

Cardiac electropharmacology

David Newman MD



International Winter arrhythmia School
Collingwood ON
February 11, 2017

disclosures

Honoraria from Boehringer, Bayer, AstraZeneca

BOD cardiocom

Will talk about off label use of all devices

(where labels exist)

From the IWAS steering committee meeting.....

Eugene: time we had a electropharmacology talk

David : OK, for afib, idio VT or in device management?

Eugene: more of a larger overview, what does David Newman do?

David: you mean like a grand overview

Eugene: Exactly

Daivd: you mean ALL of electropharmacology?

Eugene : yup

David: in 15 min!!!

Eugene: 5 min for questions always appreciated

David: oy...

I will never complain about my job again.



Key points:

Drug therapy is never strictly rational (like people)

Goals of therapy always have to be clear

Upstream effects are myriad and count a lot

Principles of use count:

- nocebo responses are powerful

- bb

- 1C is your friend in a normal heart

- applied amiodaroneology can work with caution

- low dose of two agent may be better

Toxicity and its prediction

Applied alchemy

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The Sicilian Gambit

DRUG	CHANNELS						RECEPTORS				PUMPS
	Na			Ca	K	I _f	α	β	M ₂	P	Na/K ATPase
	Fast	Med	Slow								
Lidocaine	●										
Mexiletine	●										
Tocainide	●										
Moricizine	I										
Procainamide		A			●						
Disopyramide		A			●				●		
Quinidine		A			●		●		●		
Propafenone		A						●			
Flecainide			A		●						
Encainide			A								
Bepiridil	●			●	●						
Verapamil	●			●			●				
Diltiazem				●							
Bretium					●		●	●			
Sotalol					●			●			
Amlodarone	●			●	●		●	●			
Alinidine					●	●					
Nadolol								●			
Propranolol	●							●			
Atropine									●		
Adenosine										○	
Digoxin									○		●

Relative blocking potency: ○ Low, ● Moderate, ● High
 ○ = Agonist, ● = Agonist/Antag.
 A = Activated state blocker, I = Inactivated state blocker

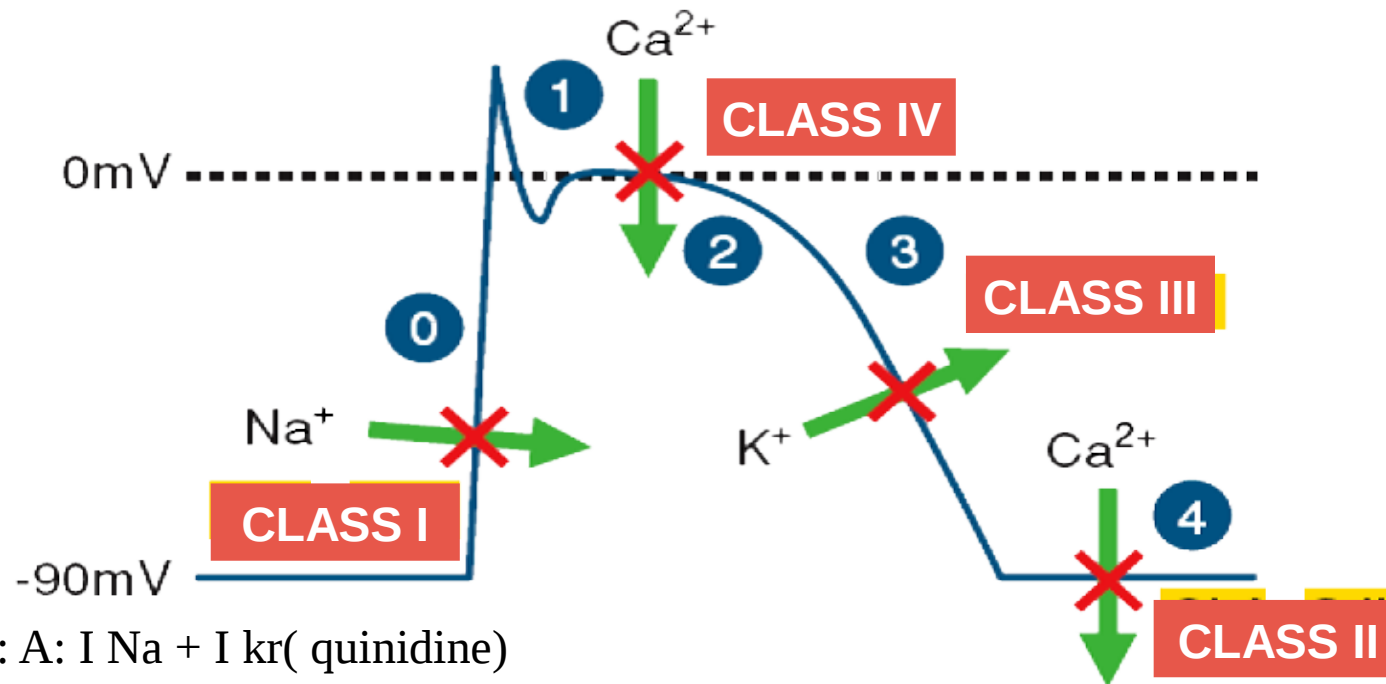
The New York Times

Warning Issued on 2 Heart Drugs After Deaths of Patients in a Test

Researcher Links Heart Drugs to 2,250 Deaths

Vaughan Williams Classification

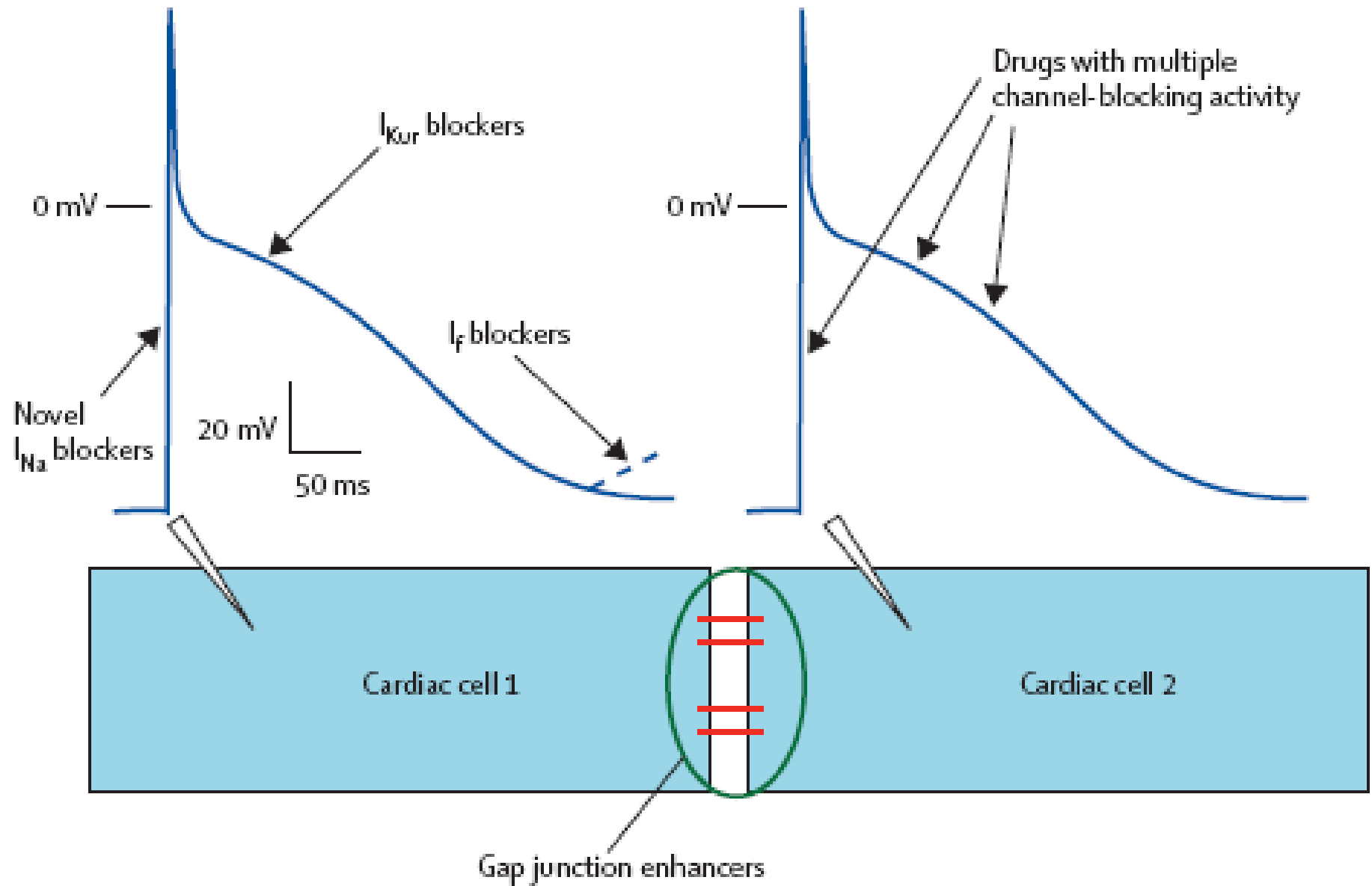
- ▶ AADs have distinct characteristics depending on which ion channels they block.



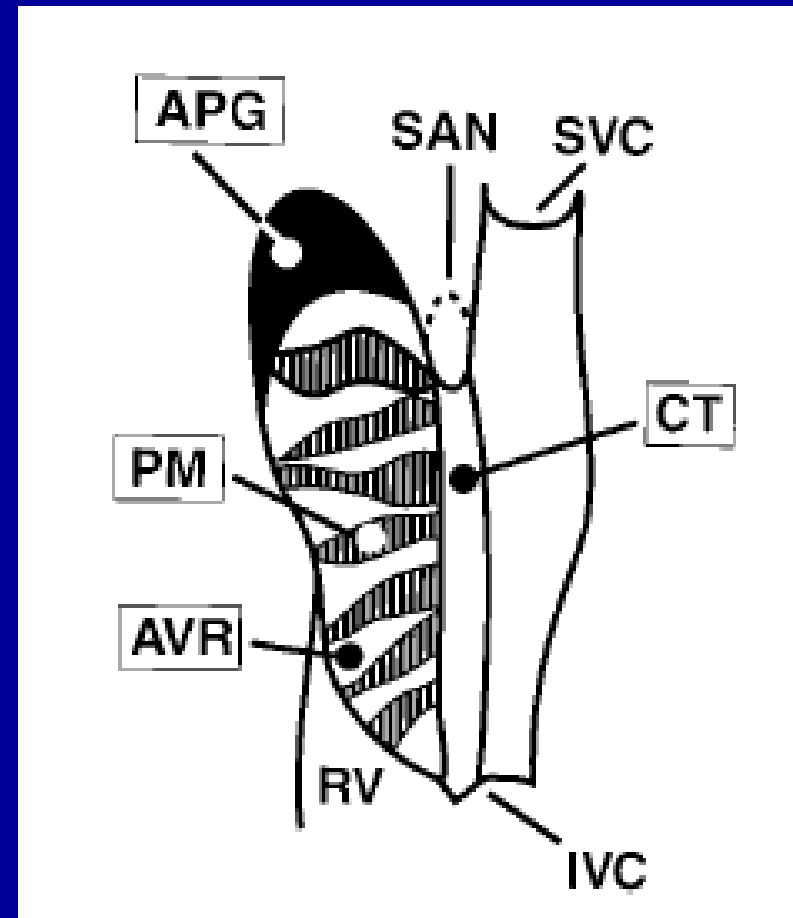
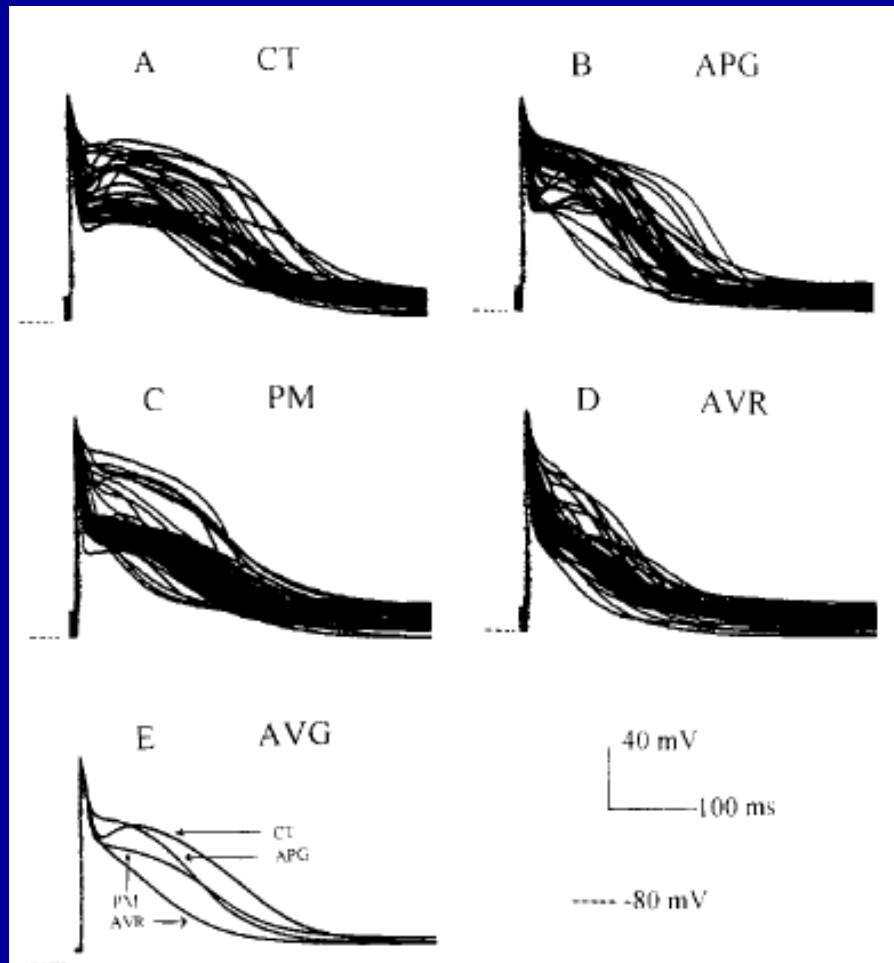
Harrison: A: I Na + I kr(quinidine)

