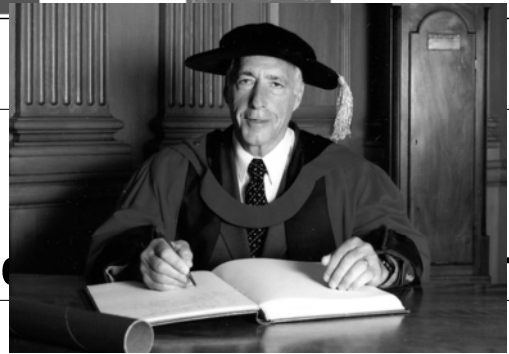


Rational Approach to Improving Cardiac Arrhythmia Therapy

Stanley Nattel, MD

SN.2003

Cardiac Arrhythmia Therapy



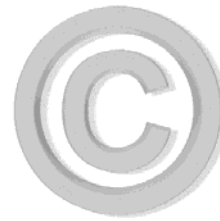
Stanley Nattel, MD

DEDICATED TO THE MASTER OF RATIONAL THERAPEUTICS

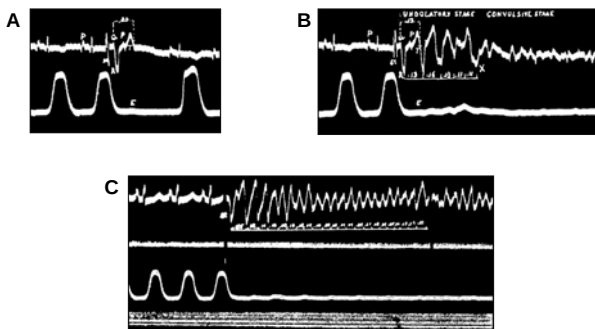
SENAC:
Cinchona bark for palpitations (1749)



FREY: On atrial fibrillation in humans
and Its Elimination by Quinidine (1918)

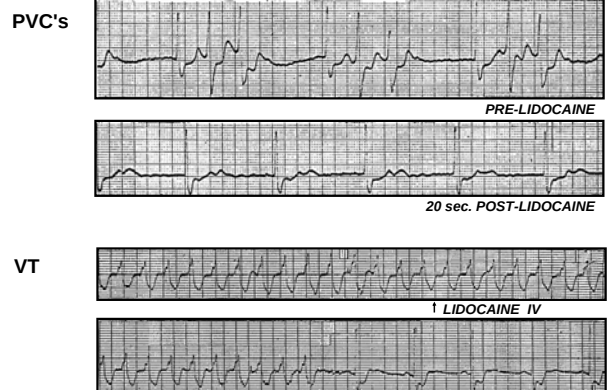


Ventricular fibrillation as an electrical accident



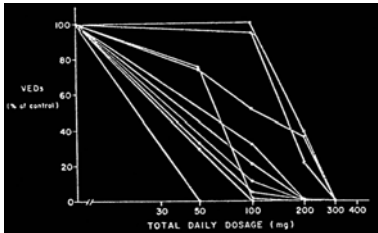
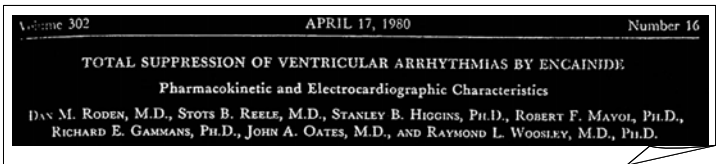
WIGGERS CJ, *Am Heart J* 20:399-412, 1940

Lidocaine to treat ventricular ectopy post-MI



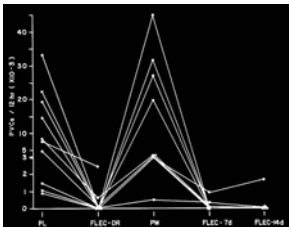
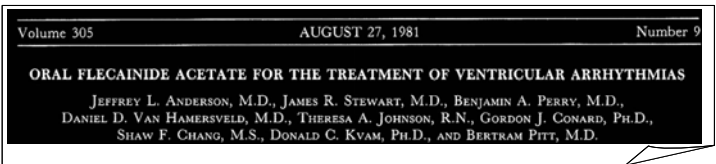
GIANELLY R et al, *NEJM* 277:1215-1219, 1967

Total suppression of ventricular arrhythmias by encainide



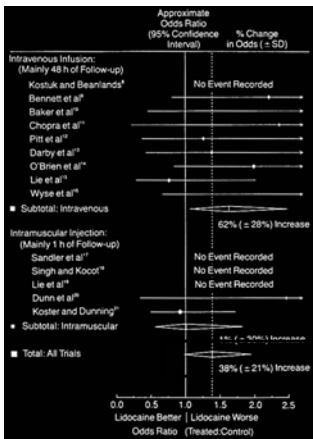
RODEN DM et al, NEJM 302 :877-882, 1980

Oral flecainide acetate for the treatment of ventricular arrhythmias



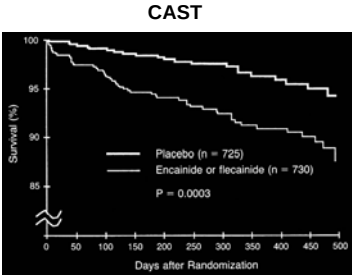
ANDERSON JL et al, NEJM 305 :473-477, 1981

Odds ratio for total mortality 1-48 hr post-MI



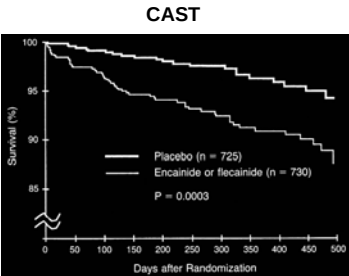
MACMAHON S et al, JAMA 260:1910-1916, 1988

