대한심장학회 춘계학술대회 2008

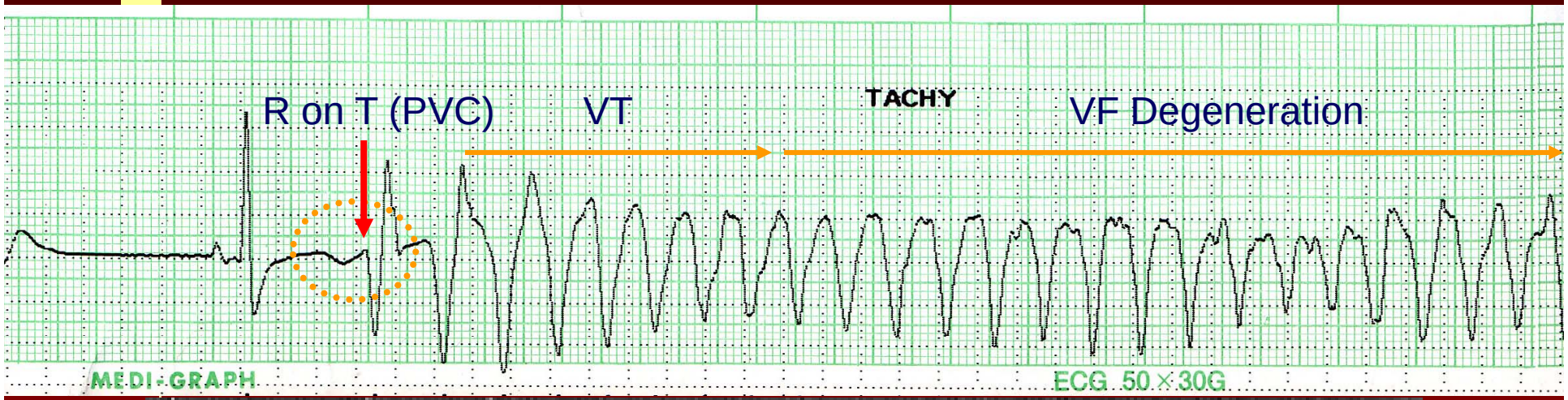
Clinical Use of Class I & III Anti-arrhythmic Drugs

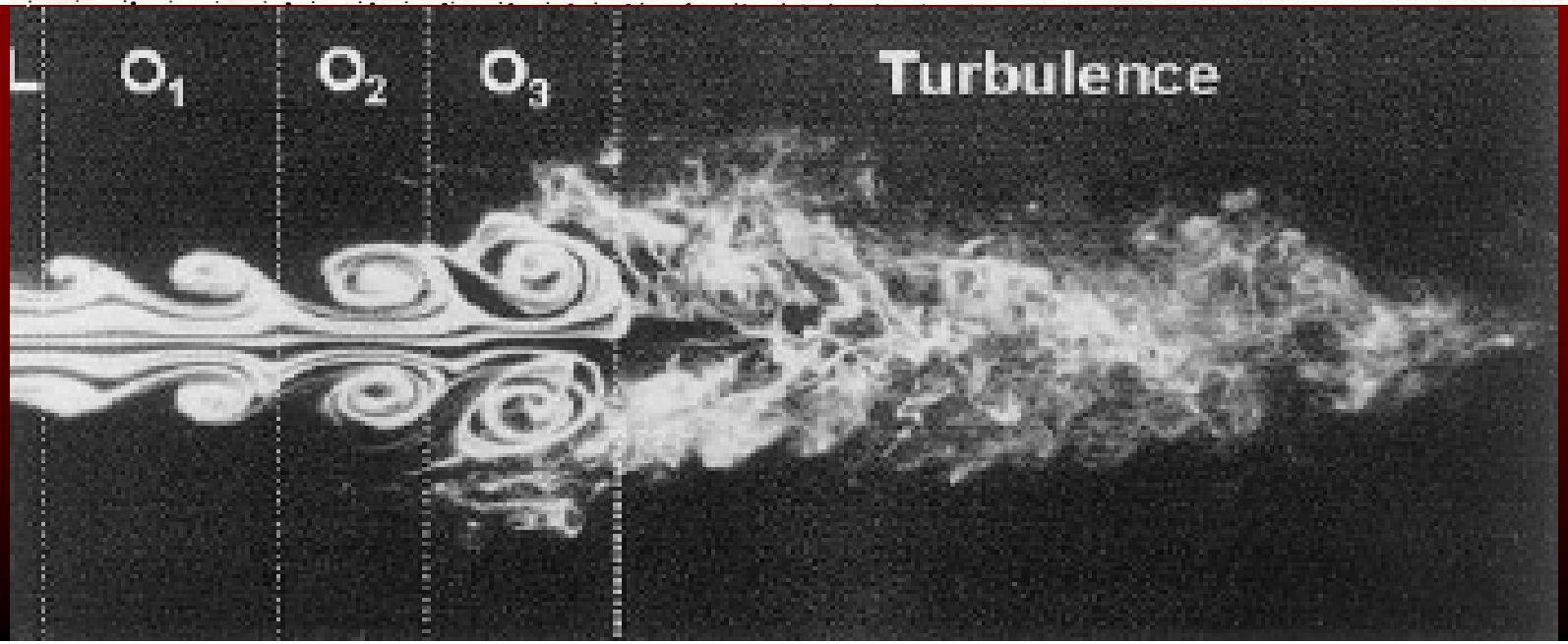
Hui-Nam Pak, MD,PhD.

Arrhythmia Center, KUMC
www.korea-heartrhythm.com

Korea University Medical College
Seoul, Korea

R on T Phenomenon

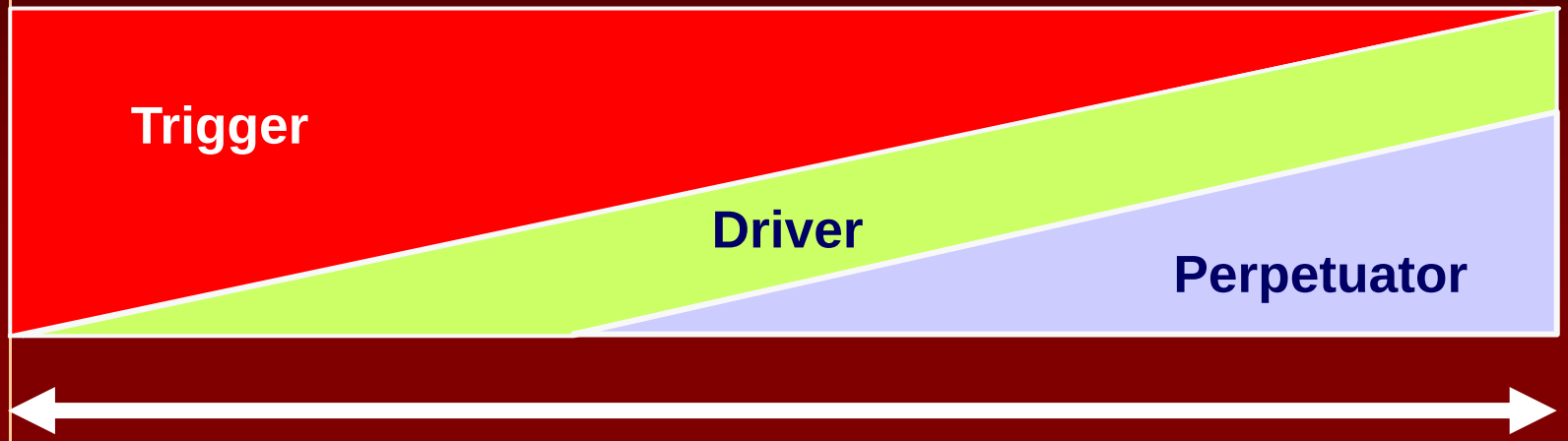




Induction of AF

Pak et al. JCE 2006;17:818

The Mechanism of Arrhythmias



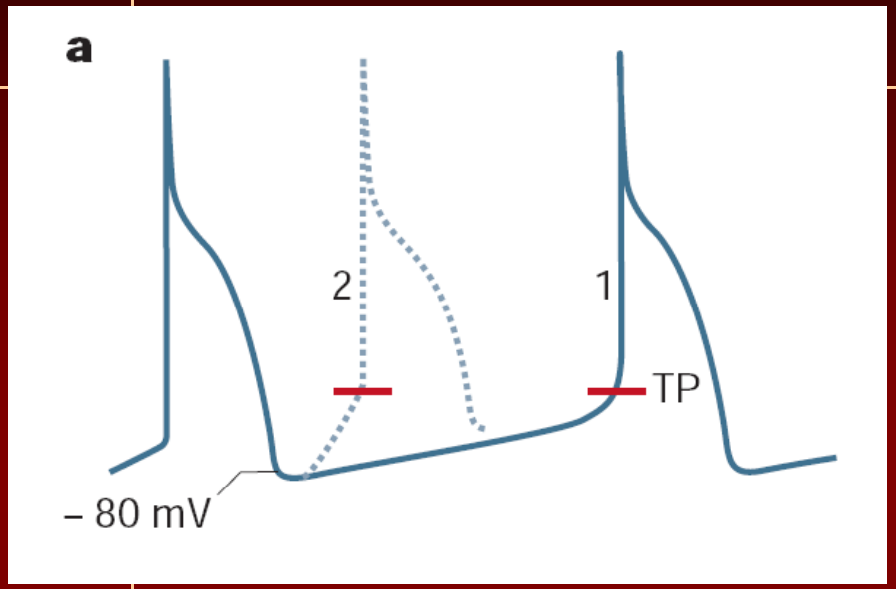
- AT
- PAF (PV Tachy)
- PVC
- RVOT-VT
- AC-VT

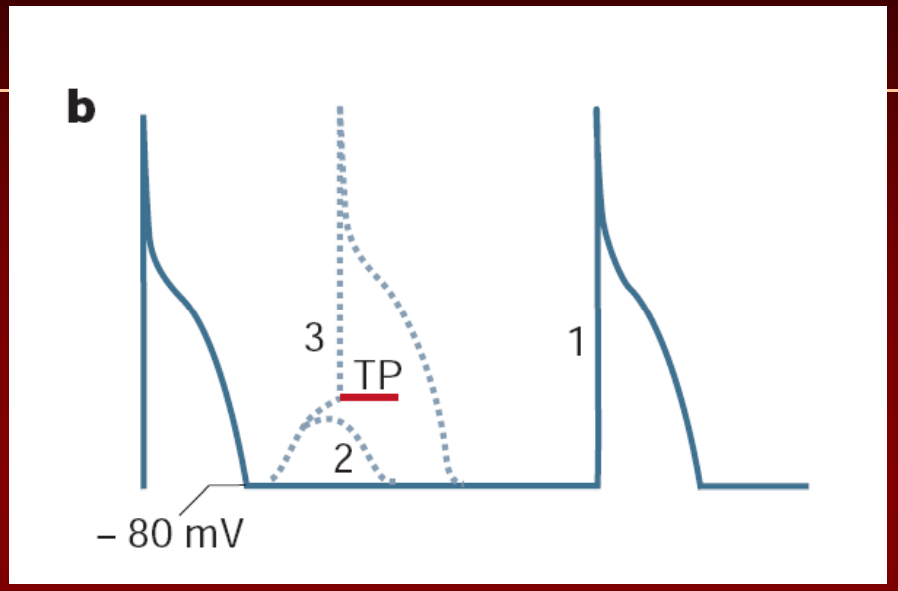
- SNRT
- PAF/ AFL
- PeAF
- AVNRT/AVRT
- ILVT
- Ischemic VT
- MVT

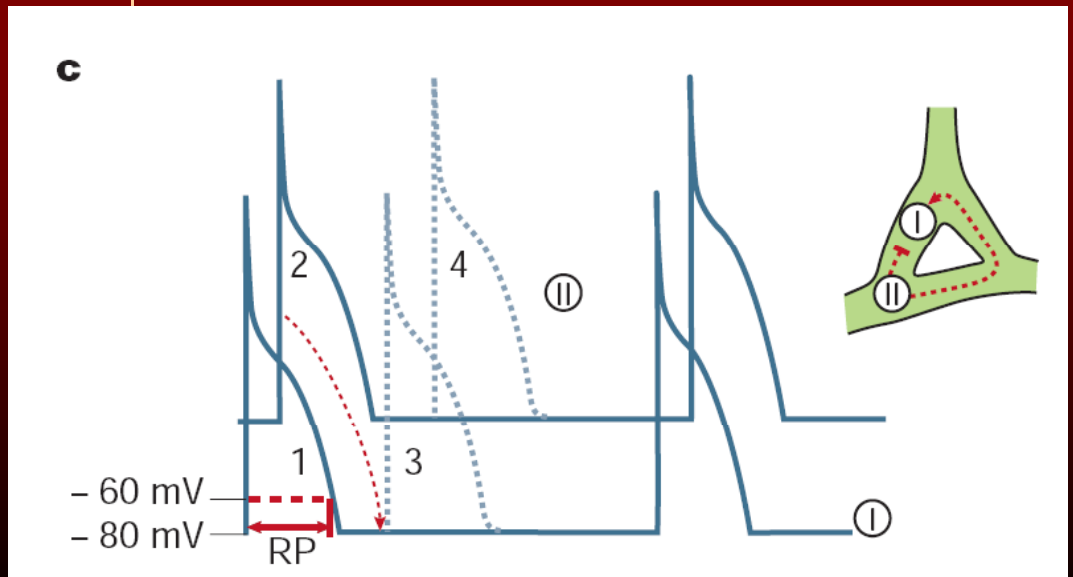
- PeAF/ PtAF
- VF
- Brugada
- LQTs
- ARVD
- HCM

How to Control Arrhythmias?