B: fast kinetics, voltage dependent (lido)

C: slow kinetics , potent (flec, propaf)



Ionic Mechanisms of Regional Action Potential Heterogeneity in the Canine Right Atrium



Effects of Experimental Heart Failure on Atrial Cellular and Ionic Electrophysiology

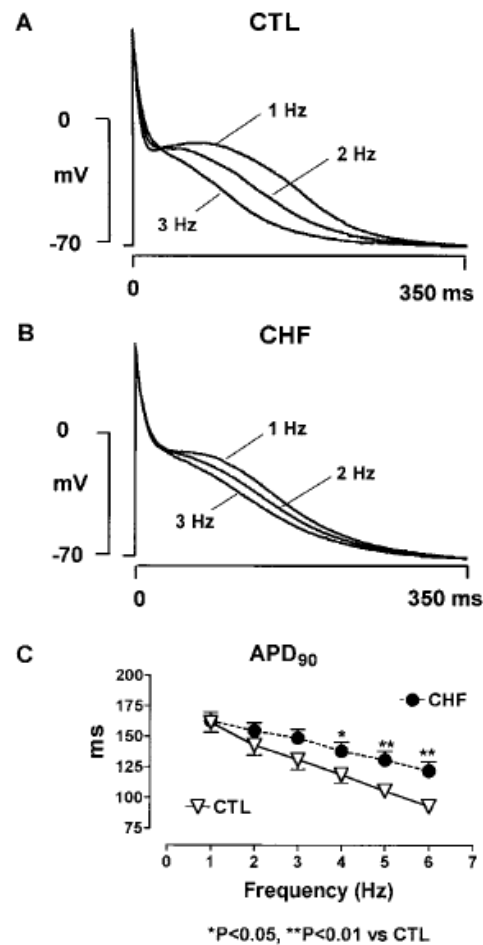


Figure 1. AP recordings from control (CTL, A) and CHF (B) atrial myocytes. C, APD at 90% repolarization (APD₉₀) in vitro (n=20 per group).

Circulation. 2000;101:2631-2638

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Electrophysiology at a crossroads: A revisit

...acceptance of the philosophy that no patients should remain on an antiarrhythmic agent and that all arrhythmias should be “cured” by ablation.

.....physician's role is to make patients feel better , not worsePVI and an antiarrhythmic agent that prevents clinical AF should be considered a therapeutic success, not a failure...

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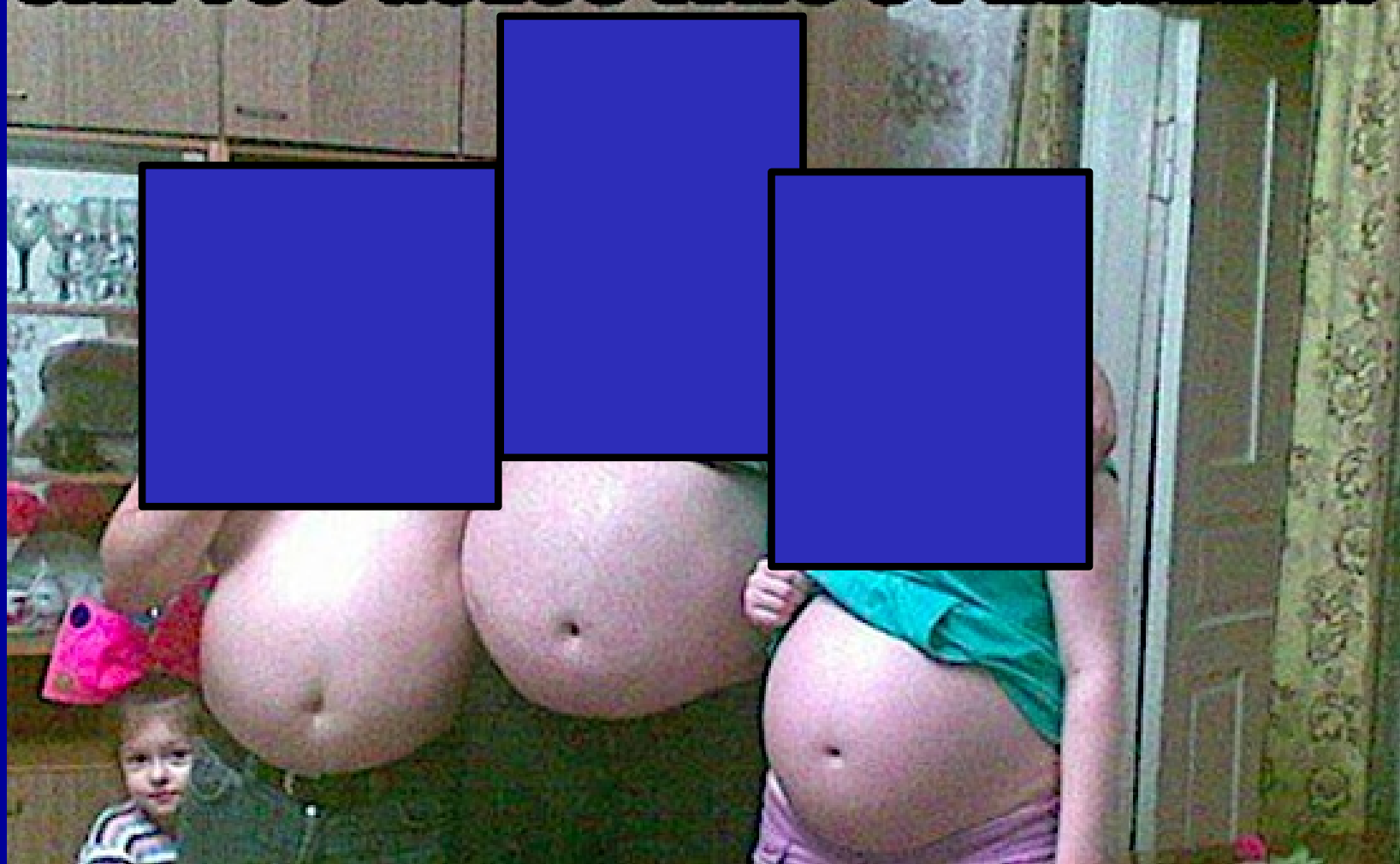
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Applied alchemy

CAN YOU GUESS WHO'S PREGNANT?

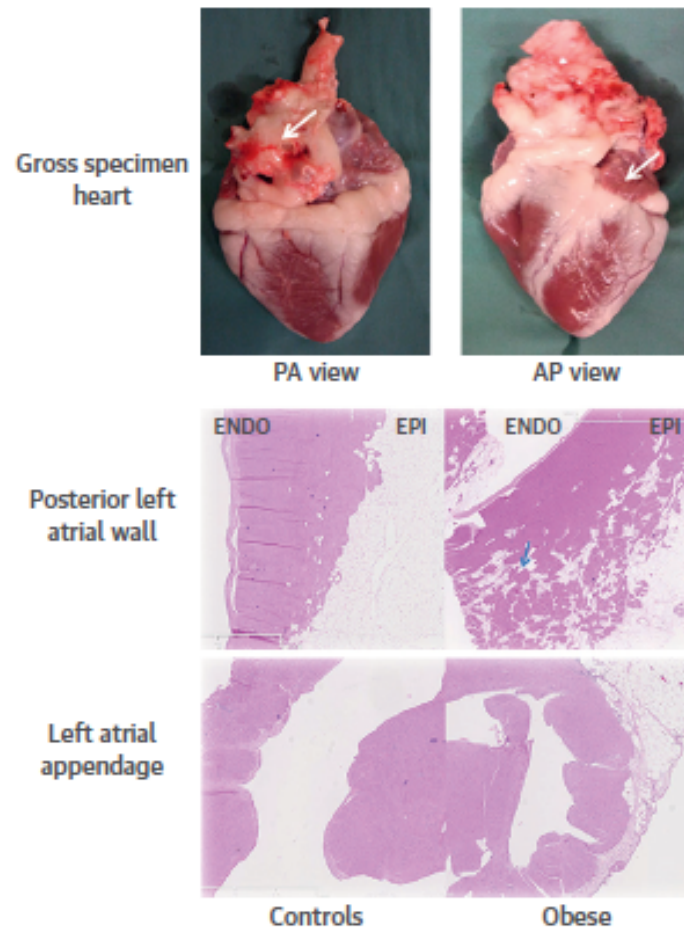


CAN YOU GUESS WHO'S PREGNANT?