Effects of class 1C antiarrhythmias on post-MI mortality



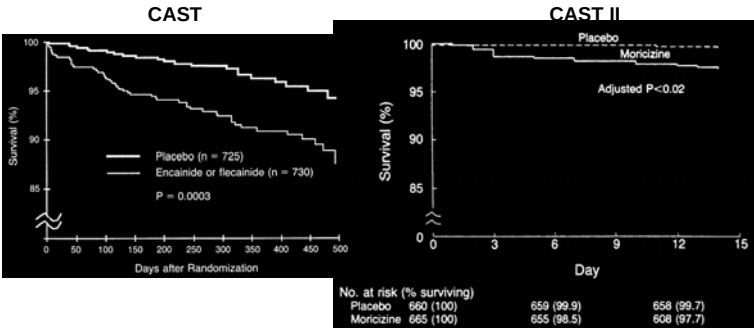
NEJM 321:406-412, 1989

Effects of class 1C antiarrhythmias on post-MI mortality



NEJM 321:406-412, 1989

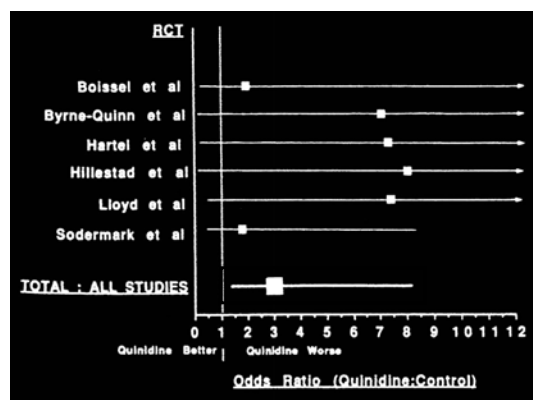
CAST II



NEJM 321:406-412, 1989

CAST II Investigators, NEJM 327 :227-233, 1992

Meta-analysis of quinidine effects on mortality in AF patients



COPLEN et al, *Circulation* 82:1106-1116, 1990

OK, Class I drugs are bad. Class III is the future.

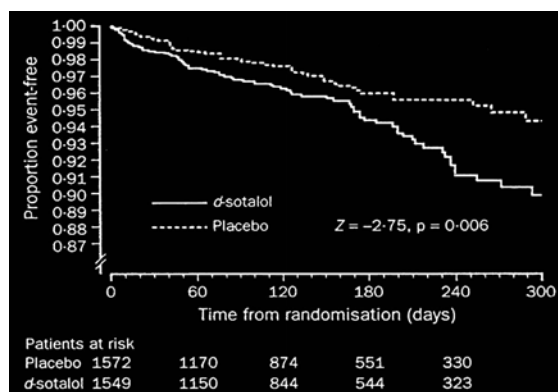
Am J Cardiol. 1996 Aug 29;78(4A):28-33.

From first class to third class: recent upheaval in antiarrhythmic therapy – lessons from clinical trials.

Lazzara R.

LAZZARA R, *AJC* 78(4A):28-33, 1996

Effects of a pure class III drug on post-MI mortality



WALDO AL et al, *Lancet* 348:7-12, 1996

Something doesn't fit!

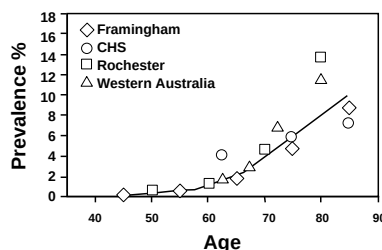
Something doesn't fit!



Look for the finding that doesn't fit. THAT is the clue to great discoveries!!

Focus on a specific arrhythmia

Age-Related Prevalence of AF

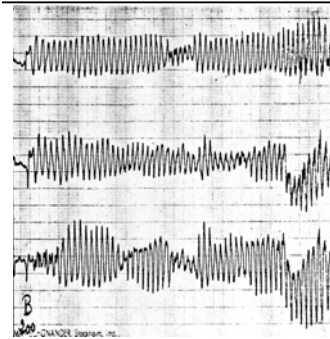


FEINBERG WM ET AL, *Arch Intern Med* 1995; 155:469-473

New antiarrhythmic drug development approaches for AF

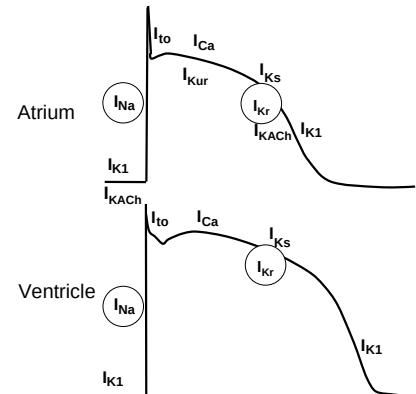
Novel ion channel targets

Problem of ventricular proarrhythmia

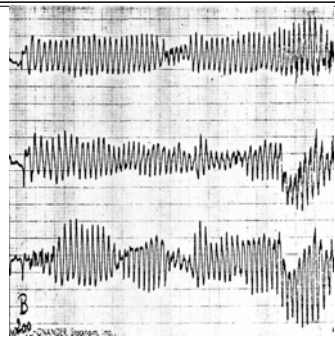


Agrandissement des 3 dérivations synchrones montrant en D III les torsades de pointes.

DESSERTENNE, Arch. des Mal. du Cœur 1966; 59:263-272

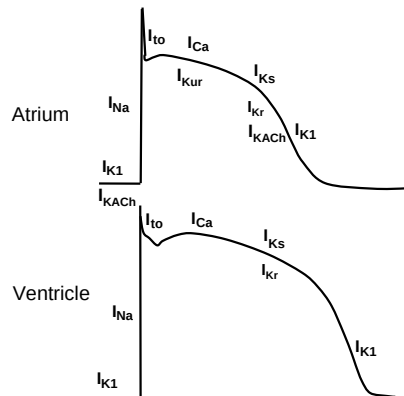


..... and strategy of atrial-selective therapies



Agrandissement des 3 dérivations synchrones montrant en D III les torsades de pointes.

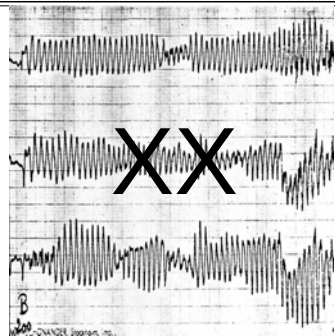
DESSERTENNE, Arch. des Mal. du Cœur 1966; 59:263-272



K⁺ channel blockers with atrial selectivity

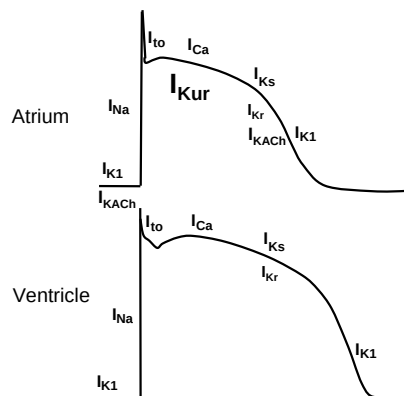
Atrial-selective therapies

I_{Kur}

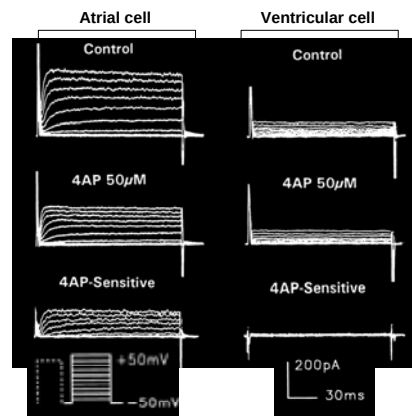


Agrandissement des 3 dérivations synchrones montrant en D III les torsades de pointes.

