Fisiopatología de la arritmias
Efectos de los anti arrítmicos

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DEPARTAMENTO DE CARDIOLOGIA

CATEDRA DE FISIOLOGÍA

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Drogas anti arrítmicas

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VAUGHAN WILLIAMS CLASSIFICATION

Class I: block Na^+ channels

Ia (quinidine, procainamide, disopyramide) (1-10s)

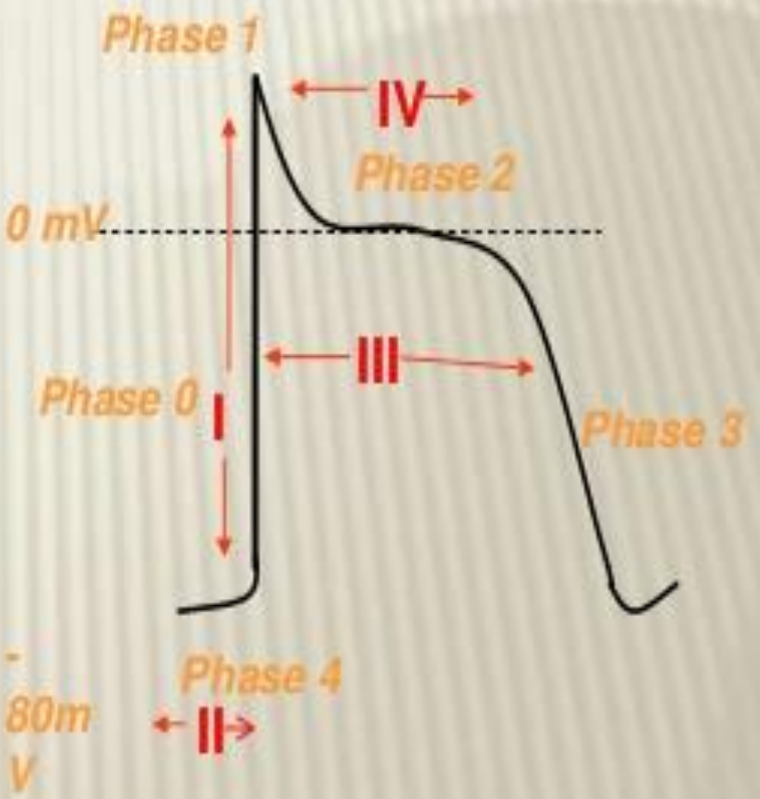
Ib (lignocaine) (<1s)

Ic (flecainide) (>10s)

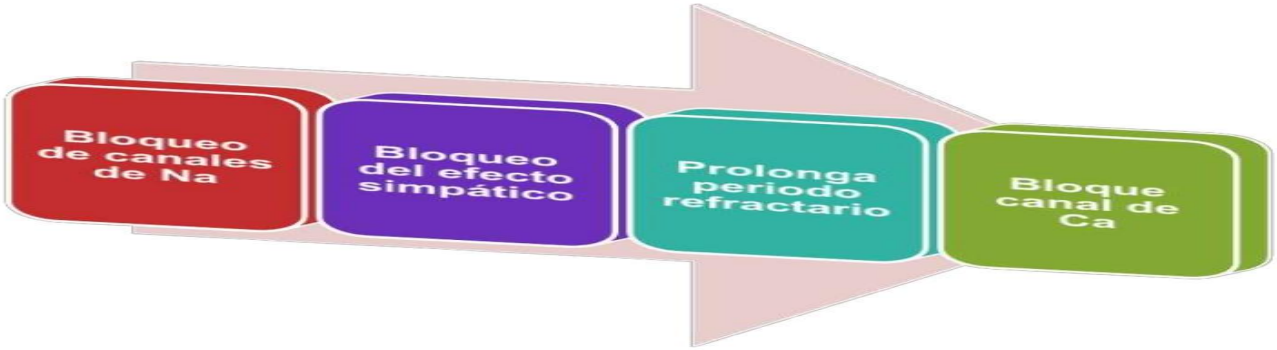
Class II: ß-adrenoceptor antagonists (atenolol, sotalol)

Class III: block K^+ channels (amiodarone, dofetilide,sotalol)

Class IV: Ca^{2+} channel antagonists (verapamil, diltiazem)



MECANISMOS DE ACCIÓN GENERAL



I

Bloqueo de canal de Na→ Potencial de acción

II

Bloqueo Simpático (beta)

III

prolongan PA: Bloqueo canal K.

IV

Bloqueo de calcio

Disminuyen conducción (PA)

Disminuyen excitabilidad

Disminuyen conducción y p. refractario

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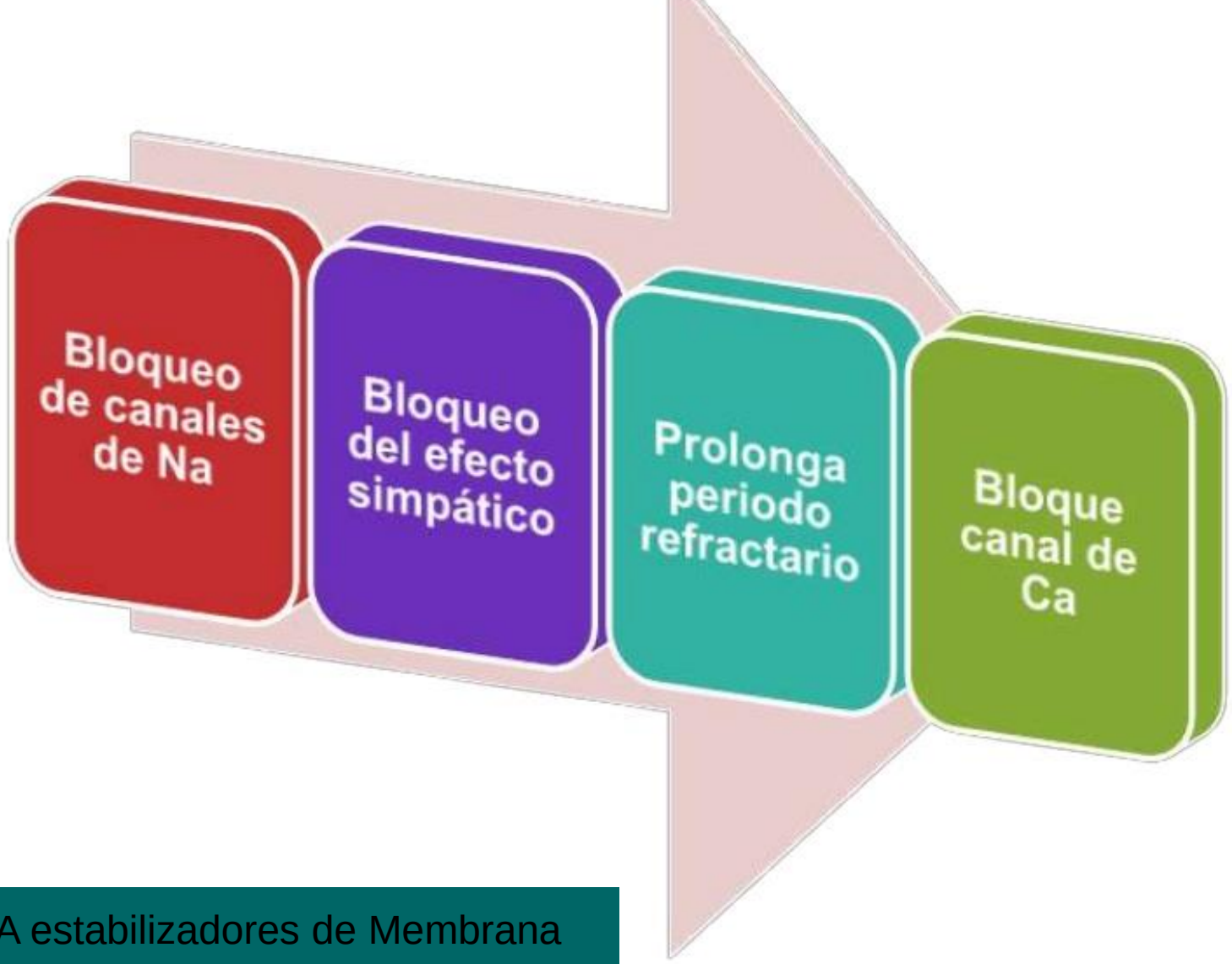

Clase I	FAA estabilizadores de Membrana
Clase II	Beta-bloqueantes
Clase III	FAA que prolongan la duración del PA
Clase IV	Calcio antagonistas

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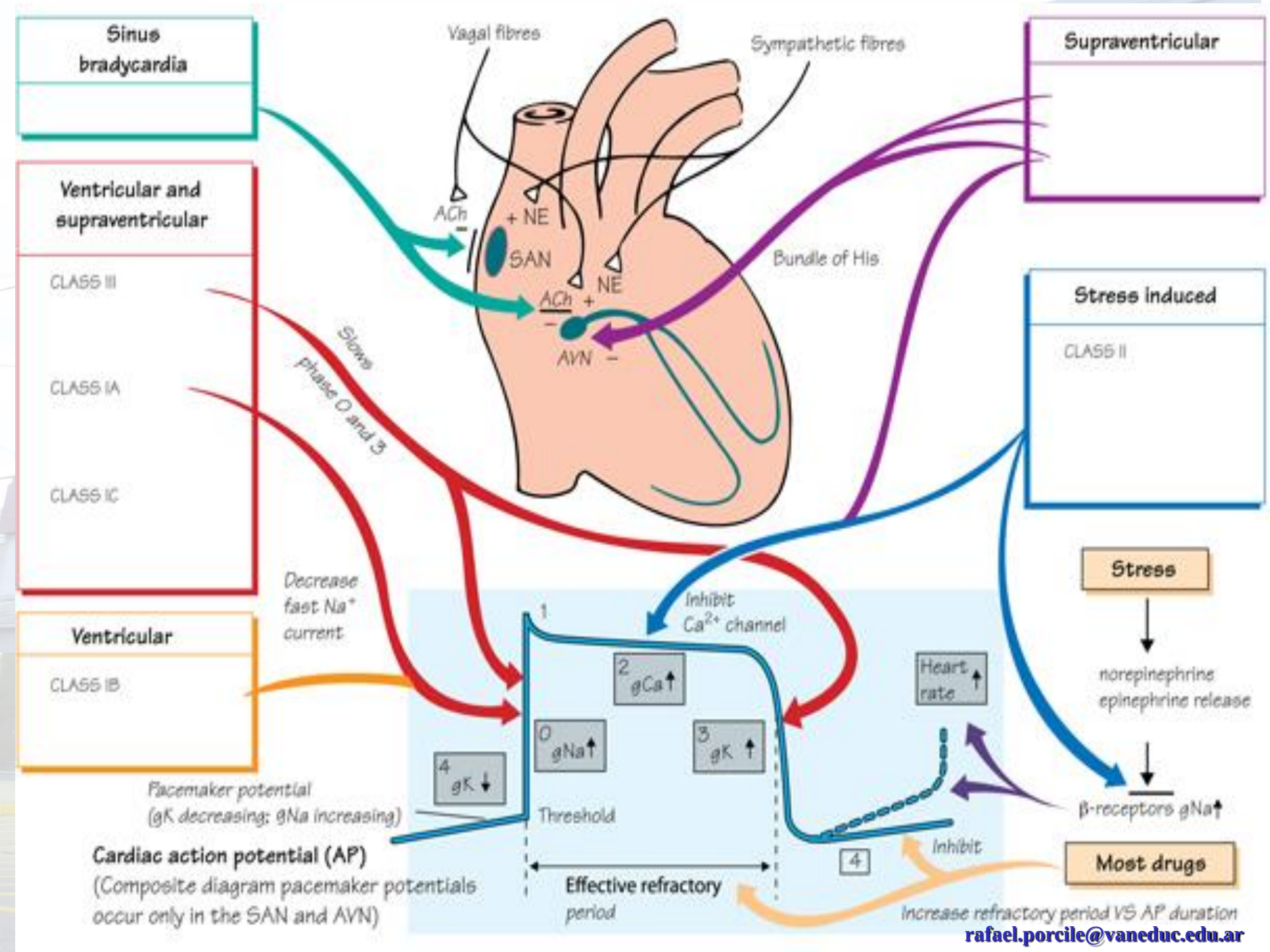

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Grupo III

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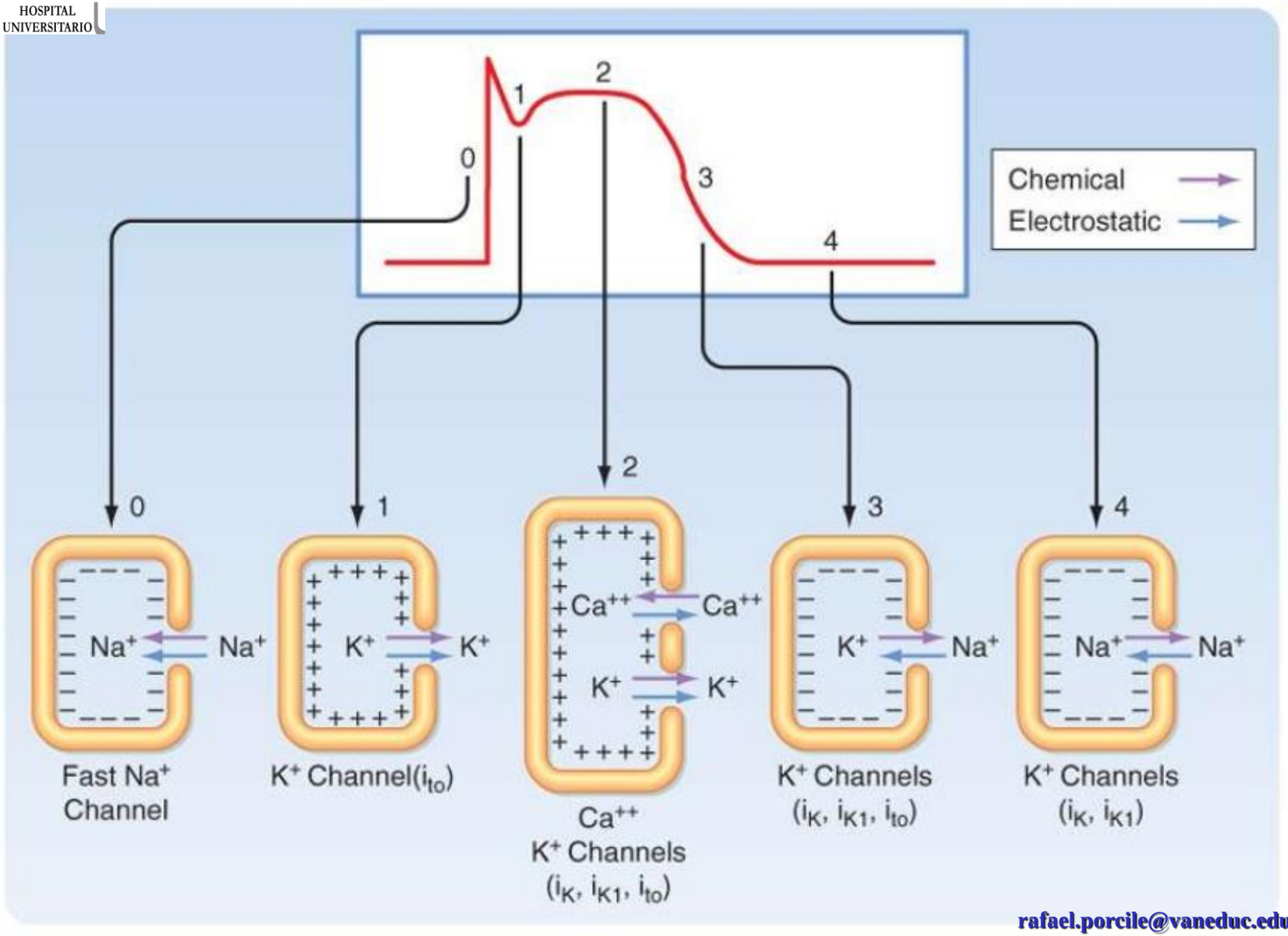

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¿Como modifican el potencial de acción?

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Clase III:

Bloquean los canales de K+:

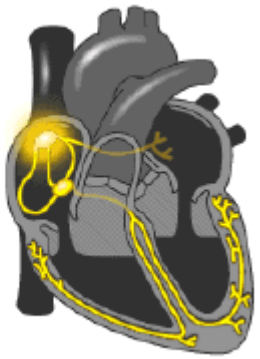
Amiodarona
Sotalol
Bretilio
Dromedarona

Clase IV:

Antagonistas de los canales de Calcio

Otras:

Adenosina
Digoxina



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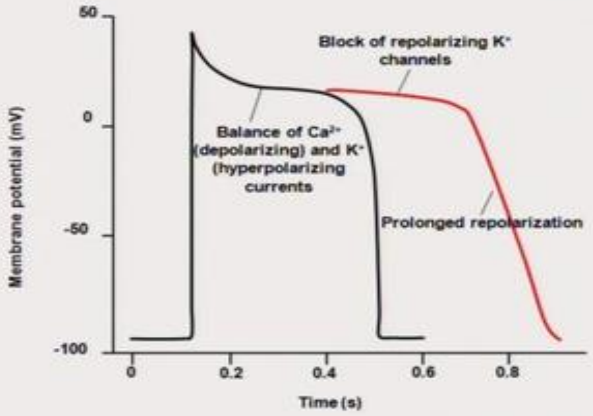
Class III Antiarrhythmics