Natel et al. Nature 2002;415:10



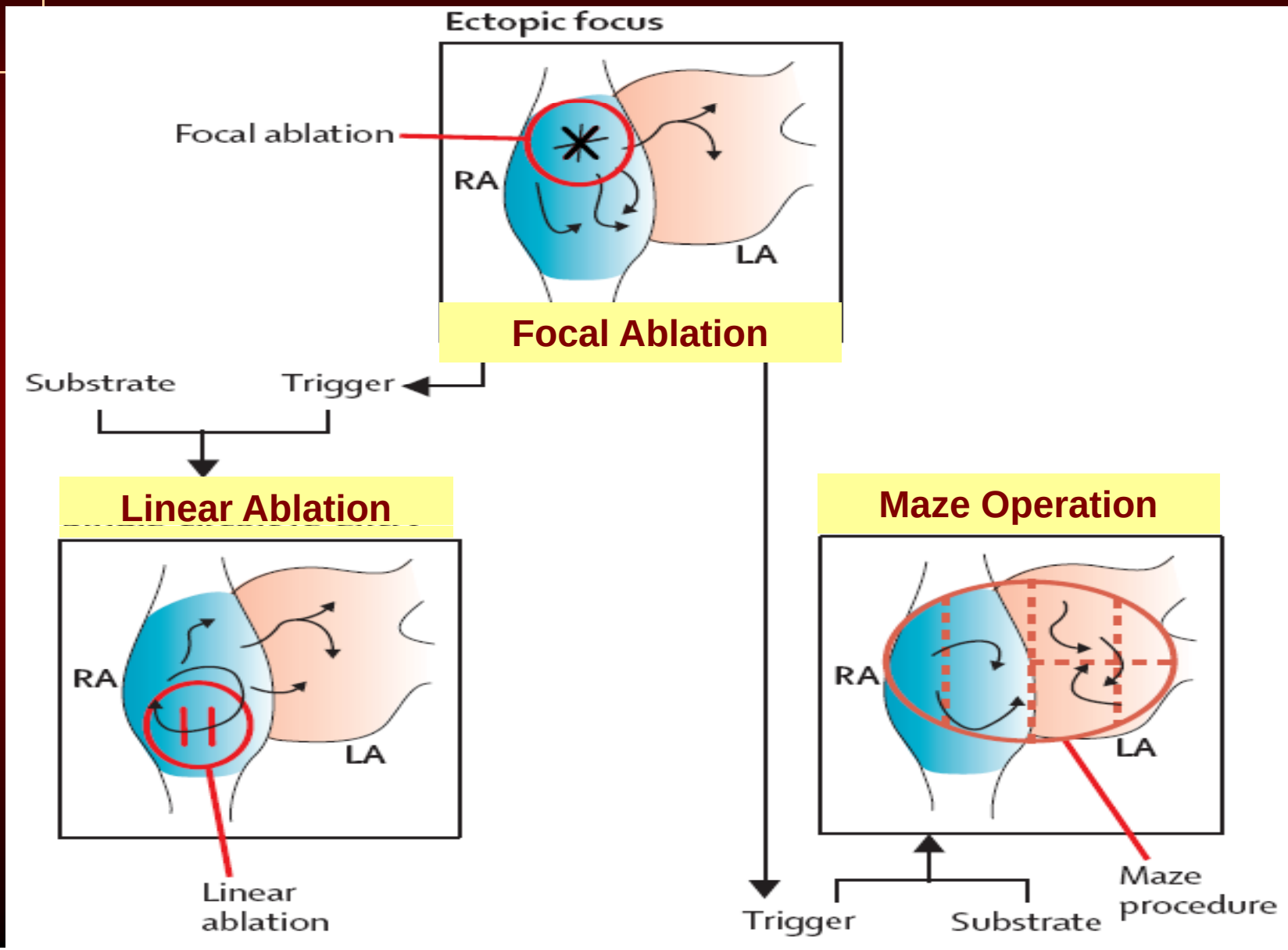




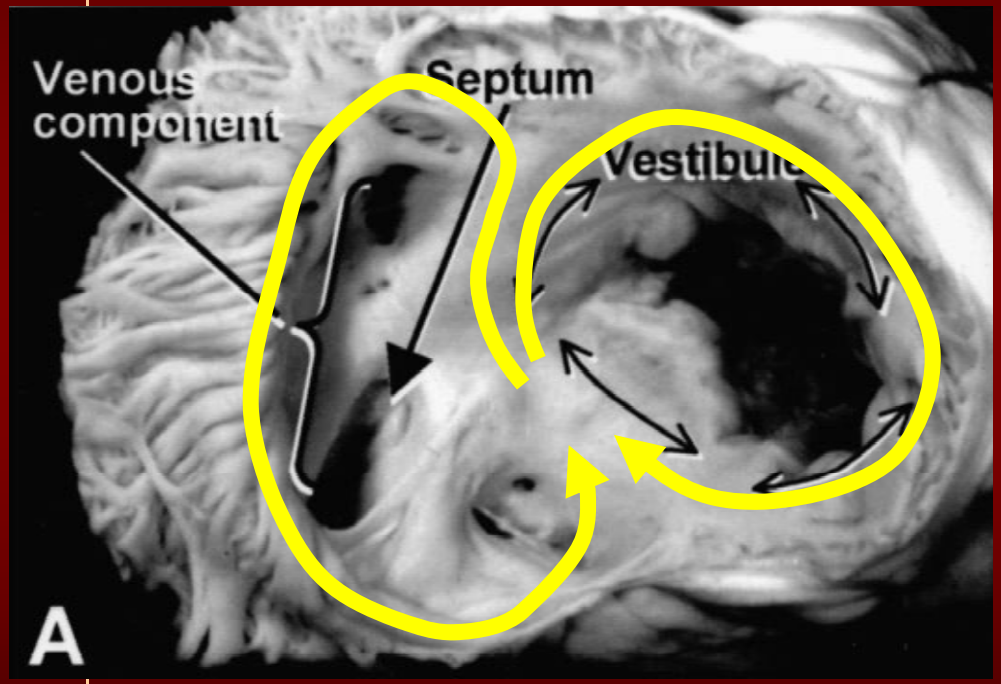
- Reducing Rate of Depol.
- Reducing Intracellular Ca by Blocking NCX
- Blocking Reentry by Reducing ERP Difference

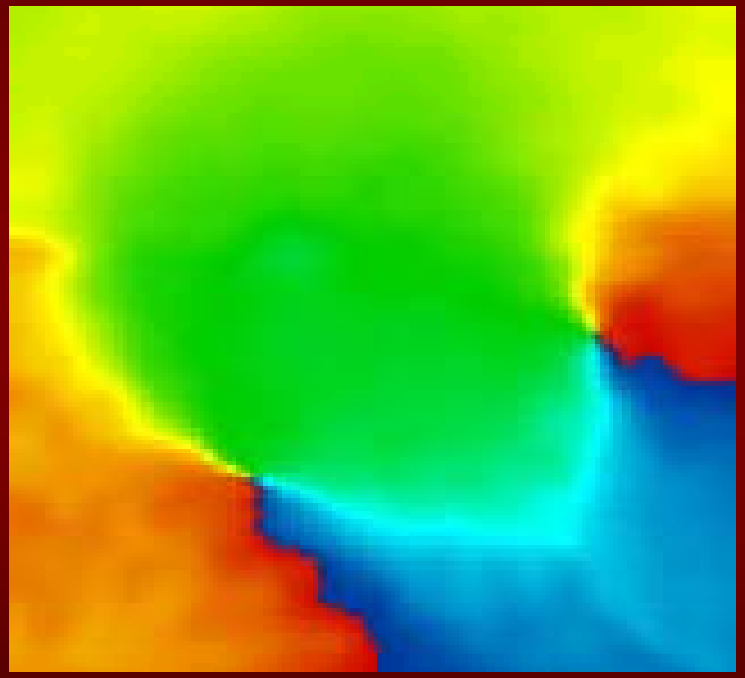
How to Control Arrhythmias?

Natel et al. Lancet 2006;367:262

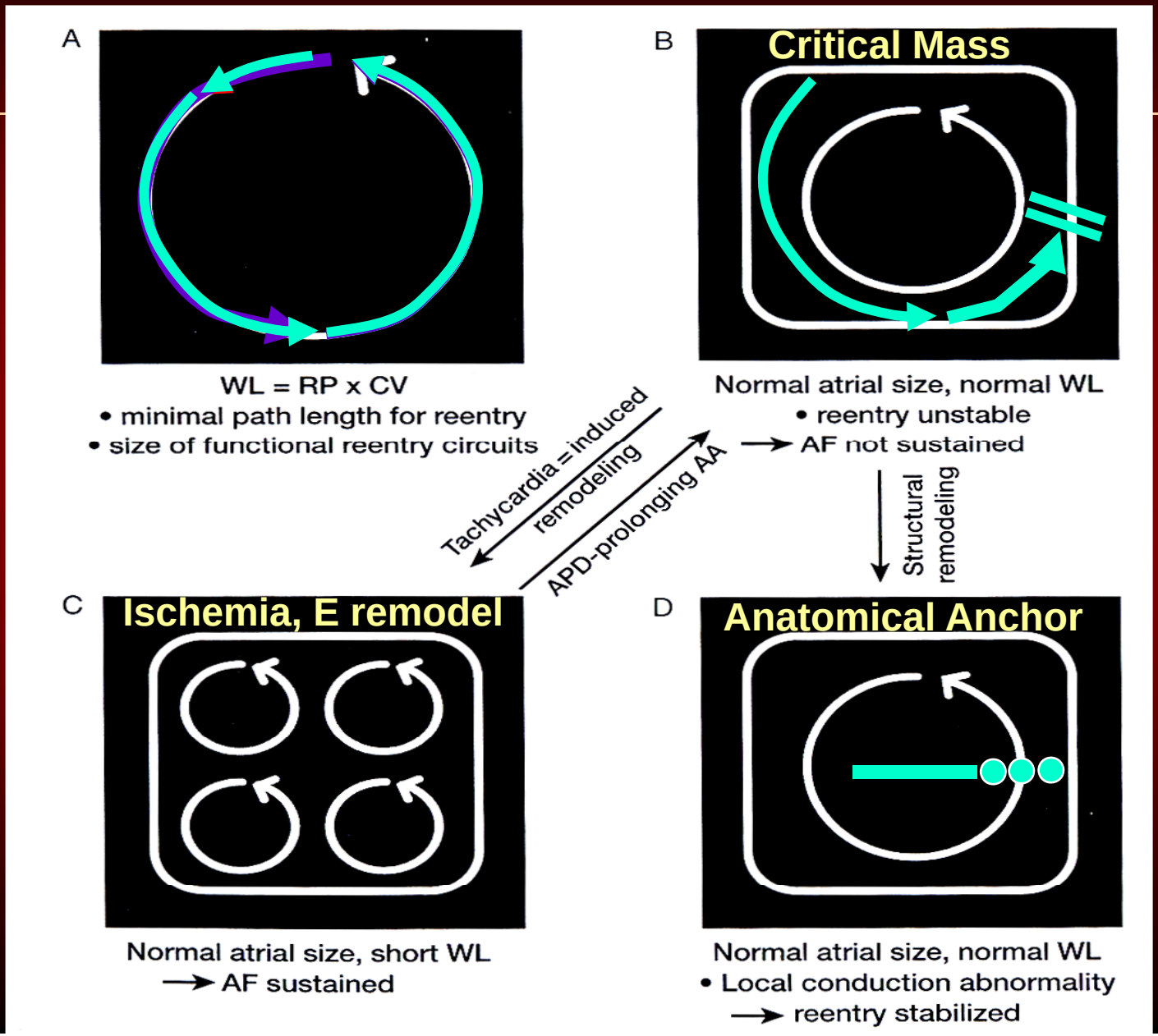


Macro-reentry & Micro-reentry



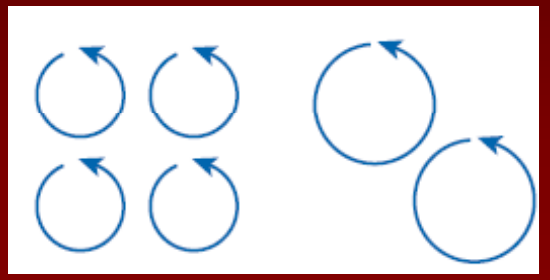


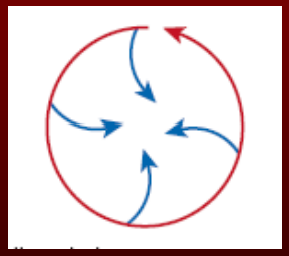
WL (λ) = RP↓ x CV↓

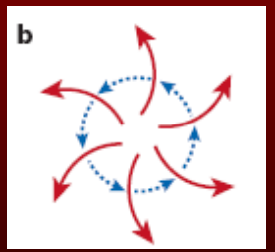

A
B
Critical Mass
WL = RP x CV
• minimal path length for reentry
• size of functional reentry circuits
Normal atrial size, normal WL
• reentry unstable
→ AF not sustained
Tachycardia = induced remodeling
APD-prolonging AA
Structural remodeling
C
Ischemia, E remodel
D
Anatomical Anchor
Normal atrial size, short WL
→ AF sustained
Normal atrial size, normal WL
• Local conduction abnormality
→ reentry stabilized

How to Control Arrhythmias?

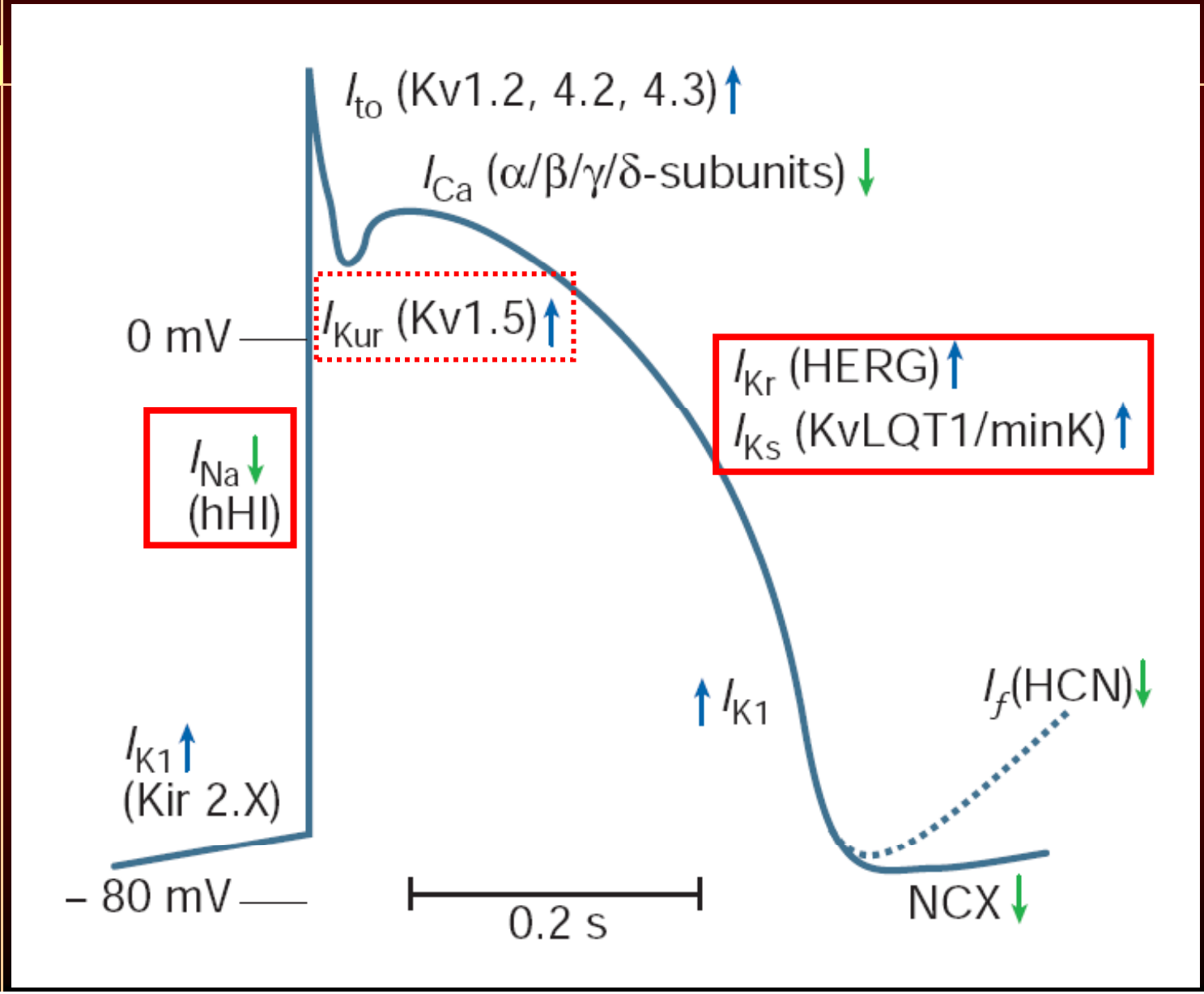
- Blocking Reentry by Increasing WL
  - Increase ERP (Class III AAD)
  - Increase CV (Gap J Enhancer)
- Relative Reduction of Critical Mass
  - Significant Reduction of CV (Class I AAD)
- Reducing Tissue Excitability (Class I AAD)
- Reducing Phase IV Depolarization (BB)
- Reducing Intracellular Calcium
  (Anti-remodeling Drugs, Amiodarone)



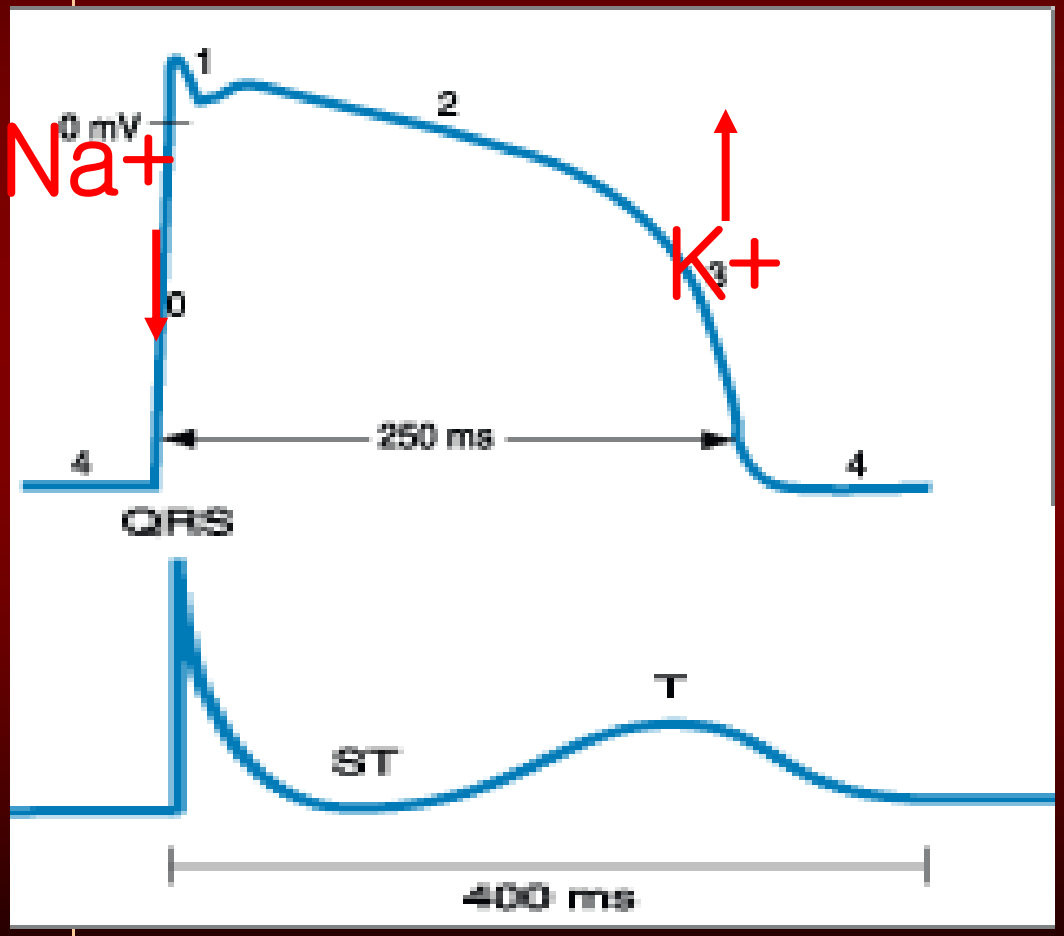




Anti-Arrhythmic Drugs



Inward Sodium Current vs. Outward Potassium Current



- I_{Na} Blocker (Class I AAD)
  - Tissue Excitability ↓
  - CV↓
  - Pharmacologic Reduction of Critical Mass
  - Automaticity ↓
  - Widen QRS width
- I_K Blocker (Class III AAD)
  - RP ↑
  - WL ↑
  - Blocking Reentry
  - Prolong QTc

Vaughan Williams Classification of Anti-Arrhythmic Drugs

- Class I: I_{Na} blocker
  - Class IA (QT↑): quinidine, procainamide, disopyramide
  - Class IB (QT↓): lidocaine, mexiletine, phenytoin
  - Class IC (QT→, QRS↑): flecainide, propafenone, moricizine
- Class II: β-blocekr
- Class III: I_K blocker
  - sotalol, amiodarone, bretylium
  - QT prolongation
- Class IV: I_{Ca}-l blocker

항부정맥제 사용의 원칙

- 항부정맥제는 부정맥 억제에 효과적이지 못하다.
  - Sudden death 위험이 있는 자에서는 피한다.
  - 심방세동 환자에서 혈전예방 요법을 게을리 해서는 안된다.