DESSERTENNE, Arch. des Mal. du Cœur 1966; 59:263-272

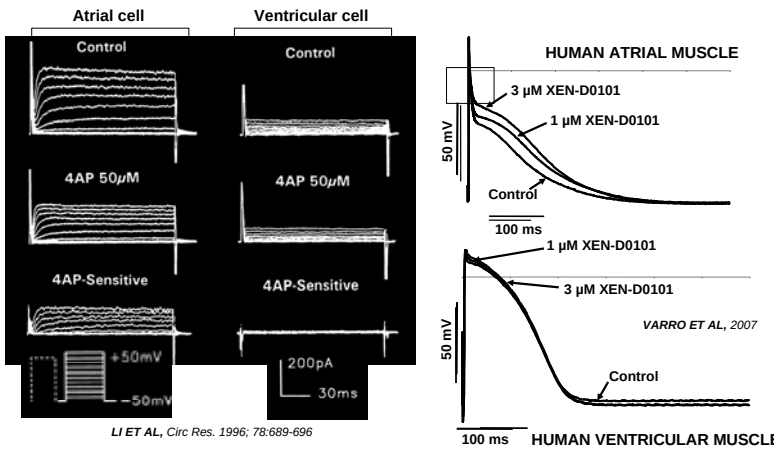


I_{Kur} (ultra-rapid delayed rectifier) is Atrial-specific in Man

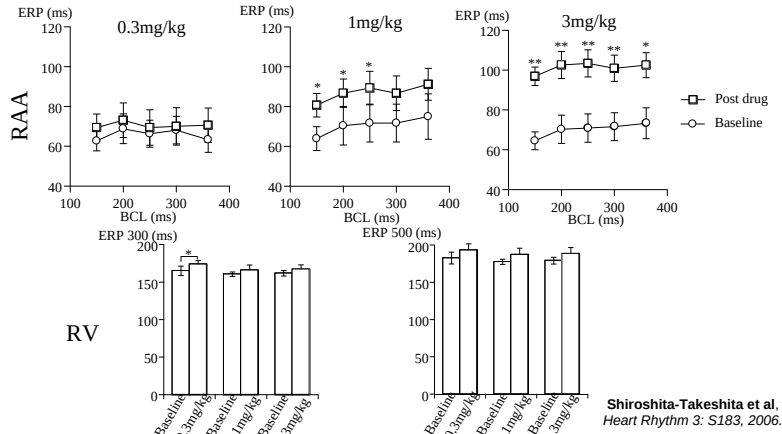


LI ET AL, Circ Res. 1996; 78:689-696

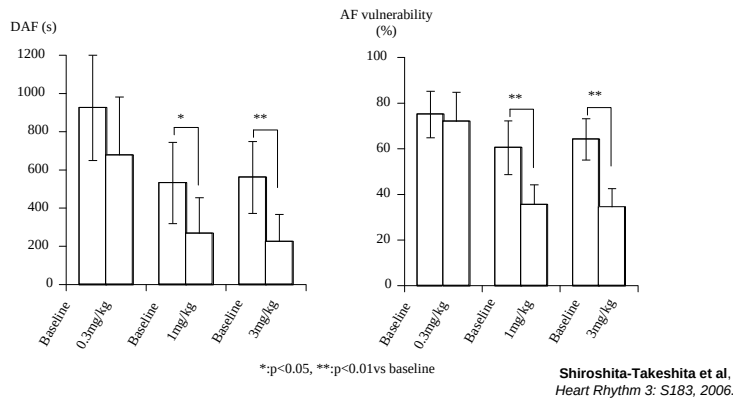
I_{Kur} (ultrarapid delayed rectifier) is Atrial-specific in Man



Efficacy of an I_{Kur} blocker (Xen-D0101) on atrial and ventricular ERPs in AT-remodeled dogs



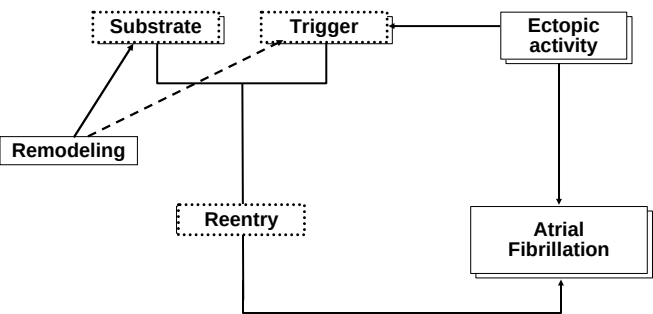
Efficacy of an I_{Kur} blocker (Xen-D0101) on AF in dogs with atrial tachycardia remodeling



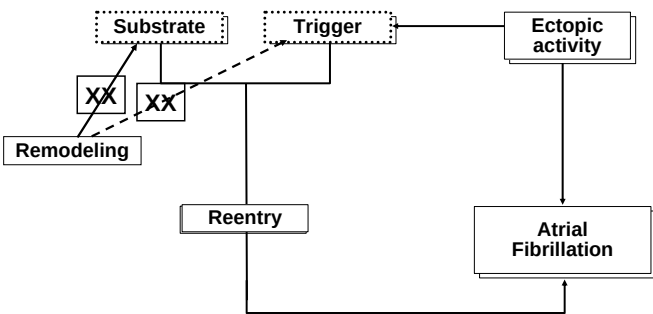
New antiarrhythmic drug development approaches for AF