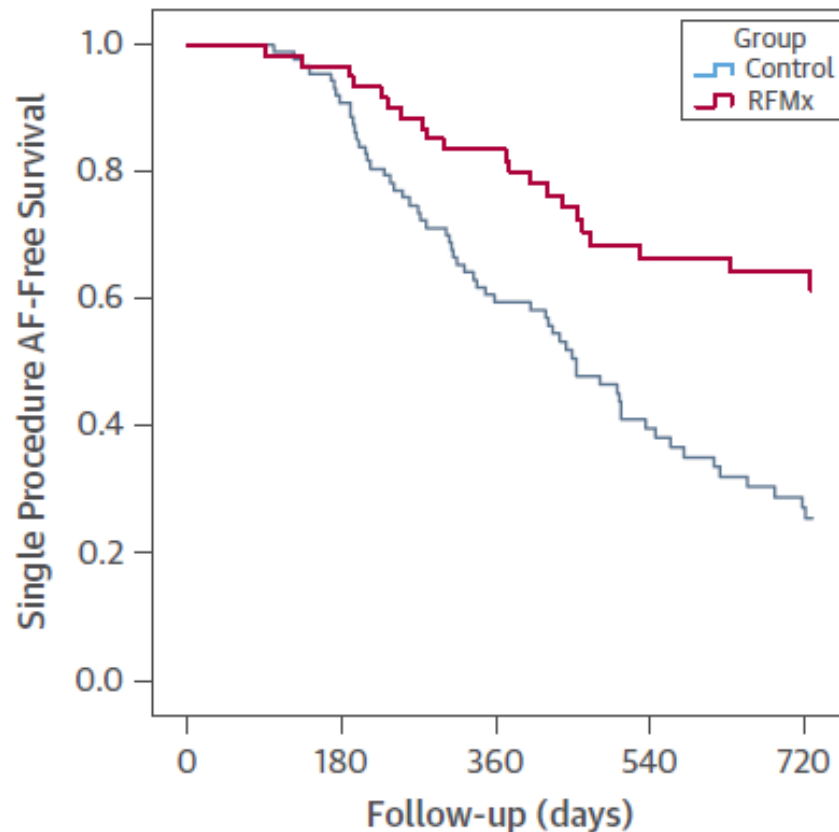
Electrophysiological, Electroanatomical, and Structural Remodeling of the Atria as Consequences of Sustained Obesity

FIGURE 4 Epicardial Fat: Novel Substrate for AF in Chronic Obesity



Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation

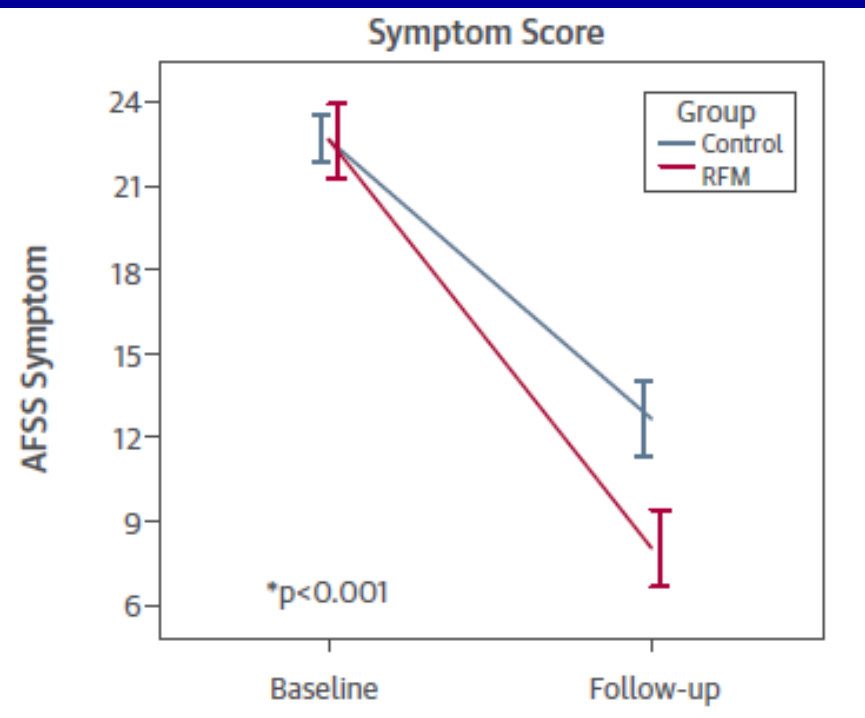
The ARREST-AF Cohort Study



Time (days)	0	180	360	540	730
RFM	61	59	48	33	27
Control	88	79	51	28	16

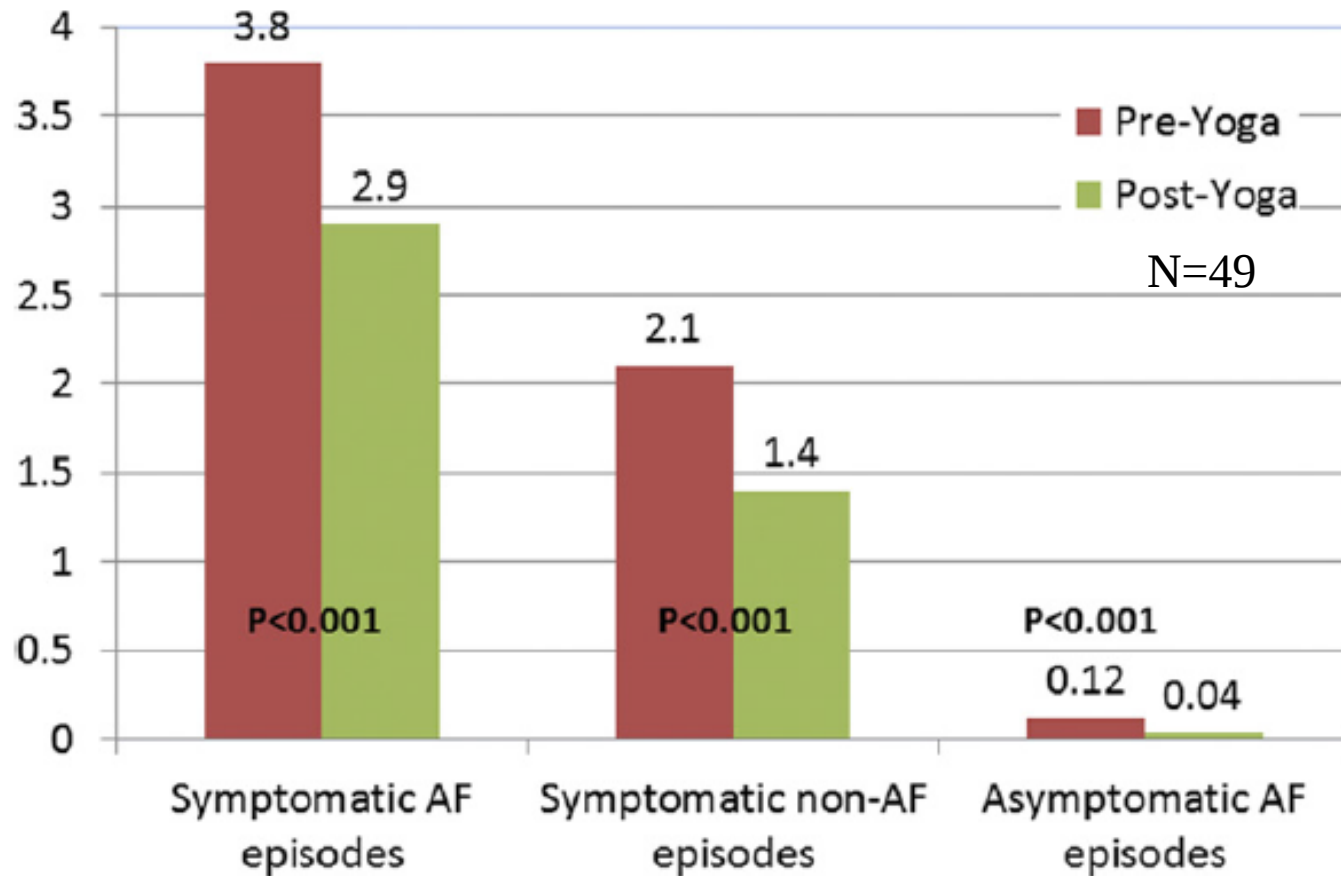
Targeted risk factor modification(RFM):

BP
Sleep
Weight
Glycemic
smoke
etOH



Effect of Yoga on Arrhythmia Burden, Anxiety, Depression, and Quality of Life in Paroxysmal Atrial Fibrillation

The YOGA My Heart Study



HOLTER REPORT

Patient : PTE.

ST. MICHAEL'S HOSPITAL
30 BOND STREET
TORONTO, ONTARIO M5B 1W8
(416) 864-5075

ID :
Age : 48(03-09-44)
Sex : F

Date : 27-AUG-93
Hook-up date : 18-AUG-93
time : 16:03:00
Duration : 16:34:59

Referred by : DR. D. NEWMAN
from : PTE.

Indications : PAF
Medications : UNKNOWN

SUMMARY

61089	QRS complexes		
8	Ventricular	ectopics which represent	<1 % of total QRS complexes
8	Supraventricular	ectopics which represent	<1 % of total QRS complexes
	Paced QRS complexes	which represent	% of total QRS complexes

NOTE: TO Jan

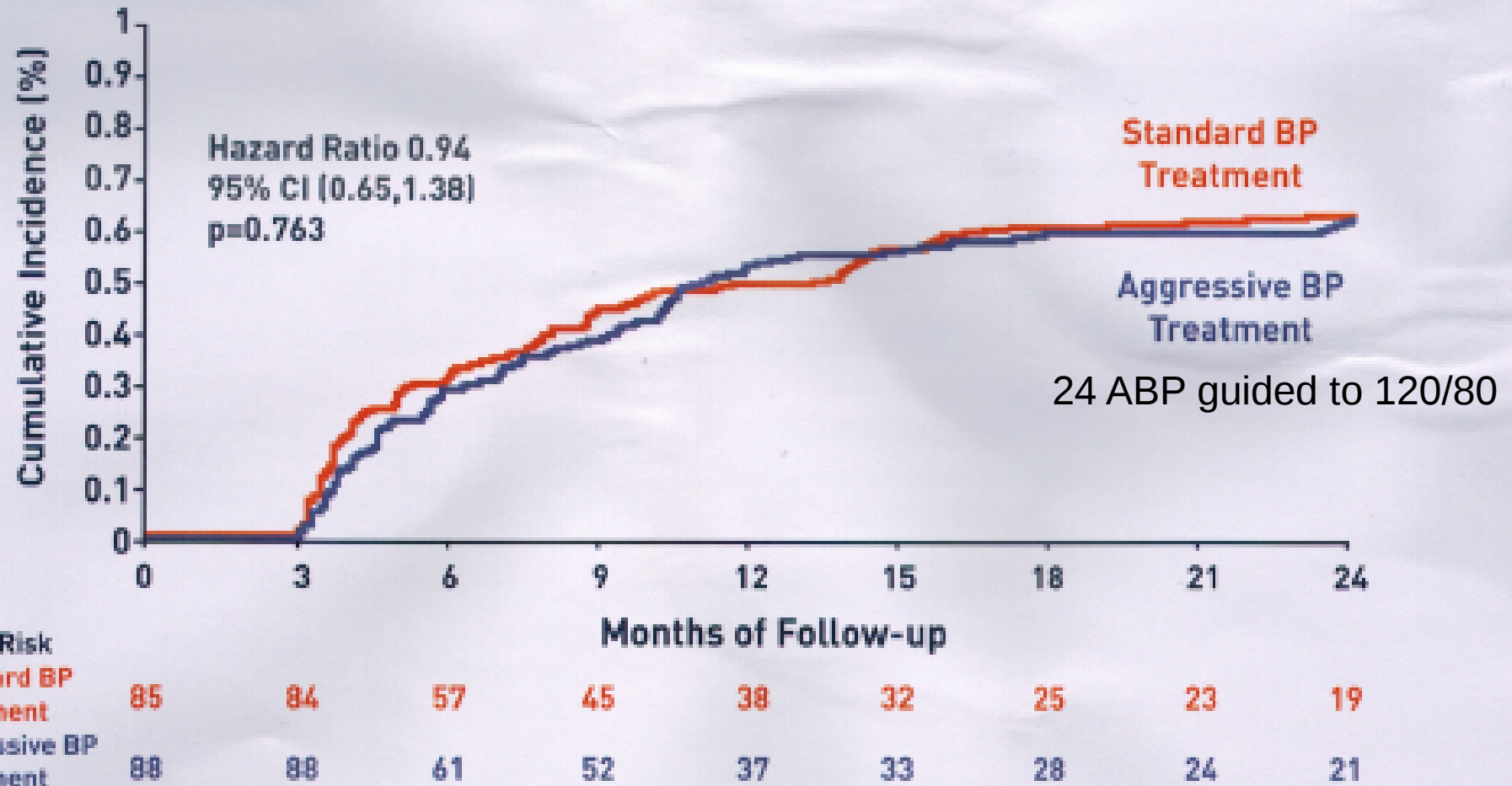
- OF COURSE -- NO fibrillation

Despite heavy duty work out
followed by 2 glasses of wine

- Holters are a sure sure

David

Atrial subsrate modification with aggressive blood pressure control to prevent atrial fibrillation (SMAC-AF)



