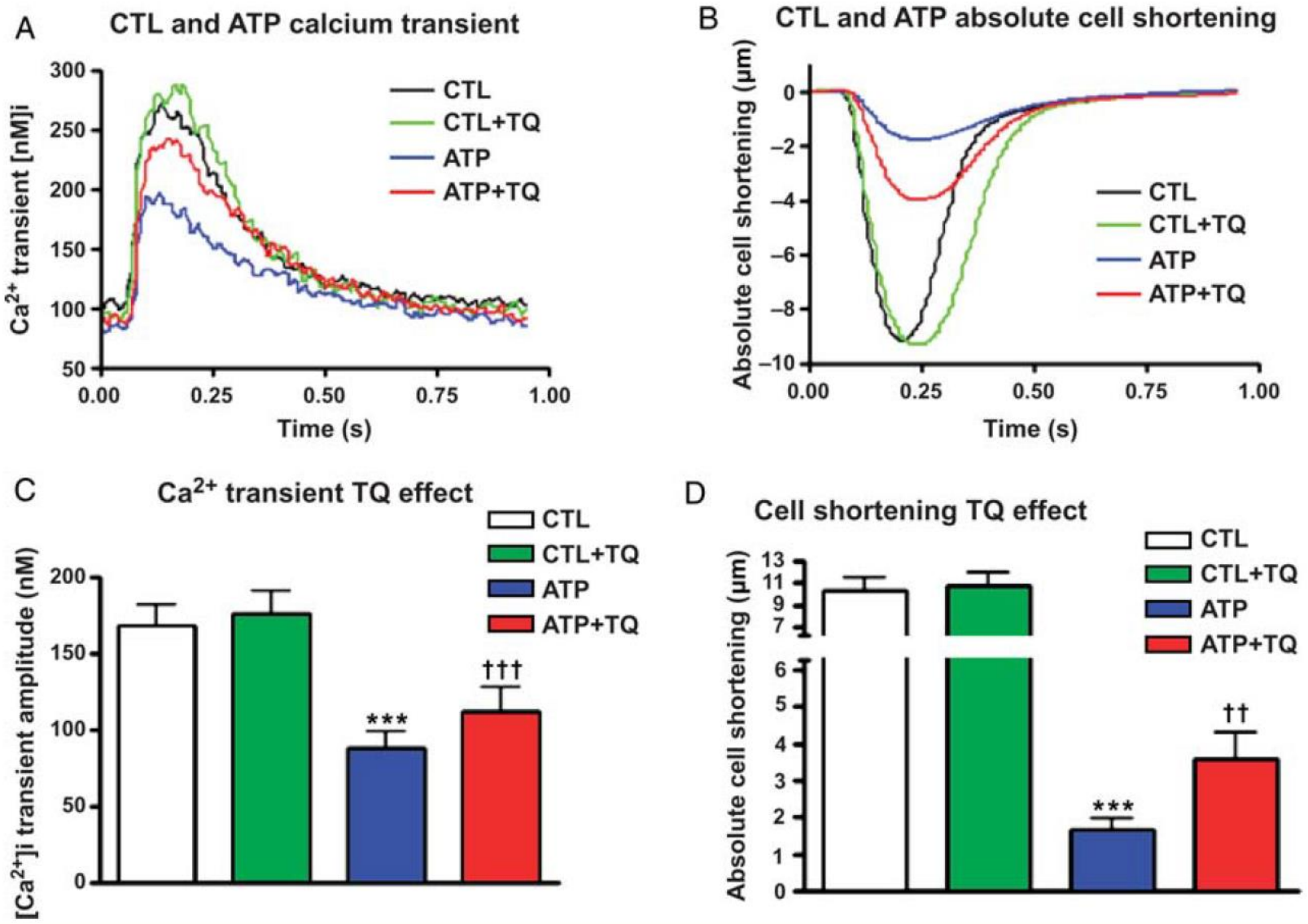
[1]Division of Cardiology, Department of Internal Medicine, Kosin University School of Medicine, 34 Amnam-Dong, Seo-Ku, Busan 602-702, South Korea; and [2]Department of Medicine and Research Center, Montreal Heart Institute and Université de Montréal, Montreal, QC, Canada

Received 6 January 2010; accepted after revision 5 July 2010; online publish-ahead-of-print 2 August 2010