Targeting the substrate

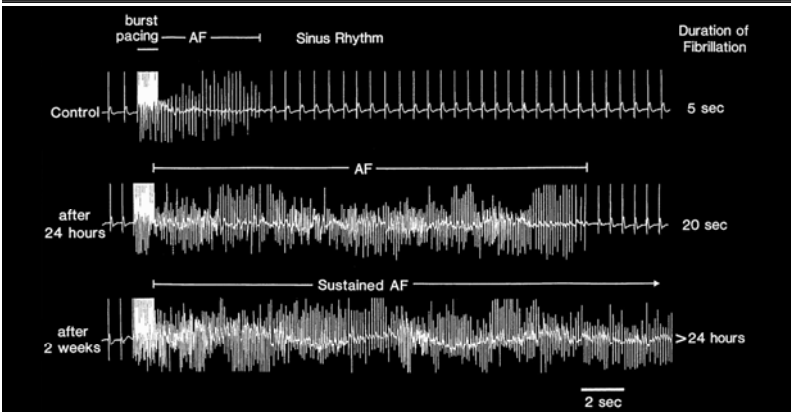
Determinants of Arrhythmia Mechanisms in AF: Role of Remodeling



Determinants of Arrhythmia Mechanisms in AF: Prevention of Remodeling

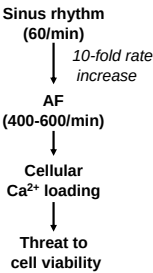


Effects of electrically maintained AF on spontaneous AF maintenance when stimulation stopped



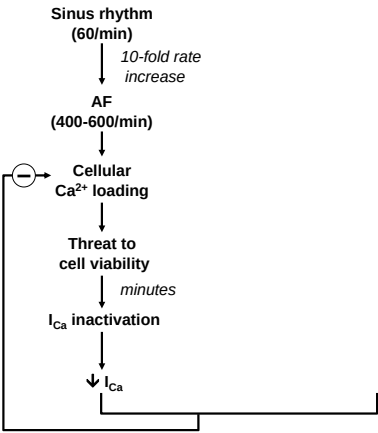
WIJFFELS MCEF, Kirchhof C.J.H.J, Dorland R, et al. Circulation 1995; 92:1954-1968