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Applied alchemy

Placebo and Nocebo in Cardiovascular Health

Implications for Healthcare, Research, and the Doctor-Patient Relationship

Healthy normal's get ADR 15-30% to blinded sham

If repeat dose rises 28%

If asked rises to 70%

β -Blocker Therapy and Symptoms of Depression, Fatigue, and Sexual Dysfunction

15 trials, N = 35,000

Ns for depression 6/1000

Fatigue 18/1000 ie : 1 report/57 treated for a year

Sexual dysfunction 5/1000 ie : 1 report /199 treated for a year

Ko, JAMA 2002;288:351

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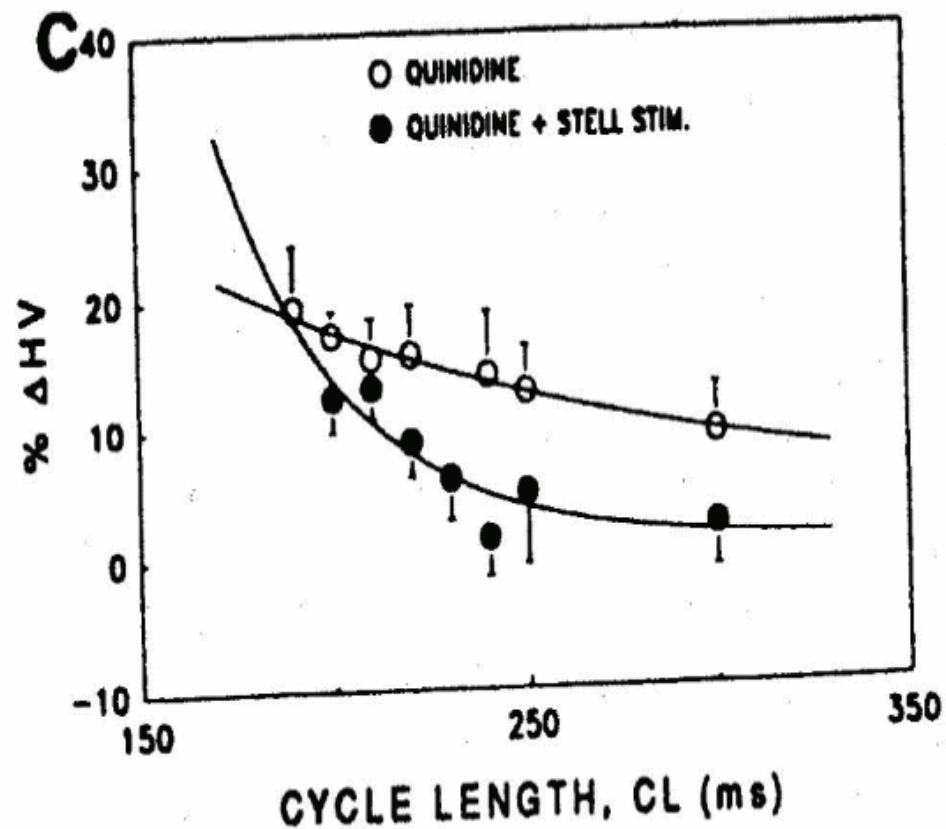
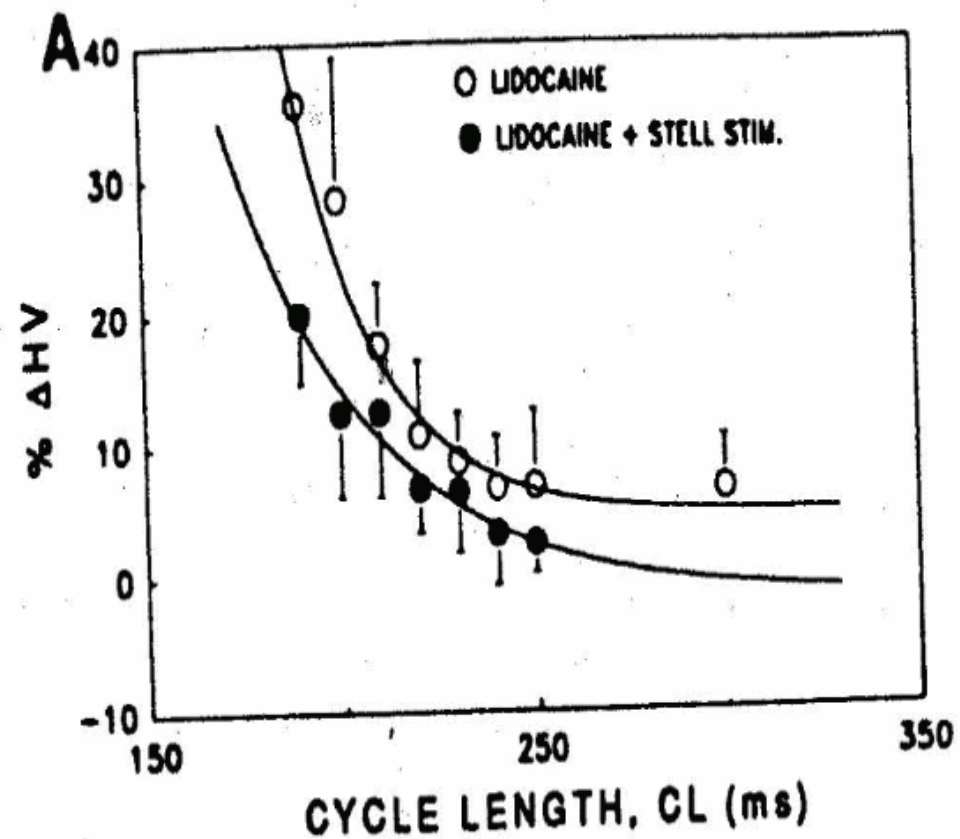
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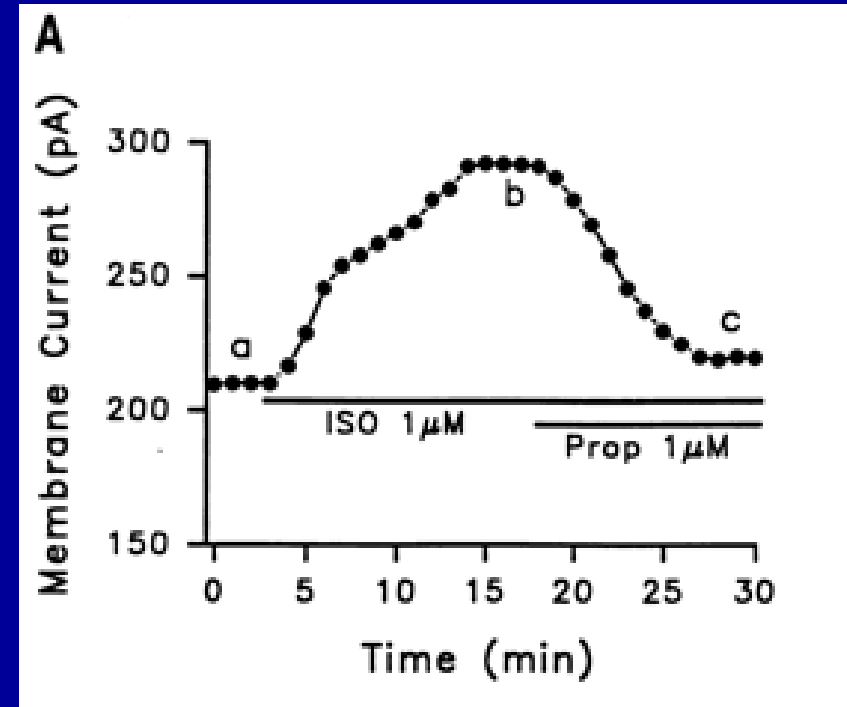
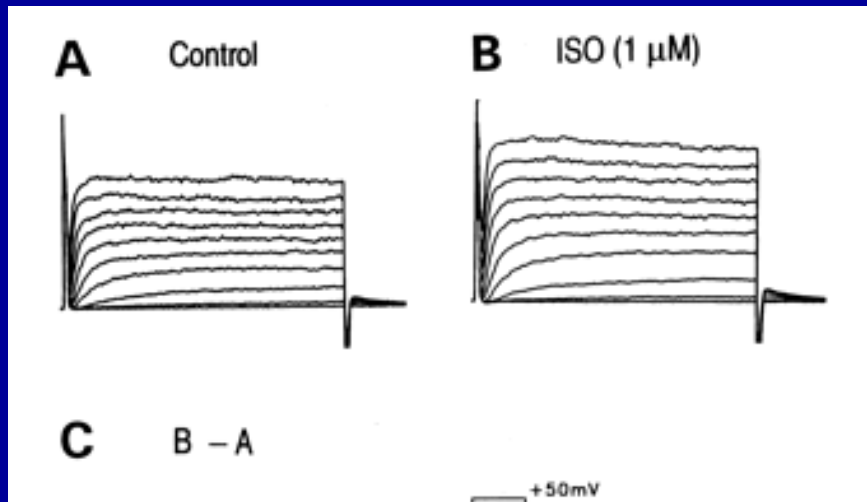
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Applied alchemy



Effect of isoproterenol (ISO) on I_{Kur} in a representative human atrial myocyte