A
TQ-sensitive current
CTL (116 pF)
–40 mV
–120 mV
4 s
B
ATP (132 pF)
200 pA
1 S
C
Current density (pA/pF)
0
–1
–2
–3
–120 –100 –80 –60 –40 –20 0 20
TP (mV)
CON
ATP


A
APD in CTL vs. CTL+TQ
CTL
CTL+TQ
25 mV
100 ms
B
APD in ATP vs. ATP+TQ
ATP
ATP+TQ
25 mV
100 ms
C
APD90 CTL vs. ATP (±TQ)
w/o TQ
TQ
APD (ms)
250
200
150
100
50
0
***
†††
CTL
ATP
D
APD50 CTL vs. ATP (±TQ)
w/o TQ
TQ
APD (ms)
130
100
70
70
40
10
***
†††
CTL
ATP


A
CTL and ATP whole LA tension
Tension unit (g)
0.6
0.4
0.2
0.0
CTL
CTL+TQ
ATP
ATP+TQ
500 ms
B
Whole LA tension
Tension unit (g)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
CTL
CTL+TQ
ATP
ATP+TQ
*
††


A
CTL and ATP calcium transient
300
250
200
150
100
50
Ca2+ transient [nM]i
0.00
0.25
0.50
0.75
1.00
Time (s)
CTL
CTL+TQ
ATP
ATP+TQ
B
CTL and ATP absolute cell shortening
0
−2
−4
−6
−8
−10
Absolute cell shortening (µm)
0.00
0.25
0.50
0.75
1.00
Time (s)
CTL
CTL+TQ
ATP
ATP+TQ
C
Ca2+ transient TQ effect
200
150
100
50
0
[Ca2+]i transient amplitude (nM)
***
†††
CTL
CTL+TQ
ATP
ATP+TQ
D
Cell shortening TQ effect
13
11
9
7
6
5
4
3
2
1
0
Absolute cell shortening (µm)
***
††
CTL
CTL+TQ
ATP
ATP+TQ

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 287, NO. 7, pp. 4925–4935, February 10, 2012

Hypercholesterolemia Induces Up-regulation of K_{ACh} Cardiac Currents via a Mechanism Independent of Phosphatidylinositol 4,5-Bisphosphate and G$\beta\gamma$*[S]

Received for publication, September 21, 2011, and in revised form, December 7, 2011 Published, JBC Papers in Press, December 15, 2011, DOI 10.1074/jbc.M111.306134

Wu Deng[‡1], Anna N. Bukiya[§], Aldo A. Rodríguez-Menchaca[‡], Zhe Zhang[‡], Clive M. Baumgarten[‡], Diomedes E. Logothetis[‡], Irena Levitan[¶], and Avia Rosenhouse-Dantsker[¶2]

From the [¶]Department of Medicine, Pulmonary Section, University of Illinois at Chicago, Chicago, Illinois 60612, the [‡]Department of Physiology and Biophysics, Virginia Commonwealth University School of Medicine, Richmond, Virginia 23298, and the [§]Department of Pharmacology, The University of Tennessee Health Science Center, Memphis, Tennessee 38163

Background: K_{ACh} channels play a key role in controlling the heart rate.
Results: K_{ACh} currents are enhanced by cholesterol enrichment and high cholesterol diet.
Conclusion: Cholesterol plays a critical role in modulating $I_{K,ACh}$ in atrial cardiomyocytes.
Significance: The increase in $I_{K,ACh}$ following cholesterol enrichment is likely to play a critical role in hypercholesterolemia-induced dysfunction of the heart.

Hypercholesterolemia is a well-known risk factor for cardiovascular disease. In the heart, activation of K_{ACh} mediates the vagal (parasympathetic) negative chronotropic effect on heart rate. Yet, the effect of cholesterol on K_{ACh} is unknown. Here we show that cholesterol plays a critical role in modulating K_{ACh} currents ($I_{K,ACh}$) in atrial cardiomyocytes. Specifically, cholesterol enrichment of rabbit atrial cardiomyocytes led to enhanced channel activity while cholesterol depletion suppressed $I_{K,ACh}$. Moreover, a high-cholesterol diet resulted in up to 3-fold increase in $I_{K,ACh}$ in rodents. In accordance, elevated currents were observed in *Xenopus* oocytes expressing the Kir3.1/Kir3.4 heteromer that underlies $I_{K,ACh}$. Furthermore, our data suggest that cholesterol affects $I_{K,ACh}$ via a mechanism which is independent of both $PI(4,5)P_2$ and G$\beta\gamma$. Interestingly, the effect of cholesterol on $I_{K,ACh}$ is opposite to its effect on I_{K1} in atrial myocytes. The latter are suppressed by cholesterol enrichment and by high-cholesterol diet, and facilitated following cholesterol depletion. These findings establish that cholesterol plays a critical role in modulating $I_{K,ACh}$ in atrial cardiomyocytes via a mechanism independent of the channel's major modulators.