Atrial Myocyte Adaptation to Ca²⁺ Loading



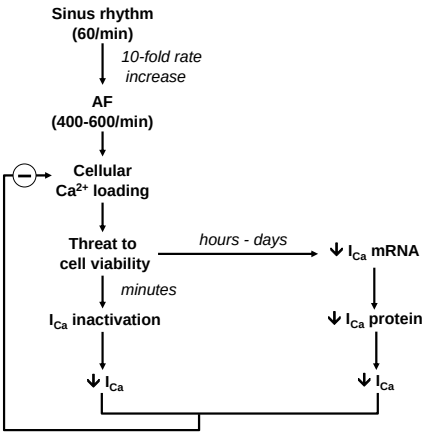
SN.2002

Atrial Myocyte Adaptation to Ca²⁺ Loading



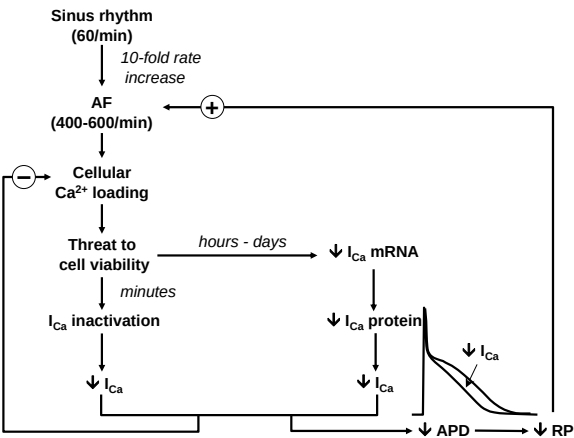
SN.2002

Atrial Myocyte Adaptation to Ca²⁺ Loading



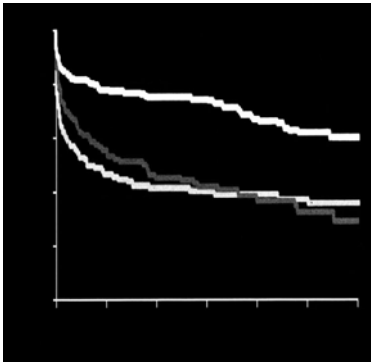
SN.2002

Atrial Myocyte Adaptation to Ca²⁺ Loading



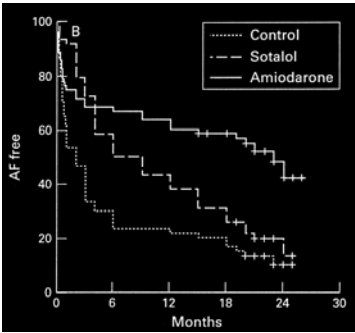
SN.2002

Superiority of Amiodarone in AF



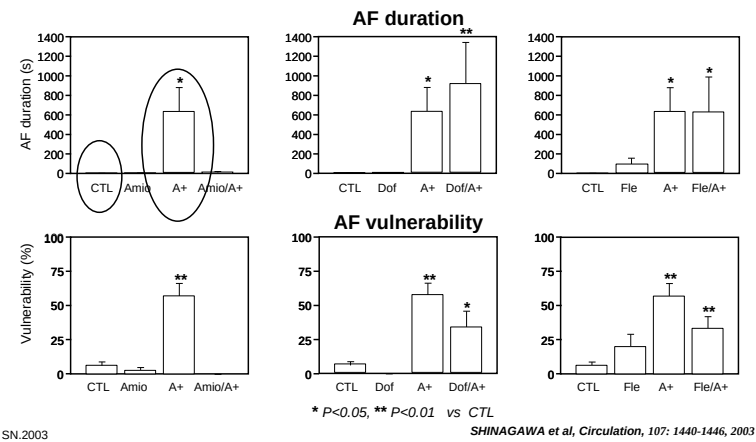
SN.2003

ROY et al, N Engl J Med 2000; 342: 913-920

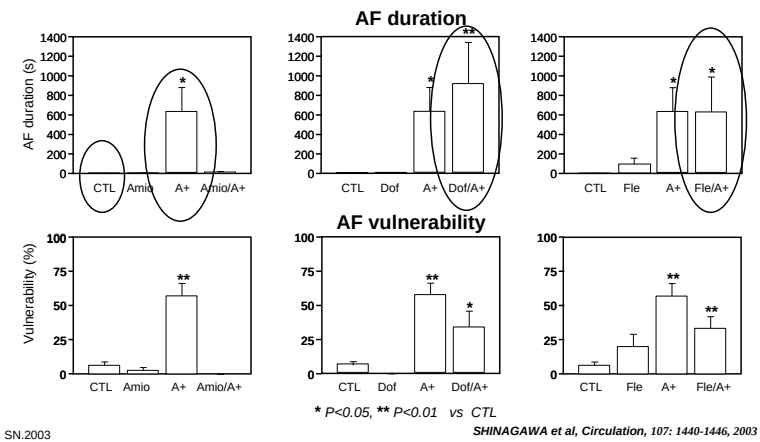


KOCHIADAKIS et al, Heart 2000; 84: 251-257

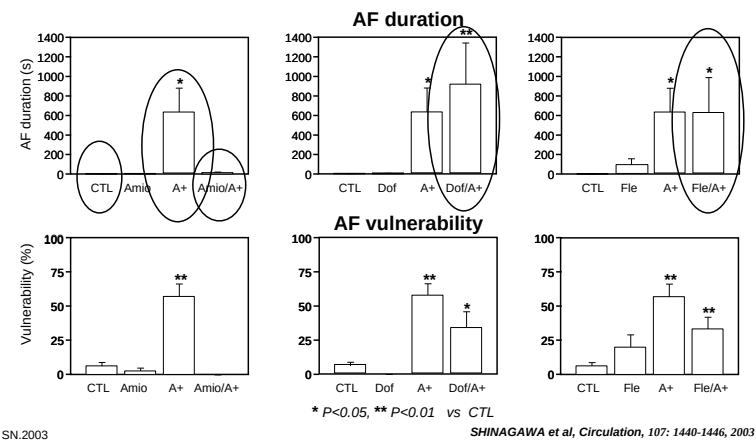
Effects of Antiarrhythmic Drugs on AF



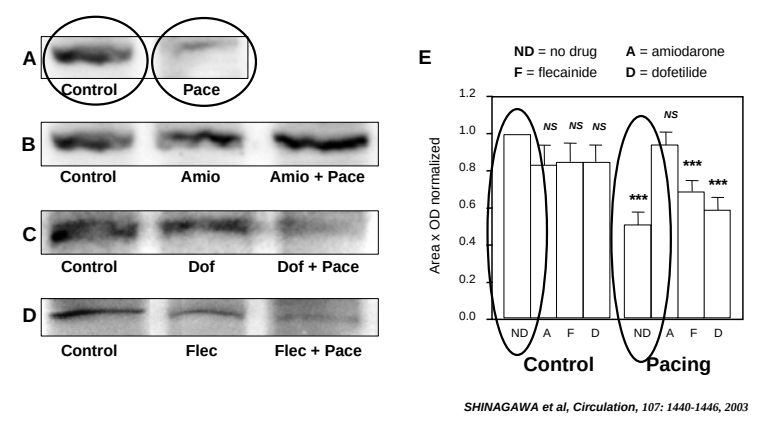
Effects of Antiarrhythmic Drugs on AF



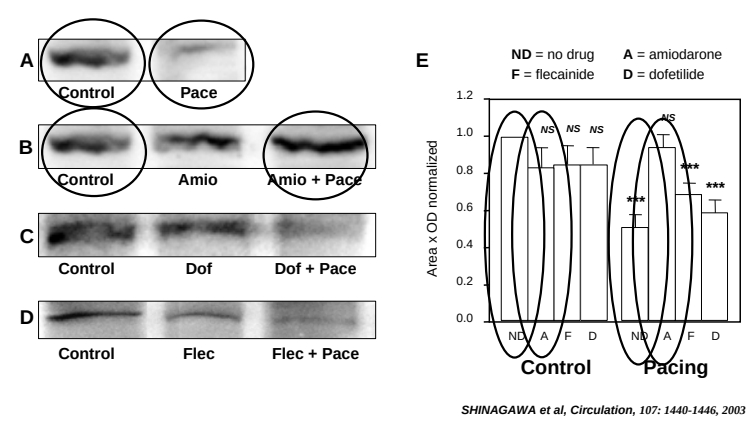
Effects of Antiarrhythmic Drugs on AF



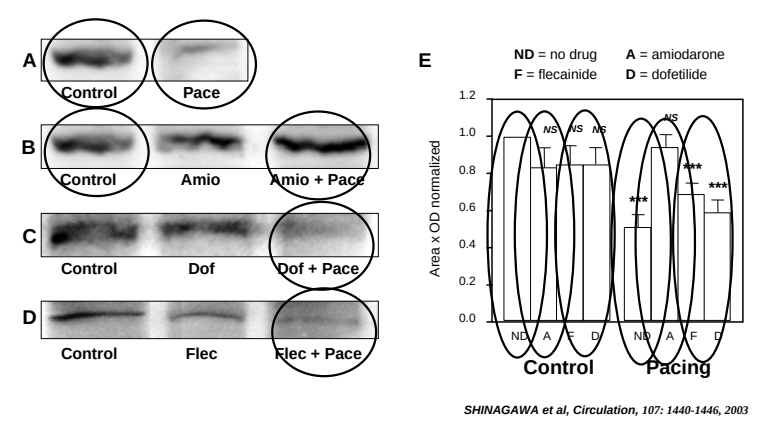
Effects of Remodeling on α_{1c} Subunit Expression



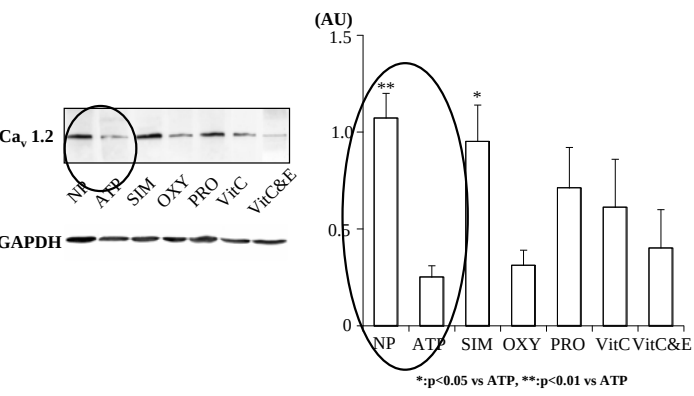
Effects of Remodeling on α_{1c} Subunit Expression