K⁺ channel blockers



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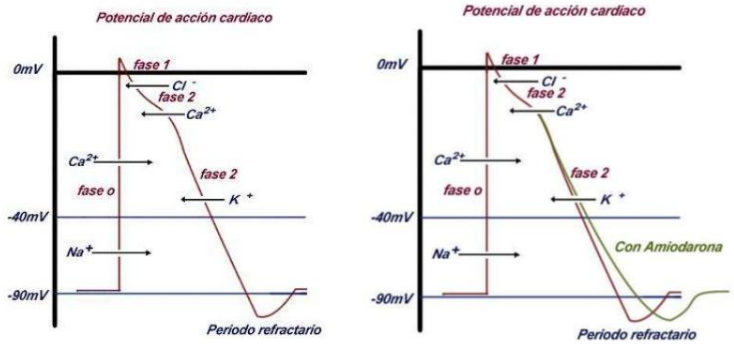
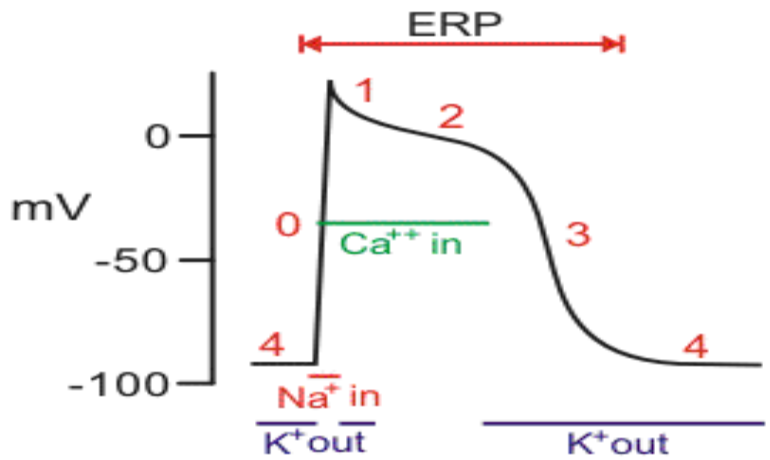
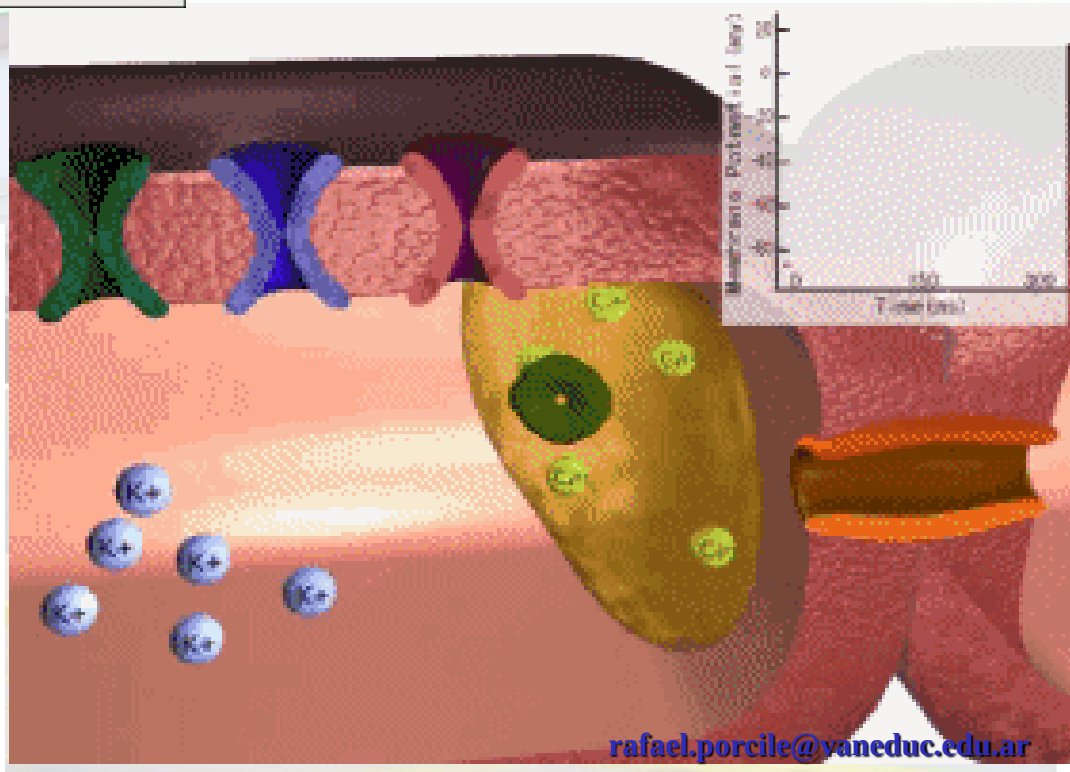
Amiodarona



Fast-Response Action Potential

(e.g., ventricular myocyte)





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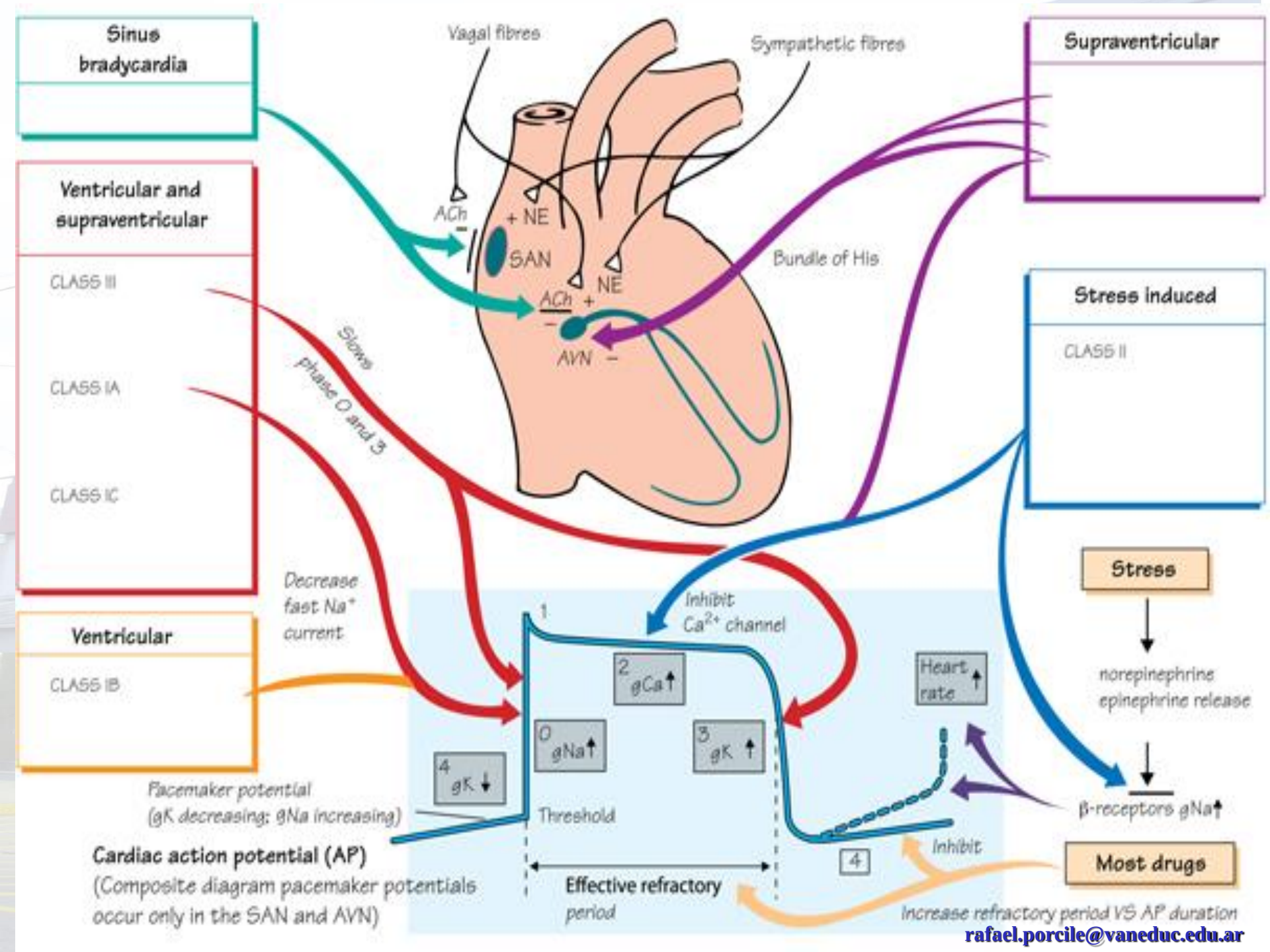

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RECONOCIMIENTO A NUESTROS MAYORES

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En la década de 1970, Rosenbaum realizó ensayos clínicos en el tratamiento de pacientes afectados por arritmias cardíacas con el anti arrítmico **amiodarona**. La labor específica consistió en ensayos para el tratamiento de sus pacientes que sufrían de arritmias ventriculares y supraventriculares con resultados notables. Asimismo, basados en los artículos escritos por Rosenbaum aplicando las teorías de Singh, algunos médicos en los Estados Unidos empezaron a prescribir amiodarona a sus pacientes con arritmias que potencialmente requerían tratamiento continuo, a finales de la década de 1970

20 de agosto de 1921 - 4 de mayo de 2003
médico cardiólogo argentino

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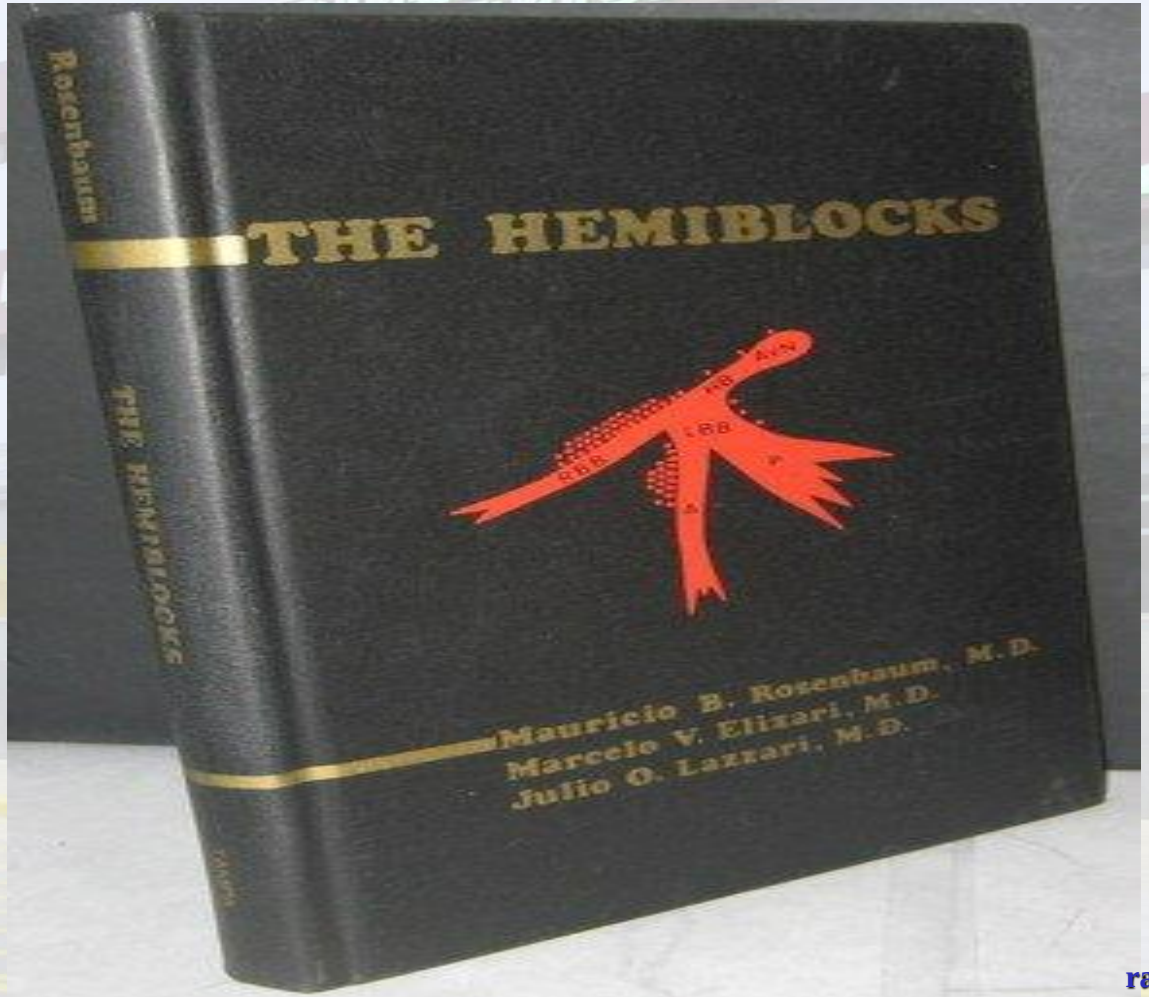
DESCRIBIO POR PRIMERA VEZ LOS HEMIBLOQUEOS



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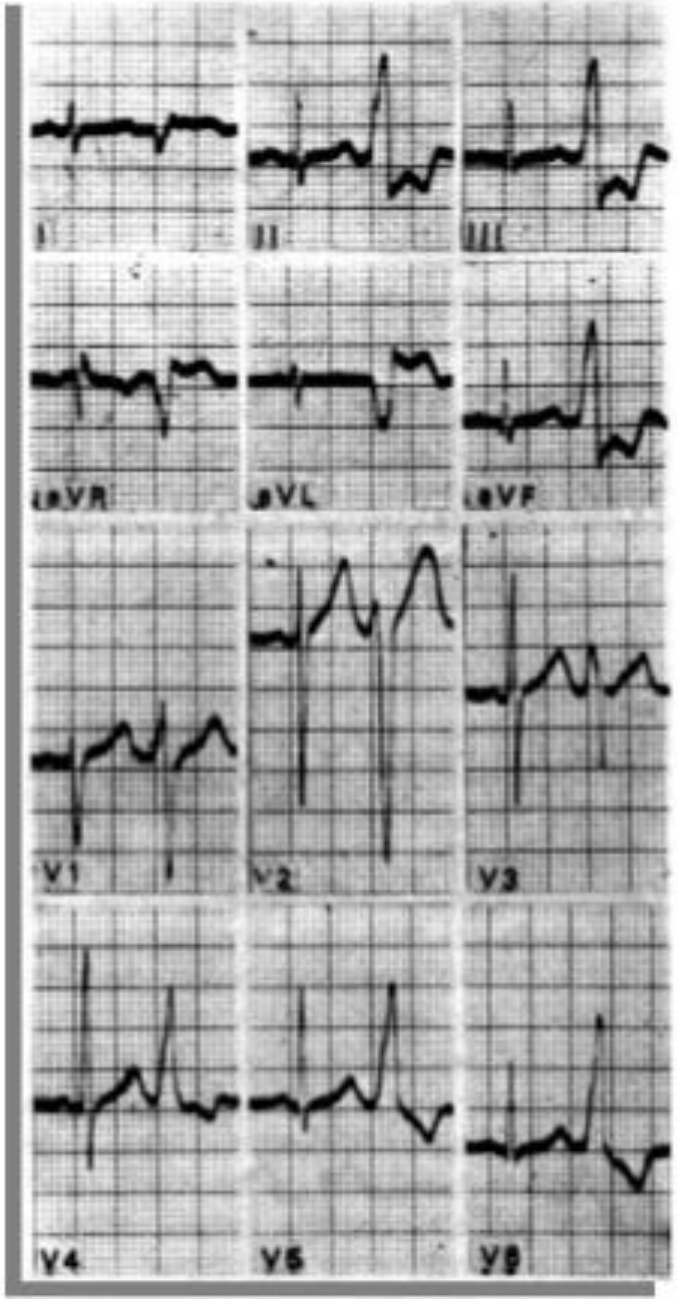
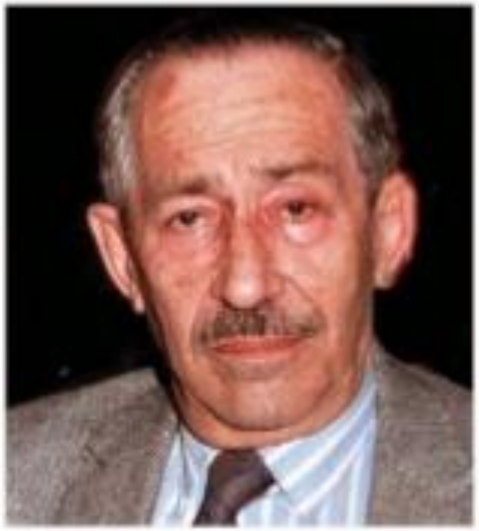
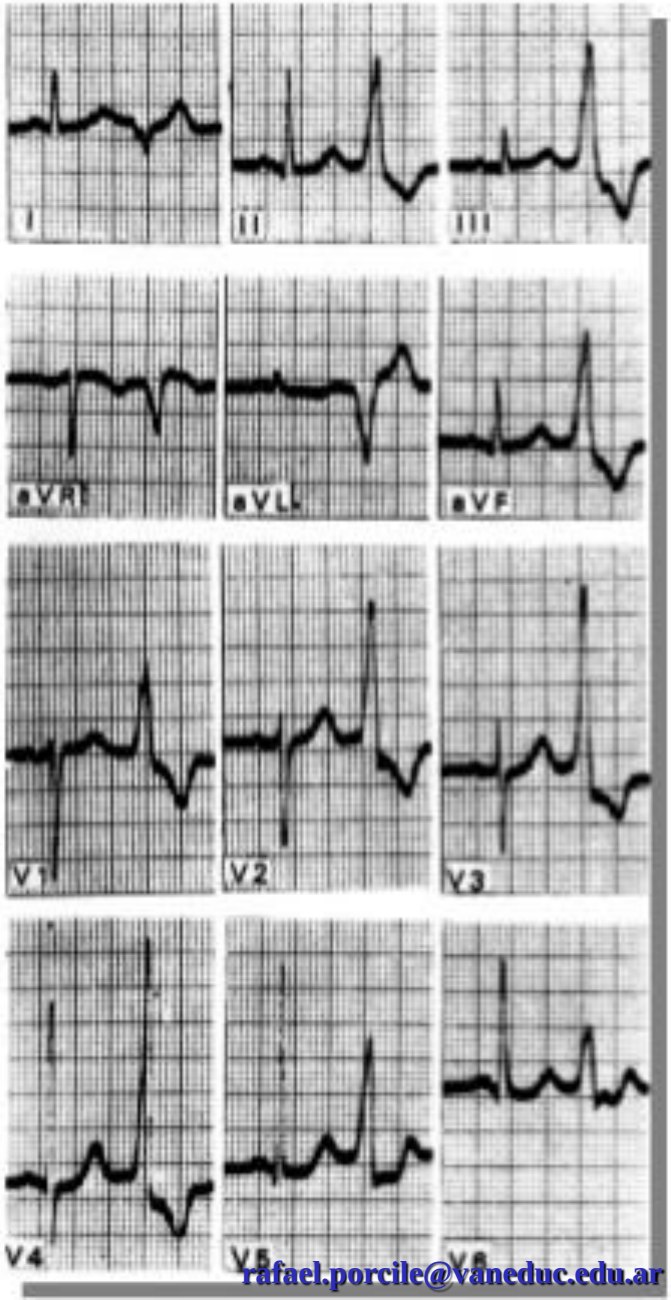
EV DEL MÚSCULO PAPILAR ANTERIOR DEL VD