brane excitability in cardiac, neuronal, and endocrine cells (5). Loss of Kir3 channel activity leads to cardiac abnormalities (6), neuronal hyperexcitability, and seizures in the brain (7, 8), hyperactivity and reduced anxiety (9). In the heart, the atrial K_{ACh} channels are heterotetrameric proteins that consist of two pore-forming subunits, Kir3.1 (GIRK1) and Kir3.4 (GIRK4) (10). Activation of K_{ACh} by acetylcholine (ACh) (6, 11, 12) via the muscarinic M2 receptor and pertussis toxin-sensitive G proteins mediates the vagal negative chronotropic effect (1–4). Thus, activation of K_{ACh} channels can terminate paroxysmal supraventricular tachycardia (PSVT), *i.e.* a rapid cardiac rhythm (13). On the other hand, vagal stimulation predisposes to atrial fibrillation (AF) (14), which can lead to thromboembolism and stroke (15, 16). Thus, while Kir3.4 knock-out mice exhibit a mild tachycardia and blunted heart rate regulation by M2 receptors (17), Kir3.4 knock-out mice are also resistant to AF caused by vagal stimulation without any change in atrioventricular node function or ventricular arrhythmias (14).

We recently reported cholesterol sensitivity of representative homomeric Kir channels using the *Xenopus* oocyte heterologous expression system (18). Kir3.4*, the highly active Kir3.4