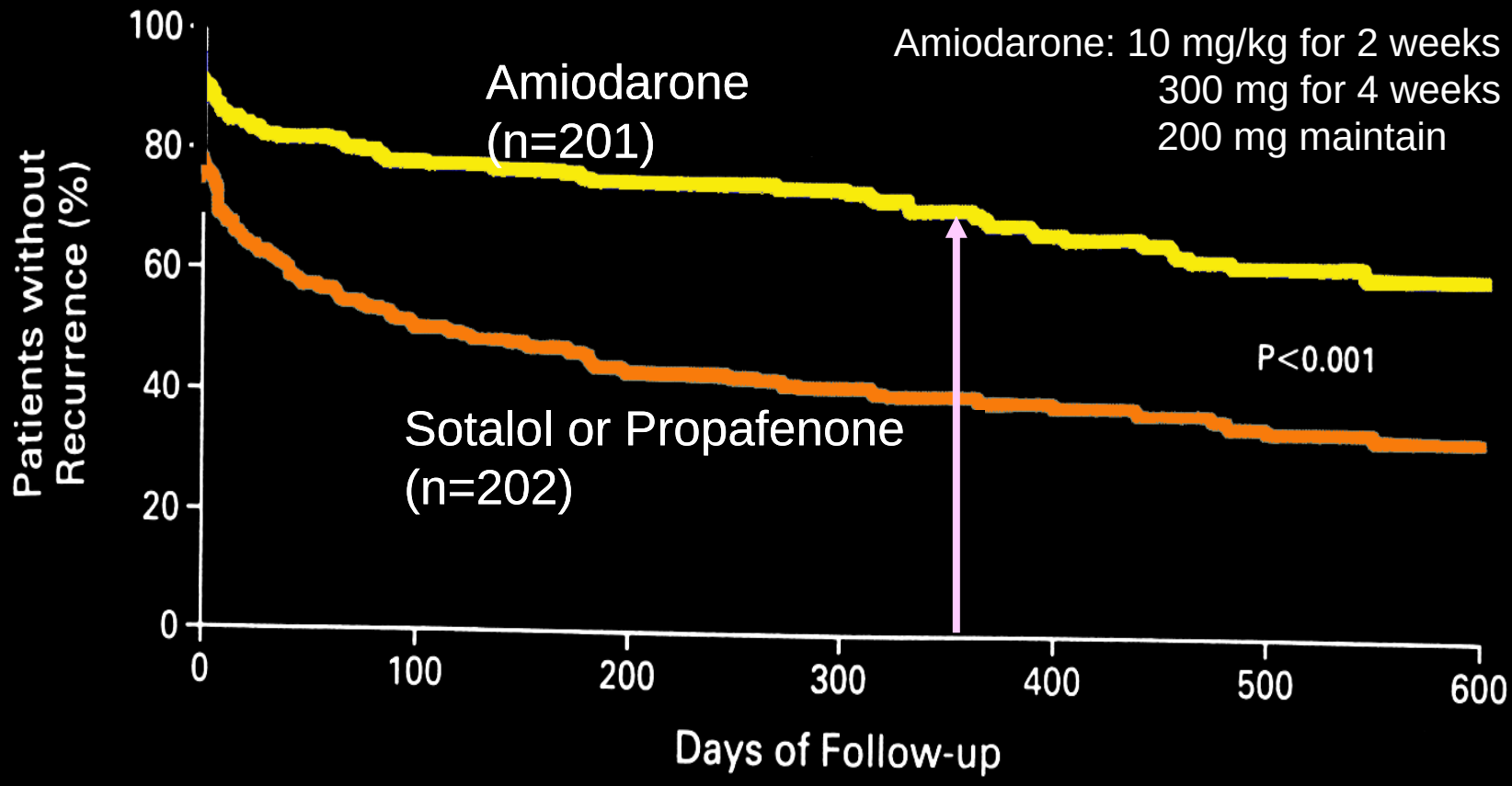
- 항부정맥제는 안전하지 않다.
  - 항부정맥제로 부정맥이 조절되어도 사망률을 감소시키지 못한다.
  - 항부정맥제가 도리어 사망률을 증가시킨다 (CAST, SWORD, AFFIRM Trials).
  - 구조적 심장질환이 있는 사람에서는 proarrhythmia의 위험이 있으므로 amiodarone, dofetilide 이외에는 피한다.
  - 항부정맥제의 급성/ 만성적 부작용에 대한 지속적인 모니터링이 필수적이다.

- 심전도로 증명이 된 부정맥에 한해서 심전도로 효과를 확인한 최소 용량을 선택적으로 사용한다.

Amiodarone to Prevent Recurrence of AF

Canadian Trial of Atrial Fibrillation Investigation

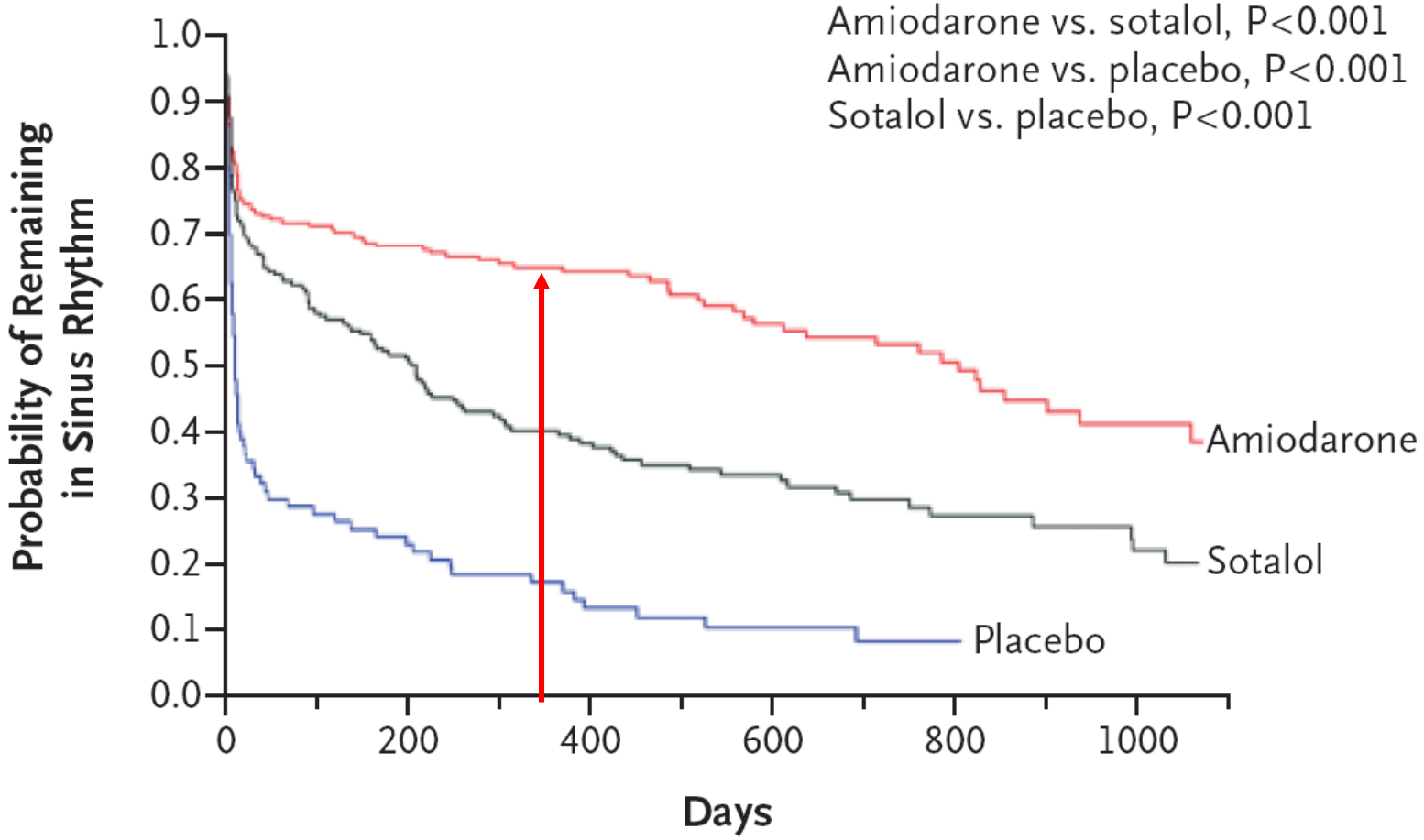
NEJM 2000;342:913-20



Amiodarone vs. Sortalol for AF

SAFE-T Investigators

Eng J Med. 2005;352:1861

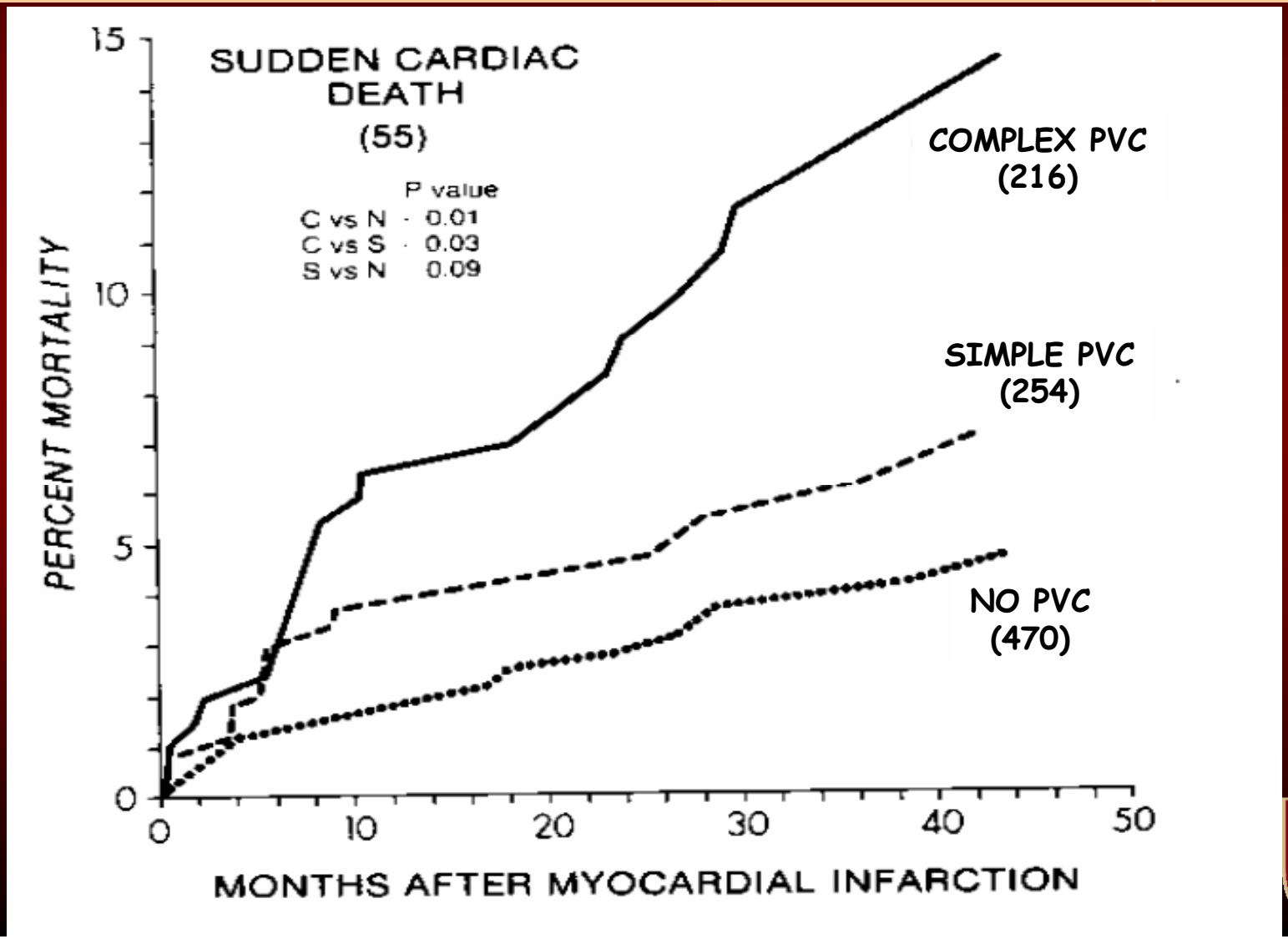


No. at Risk

Amiodarone	206	131	98	60	38	18
Sotalol	195	97	61	38	21	13
Placebo	90	21	11	8	5	2

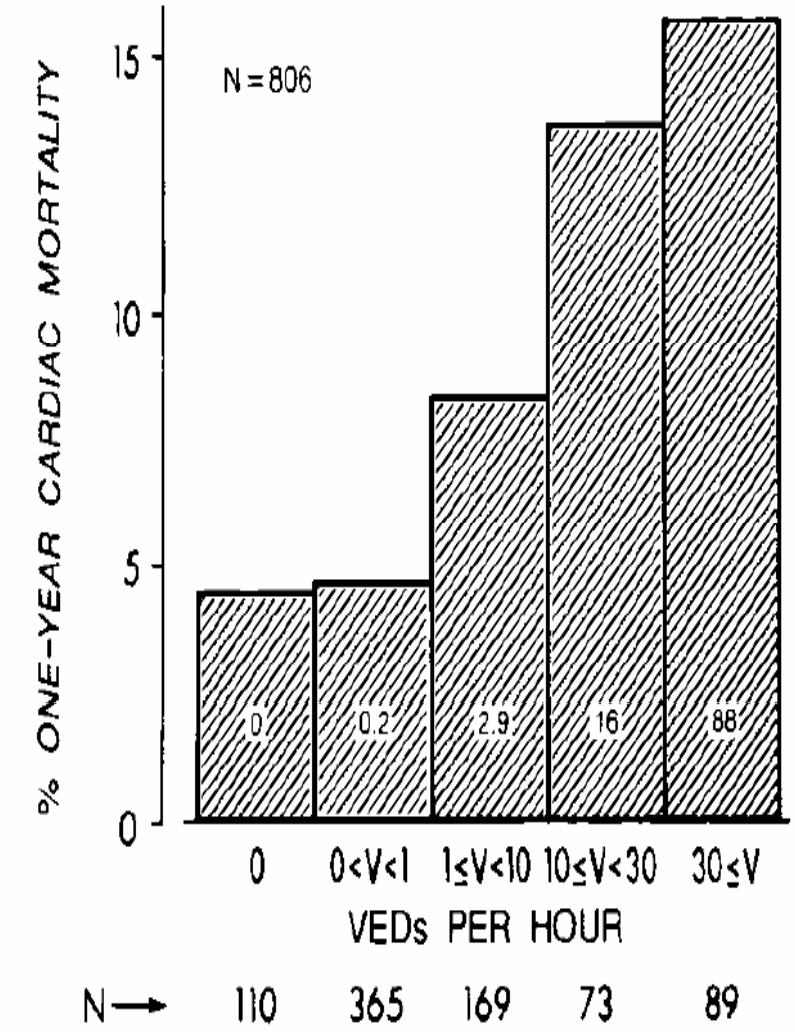
Complex PVCs Increase Mortality in Pts with CAD