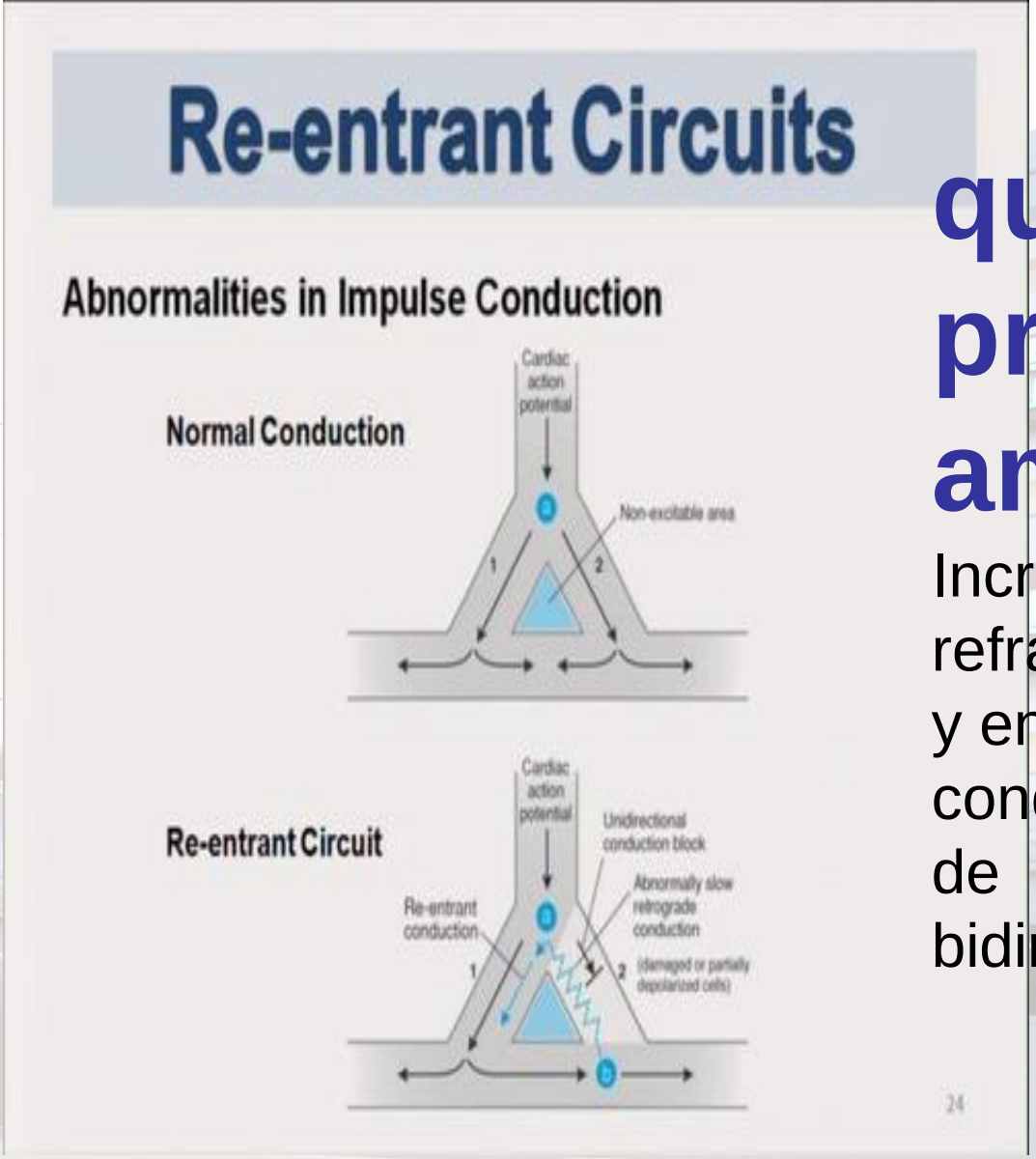




Mauricio B. Rosenbaum

EV DE LA BASE DEL VD O WOLFFIANAS





quinidina (Ia)
propranolol (II)
amiodarona (III)

Incrementan el periodo refractario
y enlentecen la velocidad de conducción convirtiendo el área de bloqueo unidireccional en bidireccional

FIBROSIS

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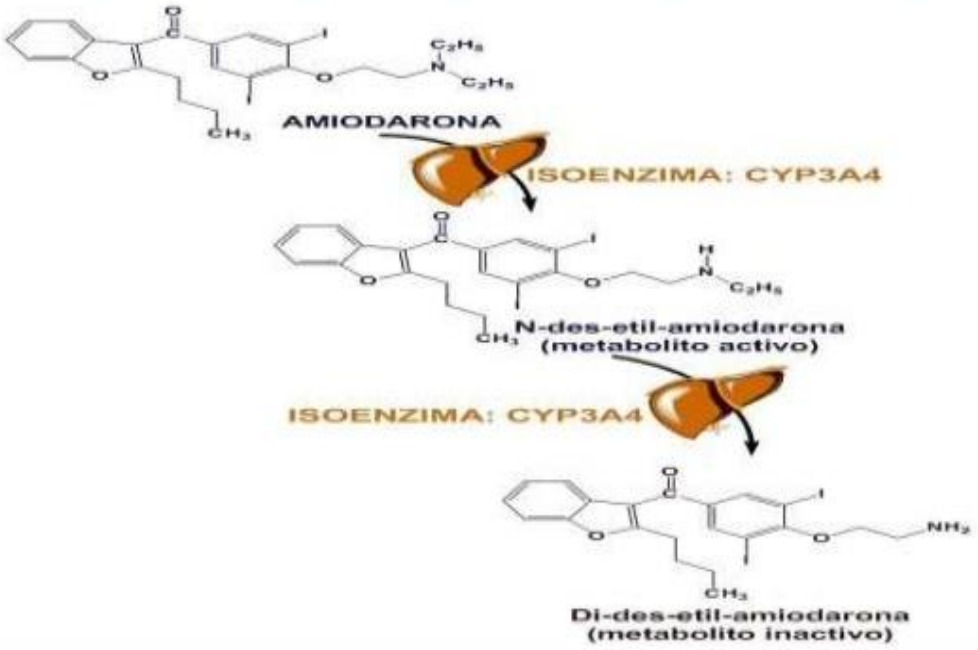
Amiodarona

Fármaco	Biodisponibilidad	Metabolismo del primer paso	Vida media	Unión a proteinas	Volumen de distribución	pKa	Metabolitos	eliminación
Amiodarona	30-50%	Si	25 – 110 d	96%	65,8L	6,56	N-des-etil-amiodarona	Heces



0,5 – 2 µg/ml

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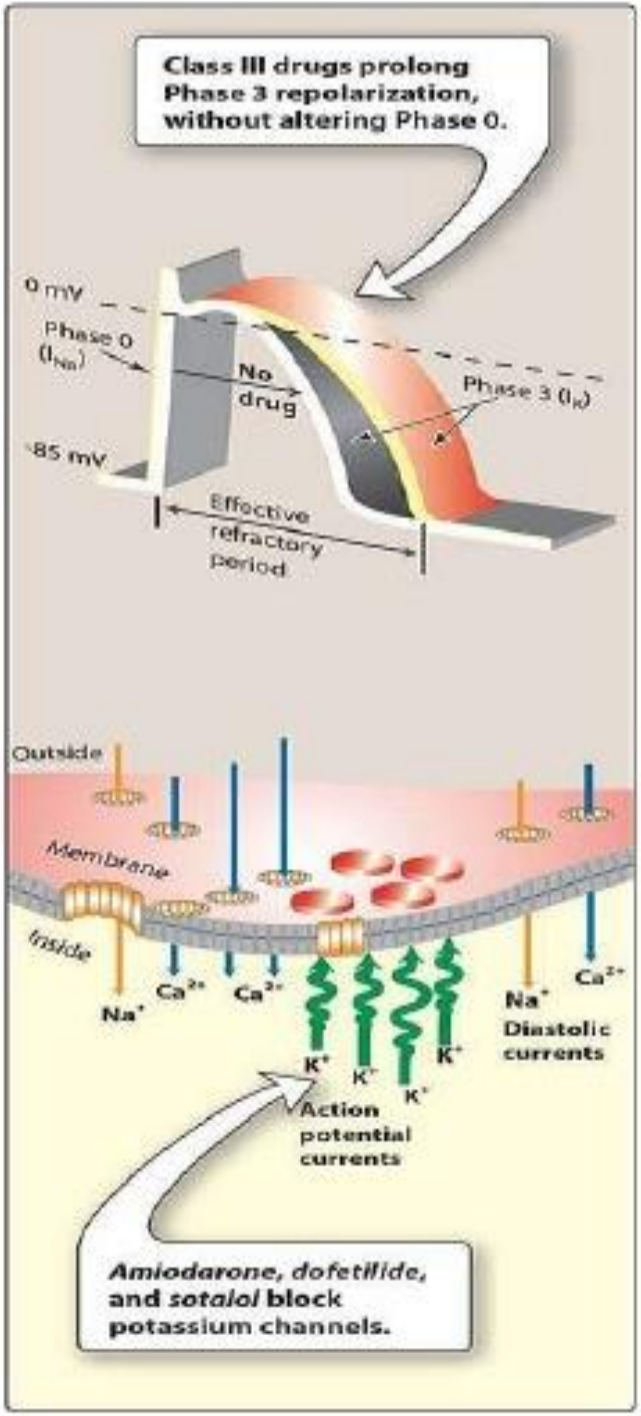
AMIODARONA

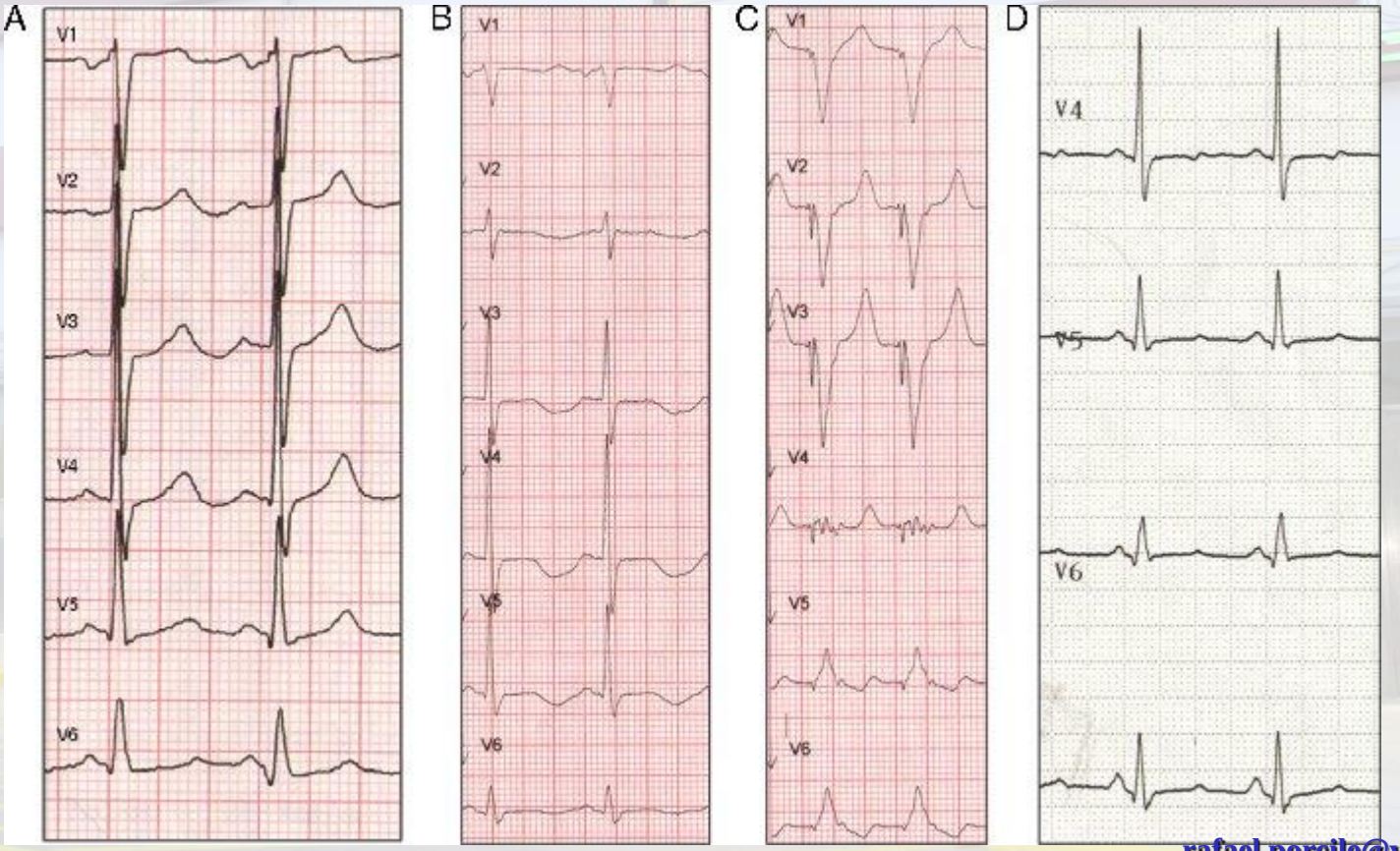

vía oral
lenta
Biodisponib
25-65%
Unión a proteinas
95-99%
Eliminación biliar
Semivida 28 – 110d
Tejido
adiposo,
pulmón,
miocardio y m
Esquelético
MECANISMO DE
ACCION
Acción directa
sobre el
miocardio
Retrasa la
despolarización y
aumenta la
duración del
potencial de
acción
Inhibe de forma
no competitiva
los receptores
alfa y ß y posee
propiedades
bloqueantes del
calcio

Amiodarone III

- Therapeutic uses: Amiodarone is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias. Despite its side-effect profile, amiodarone is the most commonly employed antiarrhythmic.
- Pharmacokinetics: Amiodarone is incompletely absorbed after oral administration. The drug is unusual in having a prolonged half-life of several weeks, and it distributes extensively in adipose issue. Full clinical effects may not be achieved until 6 weeks after initiation of treatment.



A: electrocardiograma inicial en ritmo sinusal a 90 lpm con QRS de 90 ms e intervalo QT corregido de 415 ms. B: electrocardiograma 24 h después de administrar amiodarona en ritmo sinusal a 75 lpm con QRS de 146 ms e intervalo QT corregido de 714 ms. C: marcapasos estimulando a 100 lpm. D: electrocardiograma una semana tras suspender amiodarona en ritmo sinusal a 75 lpm con QRS de 110 ms e intervalo QT corregido de 449 ms



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Amiodarona

Indicaciones:

- ✓ Arritmias ventriculares refractarias y hemodinámicamente comprometedoras que no hayan respondido a otros fármacos antiarrítmicos
- ✓ Bajas dosis prevención de arritmias ventriculares post infarto miocárdico (EMIAT Y CAMIAT)
- ✓ ICC en quienes es mucho mejor tolerada que otros fármacos
- ✓ Fibrilación ventricular recurrente y taquicardia ventricular con compromiso hemodinámico usar VEV simultáneo con carga oral (ARREST)
- ✓ Prevención de recurrencias de la FA a bajas dosis (≤200 mg/d)

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Tabla 1. Principales efectos adversos del tratamiento con amiodarona.

Microdepósitos corneales	100%
Gastrointestinales (náuseas, anorexia)	80%
Fotosensibilidad cutánea, decoloración	55-75%
Ataxia, temblores, neuropatía periférica	48%
Alteración función hepática	25%
Disfunción tiroidea	14-18%
Neumonitis intersticial, alteraciones pulmonares	10-13%
Epididimitis	11%
Bloqueo cardiaco, sinusal, bradicardia	2-3%
Ginecomastia	excepcional

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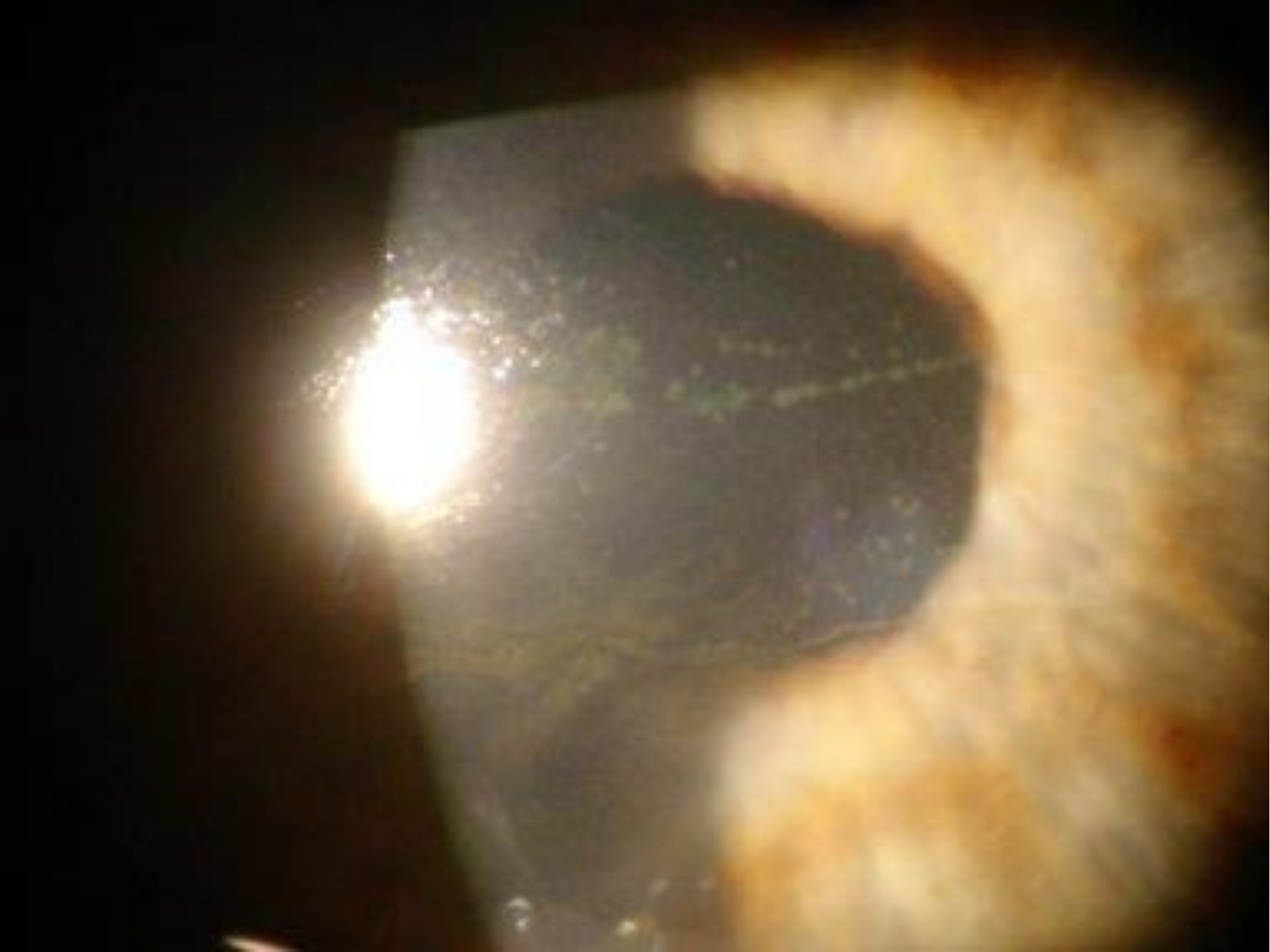