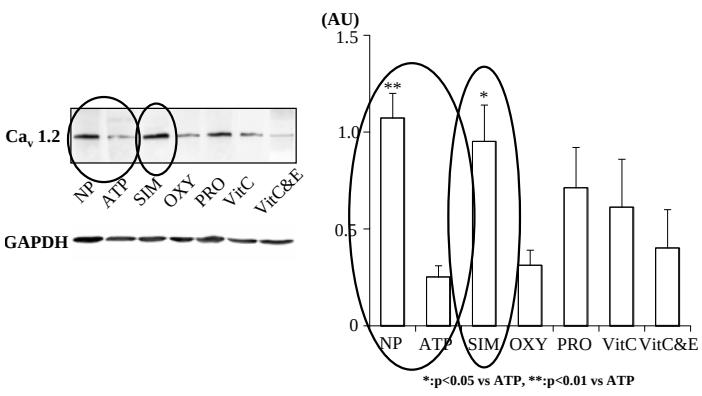
Effects of Remodeling on α_{1c} Subunit Expression



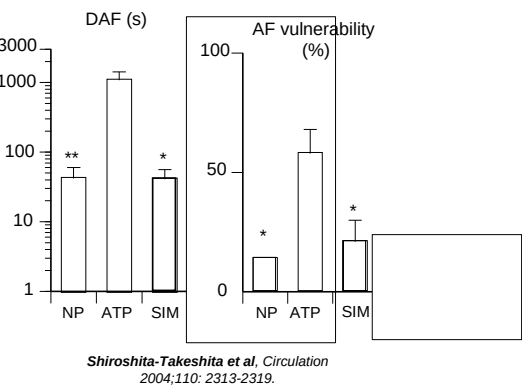
Effects of Various Agents on Ca_v1.2 Expression



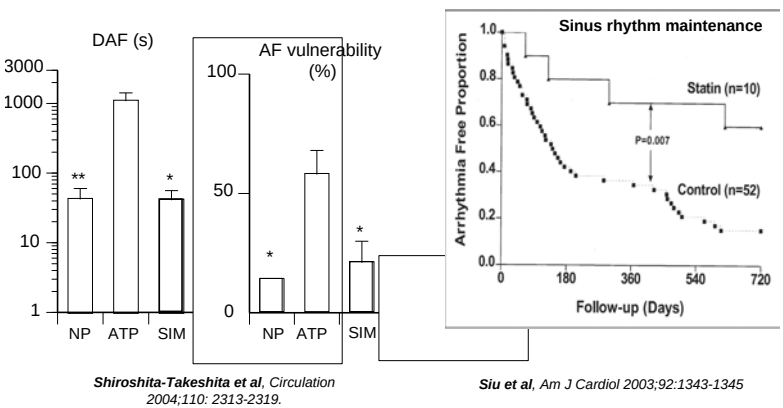
Effects of Various Agents on Ca_v1.2 Expression



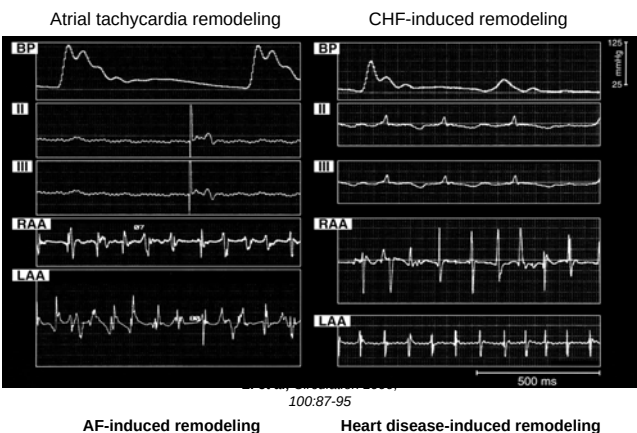
Can we identify new antiarrhythmic approaches that work by preventing atrial-tachycardia remodeling?



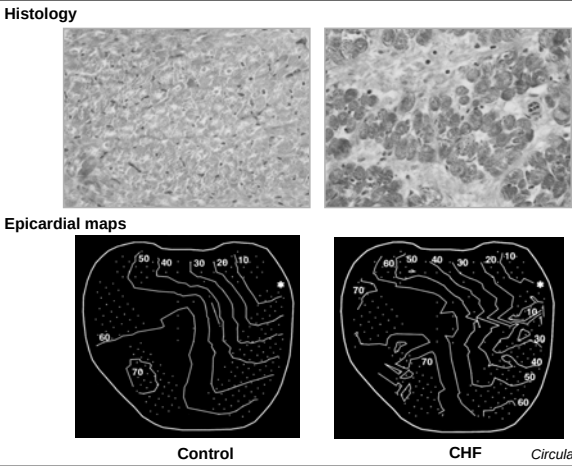
Can we identify new antiarrhythmic approaches that work by preventing atrial-tachycardia remodeling?



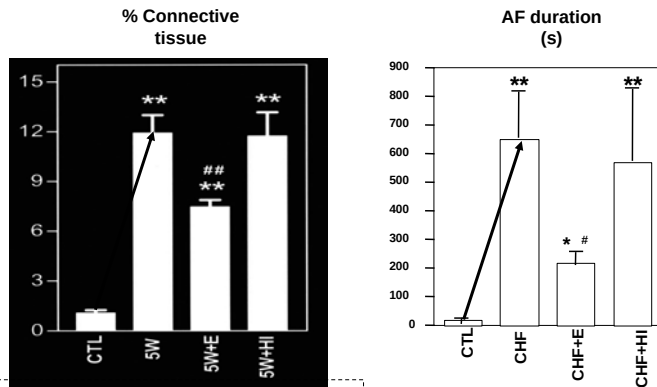
Remodeling Induces Two Clinically Relevant AF Substrates: Atrial-tachycardia Remodeling and Structural Remodeling



CHF produces a structural substrate for AF



Can Inhibiting Ang-II Formation Prevent Development of the Substrate for AF?

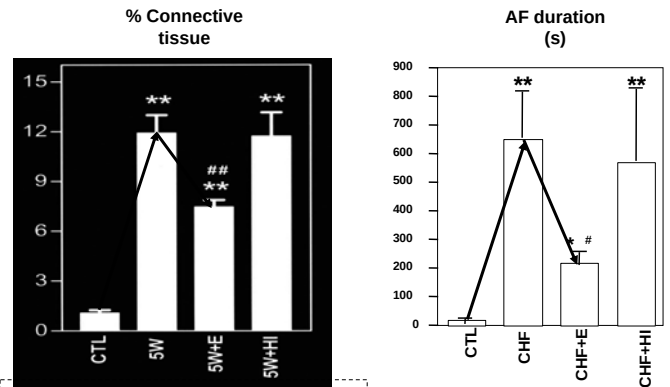


E = enalapril; HI=hydralazine/isosorbide

Li D et al, Circulation 104: 2608-2614, 2001

CHF induces fibrosis and increases AF duration

Can Inhibiting Ang-II Formation Prevent Development of the Substrate for AF?