Moss et al. Circulation 1979;60:998

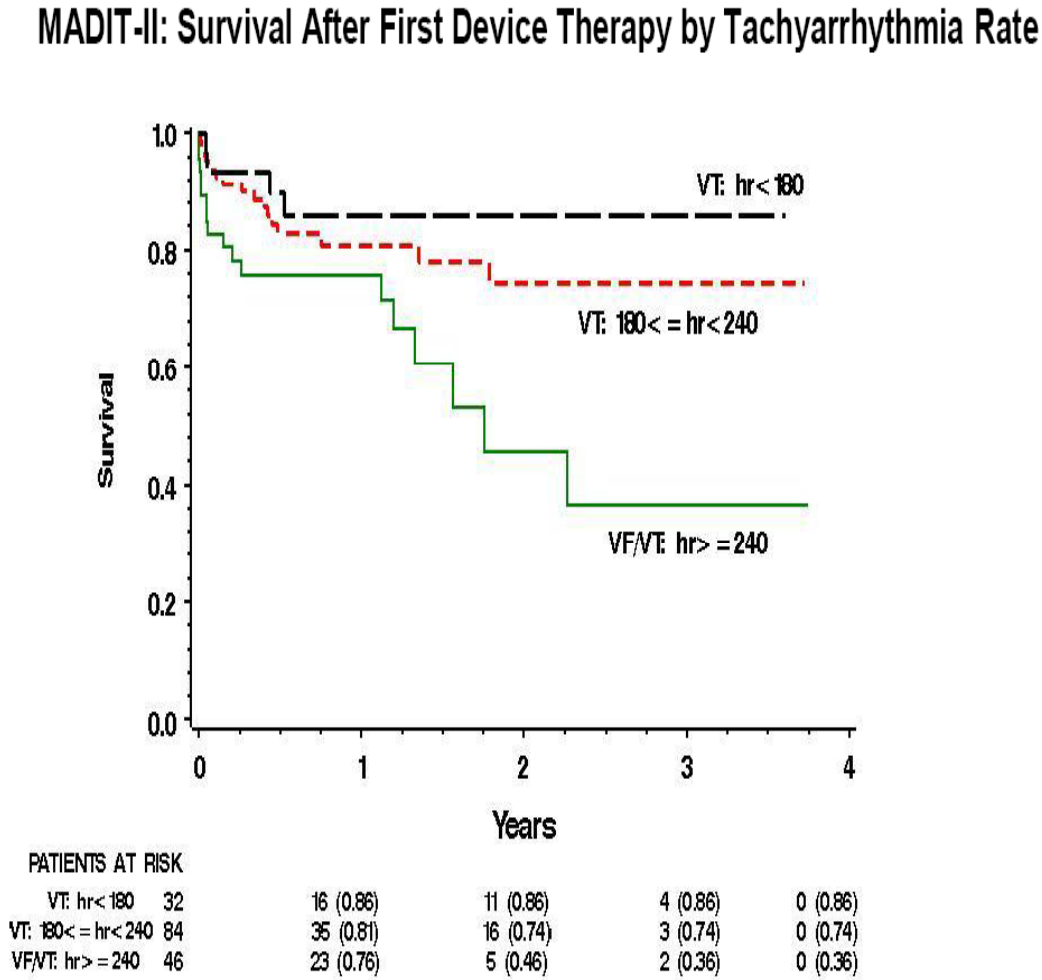


Frequent PVC Increases Mortality in Pts c CAD

Moss et al. N Eng J Med 1983



Moss et al. Circulation 2004

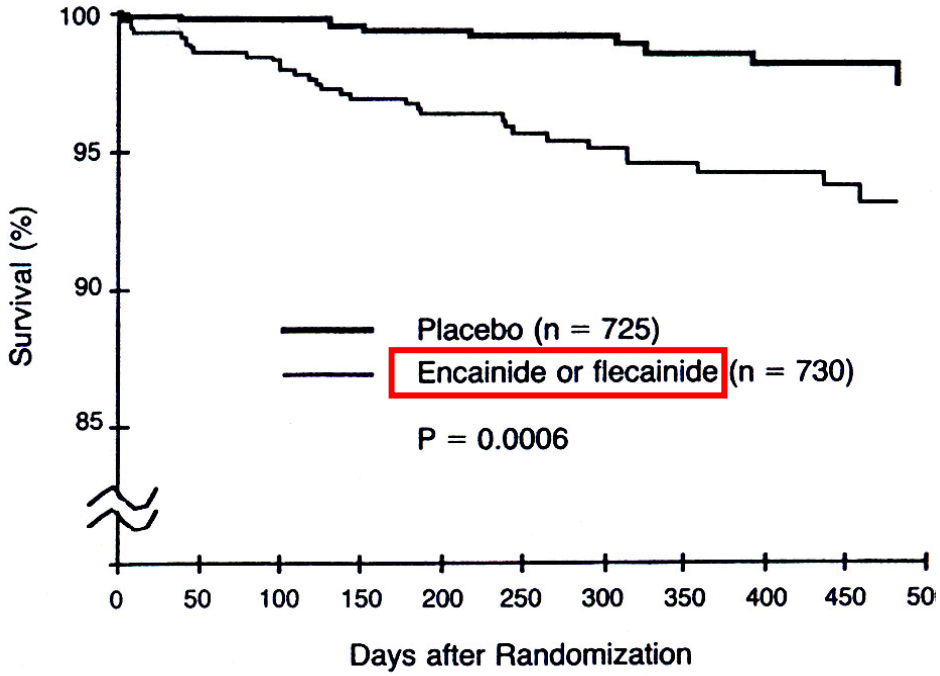


BUT!

AAD is NOT Effective NOR Safe.

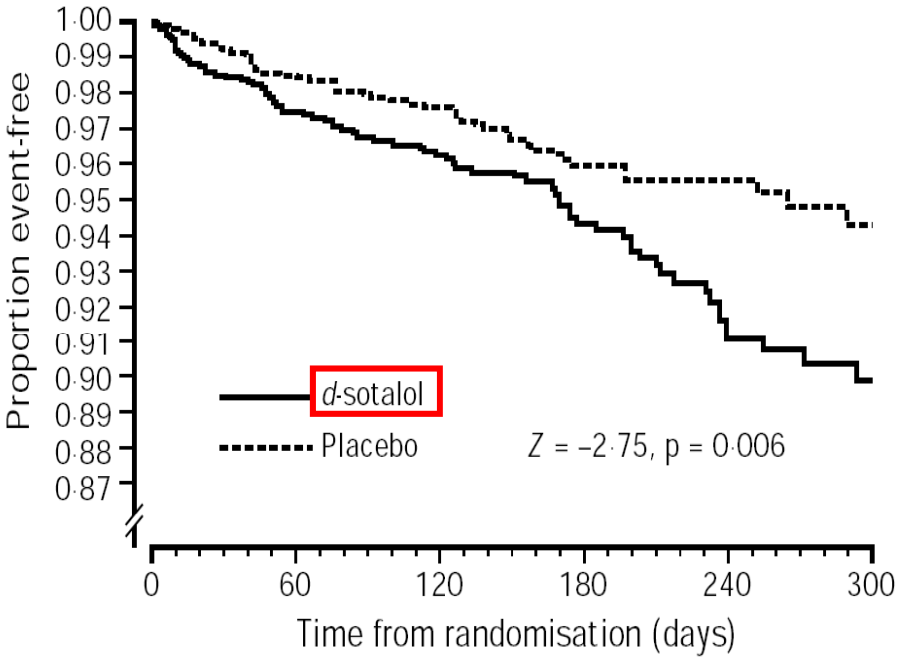
Arrhythmic Mortality / All Cause Mortality

Flecainide & Encainide (Class Ic AAD)



CAST Trial. N Engl J Med. 1989;321:406-12

Sotalol (Class III AAD)

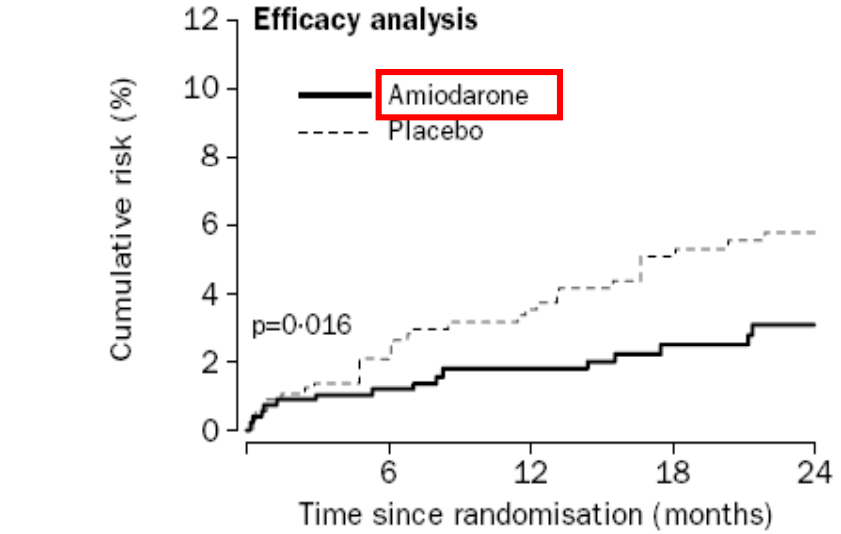


SWORD Trial. Lancet 1996;348:7-12

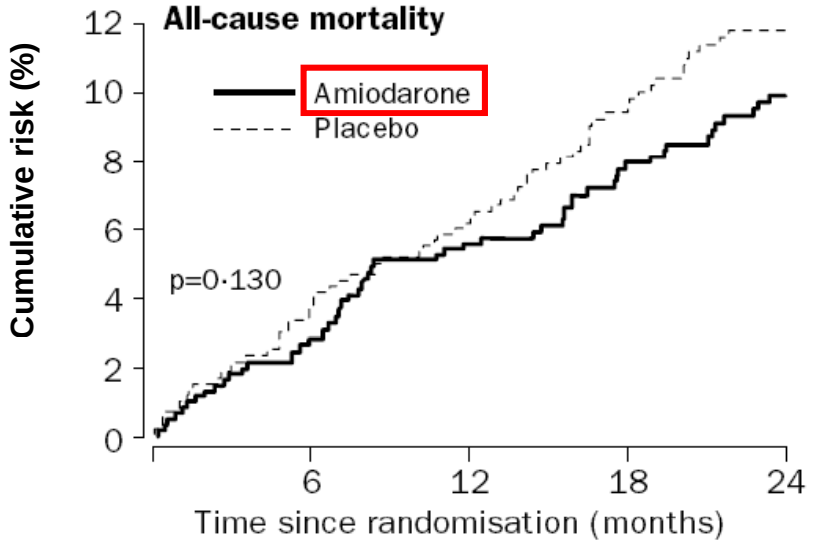
AMD Reduces Arrhythmic Mortality, but not All-cause Mortality.

Amiodarone (Class III AAD)

MI 6~45 days, PVC > 10/hr or VT



Patients at risk					
Placebo	596	523	458	383	336
Amiodarone	606	505	402	325	282

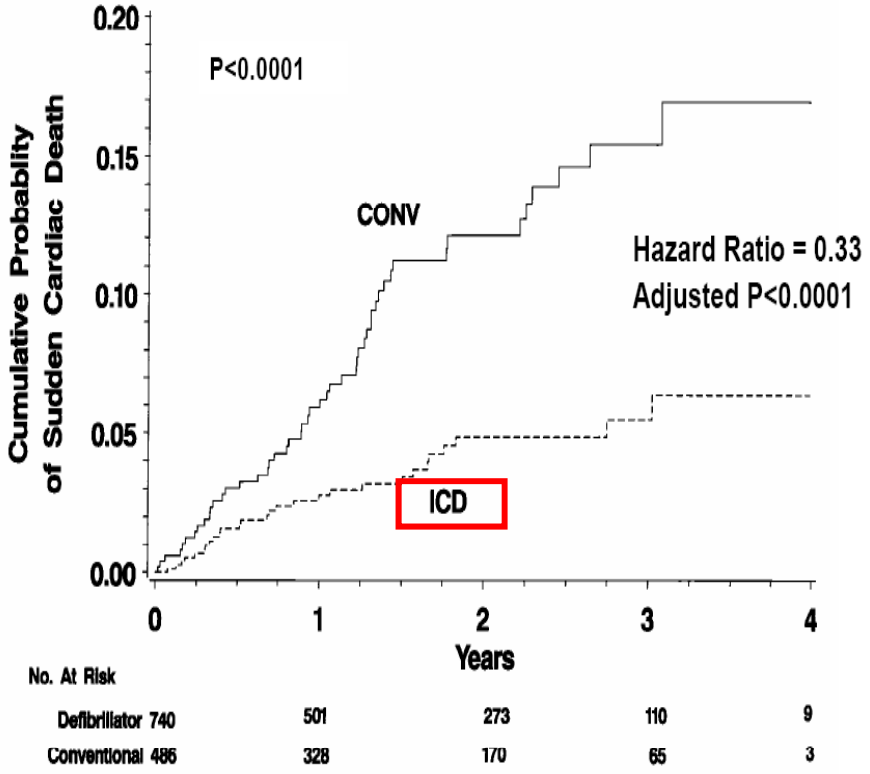


Patients at risk					
Placebo	596	574	556	480	424
Amiodarone	606	589	565	494	435

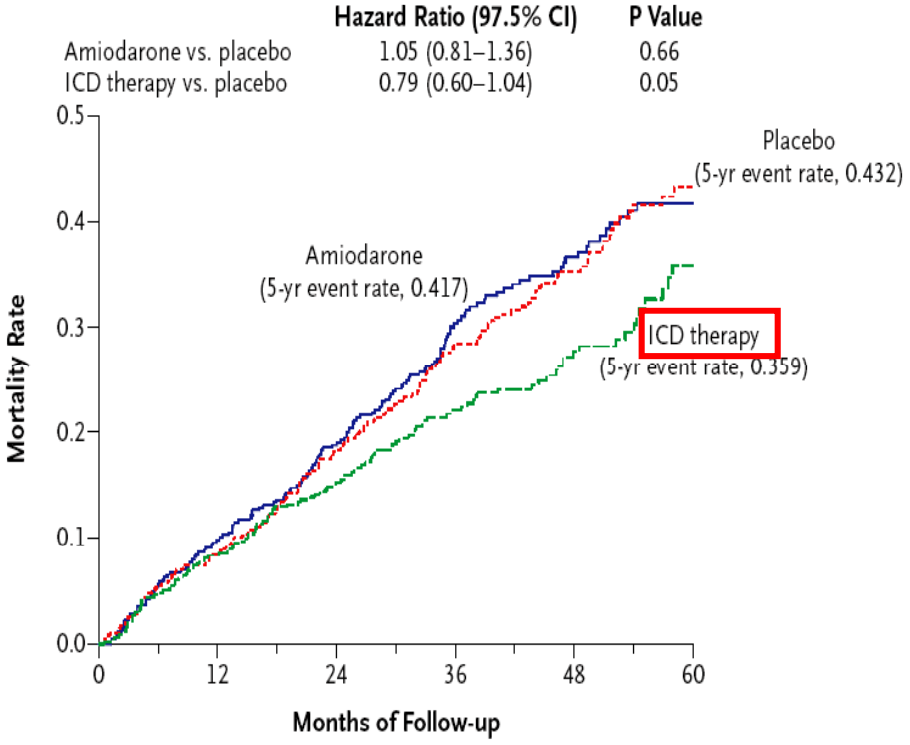
CAMIAT Trial. Lancet 1997;349:675-85

ICD Reduces Mortality in Pt with Ischemic Cardiomyopathy: MADIT-II

MADIT-II Trial
Greenberg et al. JACC 2004



SCD-HeFT Trial.
New Eng J Med. 2005;352:225-37



Benefits of Sinus Rhythm : On Treat Analysis

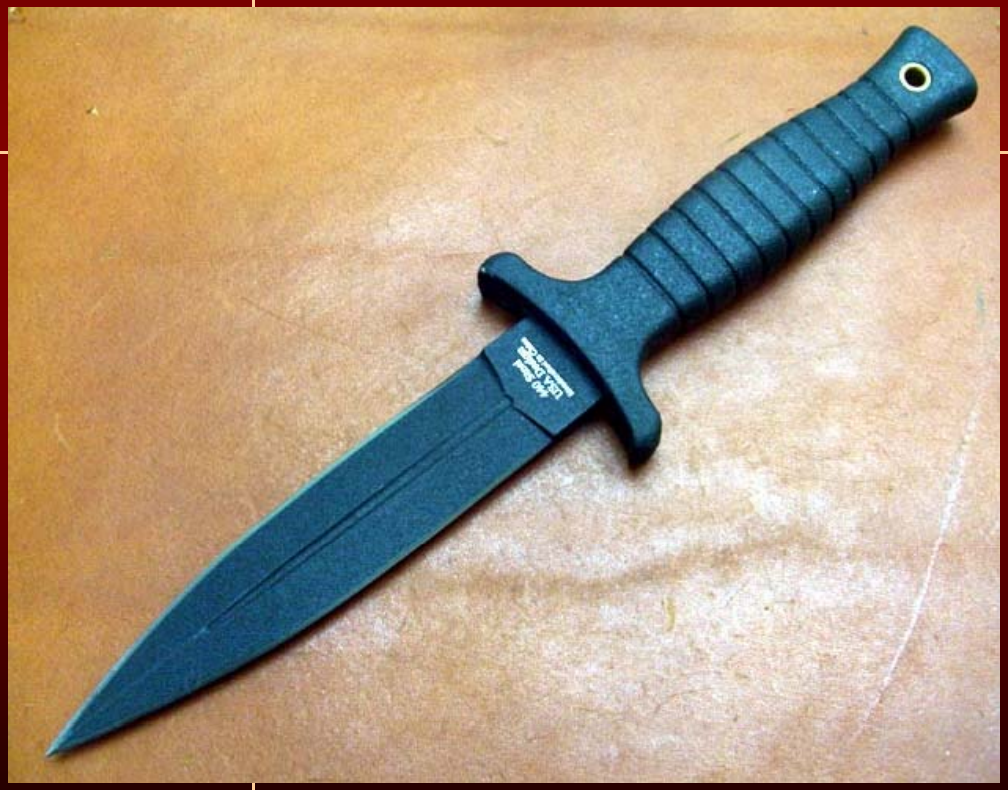
AFFIRM Investigators. Circulation 2004;109:1509-1513

TABLE 2. Covariates Significantly Associated With Survival Results With Echocardiographic Data Included

Covariate	*P*	HR	HR: 99% Confidence Limits	
			Lower	Upper
Age at enrollment*	<0.0001	1.06	1.05	1.08
Coronary artery disease	<0.0001	1.56	1.20	2.04
Congestive heart failure	<0.0001	1.57	1.18	2.09
Sinus rhythm	<0.0001	0.53	0.39	0.72
Warfarin use	<0.0001	0.50	0.37	0.69
Digoxin use	0.0007	1.42	1.09	1.86
Rhythm-control drug use	0.0005	1.49	1.11	2.01

*Per year of age.