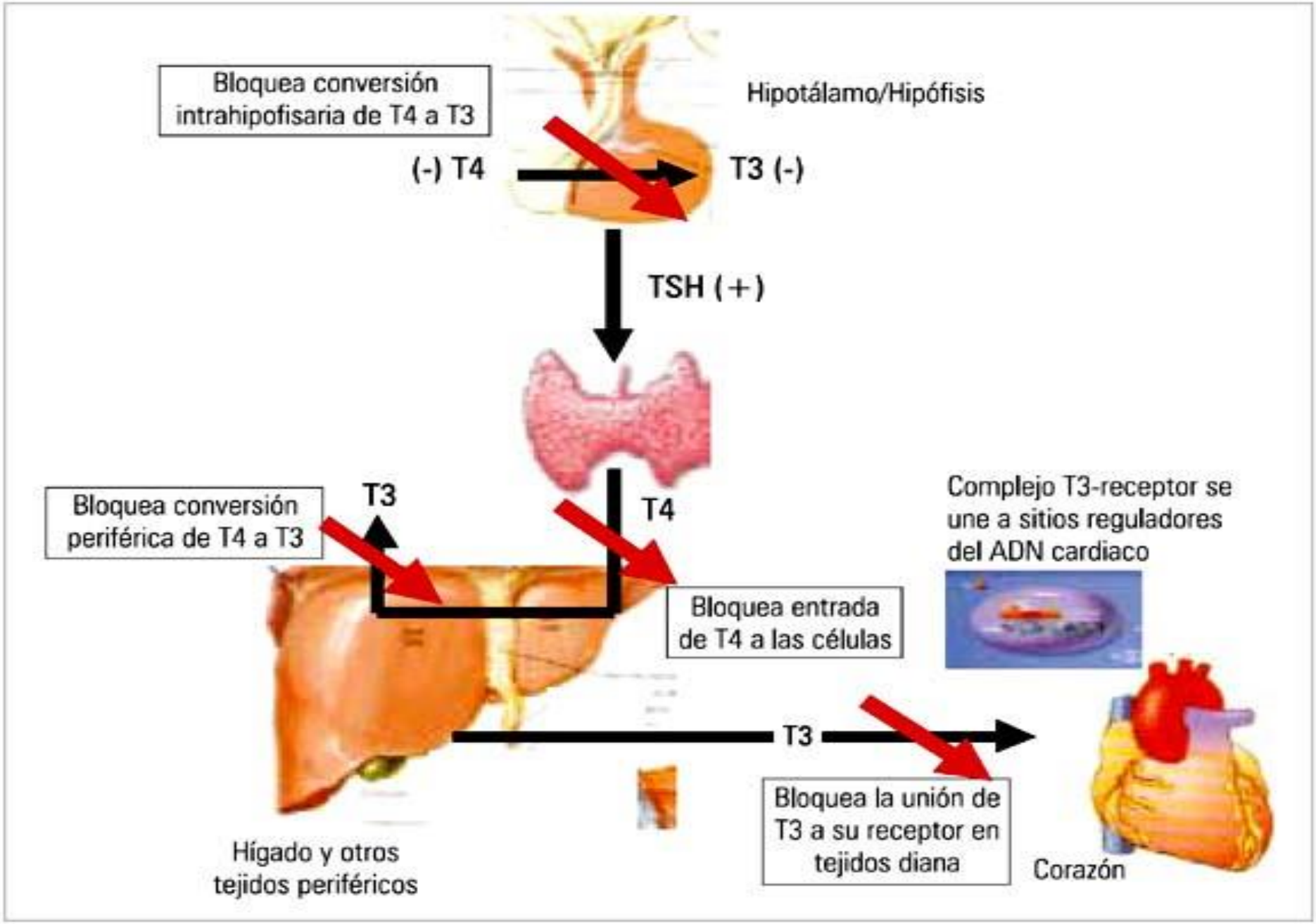
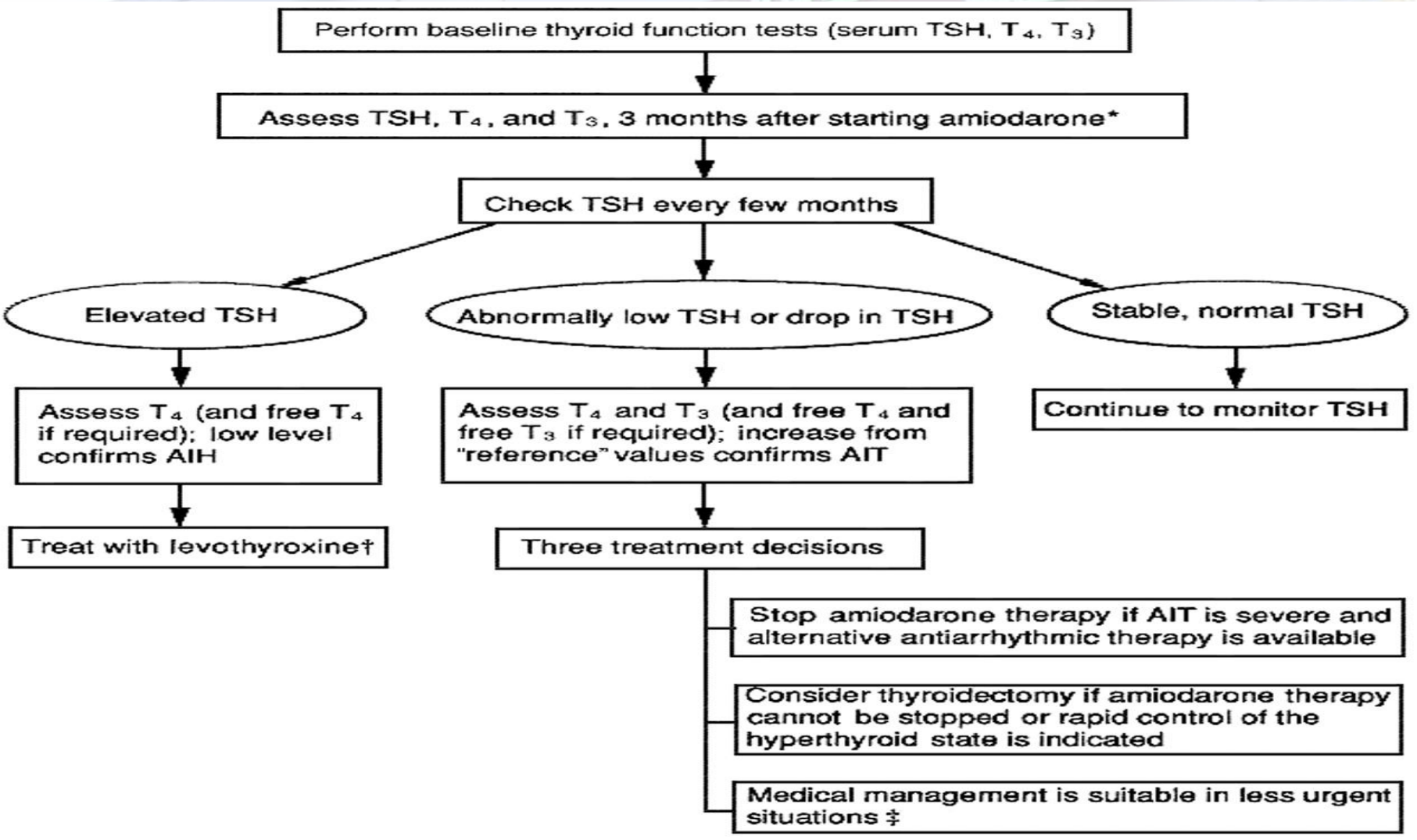


Figura 2. Efectos de la AMD sobre el metabolismo de las hormonas tiroideas (flechas rojas significan bloqueo). Adaptado de Basaria [3]. T4: tiroxina; T3: triyodotironina; TSH: tirotropina

Amiodarona y efectos tiroideos



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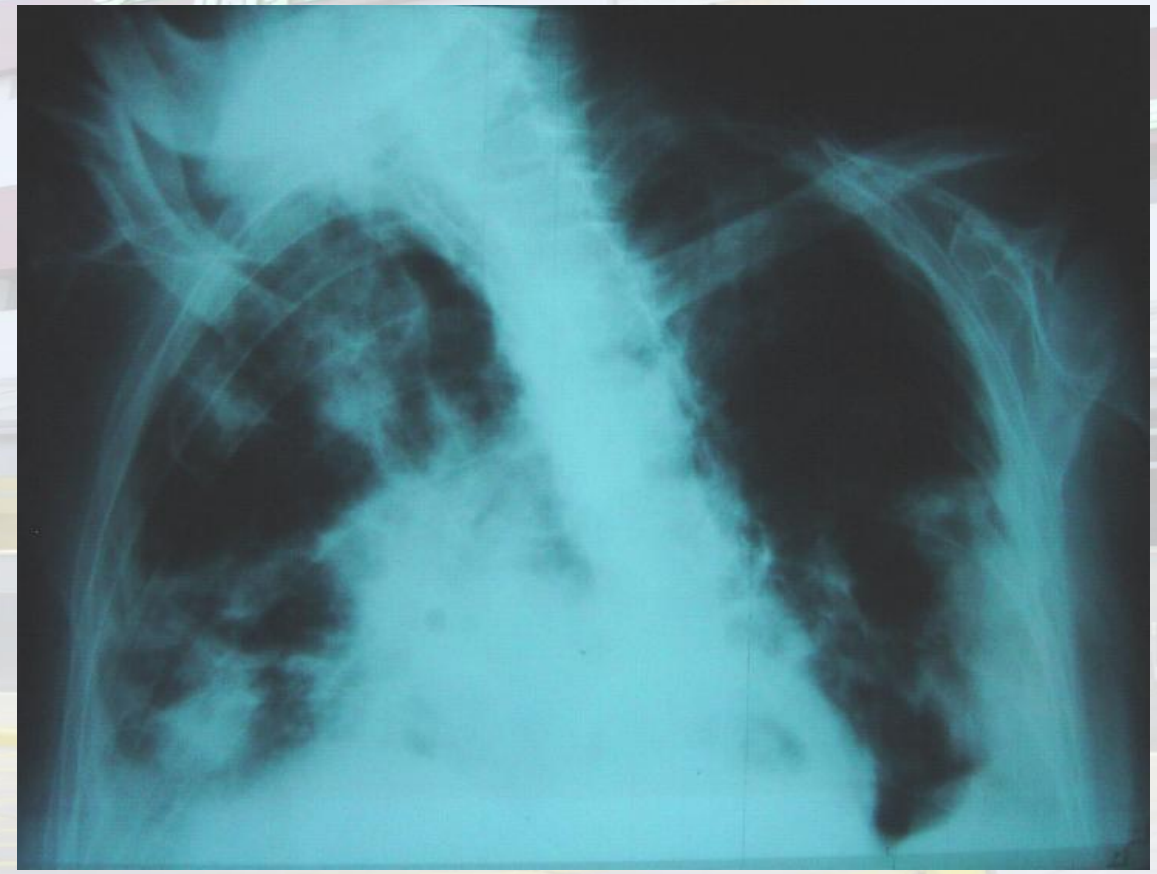
Toxicidad pulmonar por amiodarona



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Interacciones:

Aumenta el efecto de anticoagulantes orales

Aumenta el nivel sanguíneo de digoxina, quinidina, procainamida, diltiazem, flecainida y fenitoína.

No asociar con antidepresivos tricíclicos que aumentan el intervalo QT fenotiazinas, tiazidas, terfenadina, asyemizol, ketoconazol,

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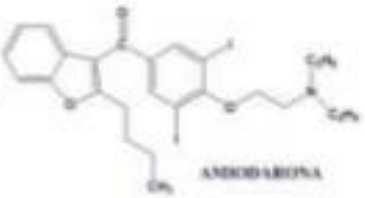
Contraindicaciones

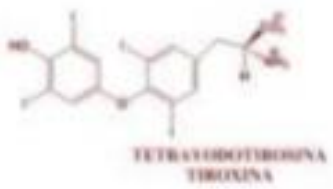
- Hipersensibilidad al yodo
- Bradicardias

(Bradicardia Sinusal, bloqueo sino-auricular; bloqueo AV, Enf. del seno sin implantar marcapasos)

- Trastornos de función tiroidea



- Embarazo y lactancia



- Por vía E.V contraindic. en: hipotensión arterial grave, colapso cardiovascular, hipotensión, insuf. respiratoria grave, miocardiopatía o insuf. cardiaca.

Carga endovenosa de Amiodarona

Hypotension is the most common adverse effect seen with Amiodarone and may be related to the rate of infusion. Hypotension should be treated by *slowing the infusion* or with standard therapy: vasopressor drugs, positive inotropic agents, and volume expansion.

The most important treatment-emergent adverse effects are hypotension (16%), bradycardia (4.9%), liver function test abnormalities (3.4%), cardiac arrest (2.9%), VT (2.4%), CHF (2.1%), cardiogenic shock (1.3%), and AV block (0.5%).

CLASE III AMIODARONA EN EL PARO CARDÍACO

American Heart Association®

Fighting Heart Disease and Stroke

RCP Avanzado

AMIODARONA

- ✓ FV / TV PERSISTENTE (3º Shock)

  Amiodarona 300 mg EV bolo.
- ✓ FV / TV RECURRENTE / REFRACTARIO

  Amiodarona 150 mg, seguido infusión 900 mg/24 horas.

  Lidocaina 1mg/Kg.
- ✓NO INTERRUMPIR RCP

CLASE III AMIODARONA EN PREVENCIÓN DE TV Y FV

Drogas que impactan sobre la muerte de causa arrítmica .

	Clinical condition	Arrhythmic mortality reduction	Cardiovascular mortality reduction	All-cause mortality reduction
Beta-blockers	**Post MI, CHF**	++	+++	+++
Amiodarone	**Post MI**	+	**Neutral**	**Neutral**
ACE-I/ARB	**Post MI, CHF**	+	+++	+++
MRB	**CHF, post MI**	+	++	++
Statins	**CAD**	+	++	++
Fish oil	**CAD, CHF**	–	–	–

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Farmacos en prevención primaria

Amiodarona

- *Amiodarona en el post IAM* (EMIAT y CAMIAT)
- *Amiodarona en IC (*GESICA SCD-HeFT, CHF-STAT)

evidenciaron reducción de la incidencia de MS sin impacto significativo sobre la mortalidad global.

Beta Bloqueantes

Múltiples estudios demostraron disminución de la incidencia de MS y mortalidad global en pacientes post IAM e Insuficiencia Cardíaca

Que los Beta Bloqueantes hayan reducido la MS y muerte global los hace fármacos de elección frente a la Amiodarona

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Eur Heart J. 2009 May;30(10):1245-53. doi: 10.1093/eurheartj/ehp100. Epub 2009 Mar 31.
Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials.

Amiodarone reduces the risk of SCD by 29% and CVD by 18%, and therefore, represents a viable alternative in patients who are not eligible for or who do not have access to ICD therapy for the prevention of SCD. However, amiodarone therapy is neutral with respect to all-cause mortality and is associated with a two- and five-fold increased risk of pulmonary and thyroid toxicity.

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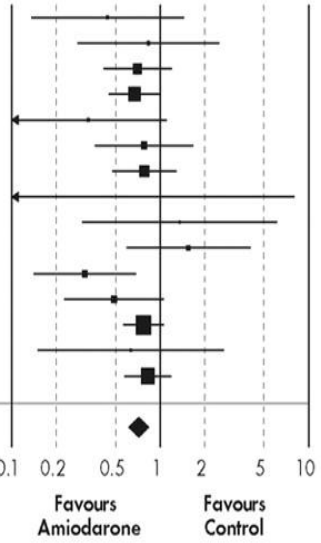
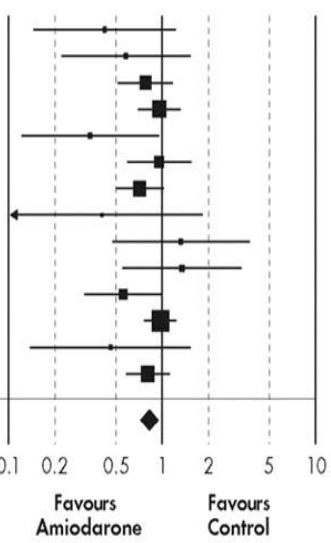
A Sudden cardiac death

Study name	Odds ratio	Lower limit	Upper limit	*P*-value	Dead/Total: Amiodarone	Dead/Total: Control
BASIS	0.443	0.134	1.459	0.180	4/98	10/114
Biswas et al	0.831	0.274	2.523	0.744	7/36	9/40
CAMIAT	0.704	0.411	1.205	0.201	24/606	33/596
EMIAT	0.670	0.446	1.006	0.054	42/743	61/743
EPAMSA	0.329	0.097	1.111	0.073	4/66	10/61
GEMICA	0.779	0.361	1.680	0.524	12/542	15/531
GESICA	0.781	0.472	1.292	0.335	32/260	39/256
Hamer	0.015	0.000	8.074	0.189	0/19	4/15
Hockings *et al.*	1.347	0.294	6.180	0.701	4/100	3/100
Nicklas *et al.*	1.550	0.588	4.086	0.376	12/49	9/52
OPTIC	0.311	0.139	0.693	0.004	9/140	25/138
PAT	0.488	0.225	1.061	0.070	10/305	20/308
SCD HeFT	0.771	0.560	1.061	0.110	75/845	95/847
SSSD	0.632	0.148	2.707	0.537	3/115	5/123
STAT CHF	0.825	0.568	1.199	0.314	64/336	75/338
Overall	0.716	0.611	0.840	0.000	302/4260	413/4262



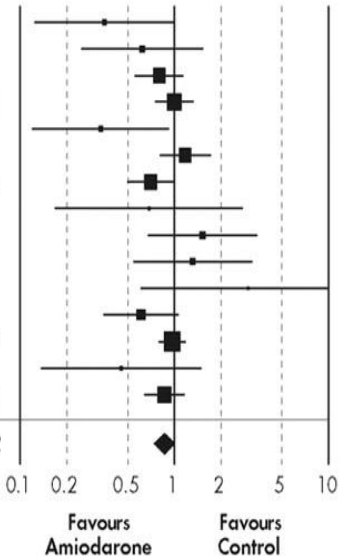
B Cardiovascular death

Study name	Odds ratio	Lower limit	Upper limit	*P*-value	Dead/Total: Amiodarone	Dead/Total: Control
BASIS	0.418	0.143	1.217	0.110	5/98	13/114
Biswas *et al.*	0.577	0.220	1.515	0.264	10/36	16/40
CAMIAT	0.770	0.509	1.165	0.216	44/606	55/596
EMIAT	0.949	0.692	1.302	0.747	85/743	89/743
EPAMSA	0.336	0.120	0.940	0.038	6/66	14/61
GEMICA	0.949	0.587	1.536	0.832	35/542	36/531
GESICA	0.708	0.493	1.016	0.061	83/260	102/256
Hamer	0.400	0.088	1.813	0.235	4/19	6/15
Hockings *et al.*	1.314	0.470	3.677	0.603	9/100	7/100
Nicklas *et al.*	1.333	0.545	3.262	0.529	14/49	12/52
PAT	0.554	0.307	0.997	0.049	19/305	33/308
SCD HeFT	0.966	0.759	1.229	0.777	162/845	167/847
SSSD	0.456	0.137	1.525	0.203	4/115	9/123
STAT CHF	0.798	0.577	1.106	0.175	98/336	115/338
Overall	0.818	0.714	0.937	0.004	578/4120	674/4124