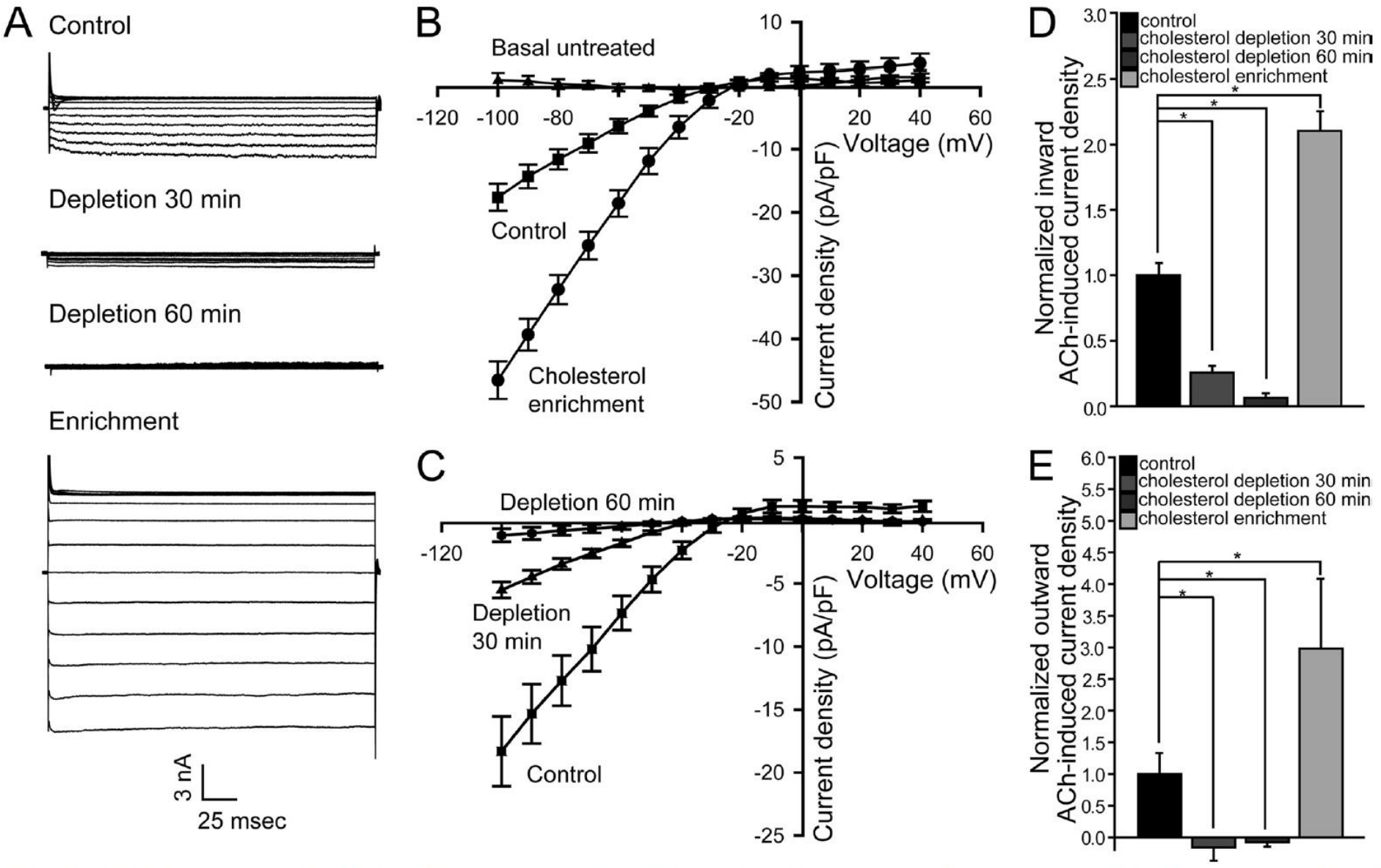


FIGURE 1. **ACh-induced currents in atrial cardiomyocytes are enhanced by cholesterol.** Tertiapin-sensitive currents (*A*) and I-V relationships (*B* and *C*) of ACh-induced current densities for control and cholesterol-treated myocytes. Also shown in *B* are tertiapin-insensitive basal current densities. Summary data: (*D*) inward ACh-induced current densities at −80mV; (*E*) outward ACh-induced current densities at +40mV. Significant difference is indicated by an *asterisk* (*, $p < 0.05$); ($n = 6–13$). Recordings were done using cells from 2–4 rabbits per treatment.