Li, Nattel. Circulation Research. 1996;78:903

Beta-blocker variables

Half-life nadanol, bisoprolol, atenolol, metoprolol LA, nebivolol

Cardio selective bisoprolol, atenolol, metoprolol, nebivolol

Antiarrhythmic sotalol

Liver metabolism metoprolol, nebivolol

Heart failure carvedilol, nebivolol

BP effect Labetolol, nebivolol

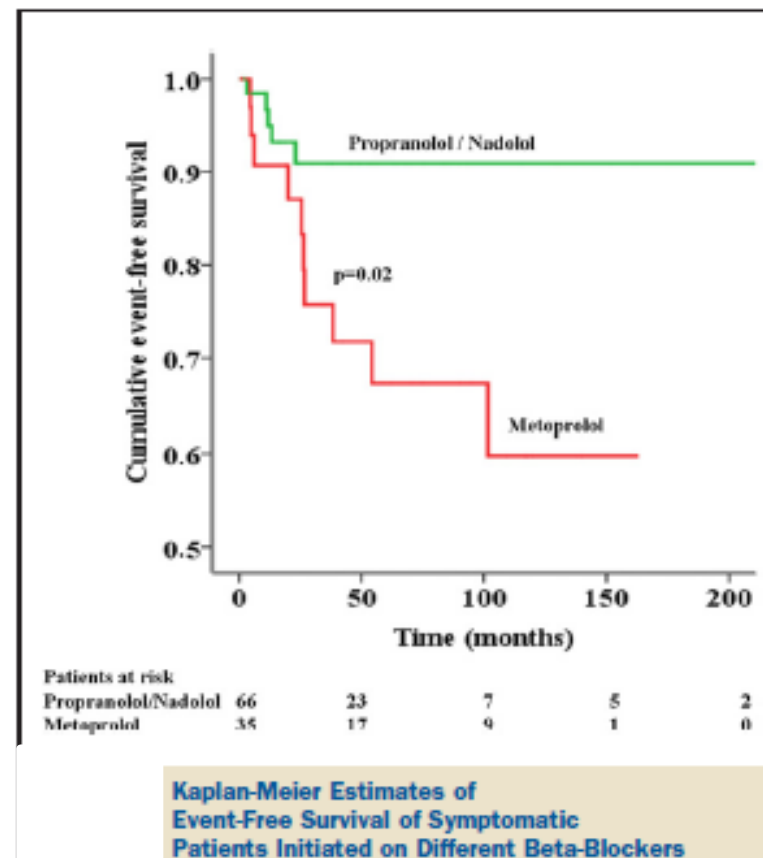
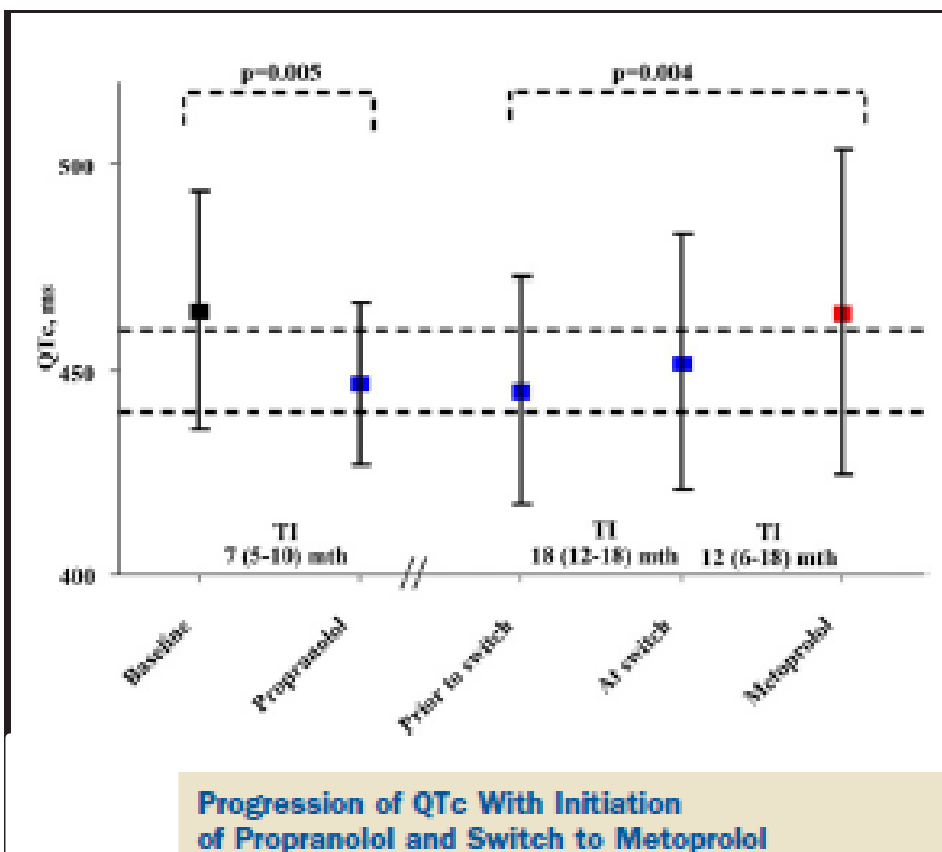
LA effect: propranolol, nadanol

ISA: (pindolol, acebutalol)

NO agonism: nebivolol

Long QT drug management

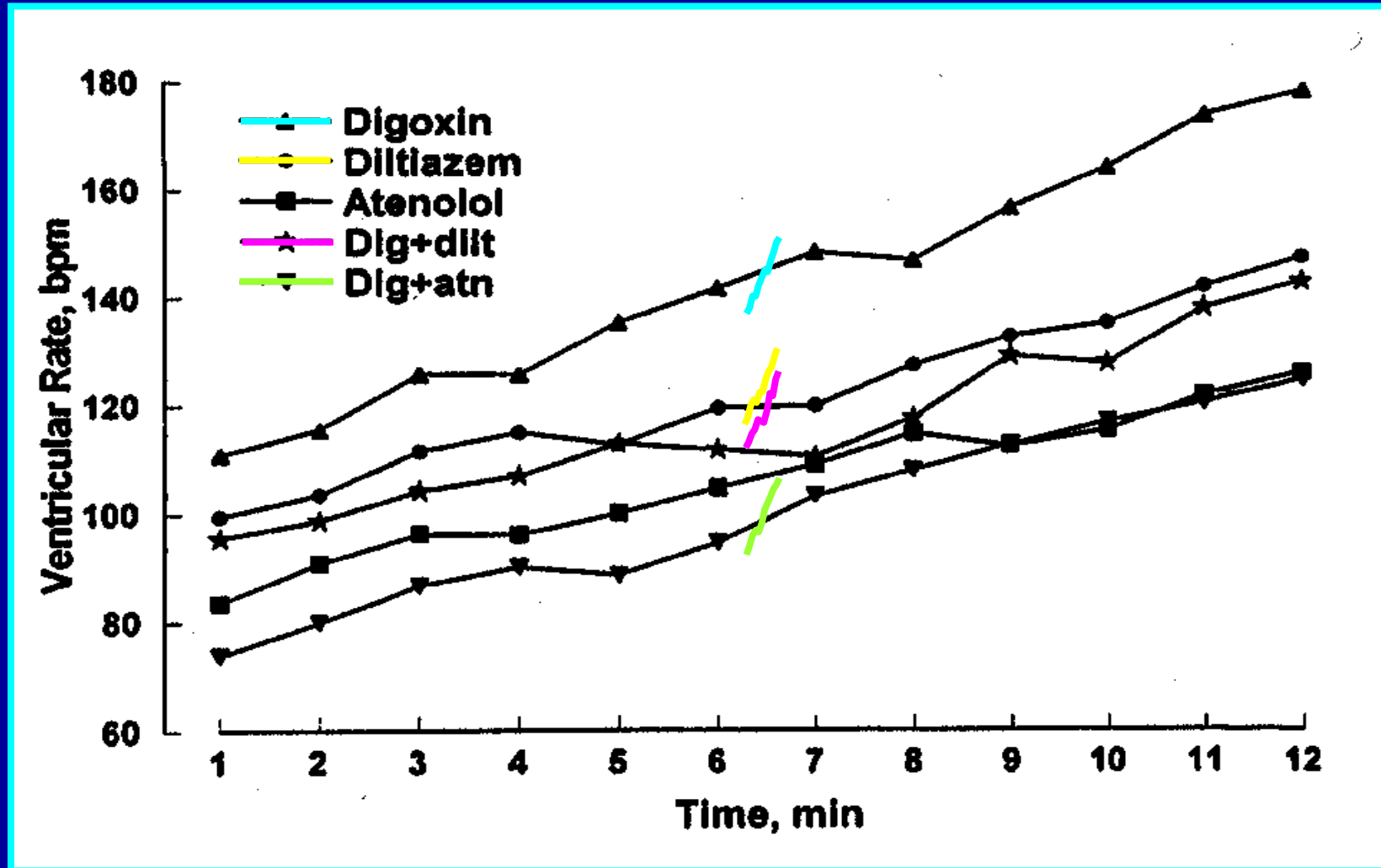
Not All Beta-Blockers Are Equal in the Management of Long QT Syndrome Types 1 and 2



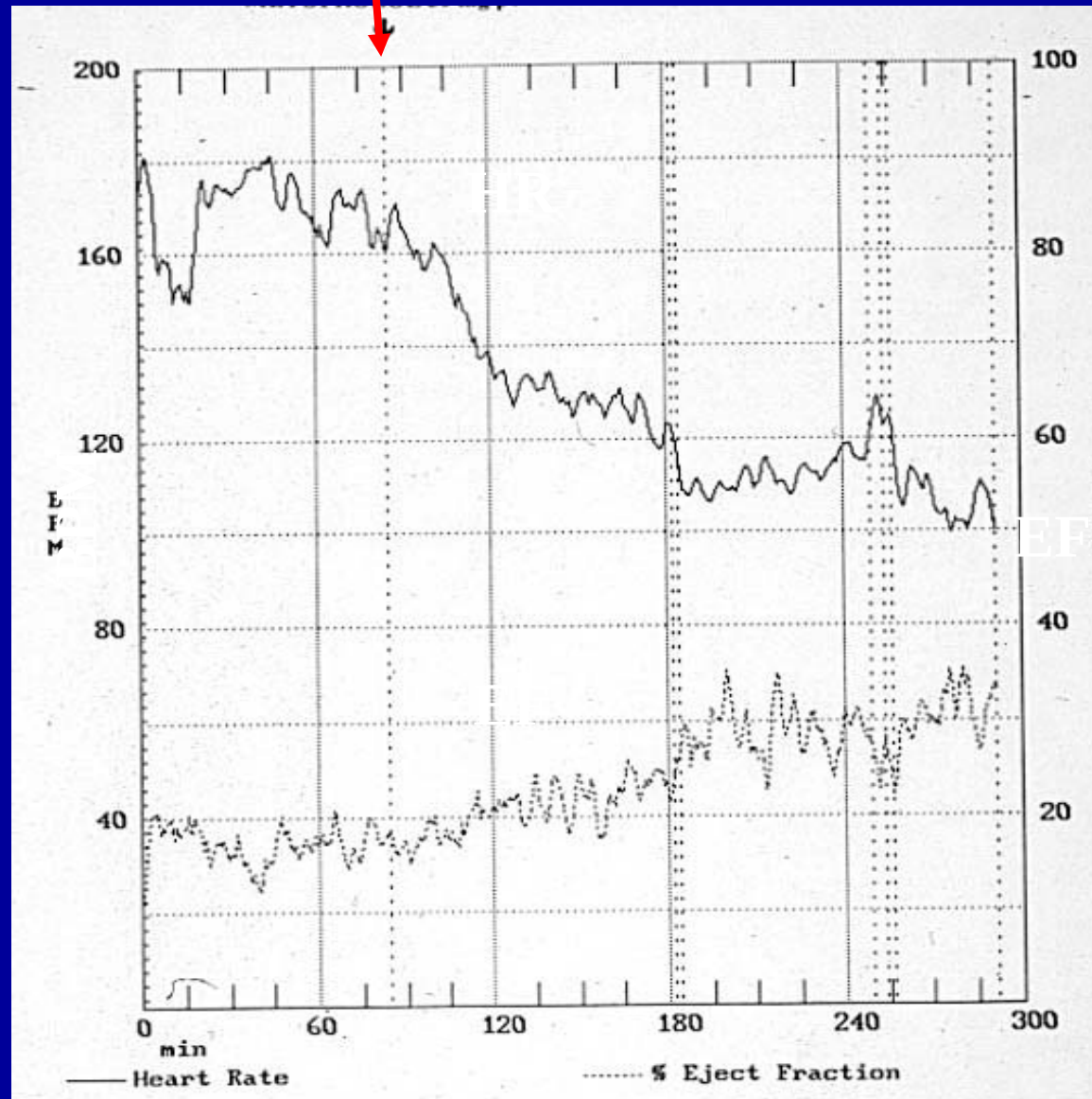
N=382

Chockalingam JACC 60:2092,2012

Effect of Pharmacologic Regimens on Exercise-induced VR in Patients with CAF



Metoprolol (25 mg)





Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com



Research Paper

Effective Management of Advanced Angiosarcoma by the Synergistic Combination of Propranolol and Vinblastine-based Metronomic Chemotherapy: A Bench to Bedside Study



Eddy Pasquier^{a,b,c,*}, Nicolas André^{a,b,d}, Janine Street^c, Anuradha Chougule^e, Bharat Rekhi^f, Jaya Ghosh^e, Deepa S.J. Philip^e, Marie Meurer^{a,g}, Karen L. MacKenzie^c, Maria Kavallaris^{c,h}, Shripad D. Banavali^{b,e,**}

^a INSERM UMR 911, Centre de Recherche en Oncologie biologique et Oncopharmacologie, Aix-Marseille University, Marseille, France

^b Metronomics Global Health Initiative, Marseille, France

^c Children's Cancer Institute Australia, Lowy Cancer Research Centre, UNSW Australia, Randwick, Australia

^d Service d'Hématologie & Oncologie Pédiatrique, AP-HM, Marseille, France

^e Department of Medical Oncology, Tata Memorial Centre, Mumbai, India

^f Department of Pathology, Tata Memorial Centre, Mumbai, India

^g Service d'Oncologie Médicale, AP-HM, Marseille, France

^h Australian Research Council Centre of Excellence in Convergent Bio-Nano Science and Technology, Australian Centre for Nanomedicine, UNSW Australia, Sydney, Australia