C All-cause death

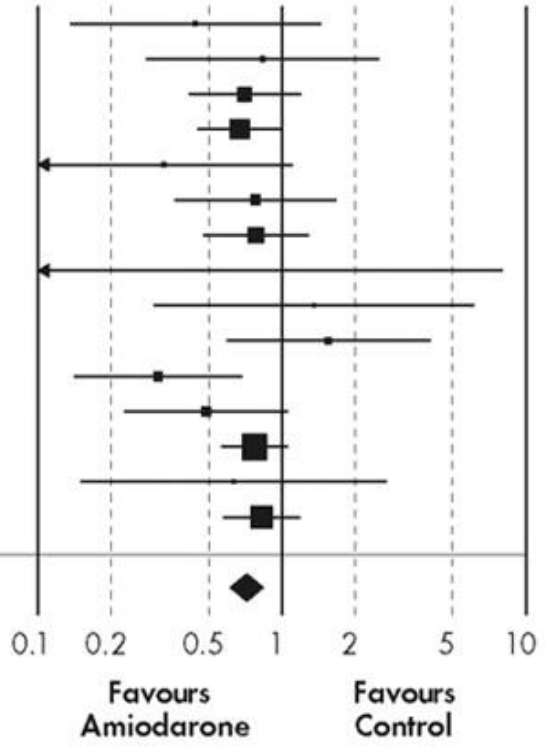
Study name	Odds ratio	Lower limit	Upper limit	*P*-value	Dead/Total: Amiodarone	Dead/Total: Control
BASIS	0.355	0.124	1.015	0.053	5/98	15/114
Biswas *et al.*	0.625	0.249	1.569	0.317	13/36	19/40
CAMIAT	0.806	0.556	1.169	0.256	57/606	68/596
EMIAT	1.011	0.753	1.358	0.940	103/743	102/743
EPAMSA	0.336	0.120	0.940	0.038	6/66	14/61
GEMICA	1.190	0.806	1.757	0.382	62/542	52/531
GESICA	0.712	0.497	1.018	0.063	87/260	106/256
Hamer	0.692	0.168	2.850	0.611	6/19	6/15
Hockings *et al.*	1.541	0.676	3.512	0.303	16/100	11/100
Nicklas *et al.*	1.333	0.545	3.262	0.529	14/49	12/52
OPTIC	3.045	0.604	15.355	0.177	6/140	2/138
PAT	0.616	0.348	1.091	0.097	21/305	33/308
SCD HeFT	0.980	0.794	1.211	0.854	240/845	244/847
SSSD	0.456	0.137	1.525	0.203	4/115	9/123
STAT CHF	0.871	0.641	1.185	0.380	131/336	143/338
Overall	0.874	0.746	1.023	0.093	771/4260	836/4262



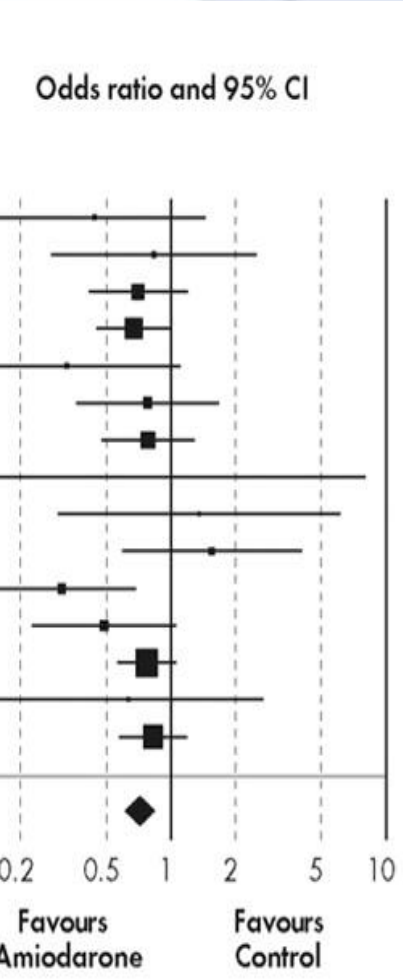
Muerte súbita y amiodarona

A Sudden cardiac death

Study name	Statistics for each study				Dead/Total		Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	*P*-value	Amiodarone	Control	
BASIS	0.443	0.134	1.459	0.180	4/98	10/114	
Biswas et al	0.831	0.274	2.523	0.744	7/36	9/40	
CAMIAT	0.704	0.411	1.205	0.201	24/606	33/596	
EMIAT	0.670	0.446	1.006	0.054	42/743	61/743	
EPAMSA	0.329	0.097	1.111	0.073	4/66	10/61	
GEMICA	0.779	0.361	1.680	0.524	12/542	15/531	
GESICA	0.781	0.472	1.292	0.335	32/260	39/256	
Hamer	0.015	0.000	8.074	0.189	0/19	4/15	
Hockings *et al.*	1.347	0.294	6.180	0.701	4/100	3/100	
Nicklas *et al.*	1.550	0.588	4.086	0.376	12/49	9/52	
OPTIC	0.311	0.139	0.693	0.004	9/140	25/138	
PAT	0.488	0.225	1.061	0.070	10/305	20/308	
SCD HeFT	0.771	0.560	1.061	0.110	75/845	95/847	
SSSD	0.632	0.148	2.707	0.537	3/115	5/123	
STAT CHF	0.825	0.568	1.199	0.314	64/336	75/338	
Overall	0.716	0.611	0.840	0.000	302/4260	413/4262	

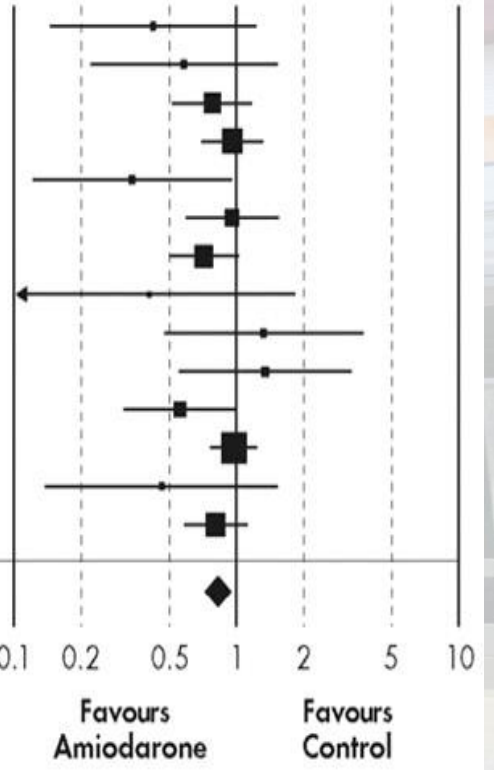


Muerte cardiovascular y amiodarona

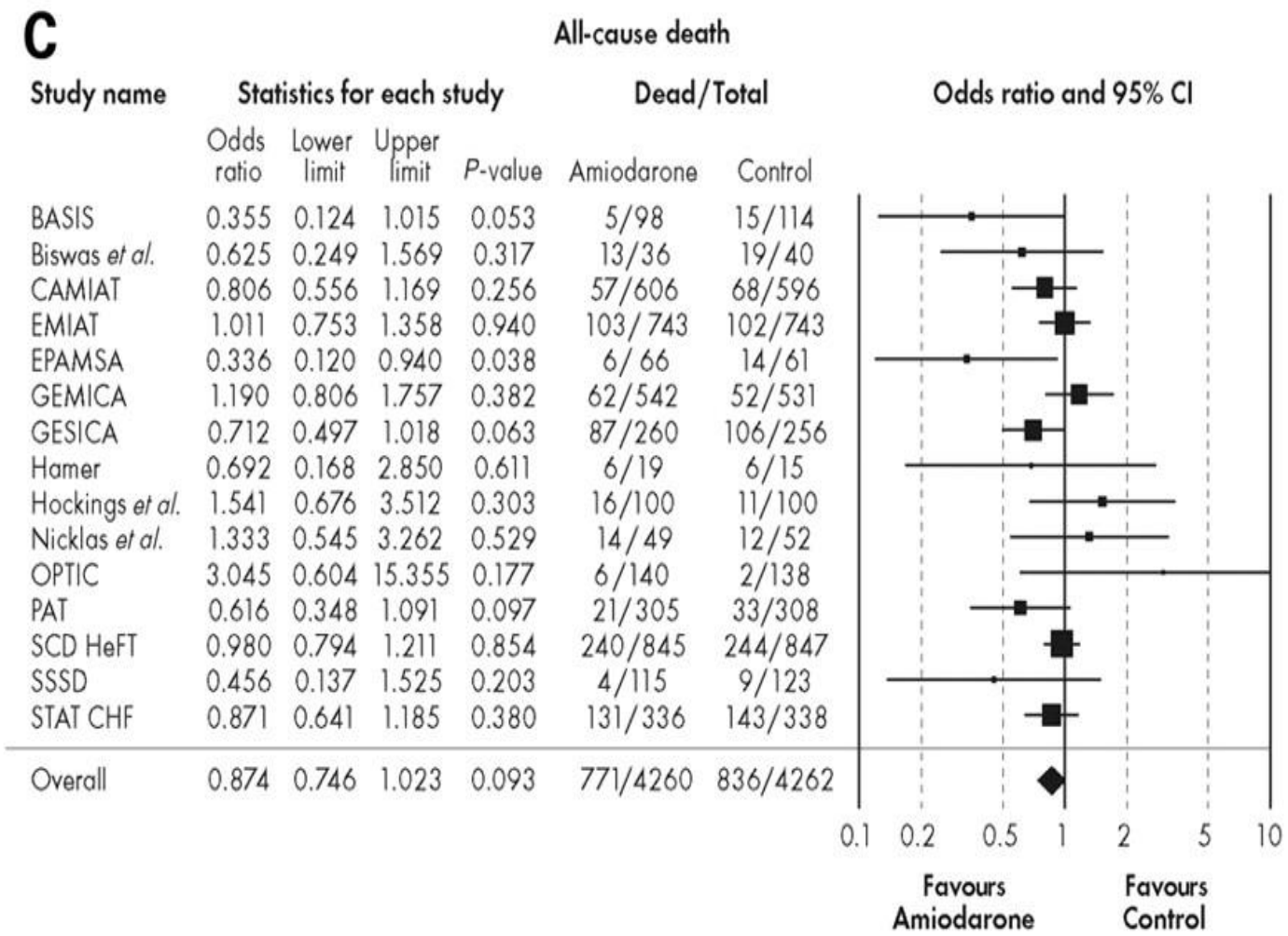


B Cardiovascular death

Study name	Odds ratio	Lower limit	Upper limit	*P*-value	Dead/Total: Amiodarone	Dead/Total: Control
BASIS	0.418	0.143	1.217	0.110	5/98	13/114
Biswas *et al.*	0.577	0.220	1.515	0.264	10/36	16/40
CAMIAT	0.770	0.509	1.165	0.216	44/606	55/596
EMIAT	0.949	0.692	1.302	0.747	85/743	89/743
EPAMSA	0.336	0.120	0.940	0.038	6/66	14/61
GEMICA	0.949	0.587	1.536	0.832	35/542	36/531
GESICA	0.708	0.493	1.016	0.061	83/260	102/256
Hamer	0.400	0.088	1.813	0.235	4/19	6/15
Hockings *et al.*	1.314	0.470	3.677	0.603	9/100	7/100
Nicklas *et al.*	1.333	0.545	3.262	0.529	14/49	12/52
PAT	0.554	0.307	0.997	0.049	19/305	33/308
SCD HeFT	0.966	0.759	1.229	0.777	162/845	167/847
SSSD	0.456	0.137	1.525	0.203	4/115	9/123
STAT CHF	0.798	0.577	1.106	0.175	98/336	115/338
Overall	0.818	0.714	0.937	0.004	578/4120	674/4124



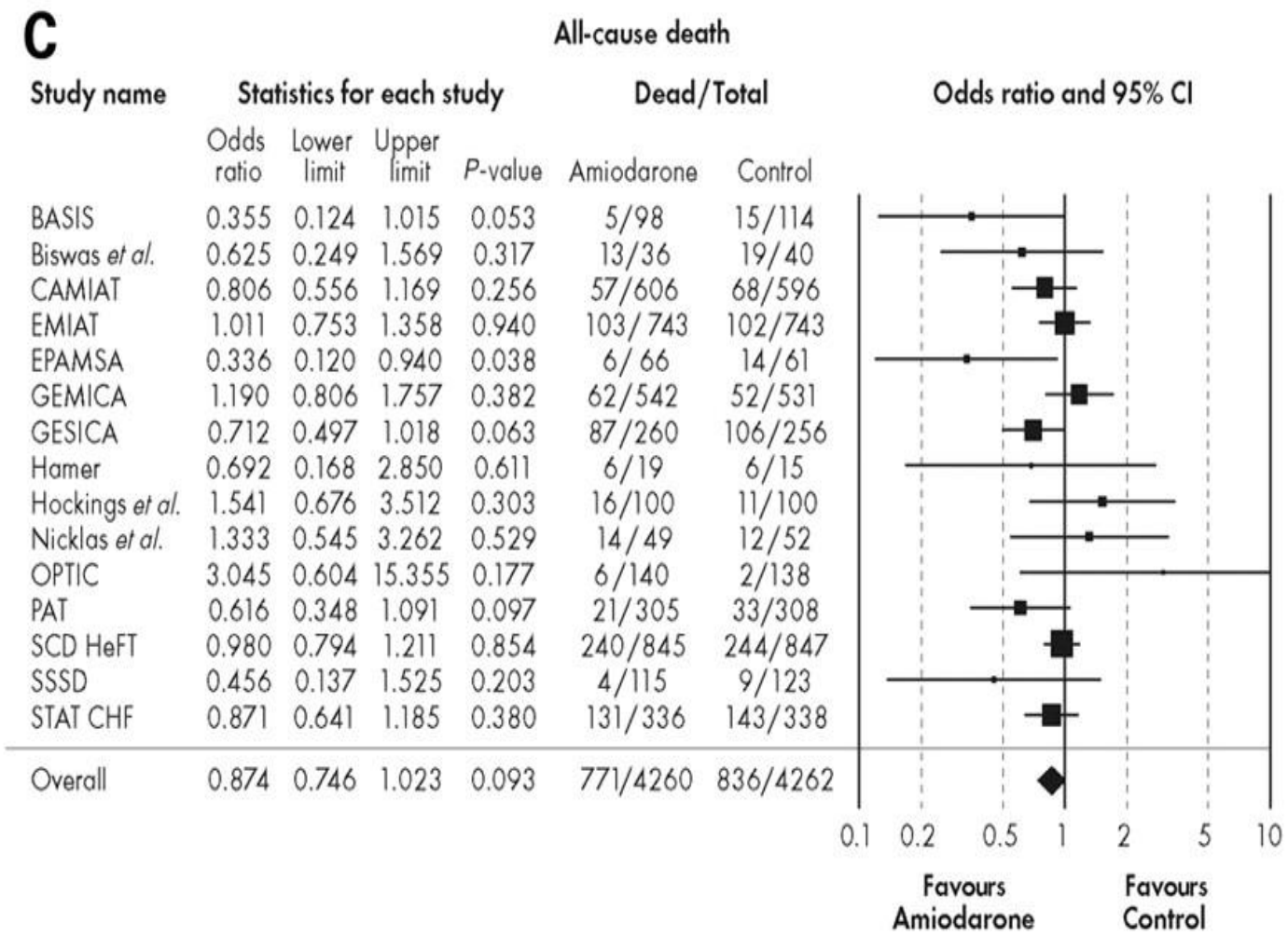
All-cause death



Muerte por cualquier causa y amiodarona

TODO DEPENDE DE PARA QUE SE INDICA

CLASE III EN FIBRILACIÓN AURICULAR



Muerte por cualquier causa y amiodarona

TODO DEPENDE DE PARA QUE SE INDICA

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¿Y EN LA FIBRILACIÓN AURICULAR?

DROMEDARONA

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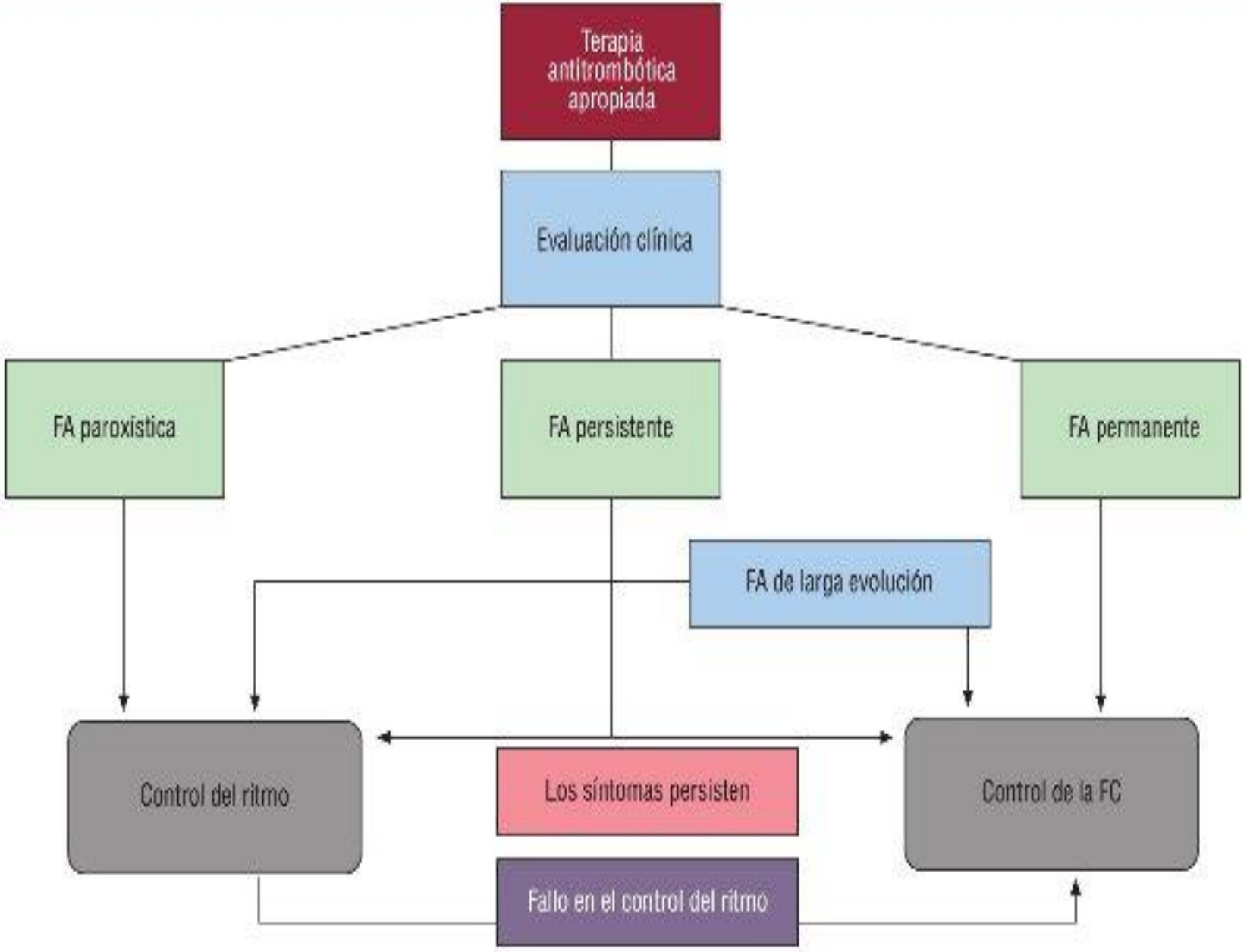