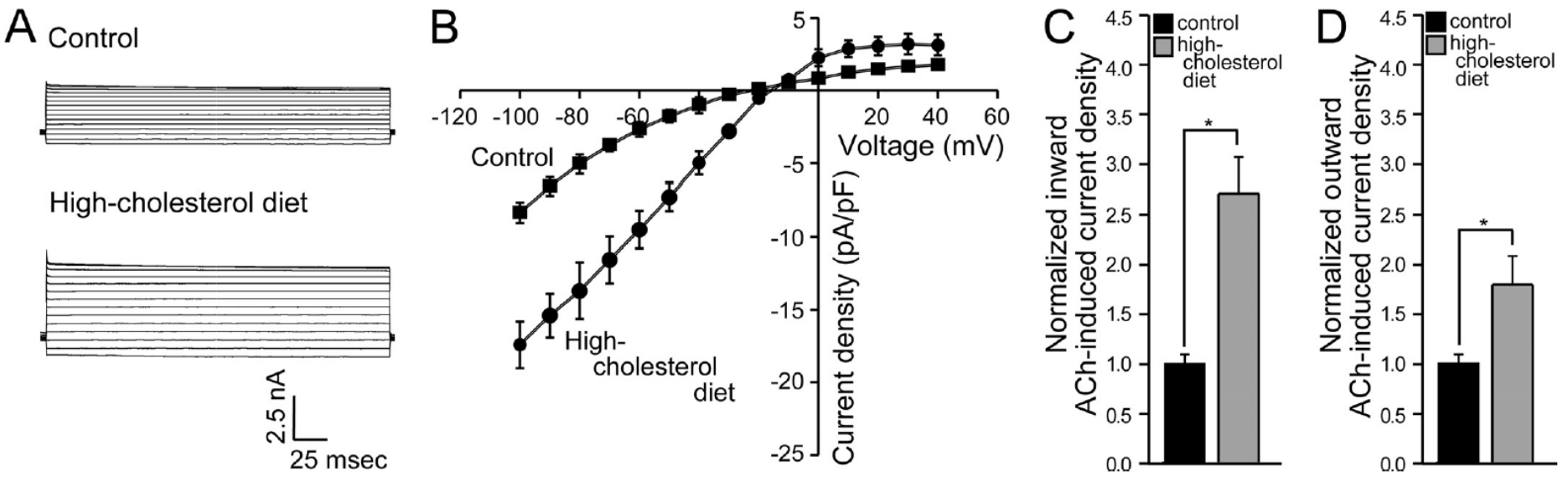


FIGURE 2. **ACh-induced currents in atrial cardiomyocytes are enhanced in hypercholesterolemic animals.** Tertiapin-sensitive currents (*A*) and I-V relationships (*B*) of ACh-induced current densities for atrial myocytes from control and hypercholesterolemic rats. Summary data: (*C*) inward ACh-induced current densities at −80 mV; (*D*) outward ACh-induced current densities at +40 mV. Significant difference is indicated by an *asterisk* (*, $p < 0.05$). Recordings were done using cells from 2 rats per condition.

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PLOS ONE

Attenuation of Acetylcholine Activated Potassium Current (I_{KACh}) by Simvastatin, Not Pravastatin in Mouse Atrial Cardiomyocyte: Possible Atrial Fibrillation Preventing Effects of Statin

Kyoung-Im Cho[1], Tae-Joon Cha[1]*, Su-Jin Lee[1], In-Kyeung Shim[1], Yin Hua Zhang[2], Jung-Ho Heo[1], Hyun-Su Kim[1], Sung Joon Kim[2], Kyoung-Lyoung Kim[3], Jae-Woo Lee[1]

1 Cardiovascular Research Institute, Department of Internal Medicine, Kosin University College of Medicine, Busan, South Korea, **2** Department of Physiology, Seoul National University College of Medicine, Seoul, South Korea, **3** Department of Molecular Biology, Kosin University College of Medicine, Busan, South Korea

Abstract

Statins, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, are associated with the prevention of atrial fibrillation (AF) by pleiotropic effects. Recent clinical trial studies have demonstrated conflicting results on anti-arrhythmia between lipophilic and hydrophilic statins. However, the underlying mechanisms responsible for anti-arrhythmogenic effects of statins are largely unexplored. In this study, we evaluated the different roles of lipophilic and hydrophilic statins (simvastatin and pravastatin, respectively) in acetylcholine (100 μM)-activated K^+ current (I_{KACh}, recorded by nystatin-perforated whole cell patch clamp technique) which are important for AF initiation and maintenance in mouse atrial cardiomyocytes. Our results showed that simvastatin (1–10 μM) inhibited both peak and quasi-steady-state I_{KACh} in a dose-dependent manner. In contrast, pravastatin (10 μM) had no effect on I_{KACh}. Supplementation of substrates for the synthesis of cholesterol (mevalonate, geranylgeranyl pyrophosphate or farnesyl pyrophosphate) did not reverse the effect of simvastatin on I_{KACh}, suggesting a cholesterol-independent effect on I_{KACh}. Furthermore, supplementation of phosphatidylinositol 4,5-bisphosphate, extracellular perfusion of phospholipase C inhibitor or a protein kinase C (PKC) inhibitor had no effect on the inhibitory activity of simvastatin on I_{KACh}. Simvastatin also inhibits adenosine activated I_{KACh}, however, simvastatin does not inhibit I_{KACh} after activated by intracellular loading of GTP gamma S. Importantly, shortening of the action potential duration by acetylcholine was restored by simvastatin but not by pravastatin. Together, these findings demonstrate that lipophilic statins but not hydrophilic statins attenuate I_{KACh} in atrial cardiomyocytes *via* a mechanism that is independent of cholesterol synthesis or PKC pathway, but may be via the blockade of acetylcholine binding site. Our results may provide important background information for the use of statins in patients with AF.

Citation: Cho K-I, Cha T-J, Lee S-J, Shim I-K, Zhang YH, et al. (2014) Attenuation of Acetylcholine Activated Potassium Current (I_{KACh}) by Simvastatin, Not Pravastatin in Mouse Atrial Cardiomyocyte: Possible Atrial Fibrillation Preventing Effects of Statin. PLoS ONE 9(10): e106570. doi:10.1371/journal.pone.0106570