그럼에도 불구하고...



Class IC Anti-Arrhythmic Drugs

Flecainide (Tambocor®, Fulcard®)
Propafenone (Rytmonorm®)

- Ix: AF, AT, WPW syndrome, idiopathic VT
- 구조적 심질환 (CAD, HF)이 있으면 금기
  - Proarrhythmia risk
  - CAST Trial
- AF에 사용시 V rate acceleration
  - Digoxin, BB, CCB 등을 병용
- 투약 초기 ECG, LFT 추적 및 기타 부작용에 대한 숙지가 필수

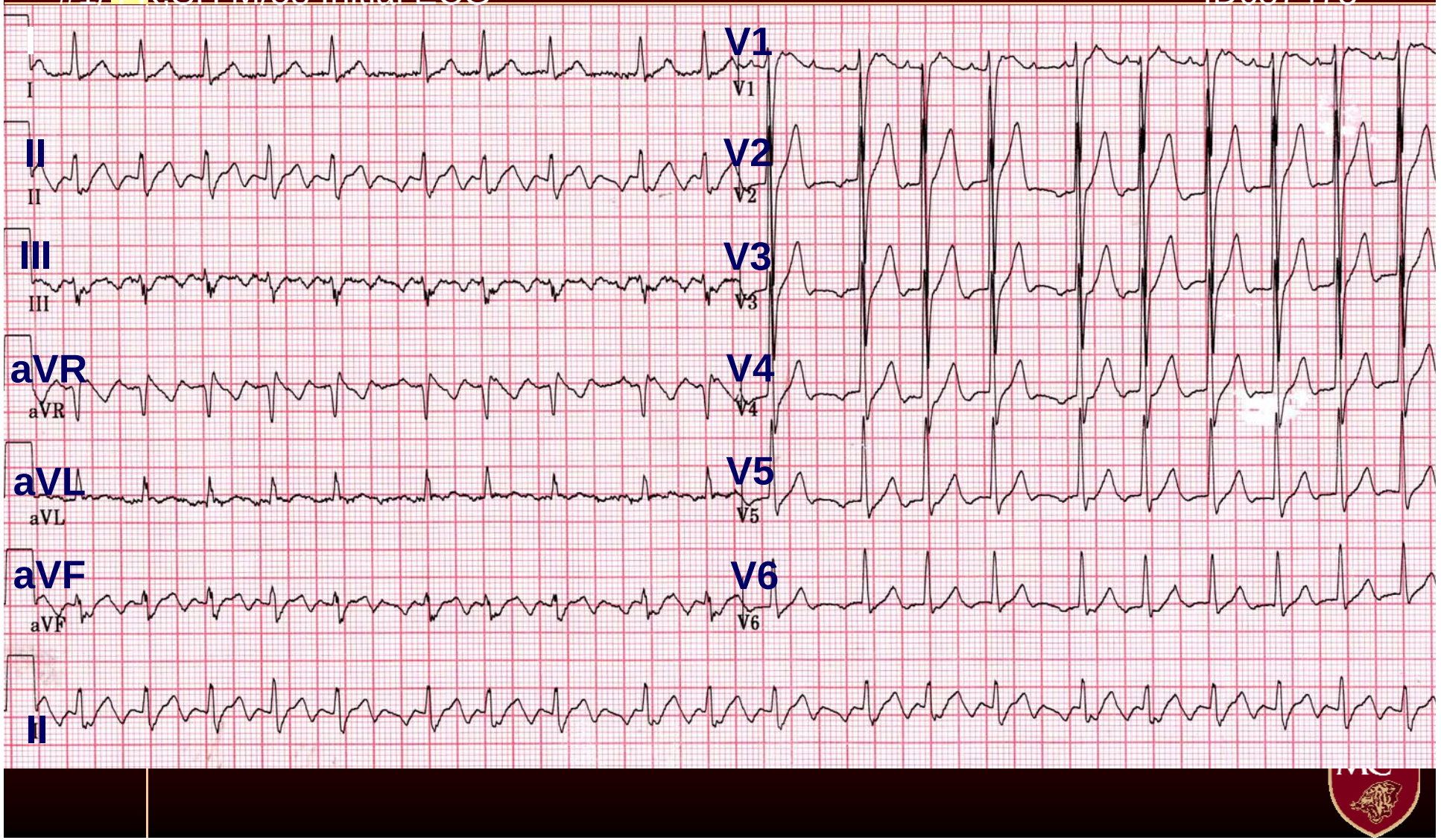
Class IC Anti-Arrhythmic Drugs

- Flecainide (Tambocor®, Fulcard®)
  - 50~100mg BP (max 400mg/day)
  - Heart block, bradycardia, proarrhythmia, HF 악화
  - 소화장애, 간기능 이상, 수면장애
  - 발한, 열감, 피로감
  - 마비, 두통, 어지러움, 시각장애, 배뇨장애

- Propafenone (Rytmonorm®)
  - 150~300 mg TP (max 1200 mg/day)
  - Ikr, β-blocking effect
  - Brady, pause, hypotension, HF 악화
  - 소화장애, 간기능 이상, 감각이상, 두통, 불안증, 근육경련
  - 발진, leukopenia, asthma attack

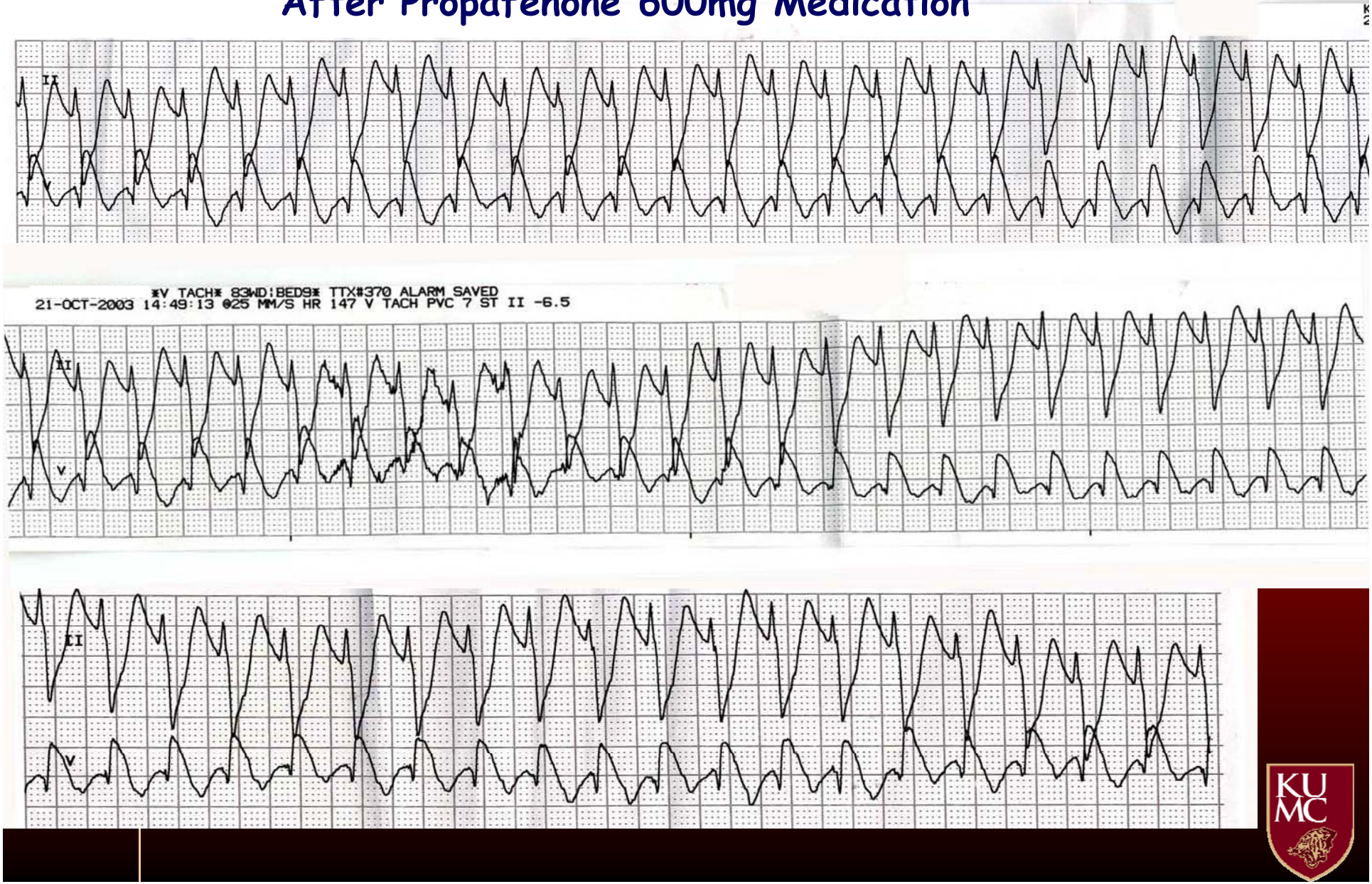
증례1. Use Dependency

M/58 Chest Fluttering



증례1. Use Dependency

After Propafenone 600mg Medication



Q1. Flecainide Over-dose 때 흔히 나타나는 심전도 소견이 아닌 것은?

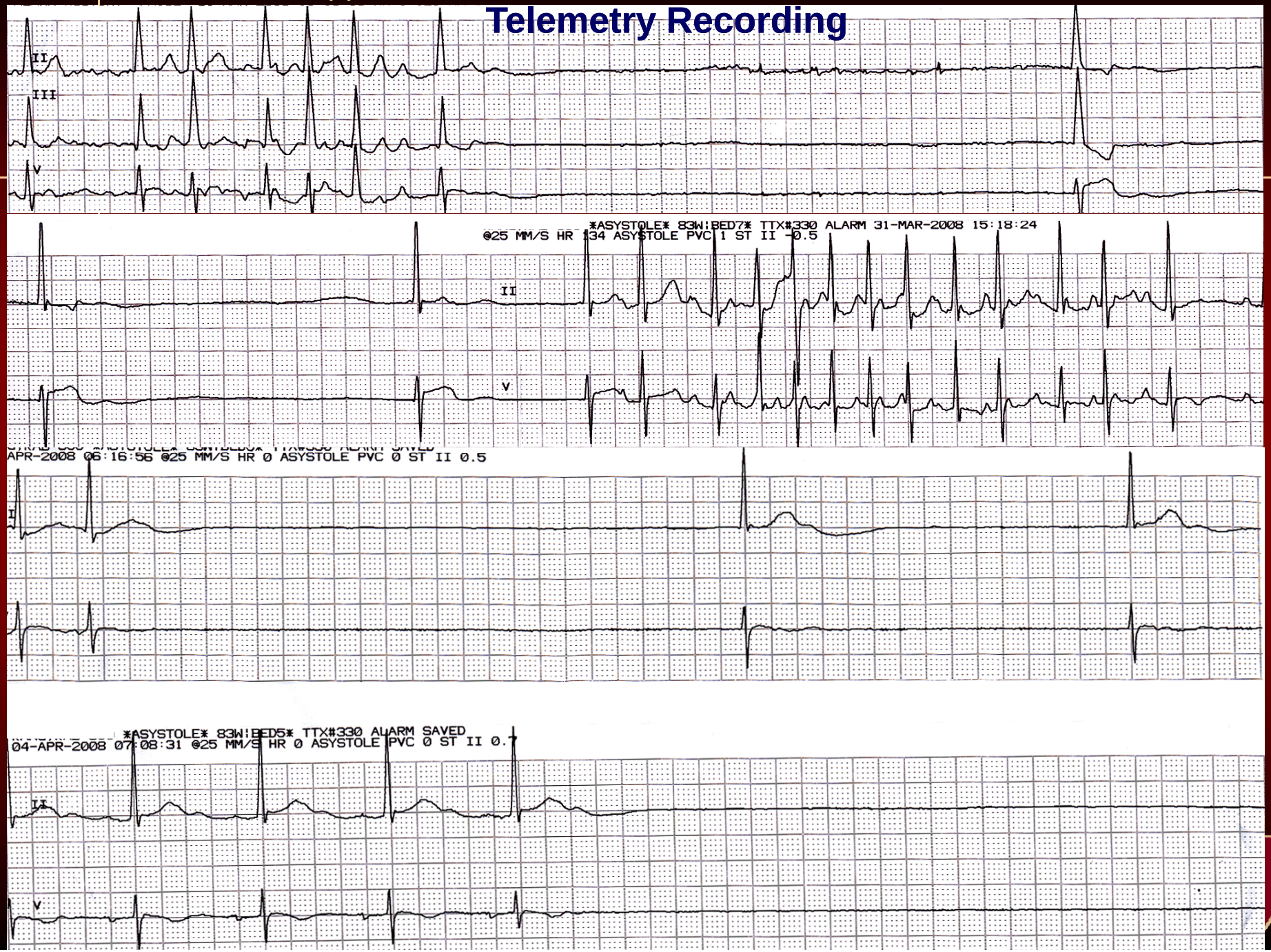
1. Sinus Pause
2. PR Prolongation
3. QRS Widening
4. New Onset RBBB
5. QTc Prolongation

증례2. F/60 PAF, s/p MVR

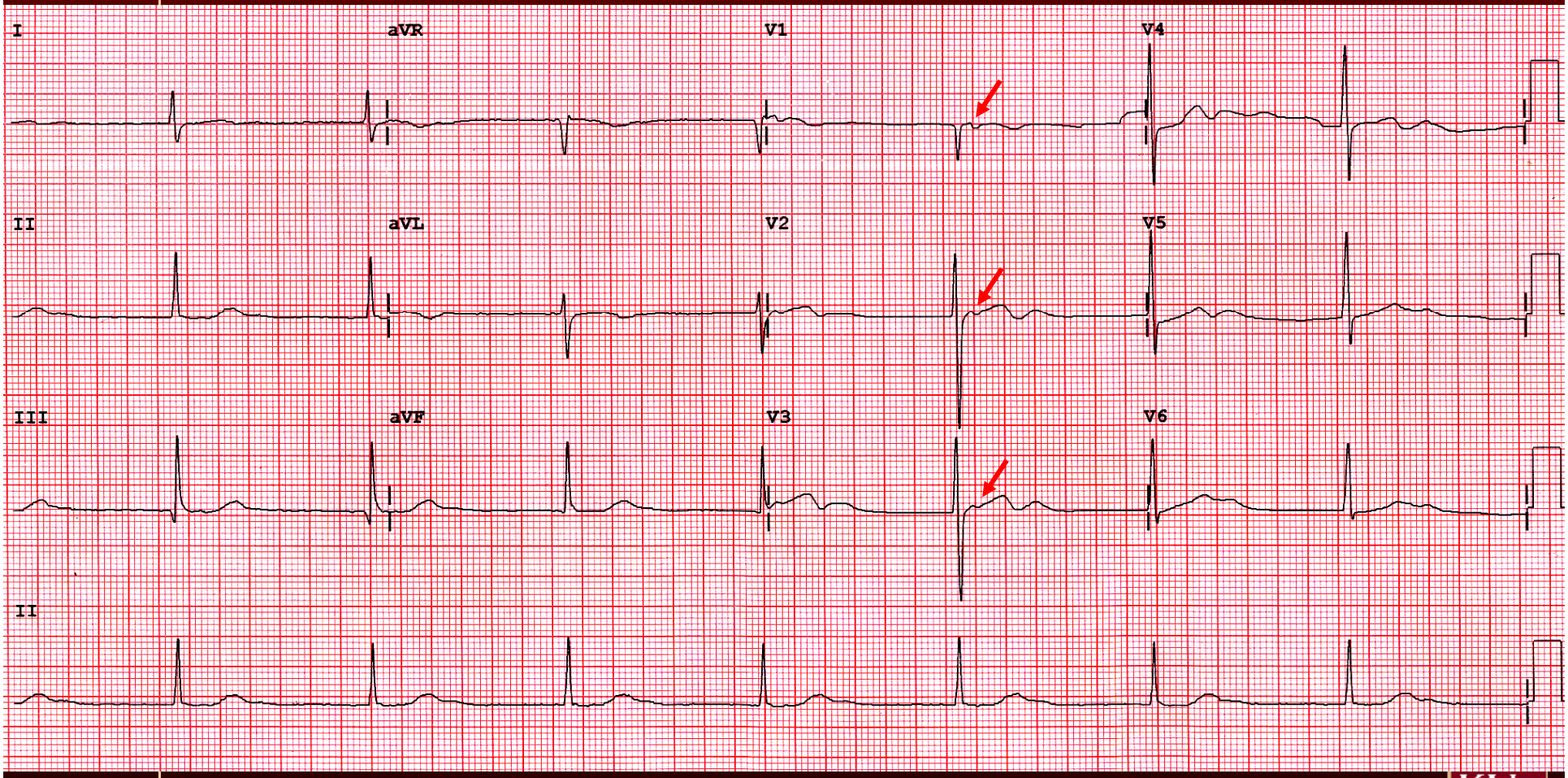
- 3년 전 Mitral stenosis로 MVR 시행한 환자로 수개월 전부터 심계항진과 어지러움증이 반복되어서 내원함.
- 증명된 심전도는 심방세동이었으며 이를 조절하기 위하여 Rytmonorm 225mg BP를 처방함.
- 항부정맥제 투여 후 syncope가 2차례 발생하여 응급실로 내원함.