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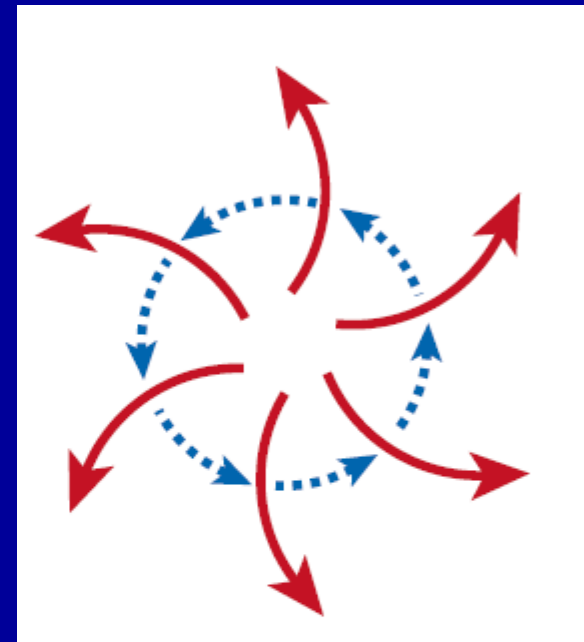
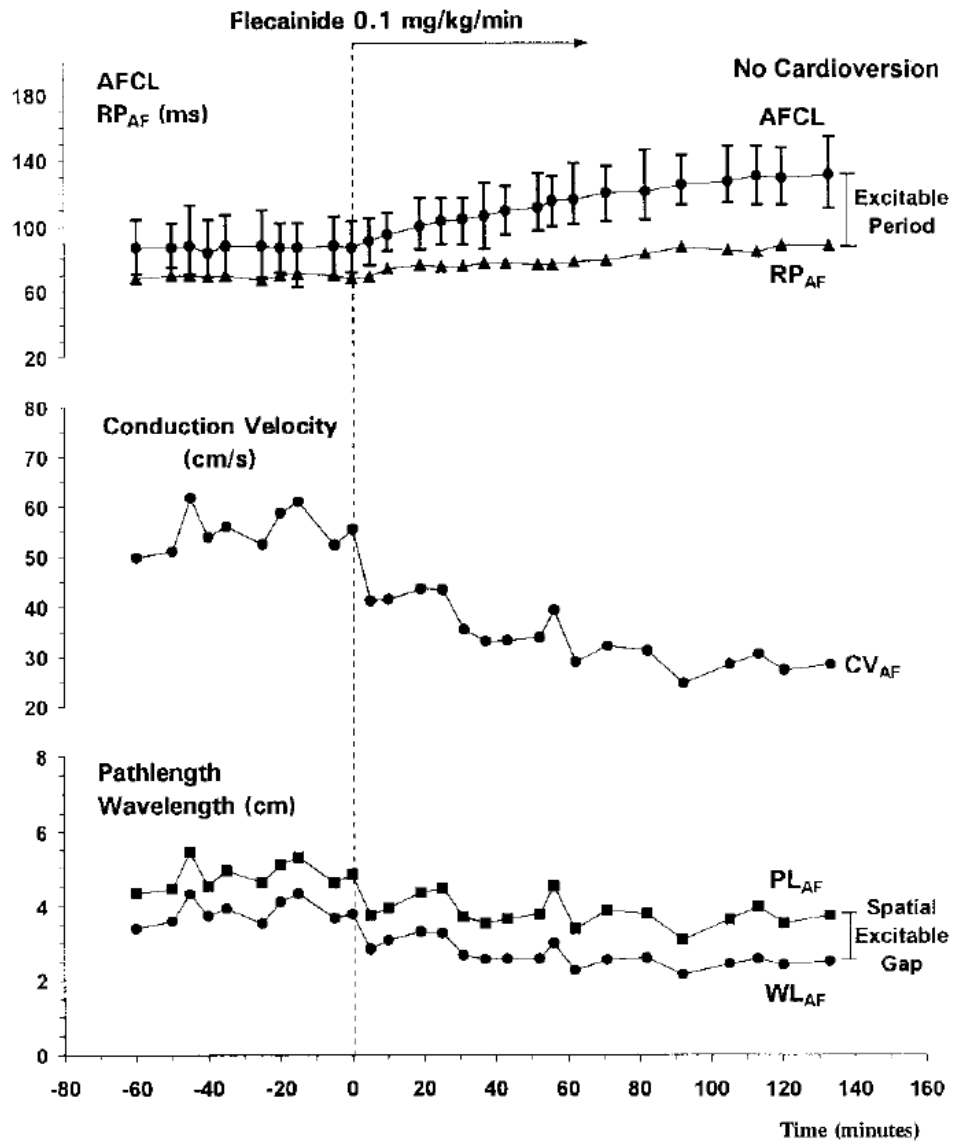
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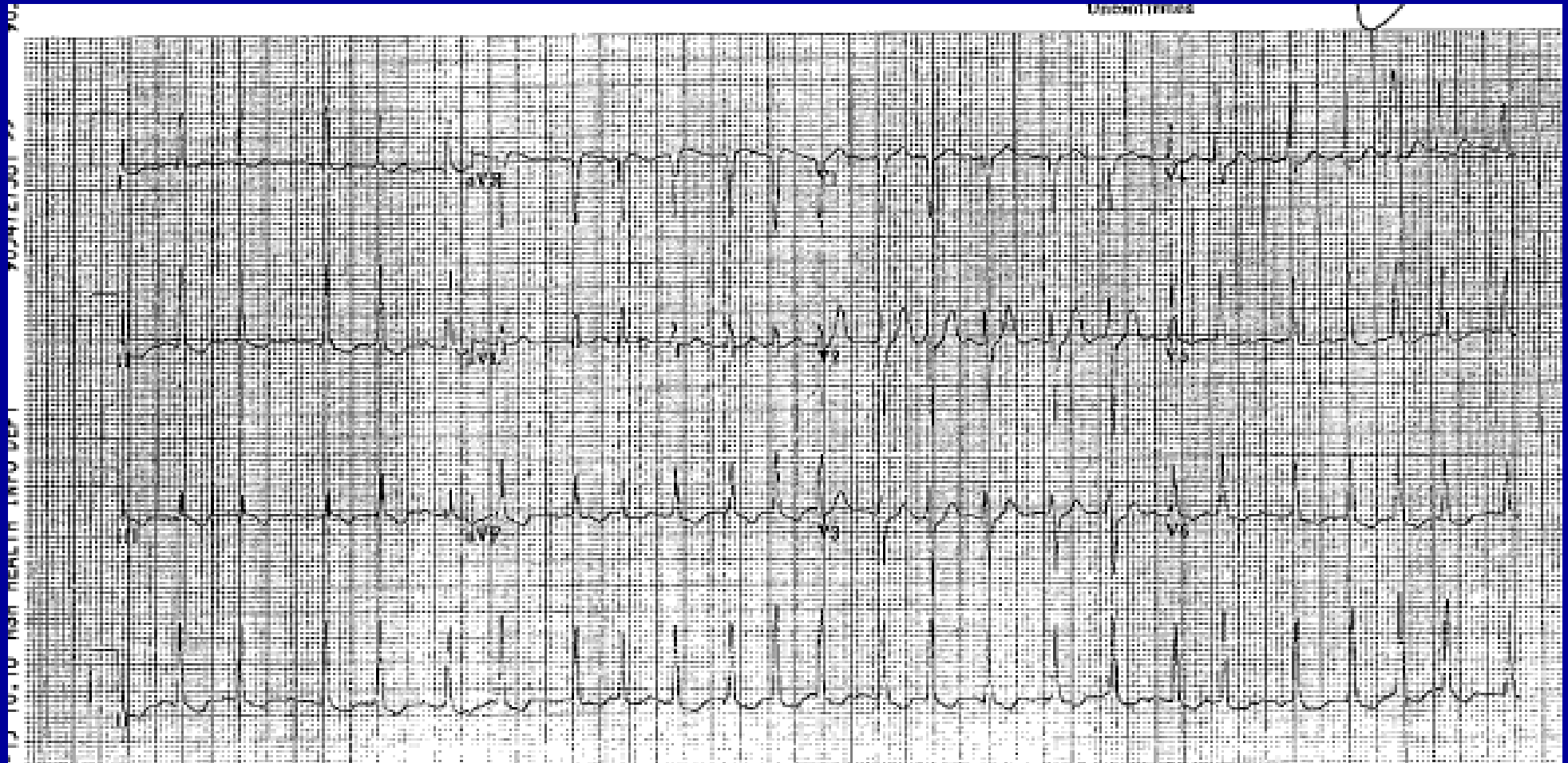
Wijffels, Allessie, Circulation. 2000;102:260-267

Outpatient Treatment of Recent-Onset
Atrial Fibrillation with the “Pill-in-the-Pocket”
Approach

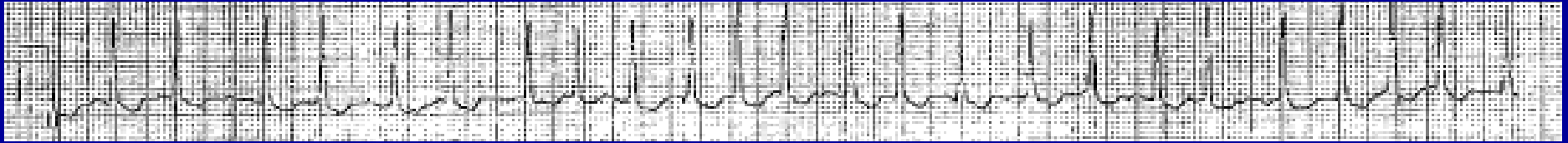
Flecainide 300 mg stat oral dose (200 mg < 70 kg)
Propafenone 600 mg (450 mg < 70 kg)