Editor: Thomas Hund, The Ohio State University, United States of America

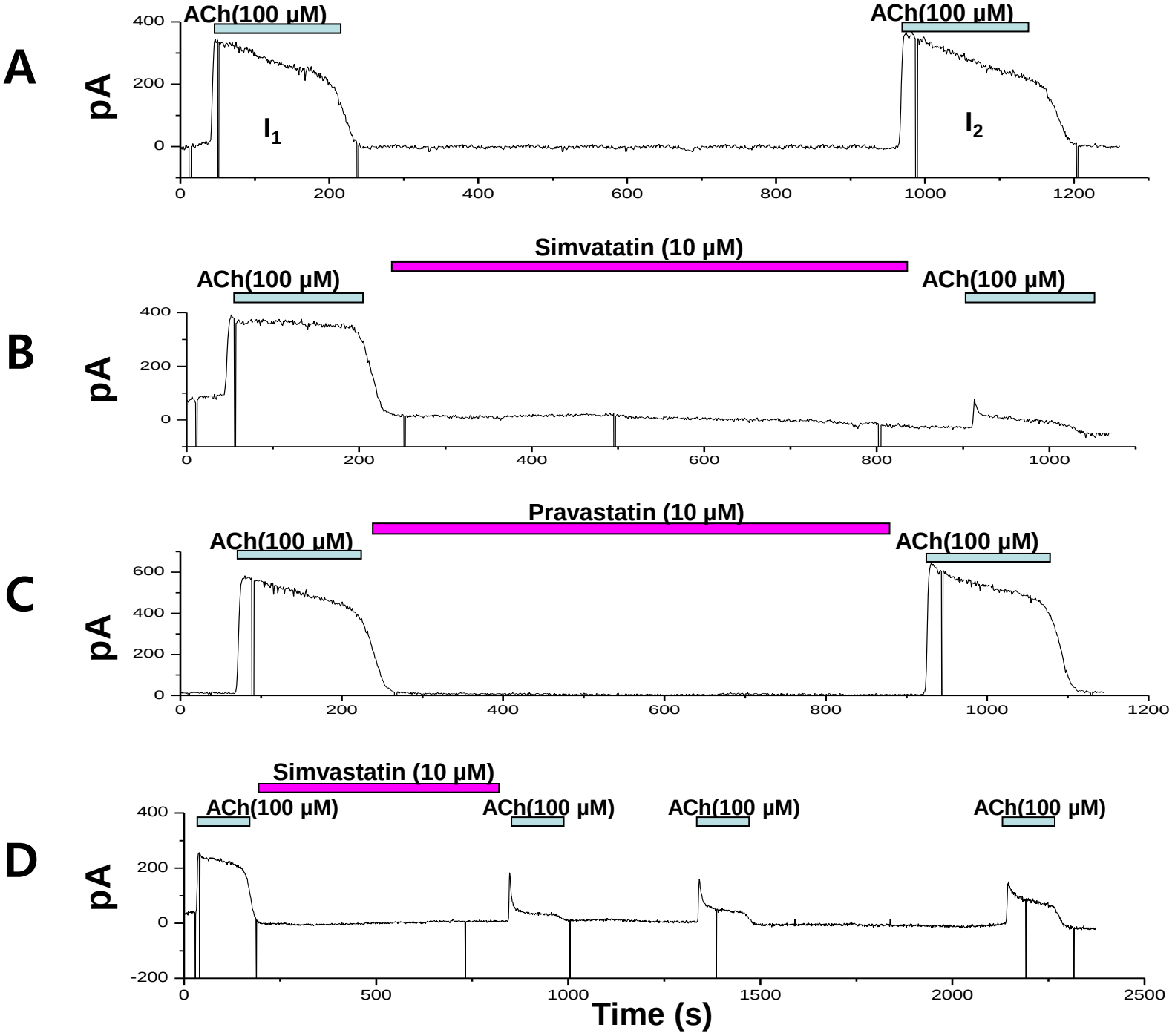
Received March 23, 2014; **Accepted** July 30, 2014; **Published** October 16, 2014

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

Funding: This study was supported by grants from the Korea Heart Rhythm Society (KHRS 2011-1) and Kosin University College of Medicine (2011). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* Email: chatjn@gmail.com


A
ACh(100 μM)
ACh(100 μM)
pA
I1
I2
B
Simvatatin (10 μM)
ACh(100 μM)
ACh(100 μM)
pA
C
Pravastatin (10 μM)
ACh(100 μM)
ACh(100 μM)
pA
D
Simvastatin (10 μM)
ACh(100 μM)
ACh(100 μM)
ACh(100 μM)
ACh(100 μM)
pA
Time (s)

Thank you!