증례2. Sinus Node Suppression

Telemetry Recording



Sinus Arrest



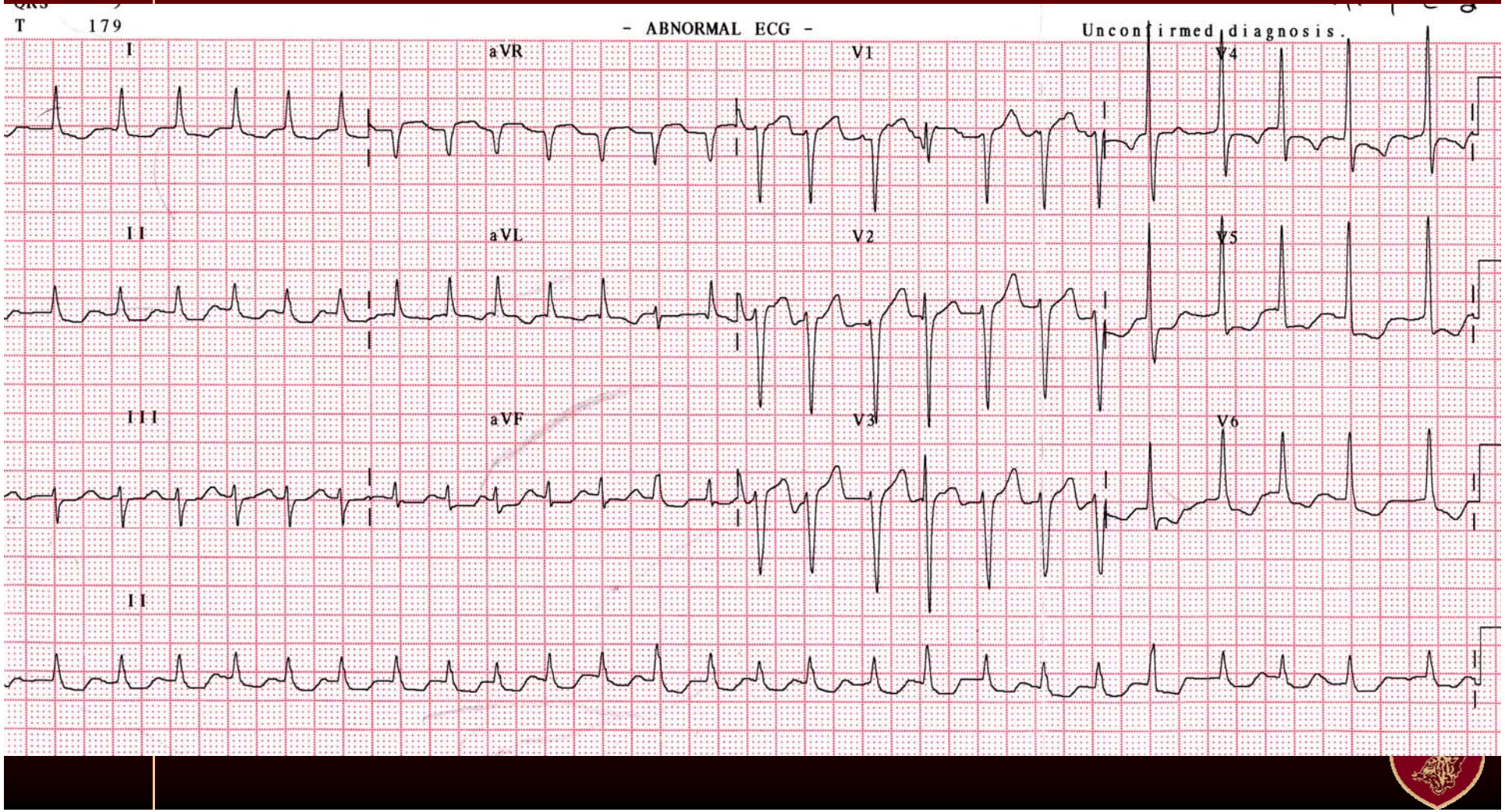
증례3. Pill in the Pocket

M/48, Paroxysmal Chest Fluttering

- 음주 후 발생한 palpitation으로 응급실에 3차례 방문한 병력이 있음. 당시 1시간30분 정도 지속되었음.
- 다른 기질적인 심질환이나 투약력은 없음.
- 평소에도 식후나 음주 후에 5~10분 지속되는 심계항진이 1개월에 1회 정도 있음.
- 심초음파/ Holter / Treadmill ECG : 모두 정상

증례 3. Paroxysmal AF with Minimal AF Burden

ER 내원 당시 심전도



적절한 치료는? ($CHADS_2$ Score 0)

1. 항응고 요법
2. ASA 100mg DP
3. Flecainide 75mg BP
4. Propafenone 300mg BP
5. Pill-in the Pocket

Flecainide 150~200mg/ Propafenone 450~600mg PRN
(Alboni et al. N Eng J Med 2004;351:2384-91)

Class III Anti-arrhythmic Drugs

Amiodarone (Cordarone®)

- I_{Kr}, β-adrenoceptor, I_{Na}, I_{Ca-l} Blocking Effects
- Ix: VT, VF, AF
- 항부정맥 효과가 높고, 심근기능 저하 적다.
- Anti-anginal effect
- 구조적 심장질환이 있은 환자에 적합
- Dosage of Oral AMD
  - VT
    - 400~800mg BP x 2 weeks
    - 200~300mg BP x 1 year
    - 200mg DP afterward
  - AF
    - 300~400mg BP x 2 weeks
    - 200mg BP x 3~6 months
    - 100~200 mg DP afterward
- IV AMD Dosage
  - 5% DW mixture
  - 150~300 mg x 10 min
  - 1 mg/min x 6 hours
  - 0.5 mg/min x 18 hours
  - Maintenance dose: 30~70% of PO dose

Class III Anti-arrhythmic Drugs

Amiodarone (Cordarone®)

- 장기 사용시 부작용 위험이 높다.
  - 75%에서 발생, 18~37%에서 중단
  - Pulmonary fibrosis (5%, 사망률 10%)
    - 3~6개월 간격 흉부 방사선, DLCO
  - Thyroid Dysfunction
  - 간기능 이상, 위장장애
  - 시신경염, 각막 이상, 추체외로 증후군
  - 피부색소 침착
  - 약물 상호 작용 (warfarin, digoxin)

Adverse Reactions of AMD

Goldschlager et al. Arch Intern Med.2000:160:1741-48.

Reaction	Incidence, %	Diagnosis*
Pulmonary	1-20	Cough, especially with local or diffuse infiltrates on chest x-ray film, suggesting interstitial pneumonitis; and decrease in D_LCO from baseline
Gastrointestinal tract	30	Nausea, anorexia, and constipation
	15-50	AST or ALT level greater than 2 times normal
	<3	Hepatitis and cirrhosis
Thyroid	1-22	Hypothyroidism
	<3	Hyperthyroidism
Skin	<10	Blue discoloration
	25-75	Photosensitivity
Central nervous system	3-30	Ataxia, paresthesias, peripheral polyneuropathy, sleep disturbance, impaired memory, and tremor
Ocular	<5	Halo vision, especially at night
	1	Optic neuritis
	>90	Photophobia, visual blurring, and microdeposits
Heart	5	Bradycardia and AV block
	<1	Proarrhythmia
Genitourinary	<1	Epididymitis and erectile dysfunction

KU MC

Cumulative Incidence and Primary Reason for Amiodarone Cessation

	By 12 Months	By 24 Months*	By 36 Months†
Inefficacy	27 (16%)	33 (20%)	40 (25%)
Intolerance	10 (6%)	16 (10%)	19 (12%)
Toxicity	12 (7%)	20 (12%)	30 (18%)
Overall	49 (29%)	69 (42%)	89 (55%)

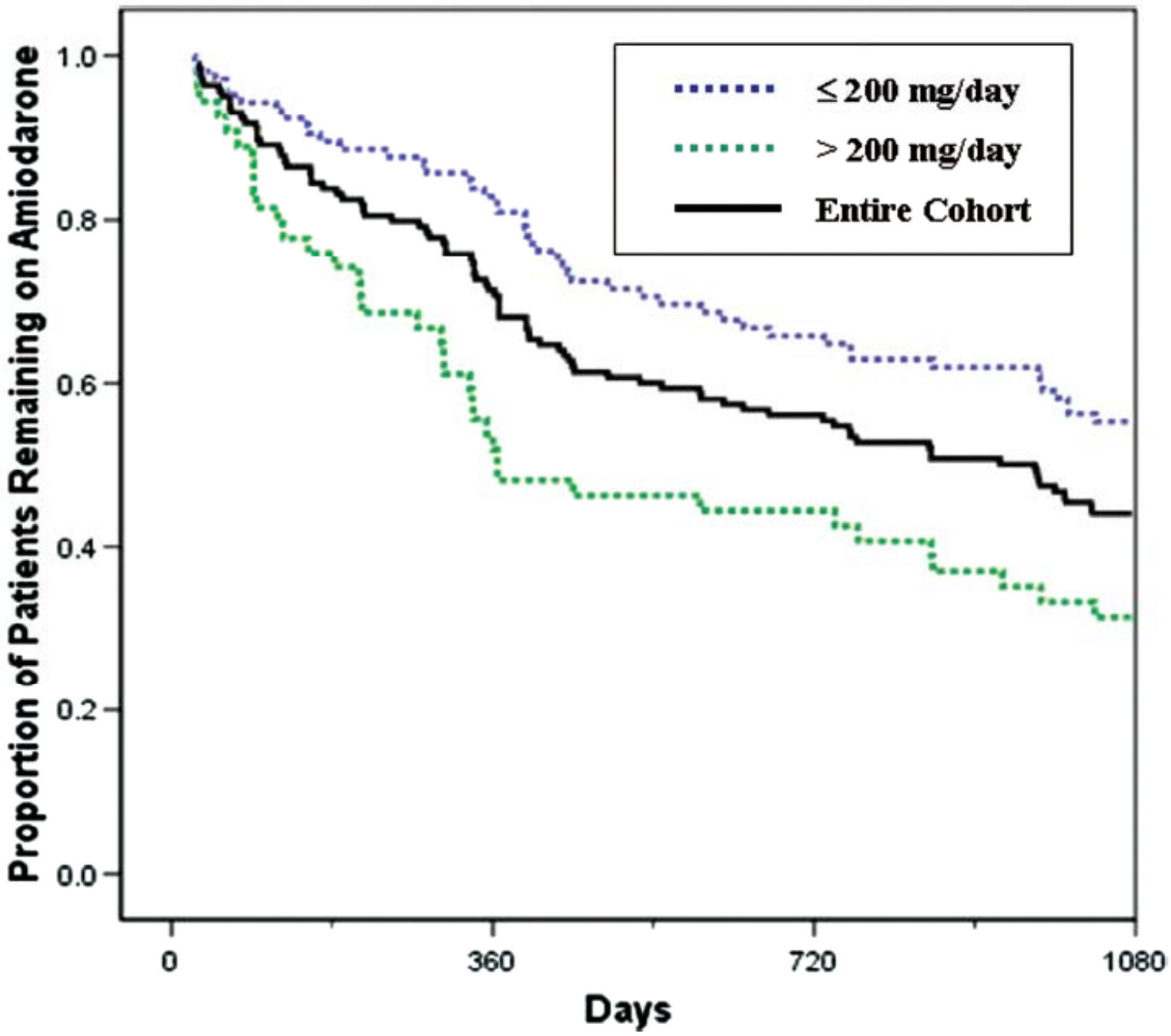
*Based on 165 patients (two deaths and one transplant censured).
†Based on 163 patients (three deaths and two transplants censured).

Cumulative Toxicity Data

	By 12 Months	By 24 Months*	By 36 Months†
Pulmonary (definite)	1 (1%)	5 (3%)	12 (7%)
Pulmonary (possible)	2 (1%)	3 (2%)	3 (2%)
Hepatic	3 (2%)	5 (3%)	5 (3%)
Thyroid	3 (2%)	5 (3%)	7 (4%)
Opthalmic	2 (1%)	3 (2%)	3 (2%)
Cardiac	1 (1%)	1 (1%)	1 (1%)

*Based on 165 patients (two deaths and one transplant censured).
†Based c

Chandhok et al. J Cardiovasc Electrophysiol.2007:18:714



Chandhok et al. J Cardiovasc Electrophysiol.2007:18:714

증례4. Pulmonary Fibrosis

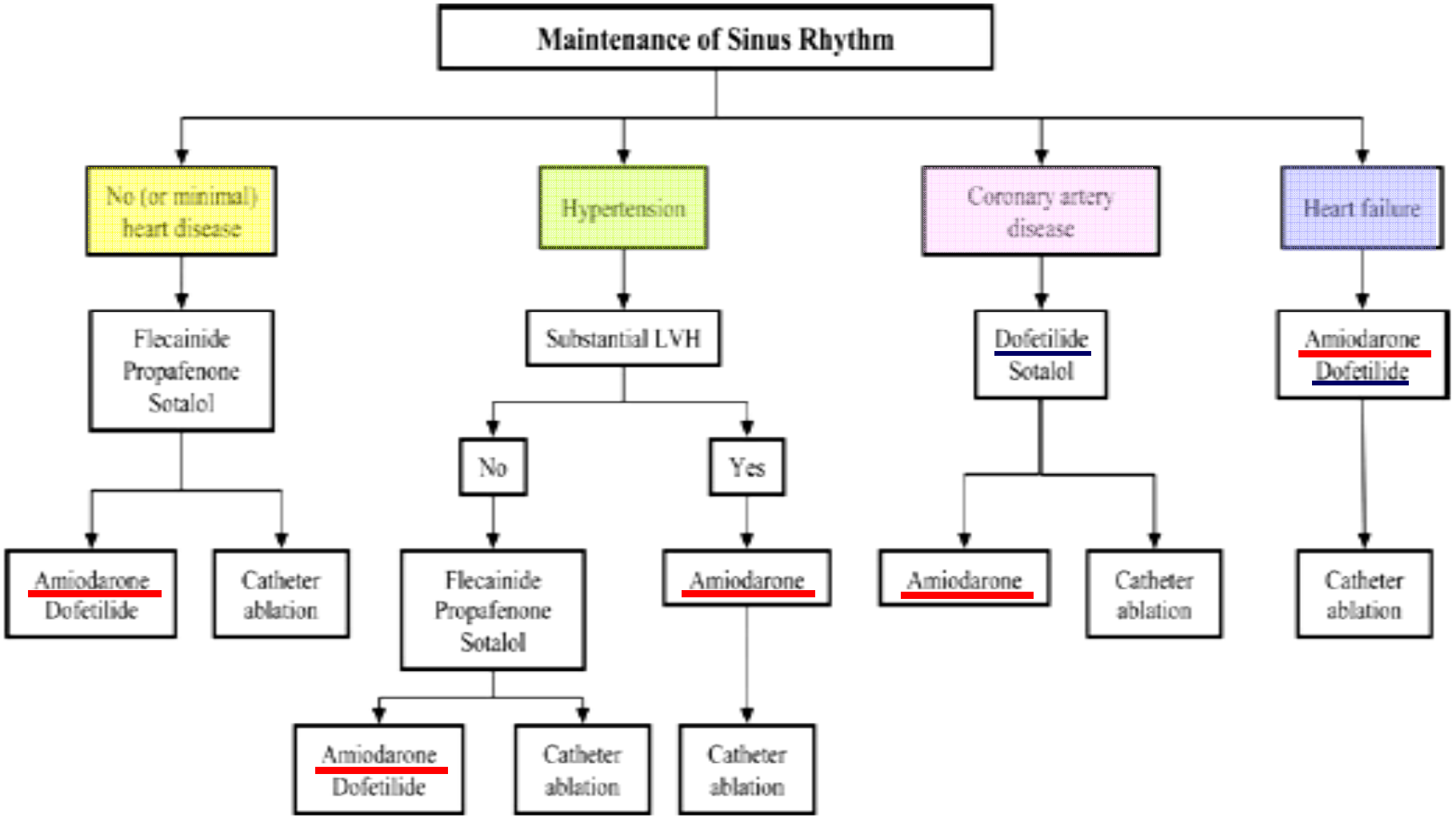
F/74 Persistent AF, s/p RFCA, AMD200mgx4Mo