Alboni. NEJM 351;2384,2004

17:25 Flecainide 300 mg po



Flecainide 300 mg po



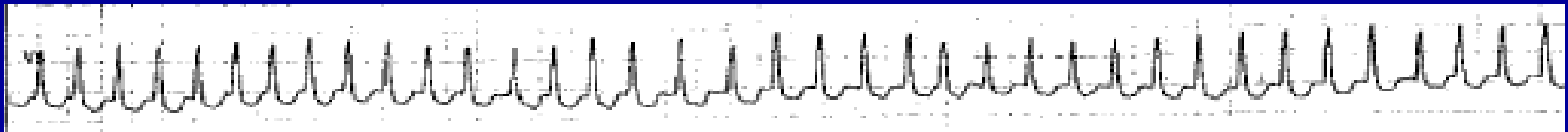
18 min



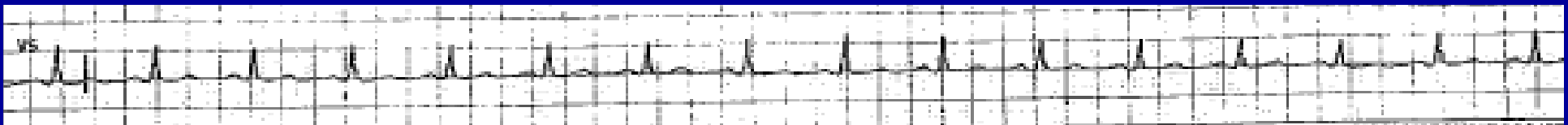
63 min



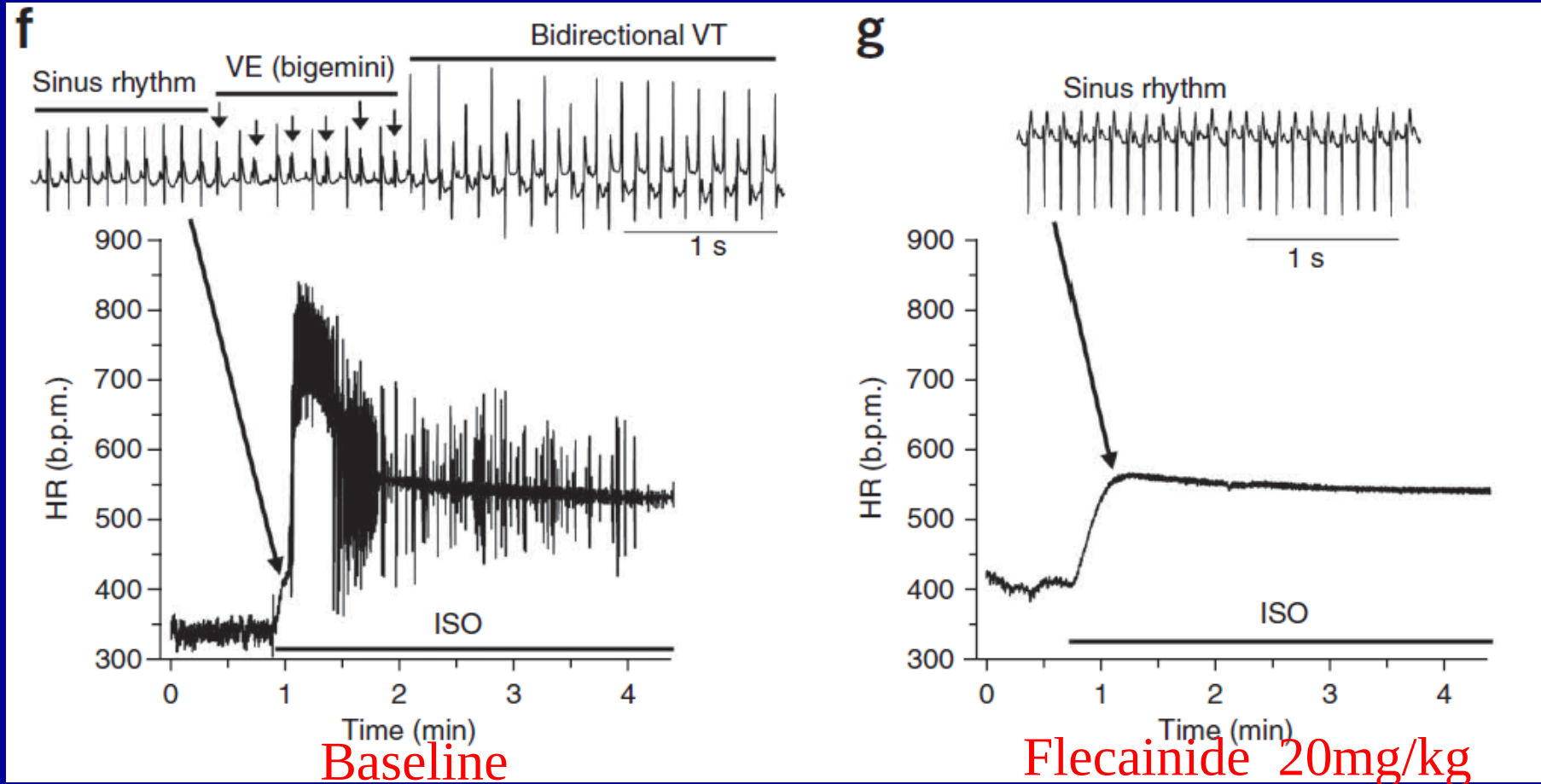
70 min



116 min



CPMVT drug management



Mouse model, RyR2 premature Ca release ; calcineurin neg KO

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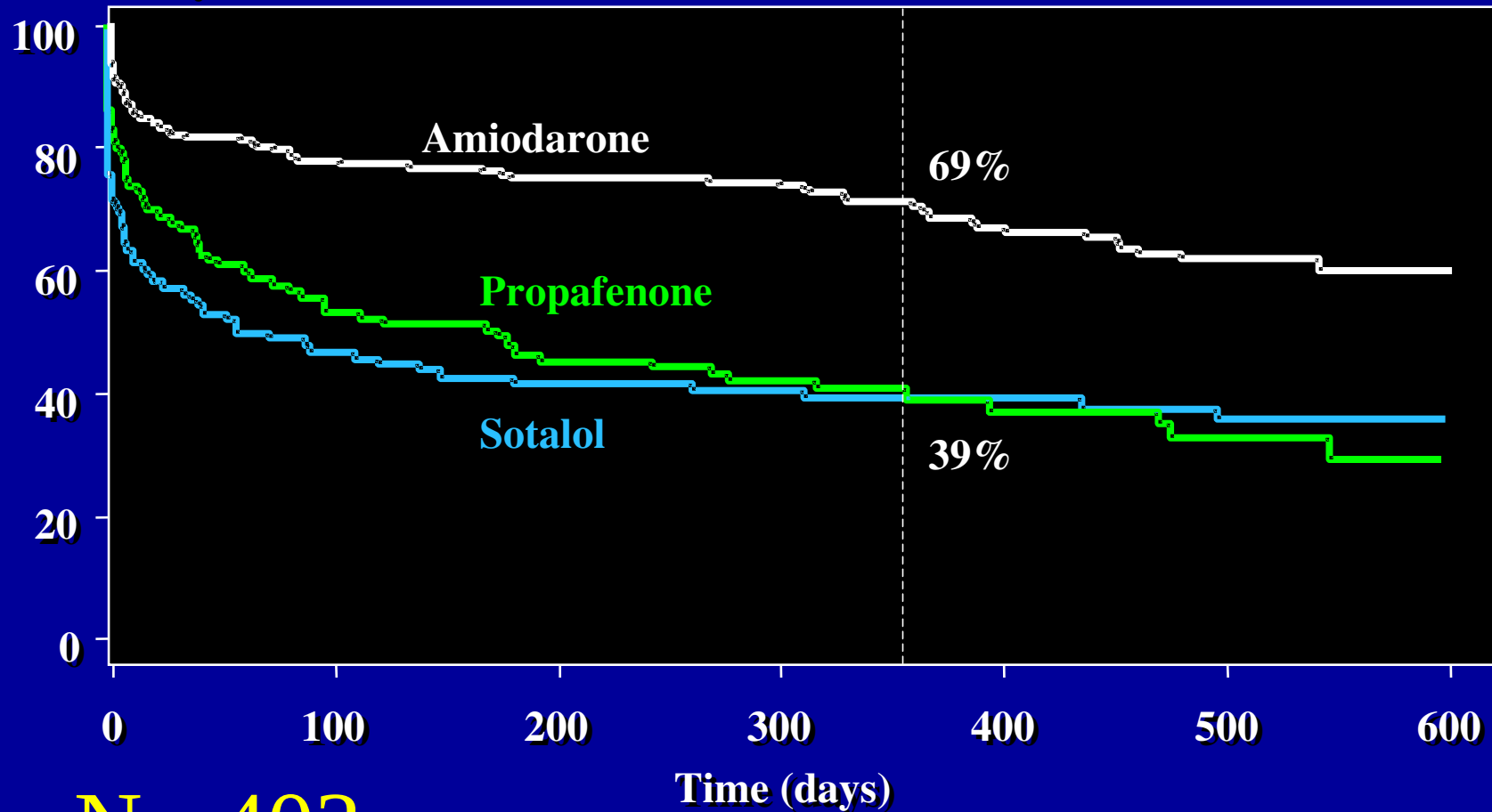
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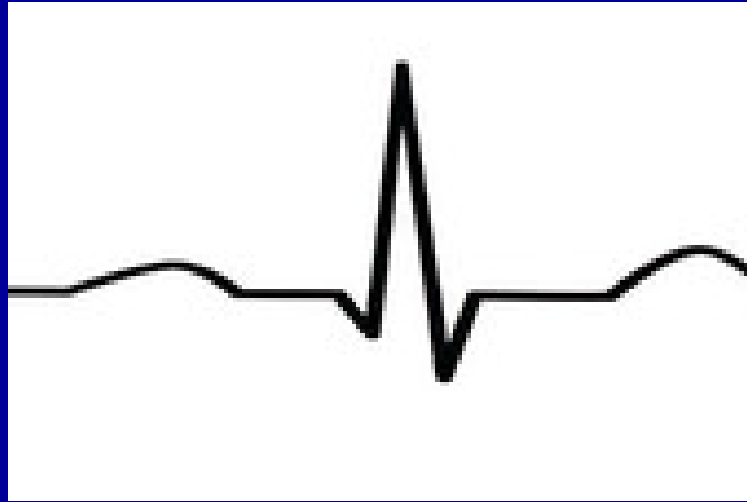
Canadian Trial Atrial fibrillation (CTAF)

% sinus rhythm

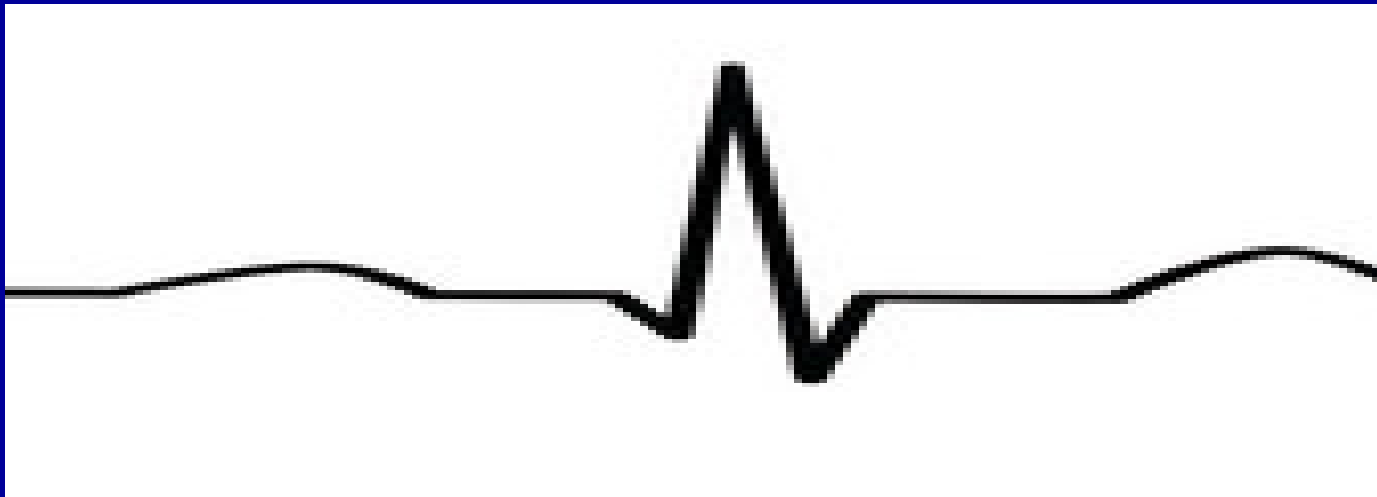


N= 403

Roy. NEJM 342:913,2000



Amiodarone= type 10 (1+2+3+4)



Amiodarone pearls.....

Efficacy:

Dirty mechanisms work

Efficacy as a beta-blocker is modest (in normal SAN)

Dose response is mysterious; in elderly 50-100 mg od

Dose loading not often needed

Total dose 25-30 g needed to saturate stores (pre cardioversion)

Probably safest in oldest

Interaction with NOACs modest,

interaction with everything else expected : Coumadin, dig, HIV meds

Can increase eGFR by 10-15% through non-toxic mechanisms

Don't forget it began life as a an antianginal (? thyroidal mechanisms)

IV is a different drug : pharmacoeversion, BB , CaCB, hypotension

Amiodarone pearls.....