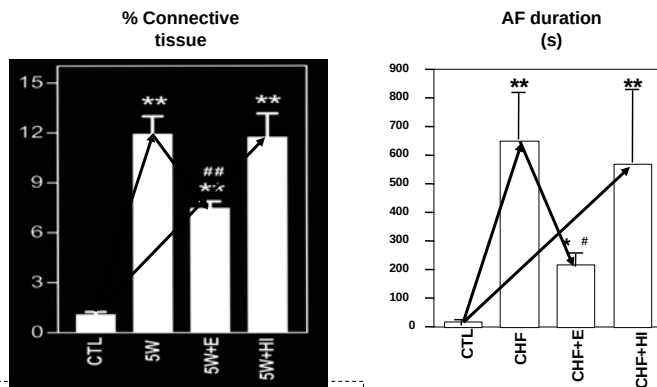


E = enalapril; HI=hydralazine/isosorbide

Li D et al, Circulation 104: 2608-2614, 2001

Enalapril attenuates fibrosis and AF duration increases

Can Inhibiting Ang-II Formation Prevent Development of the Substrate for AF?



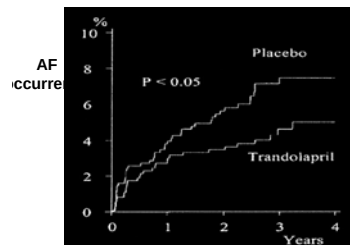
E = enalapril; HI=hydralazine/isosorbide

Li D et al, Circulation 104: 2608-2614, 2001

Vasodilator therapy does not mimic enalapril effects

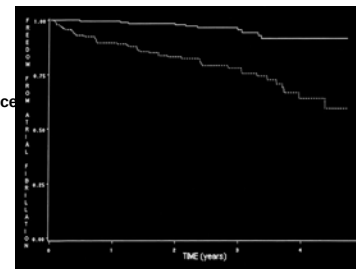
ACE antagonism and clinical AF in LV dysfunction

AF in post-MI patients with LVD



Pedersen et al, Circulation 1999; 100: 376-380

AF in SOLVD patients

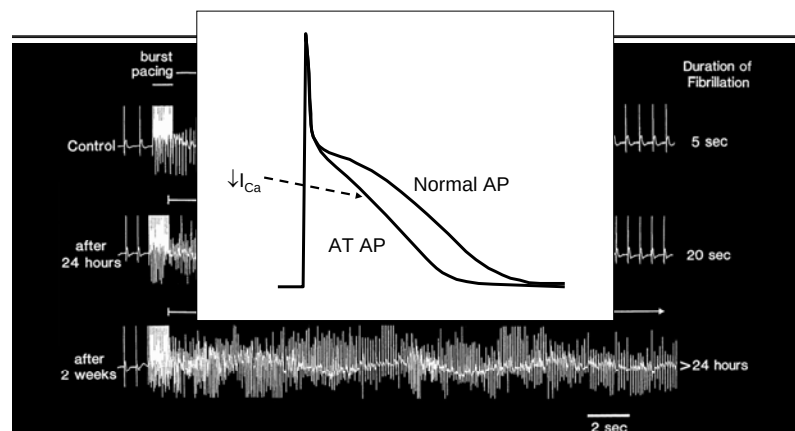


Vermes et al, Circulation 2003; 107: 2926-2931

New antiarrhythmic drug development approaches for AF

Substrate-selective ion channels

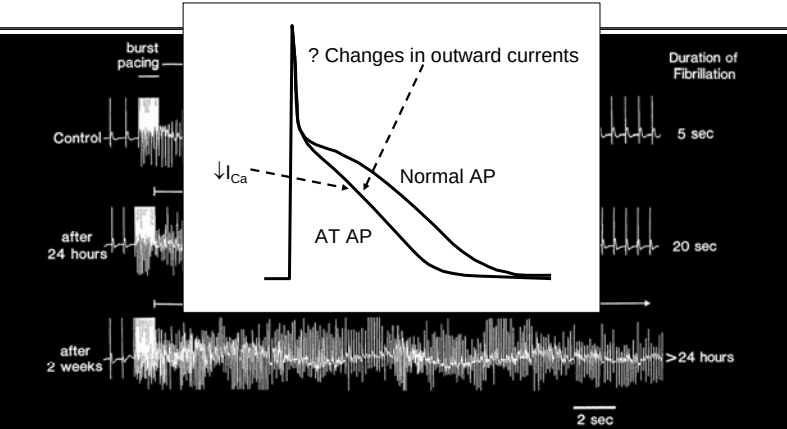
Atrial tachycardia remodeling: AF Begets AF



SN,2001

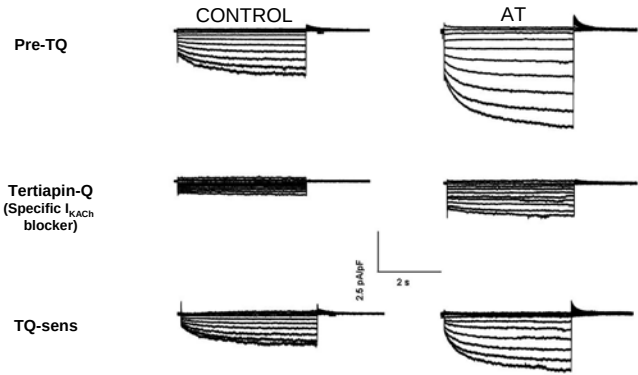
Wijffels MCEF, Kirchhof CJHJ, Dorland R, et al. Circulation 1995; 92:1954-1968

Atrial tachycardia remodeling: AF Begets AF



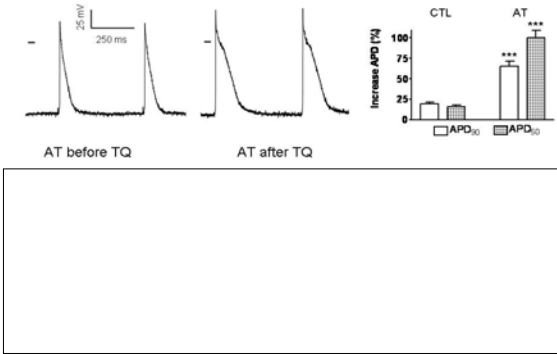
SN.2001 Wijffels MCEF, Kirchhof CJHJ, Dorland R, et al. Circulation 1995; 92:1954-1968