Recommended Adv Event Monitoring

1. Chest PA, PFT (DLCO), TFT, & LFT (per 3 mo in 1st yr, then per 6 mo)
2. Ophthalmologic Evaluation (6 mo)

Amiodarone: 2nd Line AAD for AF Control

ACC/AHA/ESC Guideline. JACC 2006;4:854



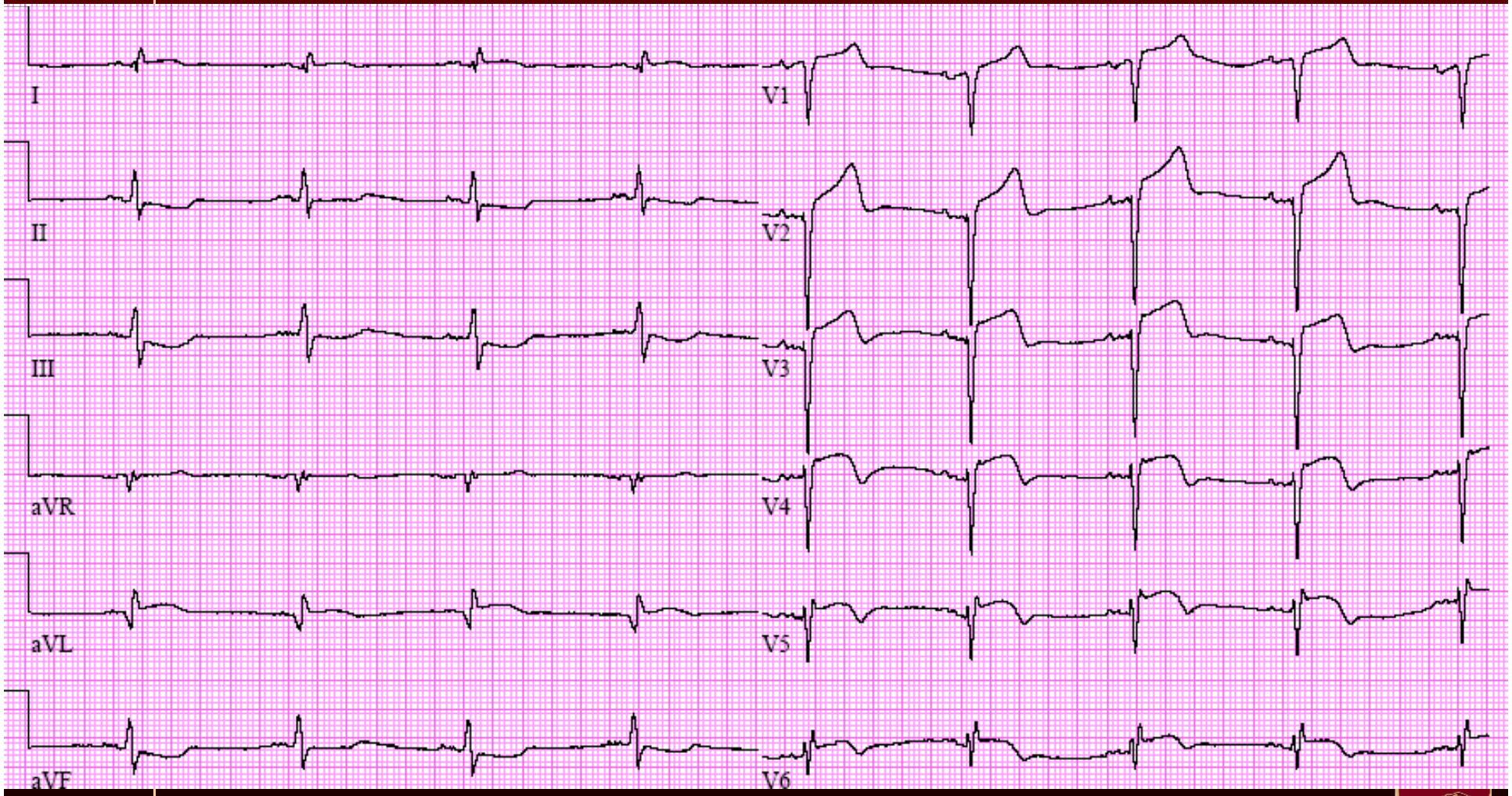
증례 5. Non-sustained VT after AMI

M/64 Chest Pain

- 4년전 급성 전벽 심근경색증으로 primary PCI 받고 지내던 분으로 별다른 증상없이 지내던 중, 1개월 전 clopidogrel 중단 후 내원 2시간 전부터 갑자기 발생한 흉통으로 내원
- 심초음파: EF30%, apical anterior wall akinesia
- Cardiac Enz: minimal increase

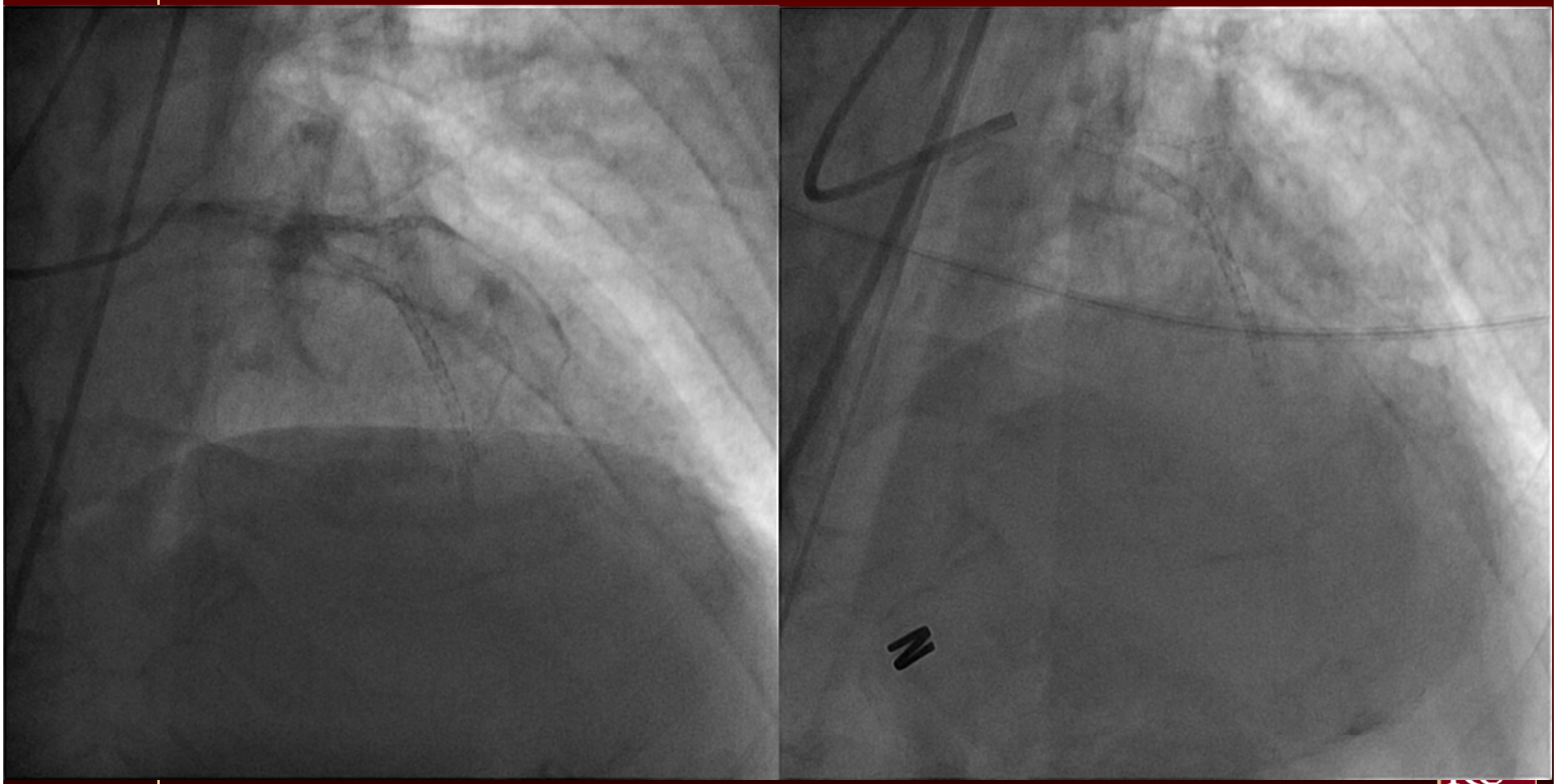
증례 5. NSVT after AMI (EF30%)

ECG



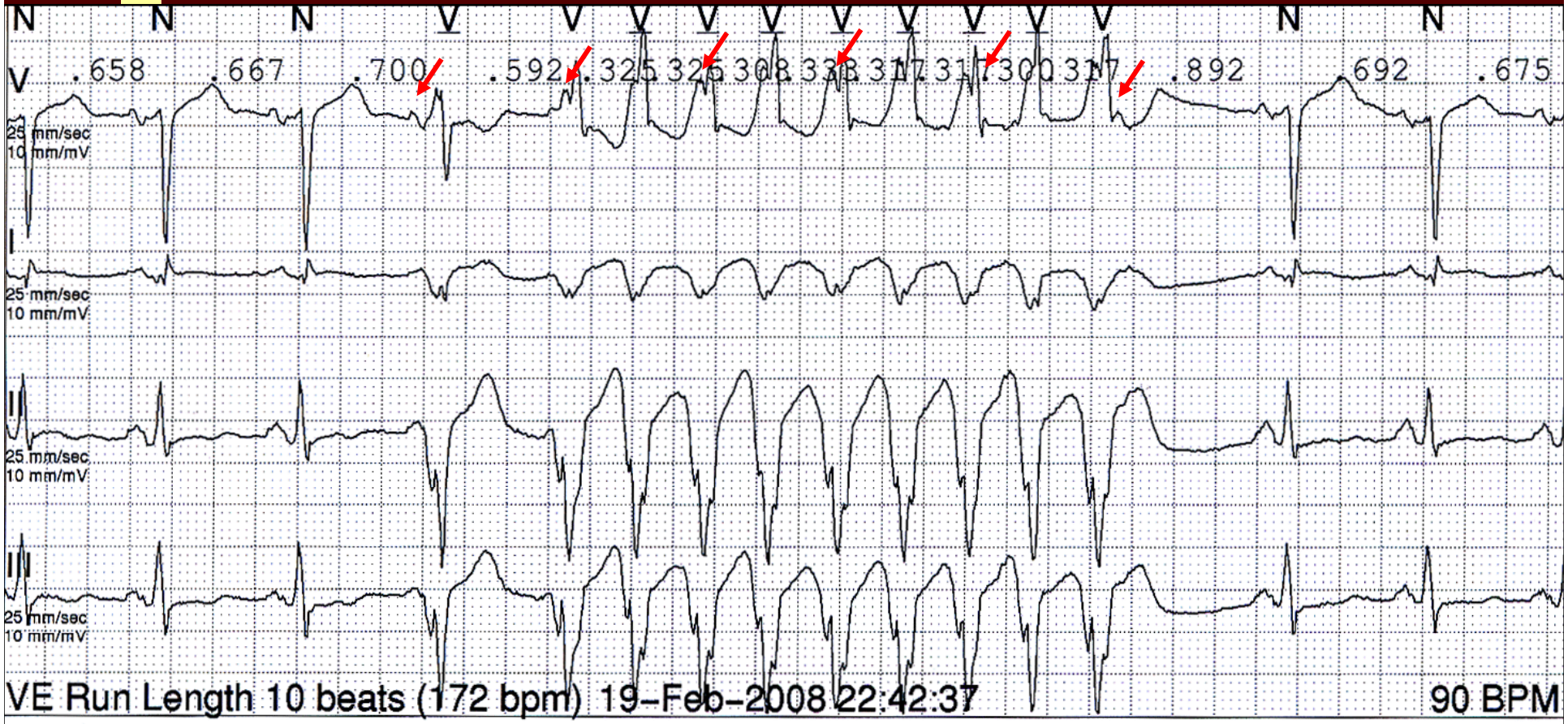
증례 5. NSVT after AMI (EF30%)

PCI



증례 5. NSVT after AMI (EF30%)

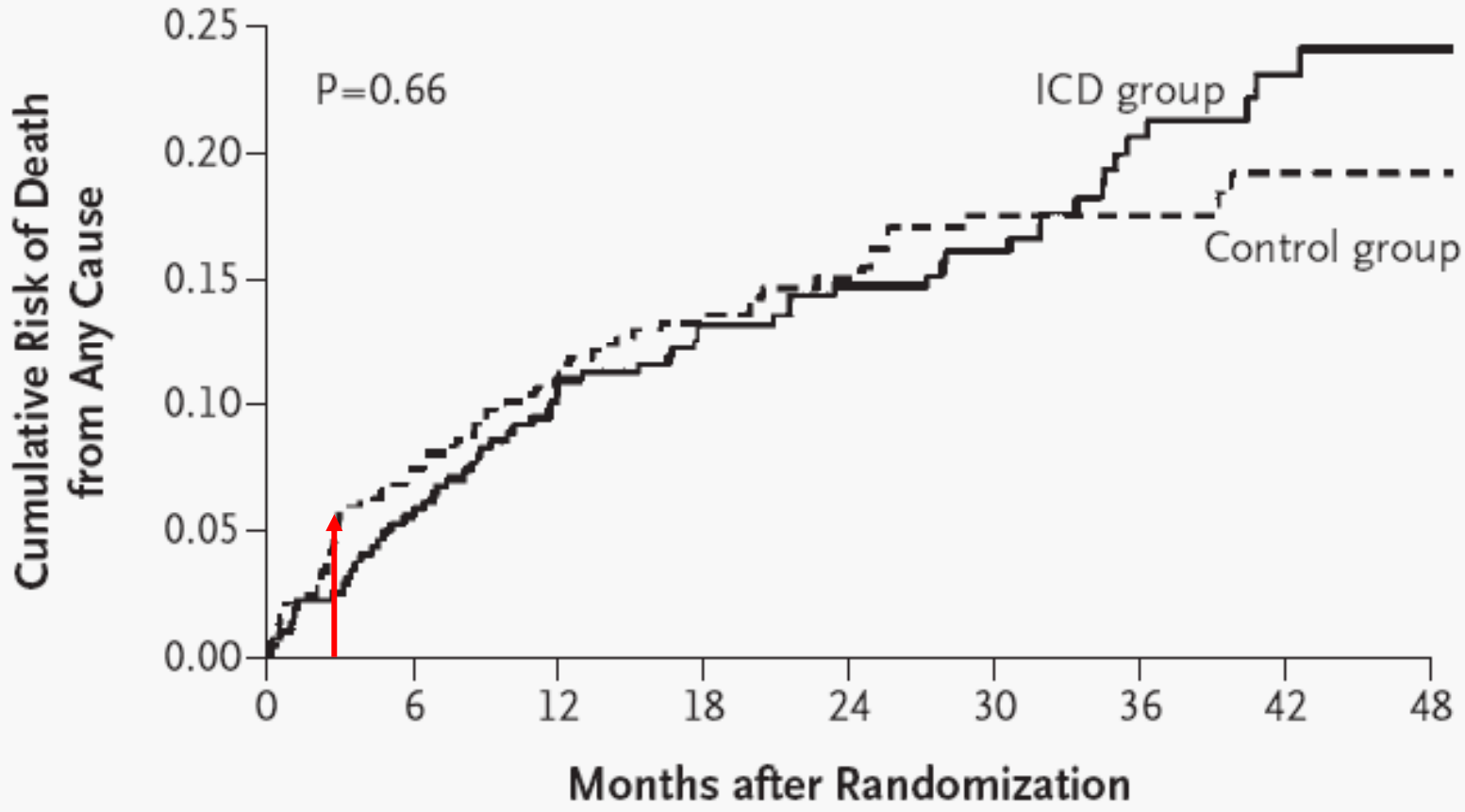
Post-PCI 4 days: No Sx



1. Amiodarone
2. ICD
3. Observation

ICD or Not?