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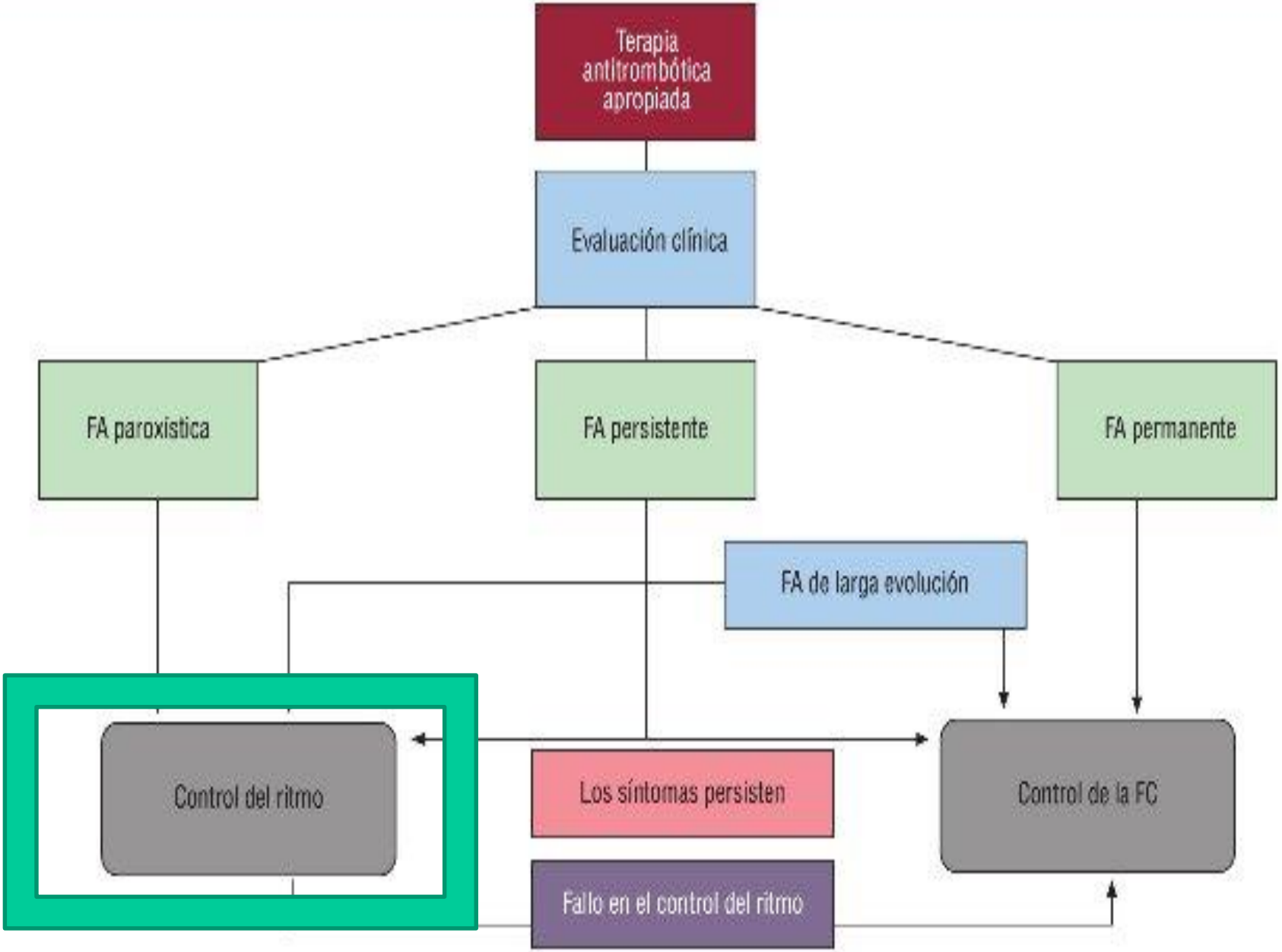

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Dromedarona en fibrilación auricular

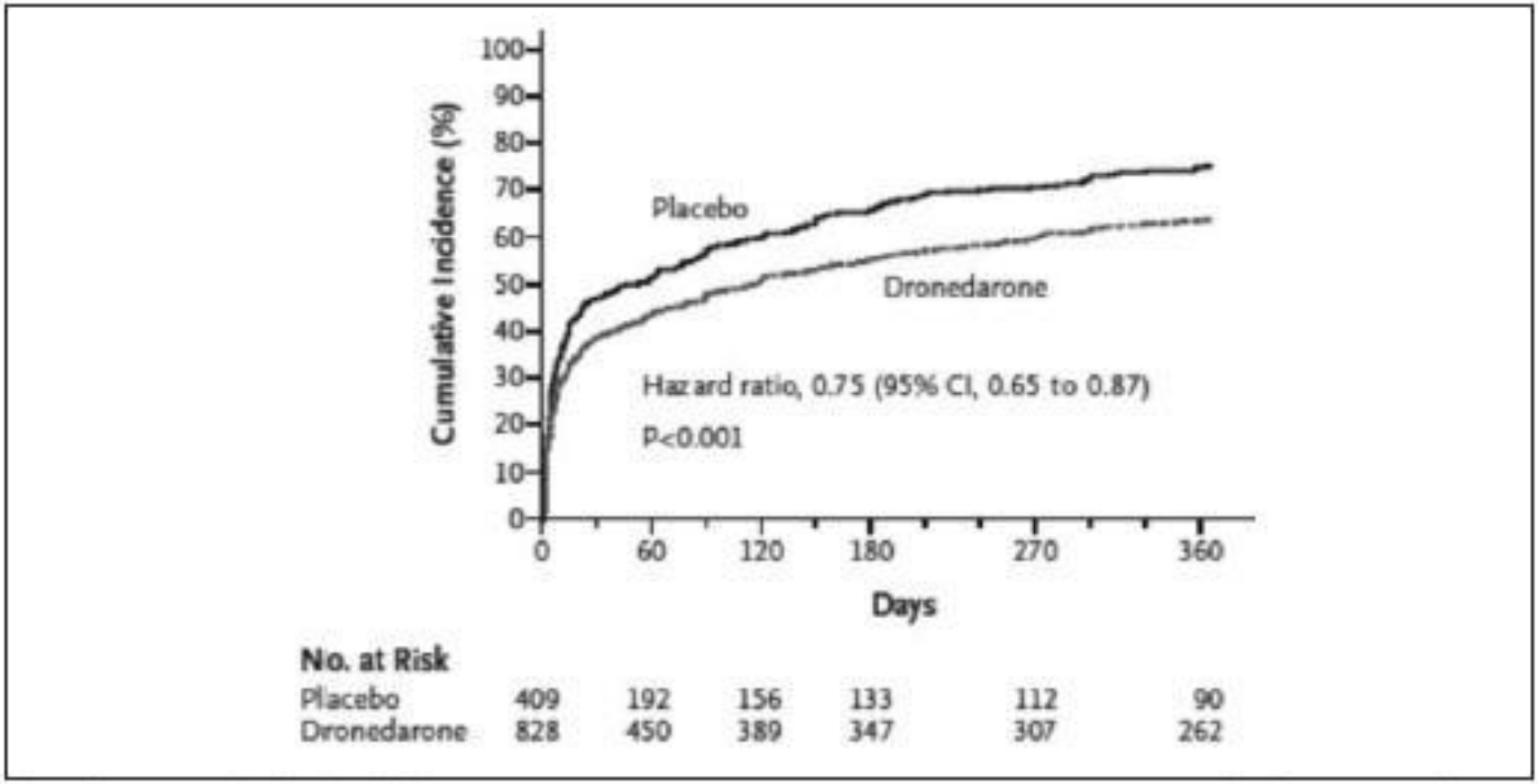

Figura 1. EURIDIS + ADONIS, Curva de Kaplan Meier, incidencia de primera recurrencia de FA o flutter. De ref. 6.

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AMIODARONA VS DROMEDARONA

La amiodarona
*más eficaz para evitar recurrencias de FA (OR 0,49; CI 95% 0,37 a 0,63, p<0,001)
*mayor incidencia de efectos adversos y una mayor mortalidad global.
De acuerdo a los resultados, los autores infieren que por **cada 1.000 pacientes** tratados con dronedarona en lugar de amiodarona habría 228 más recurrencias de FA, pero 9,6 menos muertes y 62 menos efectos adversos que obligaran a interrumpir el tratamiento

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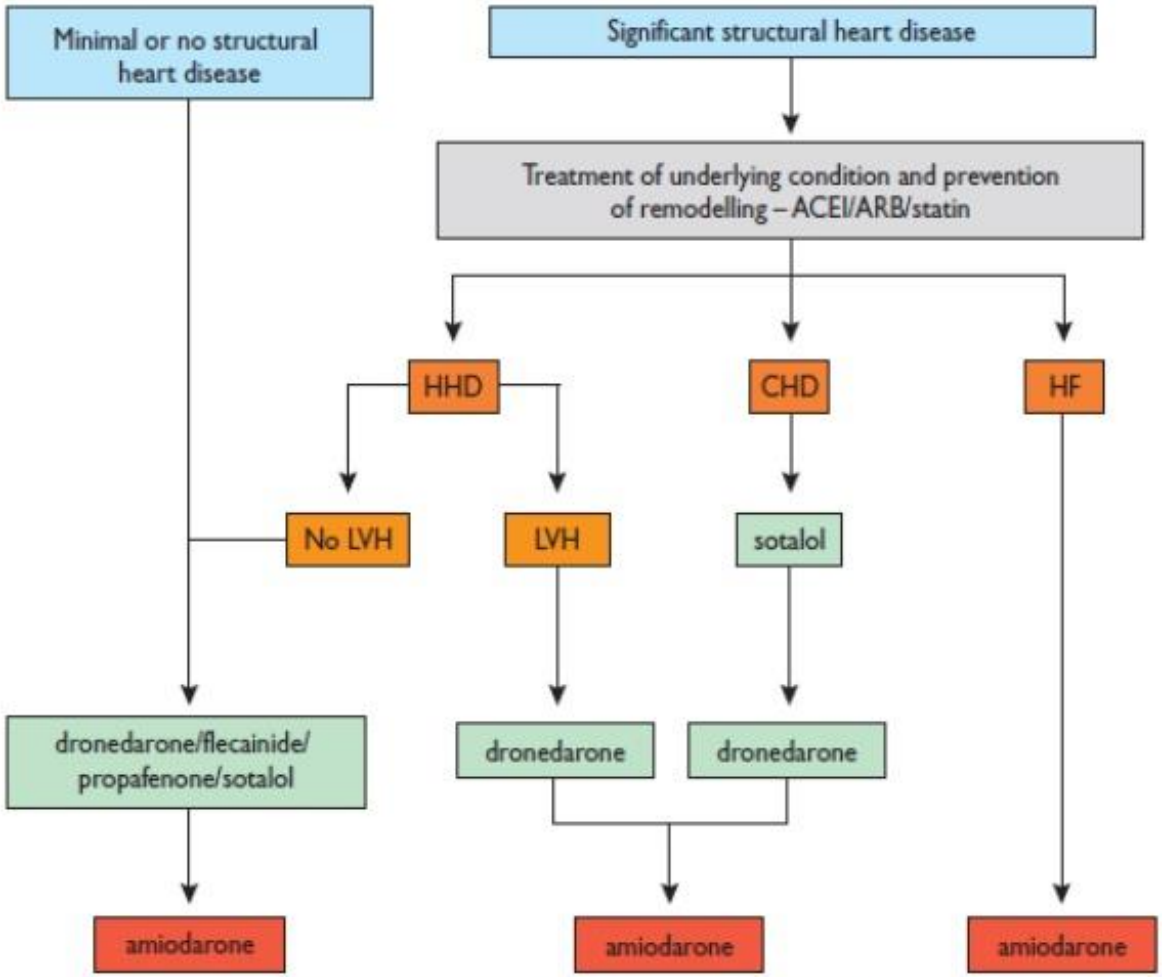
Choice of antiarrhythmic drug according to underlying pathology.



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; HHD = hypertensive heart disease; CHD = coronary heart disease; HF = heart failure; LVH = left ventricular hypertrophy, NYHA = New York Heart Association. Antiarrhythmic agents are listed in alphabetical order within each treatment box.

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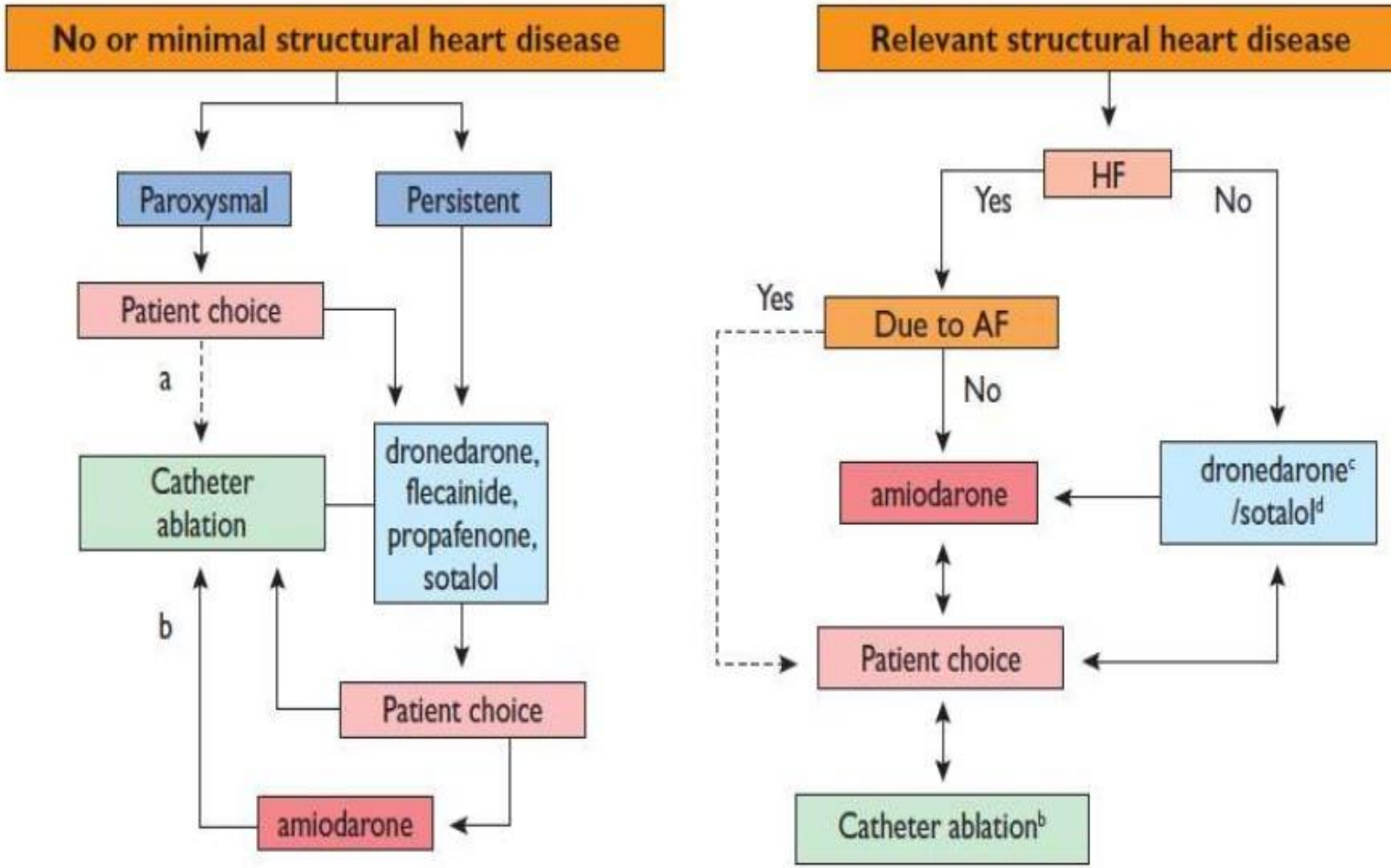

AF = atrial fibrillation; HF = heart failure. [a]Usually pulmonary vein isolation is appropriate. [b]More extensive left atrial ablation may be needed. [c]Caution with coronary heart disease. [d]Not recommended with left ventricular hypertrophy. Heart failure due to AF = tachycardiomyopathy.

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NO

- 1) in patients with permanent atrial fibrillation
- 2) previous amiodarone related liver toxicity
- 3) current symptoms or past symptoms of HF
- 4) left ventricular systolic dysfunction (EF <35%)*.

YES

- 1) for paroxysmal or persistent atrial fibrillation patients who present in sinus rhythm and are clinically stable (EMA),
- 2) in patients who are proposed to be cardioverted (FDA).

- Monitor patients on dronedarone every 3 months for their heart rhythm.
- Keep in mind that in permanent atrial fibrillation antiarrhythmic drugs carry significant risks with little benefit.
- Focus on rate control and adequate antithrombotic therapy

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En suma, dronedarona es menos eficaz que amiodarona pero tiene menos efectos colaterales; hasta que no se disponga de más información no debería usarse en pacientes con insuficiencia cardíaca

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Realidades sobre el tratamiento de la Fibrilación auricular

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•El motivo de tratar con FAA es exclusivamente mejorar los síntomas, no la mortalidad.

•• La eficacia de los FAA para mantener el ritmo sinusal es moderada.

•• Un tratamiento es eficaz si reduce el número de recidivas. Es difícil esperar una desaparición de la FA sólo con FAA.

•• Los efectos proarritmogénicos o efectos adversos extracardiacos no son infrecuentes con este tipo de fármacos.

•• Por todo ello, la seguridad, más que la eficacia, ha de ser el motivo fundamental para tratar con FAA.

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A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators

N Engl J Med
Volume 347;23:1825-1833
December 5, 2002

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GENERALIDADES DEL ESTUDIO

- There are two approaches to the treatment of atrial fibrillation: rate control, allowing atrial fibrillation to persist, and rhythm control, with cardioversion and antiarrhythmic drugs
- This North American study found that, contrary to prevailing practice, rhythm control offered no survival advantage and was associated with higher rates of adverse drug effects than rate control
- Atrial fibrillation is associated with substantial morbidity and mortality
- This study, along with another, similar study in this issue of the Journal will change the management of this common arrhythmia
- As compared with rhythm control, rate control has advantages that have previously been underappreciated

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Base-Line Characteristics of the Patients

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	OVERALL (N=4060)	RATE-CONTROL GROUP (N=2027)	RHYTHM-CONTROL GROUP (N=2033)	P VALUE
Age — yr	69.7±9.0	69.8±8.9	69.7±9.0	0.82
Female sex — no. (%)	1594 (39.3)	823 (40.6)	771 (37.9)	0.08
Ethnic minority group — no. (%)	461 (11.4)	241 (11.9)	220 (10.8)	0.28
Predominant cardiac diagnosis — no. (%)				0.29
Coronary artery disease	1059 (26.1)	497 (24.5)	562 (27.6)	
Cardiomyopathy	194 (4.8)	99 (4.9)	95 (4.7)	
Hypertension	2063 (50.8)	1045 (51.6)	1018 (50.1)	
Valvular disease	198 (4.9)	98 (4.8)	100 (4.9)	
Other	42 (1.0)	23 (1.1)	19 (0.9)	
No apparent heart disease	504 (12.4)	265 (13.1)	239 (11.8)	
History of congestive heart failure — no. (%)	939 (23.1)	475 (23.4)	464 (22.8)	0.64
Duration of qualifying atrial fibrillation ≥2 days — no. (%)	2808 (69.2)	1406 (69.4)	1402 (69.0)	0.80
First episode of atrial fibrillation (vs. recurrent episode) — no. (%)†	1391 (35.5)	700 (35.8)	691 (35.3)	0.74
Any prerandomization failure of an antiarrhythmic drug — no. (%)	713 (17.6)	364 (18.0)	349 (17.2)	0.51
Size of left atrium normal — no. (%)‡	1103 (35.3)	549 (35.3)	554 (35.3)	0.98
Left ventricular ejection fraction — %§	54.7±13.5	54.9±13.1	54.6±13.8	0.74
Normal left ventricular ejection fraction — no. (%)‡	2244 (74.0)	1131 (74.9)	1113 (73.2)	0.29

*Plus–minus values are means ±SD.