Safety/toxicity:

Monitoring: TFT, LFT, cough

Remember CAMIAT/EMIAT lesson: placebo lung toxicity = 20%; vs. 21%

AIH: Amiodarone + methimazole works when required

Hypothyroid: Thyroid monitoring: FT3 counts; TSH >15 counts

5 yr. 50% DCSE in Herre et al JACC 1988, was large dose and low EF

net cumulative dose predicts toxicity (for therapeutic trial)

Toxicity dissipates faster than efficacy

Amio cancer

Skin commonest

Law suites I have known: BOOP, retinopathy

Amiodarone long term follow up

UCSF: N=427, all post VT/VF, f/u 98 months

“Side effects were reported by 45% of patients after 1 year, by 61% after 2 years and by 86% after 5 years. Amiodarone was discontinued because of side effects in 14%, 26% and 37% of patients after 1, 3 and 5 year”

Amiodarone monitoring in 2017

TFT q 6 months or with rhythm recurrence

LFT q 6 months

Sun screen

Attention to heart rate slowing effects

Co-admin of anything

Chest X-ray /HRCT with dose held for lung Sx

See card at least q 12 mo

Expect discontinuation but low dose and normal LV



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Combination in outpatients:

BB with everything

Sotalol + selective BB

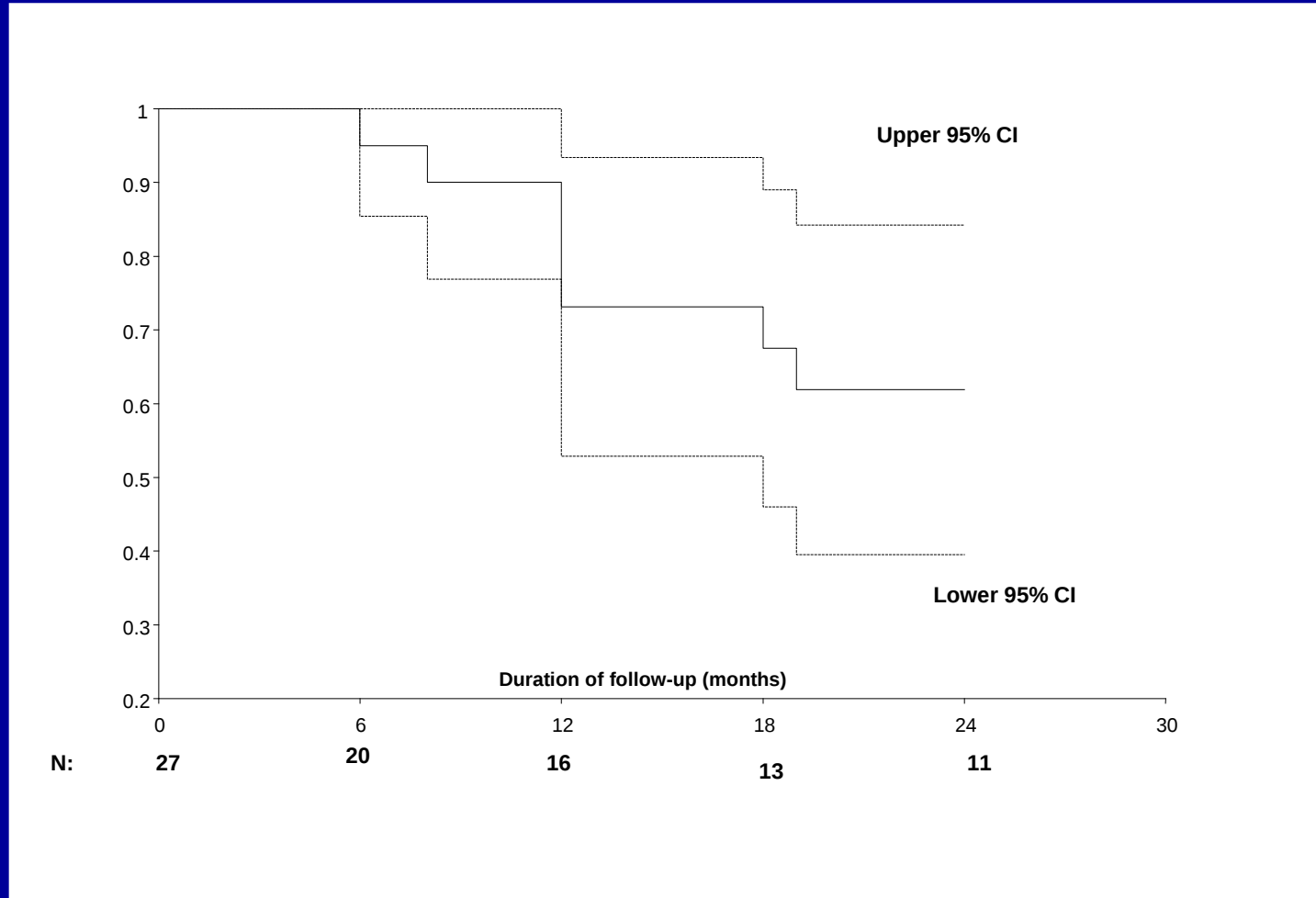
Mexilitene + quinidine (only ever rationally designed combo)

Sotalol + quinidine

Flecainide + amiodarone

Amiodarone plus Flecainide combination therapy in patients with Amiodarone refractory paroxysmal atrial fibrillation

Satisfaction with Tx



Flecainide + amiodarone for refractory atrial Fibrillation

Stop for side effects in 7 :

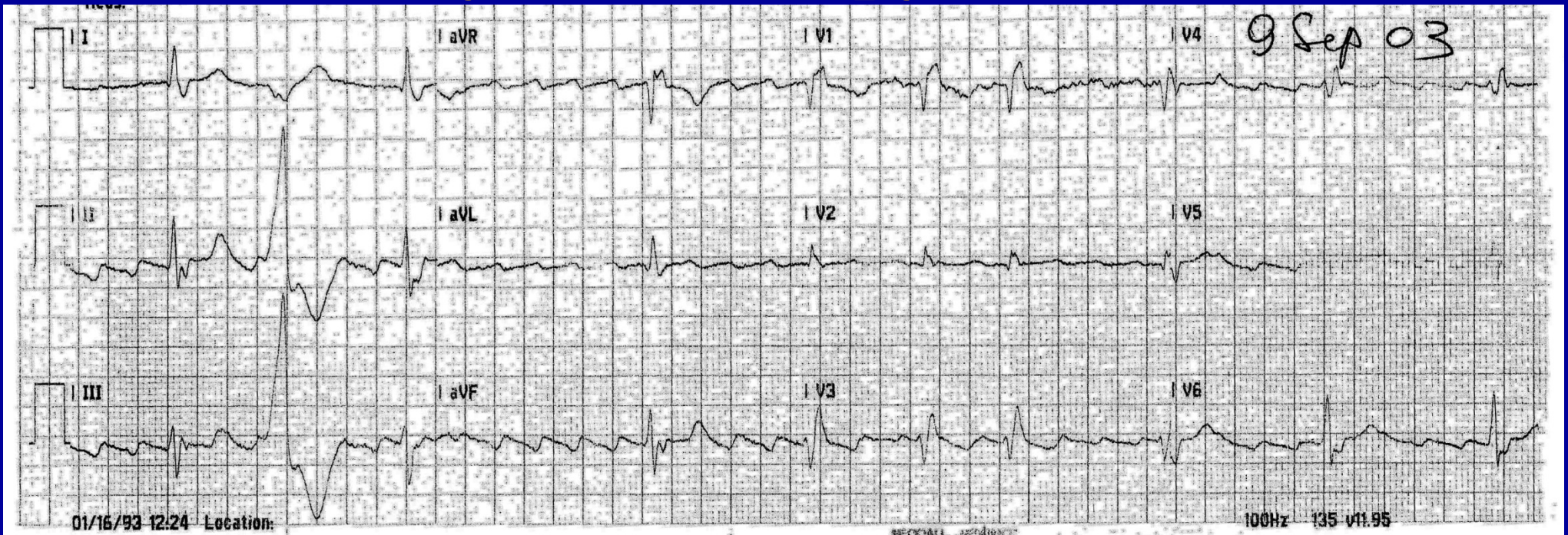
2 Asymptomatic liver enzyme elevation

1 VT (received ICD, IHSS ptnt)

4 atrial flutter; all post PVI, 2 right, 2 left . Tx RFA

2 urgent hospitalizations : VT and flutter

Hybrid therapy



71 yr. paroxysmal atrial fibrillation

amiodarone 200 mg od x 3 yr.

No SHD, Tx hypertension, no inducible ischemia

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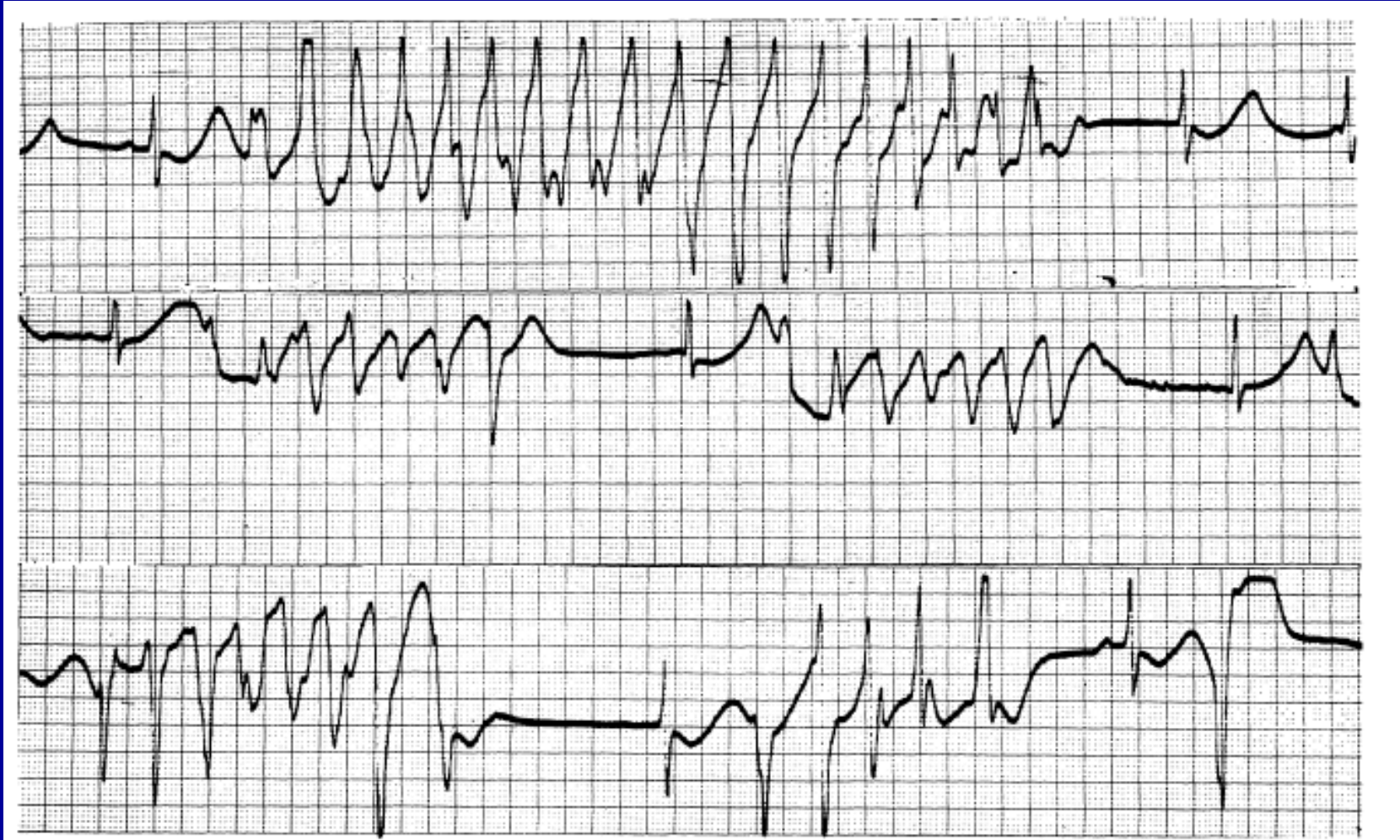
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Quinidine Syncope

**Paroxysmal Ventricular Fibrillation Occurring during
Treatment of Chronic Atrial Arrhythmias**



Uses and pitfalls of EKG's to predict *Torsades*:

- QT vs QTC
- correction formulae
- QT vs T morphology
- QT variability (measurement error, circadian postural, hysteresis, etc...)
- fixed, arbitrary “normal values”

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Generic principles that can be applied....

Pharmacokinetics

Metabolism

Pharmacogenetics/applied genomics

Treating the physiologic adjuncts

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