DINAMIT Investigators. N Eng J Med 2004;351:2481-8



No. at Risk								
ICD group	315	299	258	211	172	123	82	25
Control group	318	305	272	217	172	124	79	31

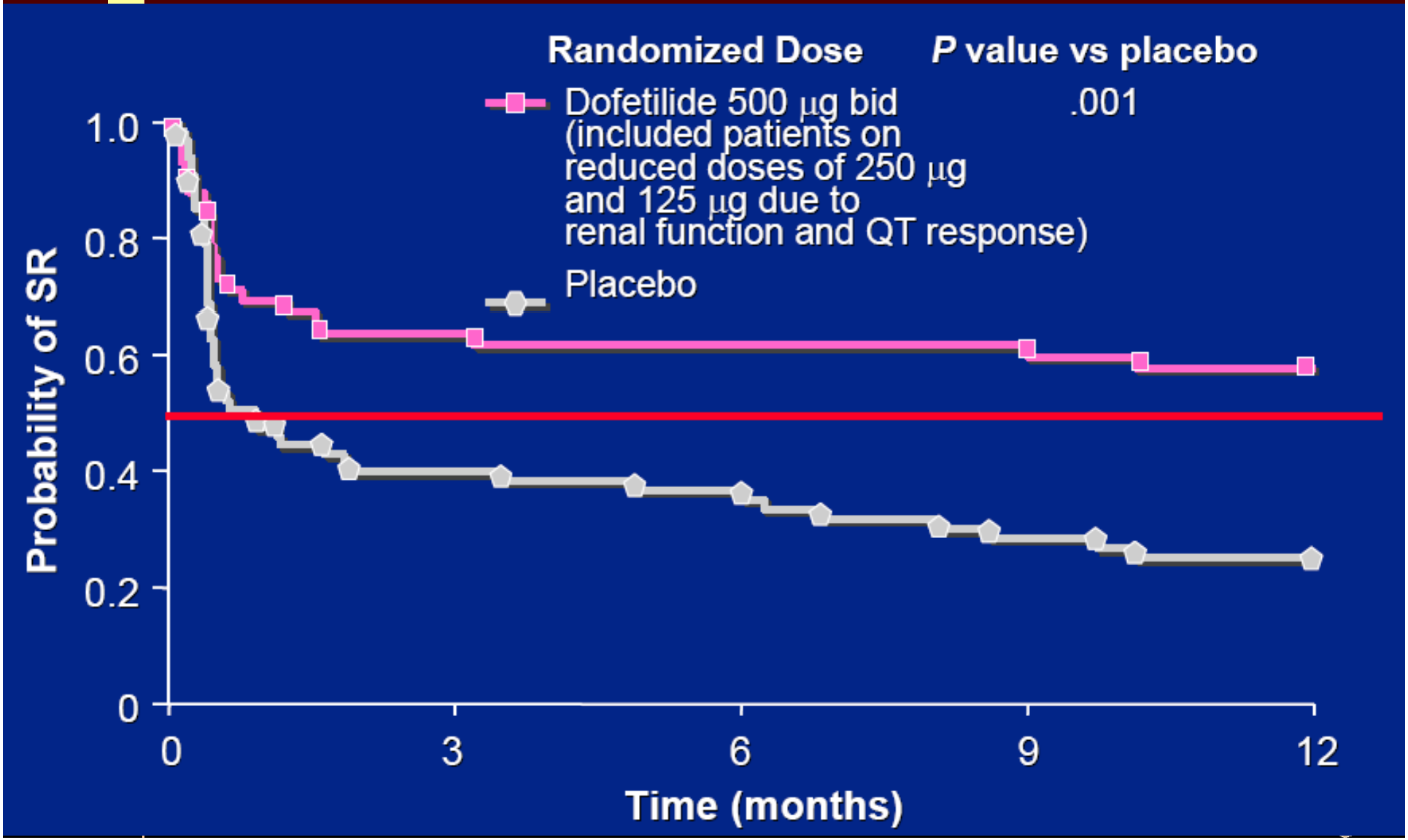
Class III Anti-arrhythmic Drugs
Dofetilide (Tikosyn®)

- I_{kr} Blocker (ERP↑ in A 30%, V 20%)
- Ix: AF, AFL
- QT prolongation, 60%가 신장으로 배설
- Contra-Ix: QTc>440ms, Ccr<20mL/min
- Dose:
  - 0.125~0.25mg BP로 시작
  - QT monitoring < 50%, CRI 환자에서 감량
- Adverse Effects
  - QT prolongation & Torsade de pointes (2-4%)

Dofetilide (Tikosyn®)

SAFIRE-D Trial

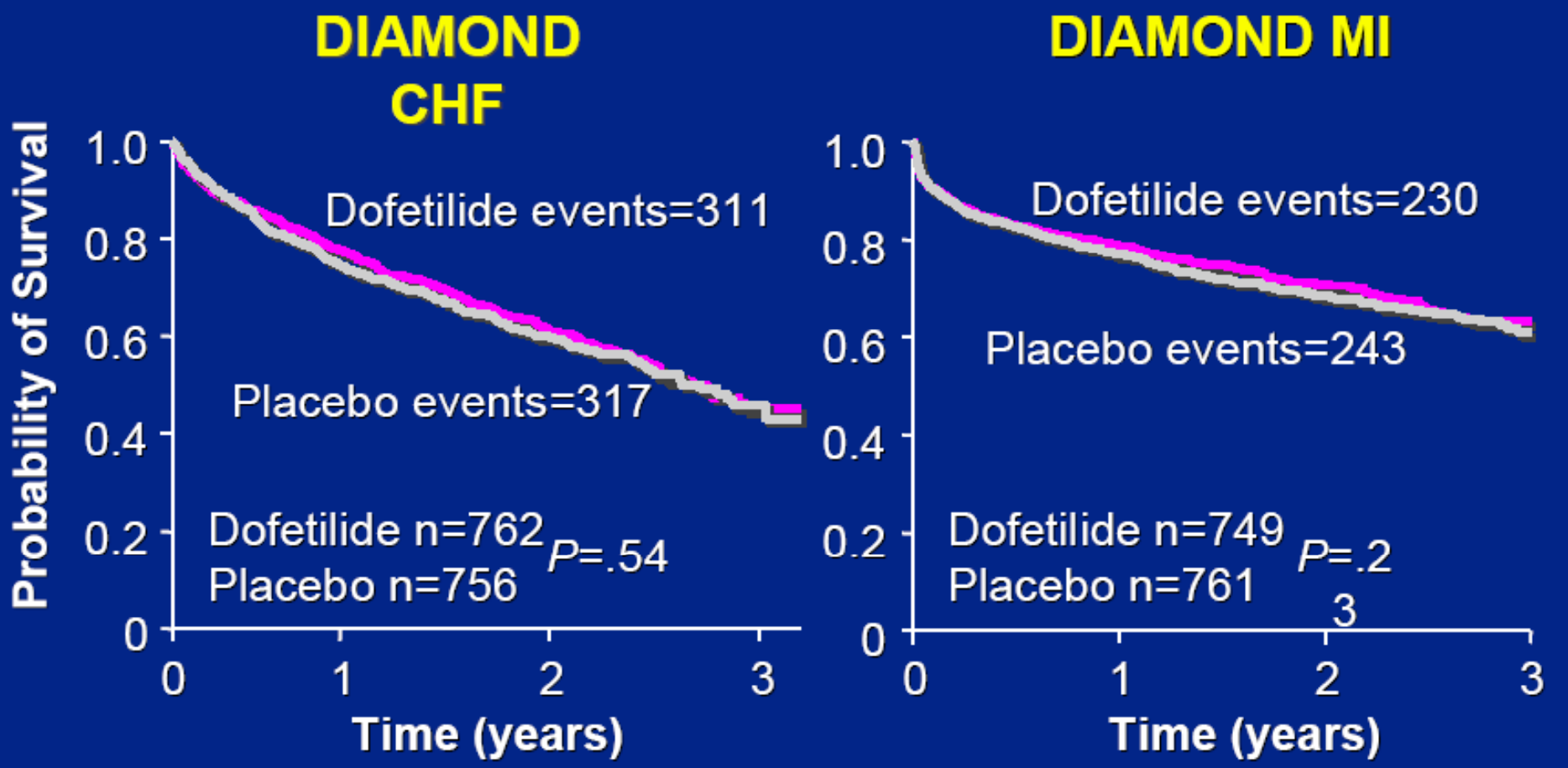
Singh et al. Circulation 2000;102:2385-90.



Dofetilide (Tikosyn®)

Torp-Pedersen et al. N Eng J Med. 1999;341:857-65.

Kober et al. Lancet 2000;356:2052-58.



Class III Anti-arrhythmic Drugs

Ibutilide (Corvert®)

- I_{Ks} Blocker
- Ix: AF, AFL, Pre-excited AF의 동율동 전환
- QT prolongation 심하고, Torsade de pointes 2%
- EKG monitor-defibrillation 준비된 상태에서 사용
- Dose: 1mg IV x 10 min
- 금기: QTc>440ms, hypokalemia, 동율동 유지목적
- 신장으로 배설,반감기 6시간
- 동율동 전환 후 6~8시간 심전도 모니터링

Class III Anti-arrhythmic Drugs

Sotalol (Rentobloc®)

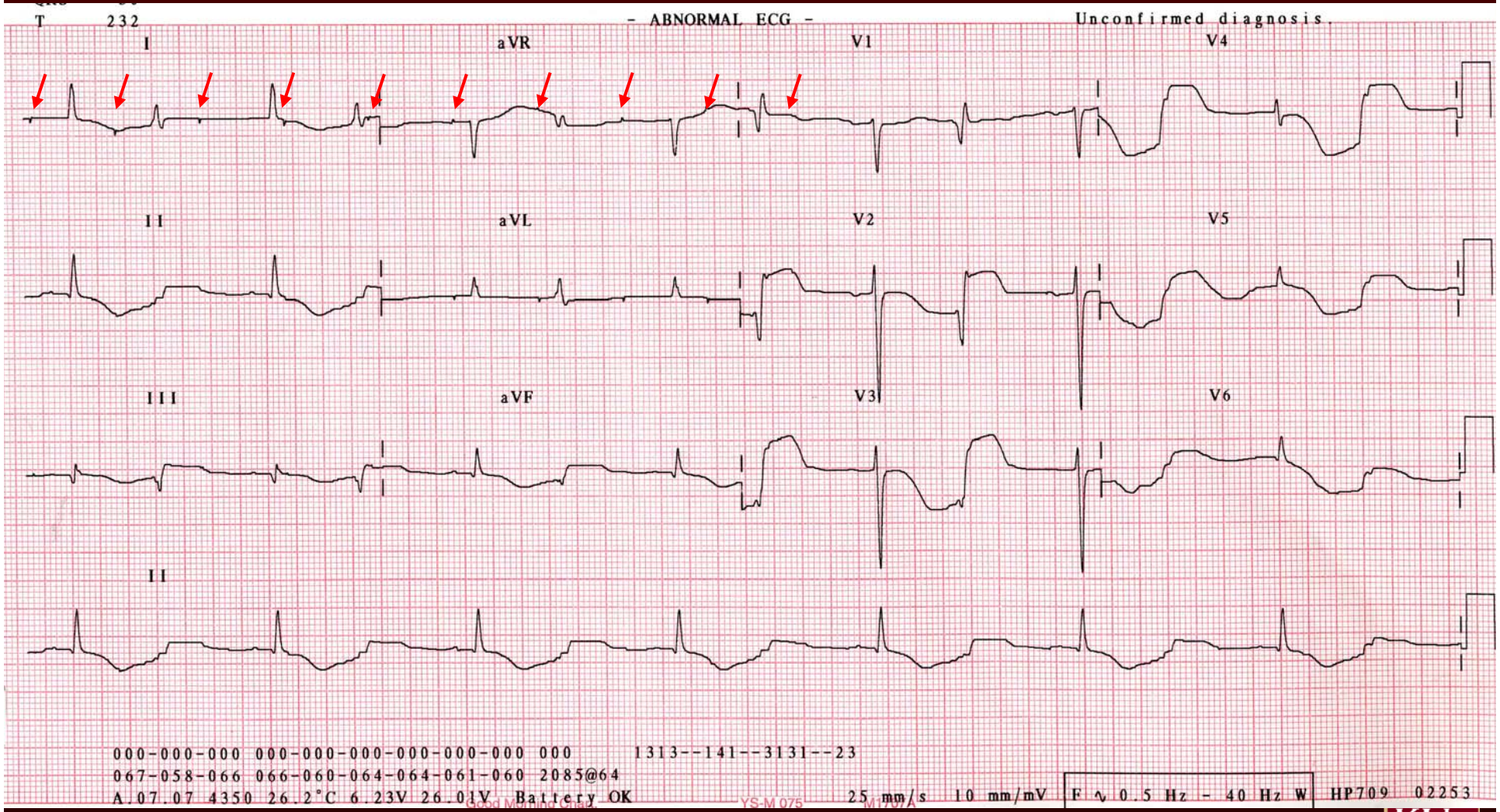
- I_{Kr}, β-adrenoceptor Blocker
- Ix: VT, AF, ARVD, PSVT
- QT prolongation 심하고, 신장으로 배설
- Reverse Use-dependency, DFT 변화적다.
- Dose:
  - 40~80mg BP로 시작, 120~160mg BP까지
  - Max, 480~640mg/ day
  - CRI 환자에서 감량
- Adverse Effects
  - QT prolongation & Torsade de pointes (4%)
  - 심부전 악화
  - Bradycardia

증례6. Reverse Use-Dependency
F/48 Post-DVR

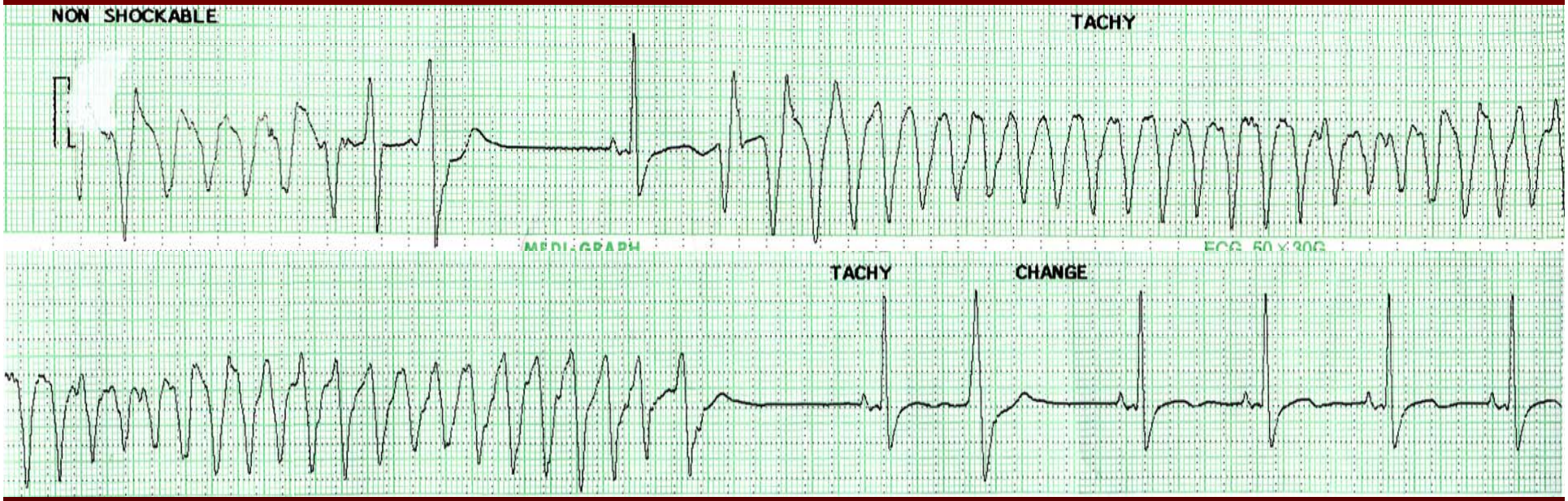
- Sever AS, MSR로 double valve replacement 수술 받으신 분으로 Post-OP arrhythmia로 sotalol 투약 중 severe bradycardia 발생.

- POD#2일, Temporary pacing으로 증상 및 혈압 안정되었으나 새벽 2시 경 서맥이 심해지면서 심전도가 바뀜.

증례 6. Reverse Use-dependency of Sortalol



증례 6. Reverse Use-dependency of Sortalol



Management of Ventricular Arrhythmias

- Anti-arrhythmic Drug
  - Does not improve survival.
  - Only Amiodarone is safe for Pts with CAD.
- Implantable Defibrillator
  - for Pts with High Risk of SCD
  - Definitely improves survival in Pts with HF.
- Catheter Ablation
  - in Pts without a Risk of SCD
  - Frequent ICD Shock/ Electrical Storm

Take Home Messages

- 항부정맥제는 부정맥 억제에 효과적이지 못하다.
- 항부정맥제는 안전하지 않다.
  - 항부정맥제가 도리어 사망률을 증가시킨다 (CAST, SWORD, AFFIRM Trials).
  - 구조적 심장질환이 있는 사람에서는 proarrhythmia의 위험이 있으므로 amiodarone, dofetilide 이외에는 피한다.
  - 항부정맥제의 급성/ 만성적 부작용에 대한 지속적인 모니터링이 필수적이다.
- 심전도로 증명이 된 부정맥에 한해서 심전도로 효과를 확인한 최소 용량을 선택적으로 사용한다.
- Non-pharmacologic Tx에 병용한 Hybrid Tx가 효과적이다.

KU MC

항부정맥제와 OOO Guideline ?

Acknowledgement

Young-Hoon Kim
Hong Euy Lim
Jong Il Choi
Jae Jin Kwak
Jin Kun Jang
Jae Seok Park
Wan Joo Shim
Soon Joon Hong
Sung Mi Park
Sang Yeup Lim

Hyun Soo Lee
Rha Seung Lim
Joon Won Kang
Woong Jin Oh
Kyung Jeong Ko
Ji Young Moon
Jin Nan Kim

Sook Kyoung Kim
Jae Hyung Park

Management of Arrhythmia in Pt c Stable CAD