†This information was not collected on the initial version of the data form and therefore is missing for 143 patients (70 in the rate-control group and 73 in the rhythm-control group).

‡Echocardiograms were obtained in 3311 patients (1650 in the rate-control group and 1661 in the rhythm-control group). The size of the left atrium was unknown in 185 cases, and left ventricular function (where normal function was defined as a left ventricular ejection fraction ≥0.50) was unknown in 279.

§A quantitative measurement of left ventricular ejection fraction was available for 894 echocardiograms.

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Drugs Used in the Rate-Control Group and the Rhythm-Control Group

TABLE 2. DRUGS USED IN THE RATE-CONTROL GROUP AND THE RHYTHM-CONTROL GROUP.*

DRUG	RATE-CONTROL GROUP		RHYTHM-CONTROL GROUP	
	USED DRUG FOR INITIAL THERAPY	USED DRUG AT ANY TIME	USED DRUG FOR INITIAL THERAPY	USED DRUG AT ANY TIME
	no. of patients (%)			
Rate control				
Data available	1957	2027	1266	2033
Digoxin	949 (48.5)	1432 (70.6)	417 (32.9)	1106 (54.4)
Beta-blocker	915 (46.8)	1380 (68.1)	276 (21.8)	1008 (49.6)
Diltiazem	583 (29.8)	935 (46.1)	198 (15.6)	610 (30.0)
Verapamil	187 (9.6)	340 (16.8)	56 (4.4)	204 (10.0)
Rhythm control				
Data available	1265	2027	1960	2033
Amiodarone	2 (0.2)†	207 (10.2)	735 (37.5)	1277 (62.8)
Sotalol	1 (0.1)†	84 (4.1)	612 (31.2)	841 (41.4)
Propafenone	2 (0.2)†	45 (2.2)	183 (9.3)	294 (14.5)
Procainamide	0	30 (1.5)	103 (5.3)	173 (8.5)
Quinidine	2 (0.2)†	14 (0.7)	92 (4.7)	151 (7.4)
Flecainide	0	29 (1.4)	88 (4.5)	169 (8.3)
Disopyramide	0	7 (0.3)	42 (2.1)	87 (4.3)
Moricizine	0	2 (0.1)	14 (0.7)	35 (1.7)
Dofetilide	0	5 (0.2)	0	13 (0.6)

*Because of changes in the data forms during the study, information on initial therapy was not recorded for some patients; the denominators therefore vary. Percentages do not total 100 because more than one drug could have been tried at the beginning of treatment and because combination therapies were allowed.

†These patients immediately crossed over to the rhythm-control group, a crossover considered to be a protocol violation.

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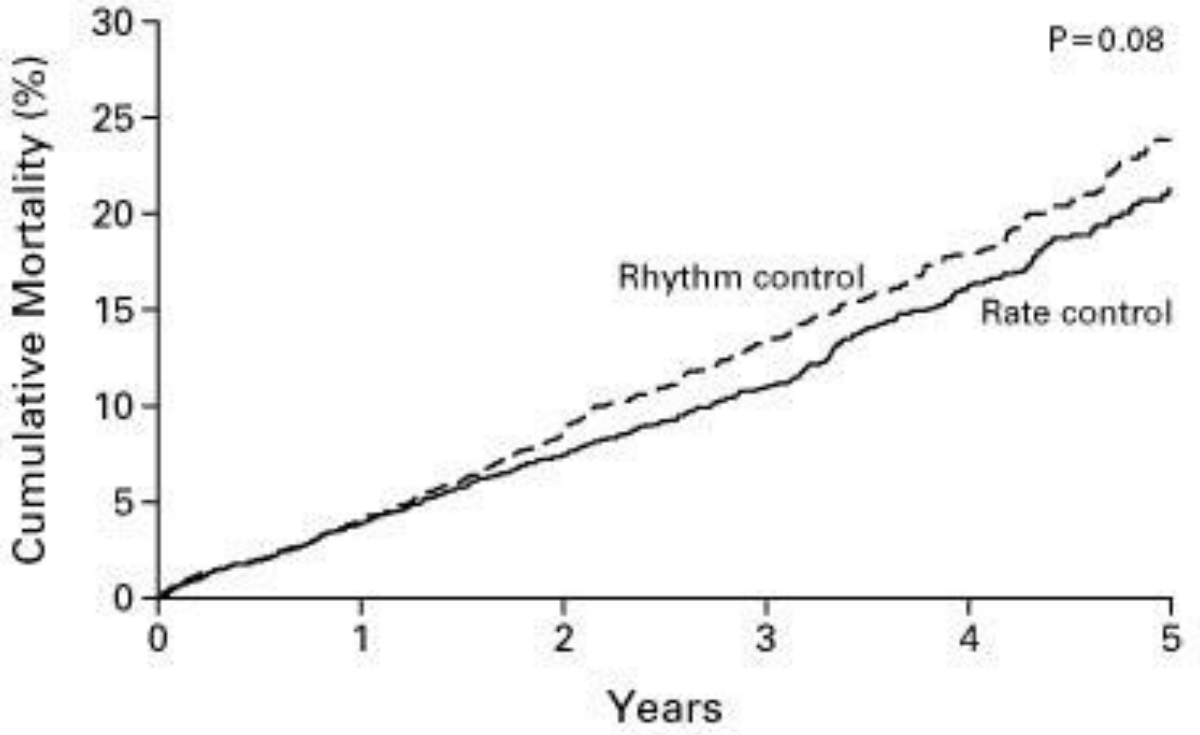
Group and the Rate-Control Group



No. of Deaths		number (percent)				
Rhythm control	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate control	0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

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Adverse Events

TABLE 3. ADVERSE EVENTS.*

EVENT	OVERALL (N=4060)	RATE-CONTROL GROUP (N=2027)	RHYTHM-CONTROL GROUP (N=2033)	P VALUE
		no. of patients (%)		
Primary end point (death)	666 (26.3)	310 (25.9)	356 (26.7)	0.08†
Secondary end point (composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest)	861 (32.3)	416 (32.7)	445 (32.0)	0.33
Torsade de pointes	14 (0.5)	2 (0.2)‡	12 (0.8)	0.007
Sustained ventricular tachycardia	15 (0.6)	9 (0.7)	6 (0.6)	0.44
Cardiac arrest followed by resuscitation				
Ventricular fibrillation or ventricular tachycardia	19 (0.6)	10 (0.7)	9 (0.5)	0.83
Pulseless electrical activity, bradycardia, or other rhythm	10 (0.3)	1 (<0.1)	9 (0.6)	0.01
Central nervous system event				
Total	211 (8.2)	105 (7.4)	106 (8.9)	0.93
Ischemic stroke§	157 (6.3)	77 (5.5)	80 (7.1)	0.79
After discontinuation of warfarin	69	25	44	
During warfarin but with INR <2.0	44	27	17	
Concurrent atrial fibrillation	67	42	25	
Primary intracerebral hemorrhage	34 (1.2)	18 (1.1)	16 (1.3)	0.73
Subdural or subarachnoid hemorrhage	24 (0.8)	11 (0.8)	13 (0.8)	0.68
Disabling anoxic encephalopathy	9 (0.3)	4 (0.2)	5 (0.4)	0.74
Myocardial infarction	140 (5.5)	67 (4.9)	73 (6.1)	0.60
Hemorrhage not involving the central nervous system	203 (7.3)	107 (7.7)	96 (6.9)	0.44
Systemic embolism	16 (0.5)	9 (0.5)	7 (0.4)	0.62
Pulmonary embolism	8 (0.3)	2 (0.1)	6 (0.5)	0.16
Hospitalization after base line	2594 (76.6)	1220 (73.0)	1374 (80.1)	<0.001

*Percentages were derived from a Kaplan–Meier analysis. P values were derived from the log-rank statistic.

†The P value in the case of death was based on the square root of the log-rank statistic, adjusted for 10 interim monitoring analyses.

‡One patient had crossed over to the rhythm-control group and was taking quinidine, and one patient had torsade de pointes 72 hours after mitral-valve replacement.

§Information on warfarin therapy was missing for two patients in the rate-control group and three patients in the rhythm-control group. Information on the presence of atrial fibrillation with the event was missing for 16 patients in the rate-control group and 13 patients in the rhythm-control group.

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Additional Adverse Events or Clinical Findings Prompting Discontinuation of a Drug

TABLE 4. ADDITIONAL ADVERSE EVENTS OR CLINICAL FINDINGS PROMPTING DISCONTINUATION OF A DRUG.*

EVENT	OVERALL (N=4060)	RATE-CONTROL GROUP (N=2027)	RHYTHM-CONTROL GROUP (N=2033)	P VALUE†
	no. of patients (%)			
Congestive heart failure	79 (2.4)	37 (2.1)	42 (2.7)	0.58
Pulmonary event	132 (4.6)	24 (1.7)	108 (7.3)	<0.001
Gastrointestinal event	162 (5.0)	35 (2.1)	127 (8.0)	<0.001
Bradycardia	169 (5.1)	64 (4.2)	105 (6.0)	0.001
Prolongation of the corrected QT interval (>520 msec)	35 (1.1)	4 (0.3)	31 (1.9)	<0.001
Other	590 (19.8)	176 (14.0)	414 (25.4)	<0.001

*Percentages were derived from a Kaplan–Meier analysis.

†P values were based on the log-rank statistic.

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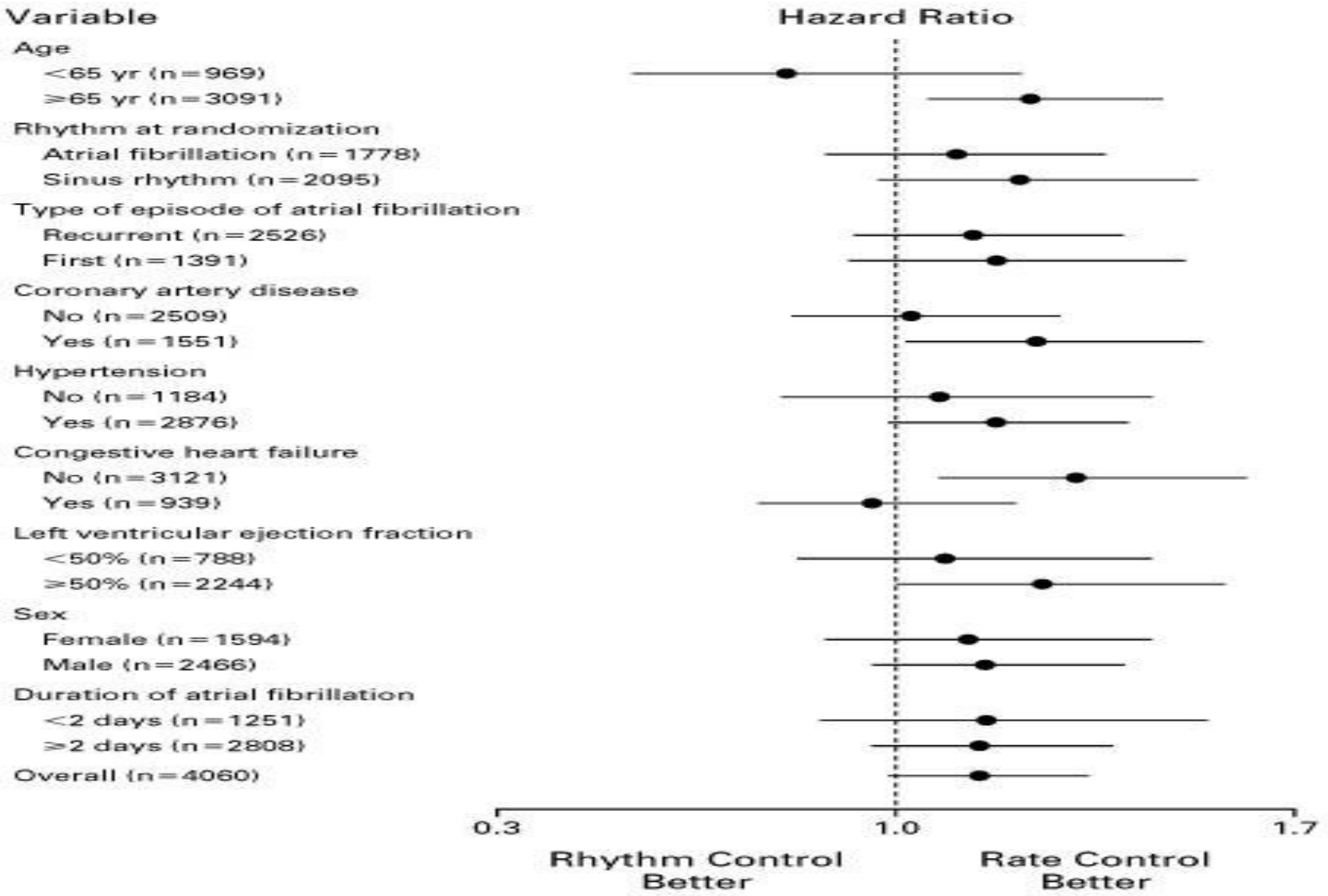
Hazard Ratios for Death in Prespecified Subgroups



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Conclusions

- Management of atrial fibrillation with the rhythm-control strategy offers no survival advantage over the rate-control strategy, and there are potential advantages, such as a lower risk of adverse drug effects, with the rate-control strategy
- Anticoagulation should be continued in this group of high-risk patients

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Estrategia de control de ritmo vs control de frecuencia cardíaca en pacientes con fibrilación auricular luego de cirugía cardíaca

Se observó FA en 33% de los pacientes. En ambos grupos se observó una estancia hospitalaria en días similar (media: 5 y 5,1 días con p=0,76). No hubieron diferencias significativas entre ambos grupos en: muerte (p=0,64), eventos adversos serios (p = 0,61), incluyendo eventos tromboembólicos y de sangrado.

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Grupo IV

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Clase III:

Bloquean los canales de K+:

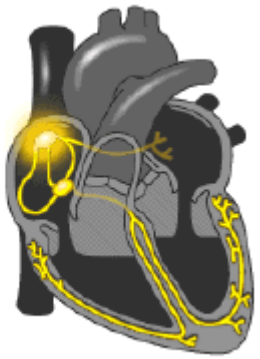
Amiodarona
Sotalol
Bretilio
Dromedarona

Clase IV:

Antagonistas de los canales de Calcio

Otras:

Adenosina
Digoxina



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Clase III:

Bloquean los canales de K+:

Amiodarona
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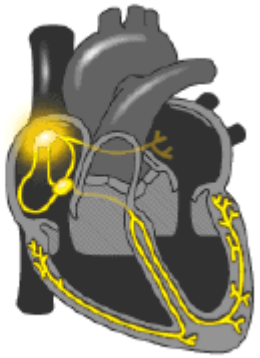
Clase IV:

Antagonistas de los canales de Calcio



Otras:

Adenosina
Digoxina

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BLOQUEANTES CALCICOS

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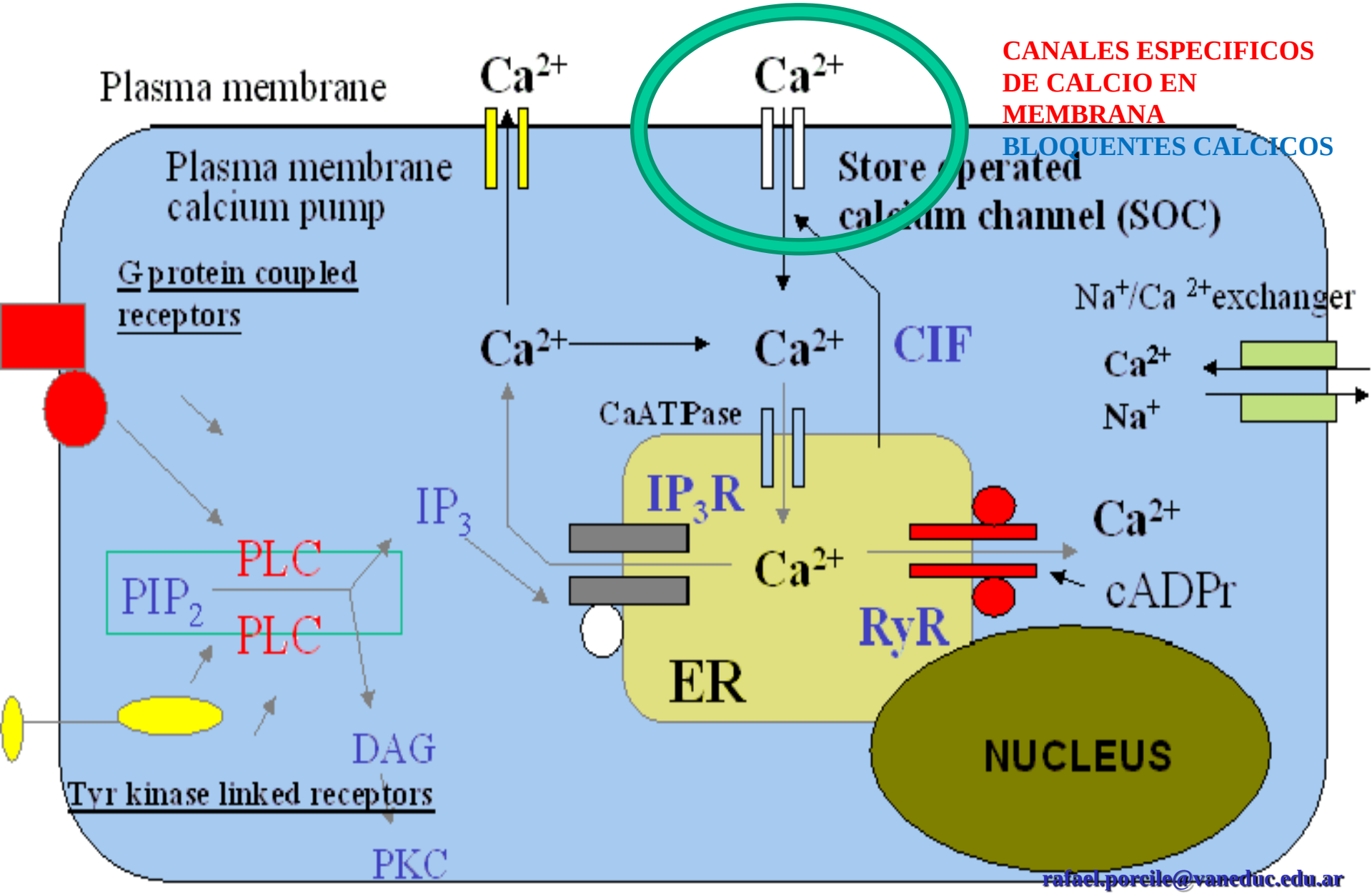
Calcium homeostasis