Constitutive I_{KACH} that is enhanced by atrial tachycardia



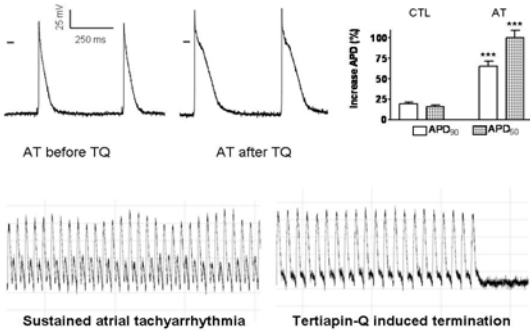
Cha TJ et al, Circulation. 2006;113:1730-7.

Effects of I_{KACH} block on APD and tachyarrhythmia



Cha TJ et al, Circulation. 2006;113:1730-7.

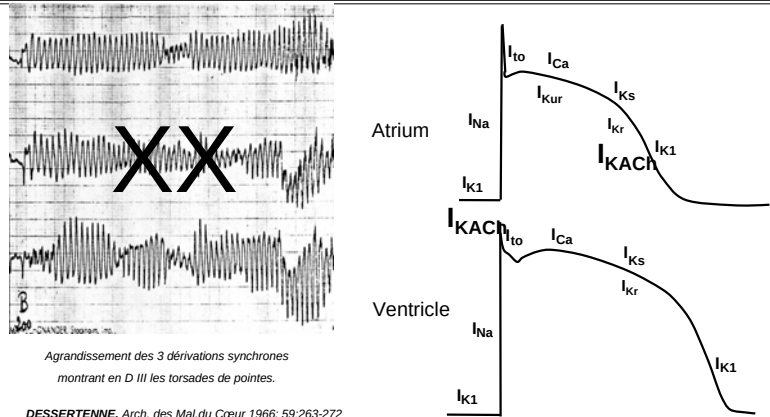
Effects of I_{KACH} block on APD and tachyarrhythmia



Cha TJ et al, Circulation. 2006;113:1730-7.

Atrial-selective therapies

I_{KACH}



DESSERTENNE, Arch. des Mal. du Cœur 1966; 59:263-272

Effects of an I_{KACH} -selective blocker (NIP 151) on AF in two canine models

compound	dose (μ g/kg/min)	AF termination		plasma conc. (ng/ml)	prevention of AF reinduction
		NO. terminated	Time sec		
vehicle		1/12	-	-	0/1
NIP-151	2	2/3	830	13	-
	5	4/5	525 $\pm$ 25	22 $\pm$ 6	1/4
dofetilide	3	1/3	558	n.d	0/1
	10	0/3	-	-	-

Aconitine-induced AF

compound	dose (mg/kg)	AF termination	
		NO. terminated	Time sec
vehicle		0/3	-
NIP-151	0.01	0/3	-
	0.03	2/3	67
	0.1	3/3	61
	0.3	3/3	55

Hashimoto N et al. Circulation. 2005;112:II-191.

Effects of an I_{KACH}-selective blocker (NIP 151) on AF in two canine models

	compound	dose (µg/kg/min)	NO. terminated	AF termination Time sec	plasma conc. (ng/ml)	prevention of AF reinduction
Vagal AF	vehicle		1/12	-	-	0/1
	NIP-151	2	2/3	830	13	-
	NIP-151	5	4/5	535±35	22±6	1/4

Collateral effects on extra-atrial (SAN) and extracardiac (GI and GU systems) need to be avoided

	compound	dose (mg/kg)	NO. terminated	Time sec	
Aconitine-induced AF	vehicle		0/3	-	
		0.01	0/3	-	
		0.03	2/3	67	
	NIP-151	0.1	3/3	61	
		0.3	3/3	55	

Hashimoto N et al.
Circulation. 2005;112:11-191.

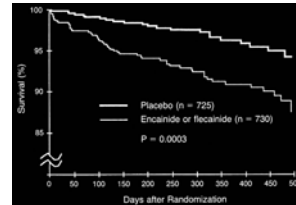
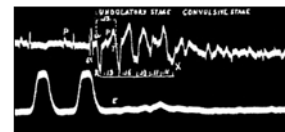
We have come a long way...



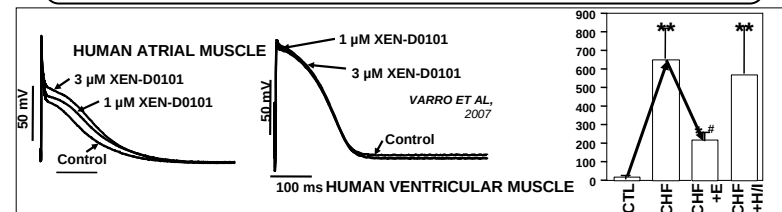
We have come a long way...



...There is still a considerable way to go...



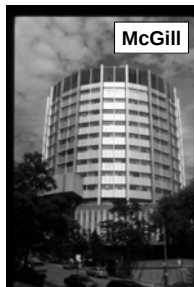
...But we do hope to get there!



MGH



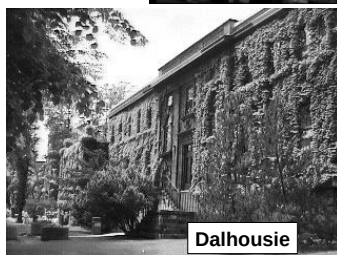
McGill



St. Paul's



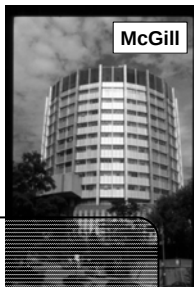
Dalhousie



MGH



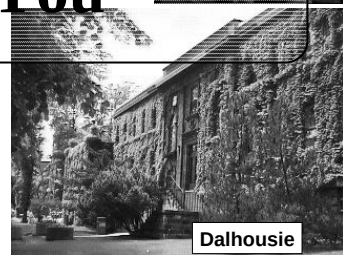
McGill



St. Paul's



Dalhousie



Thank You