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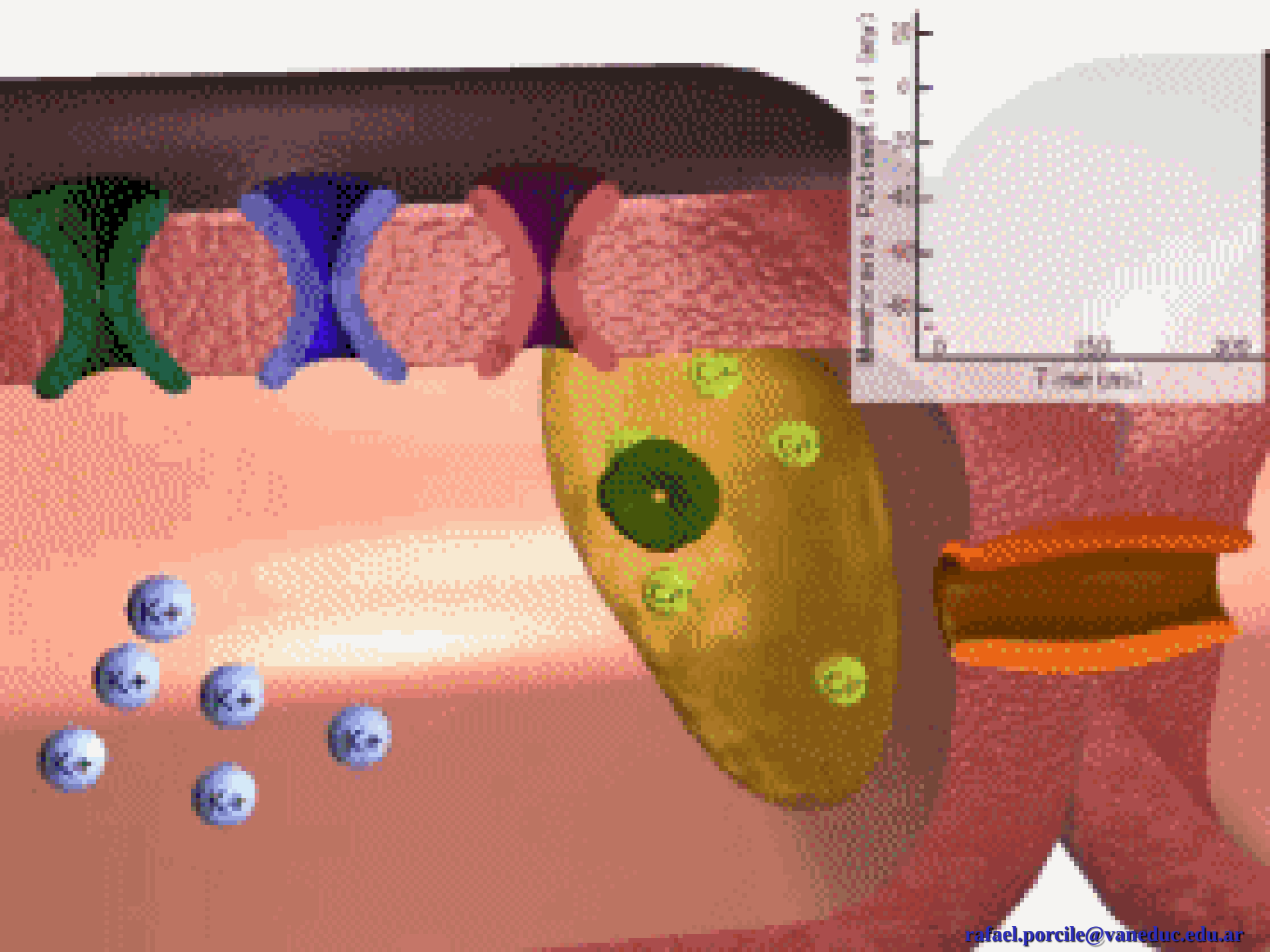

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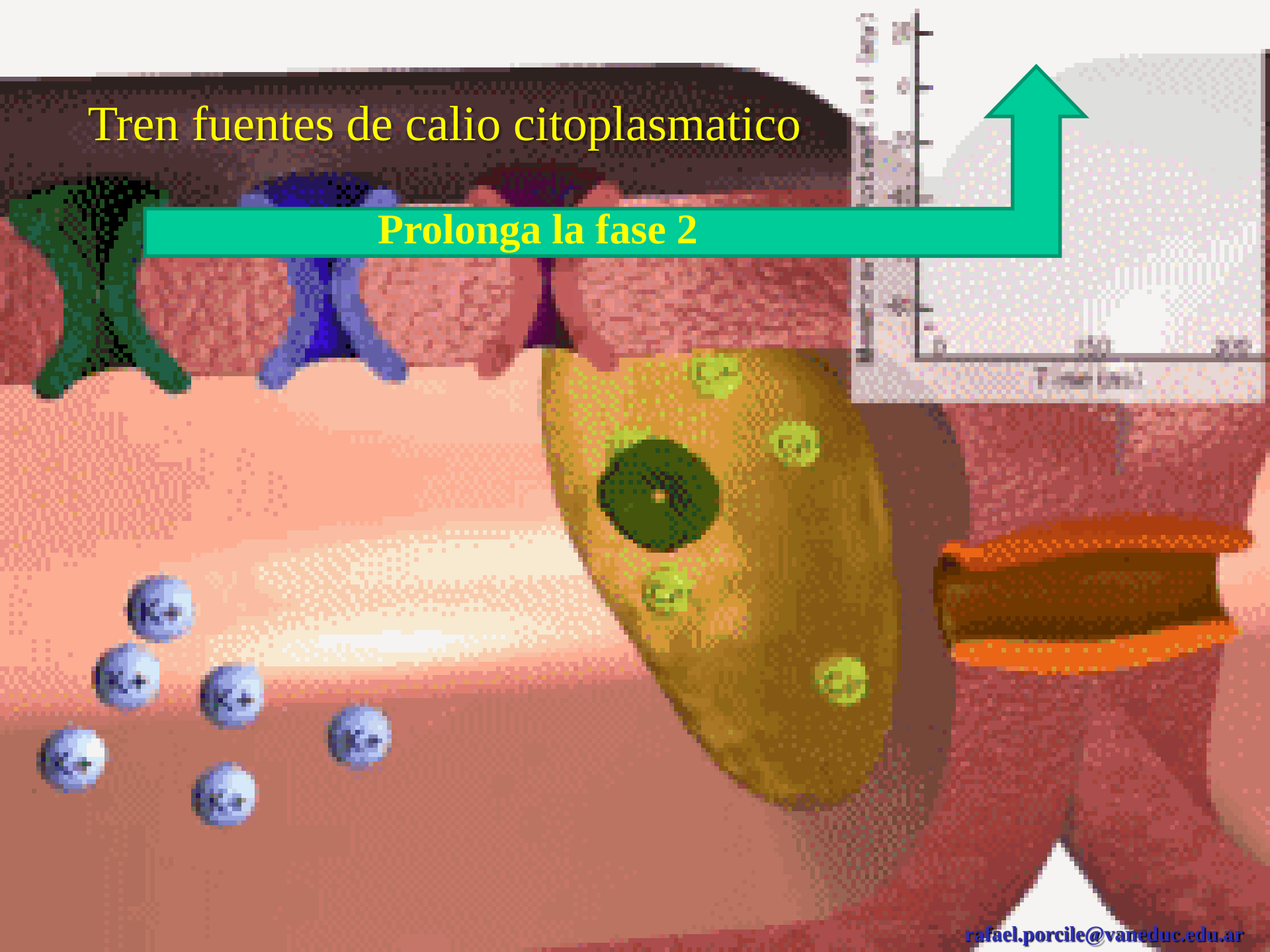

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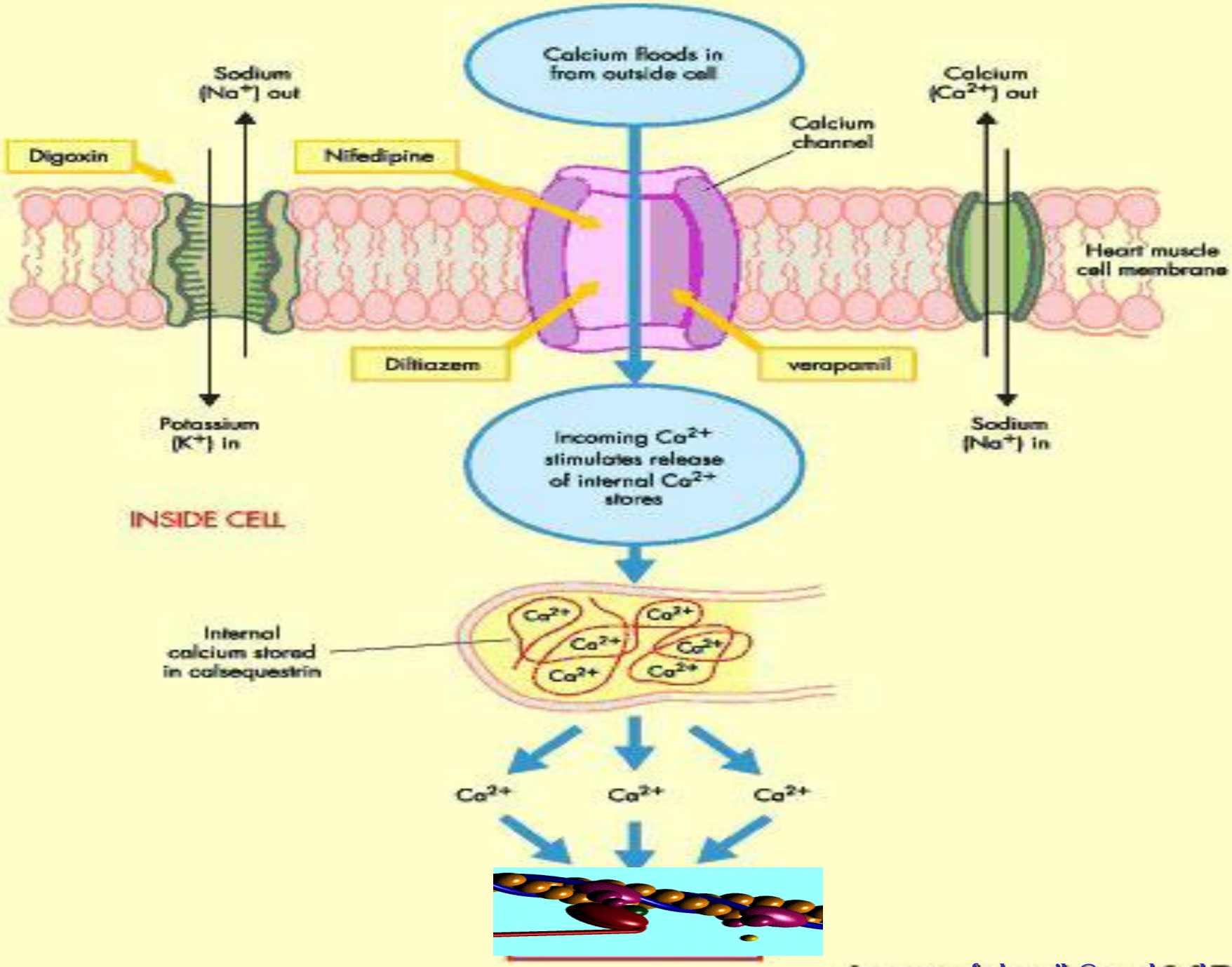

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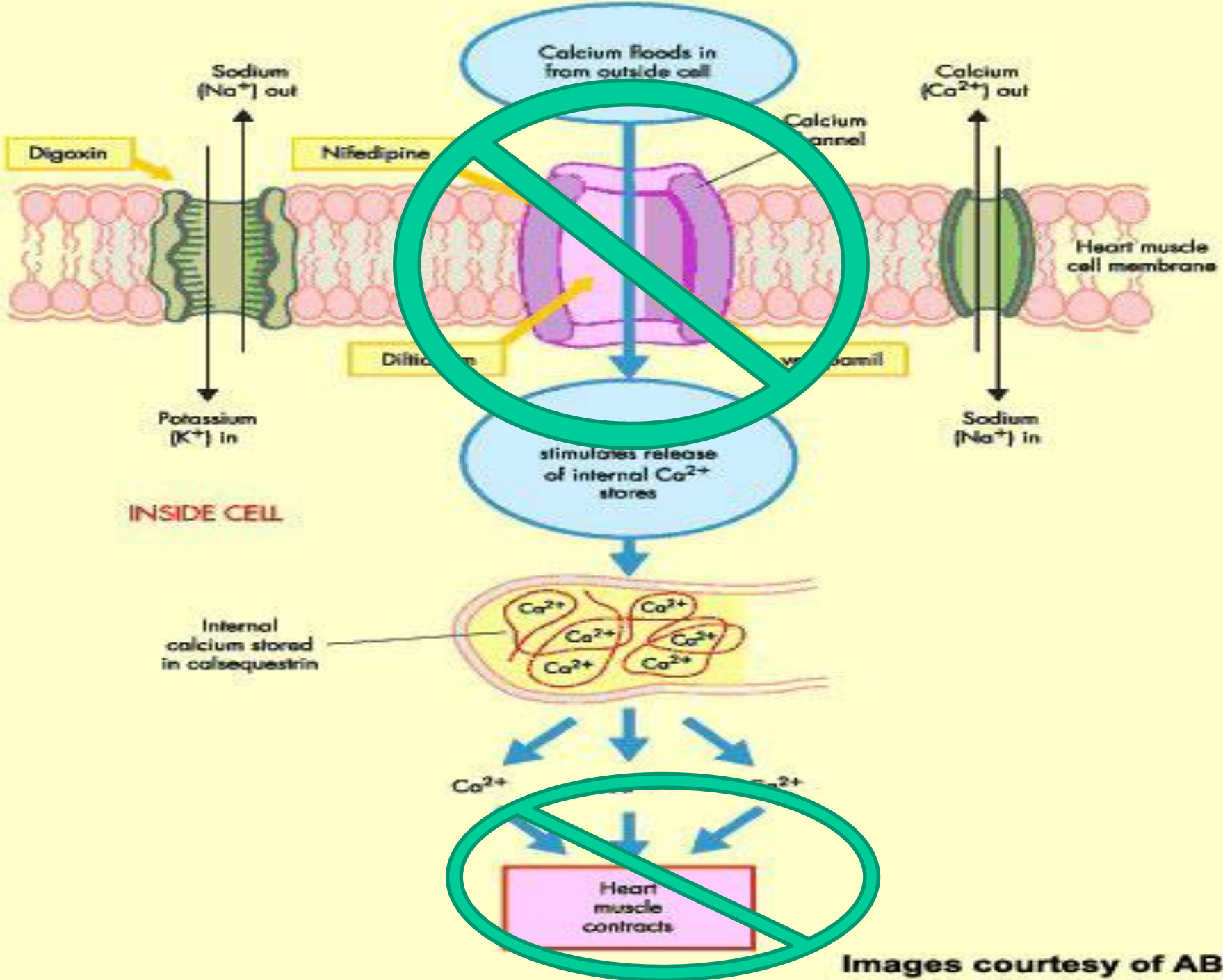
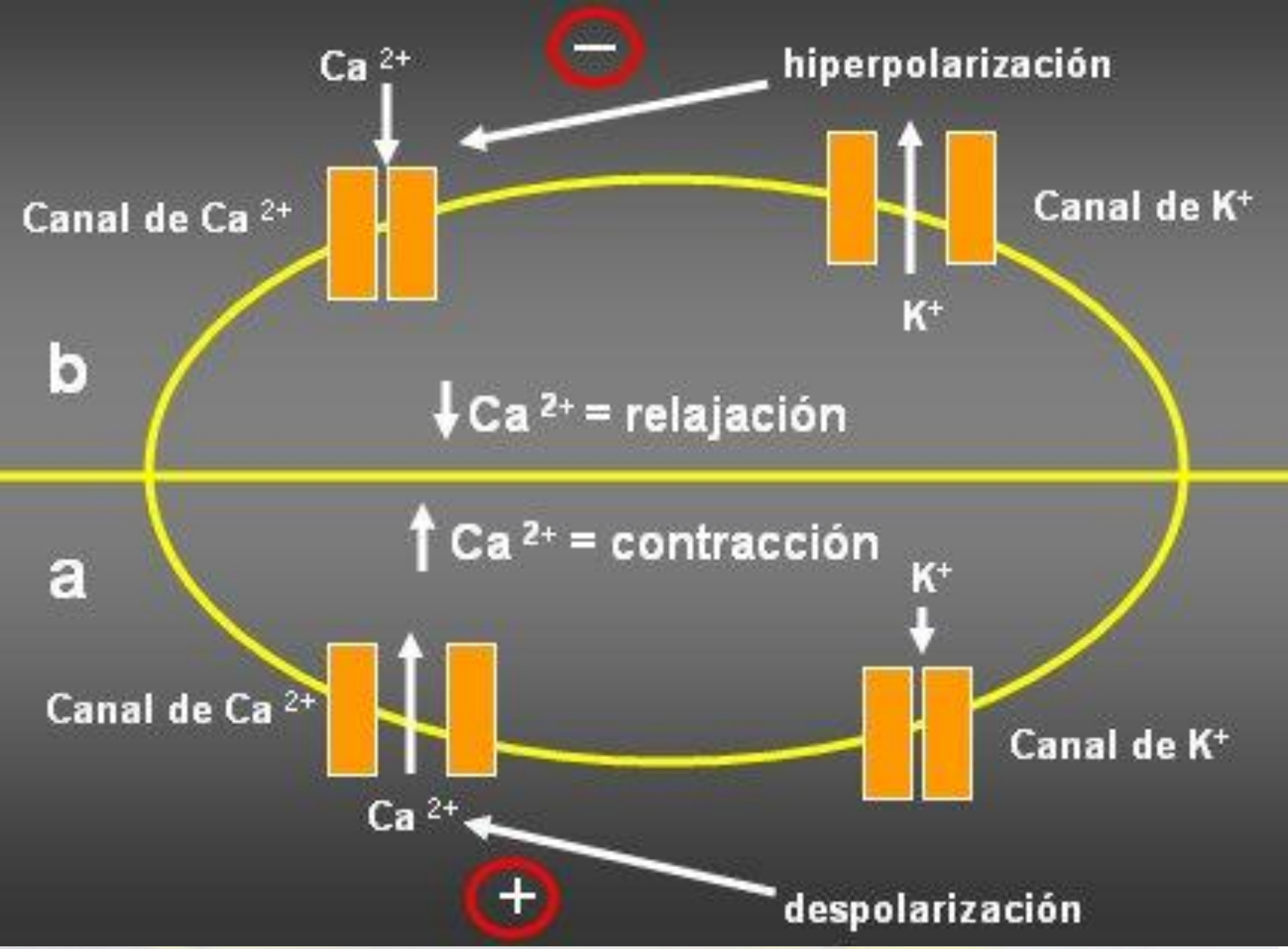
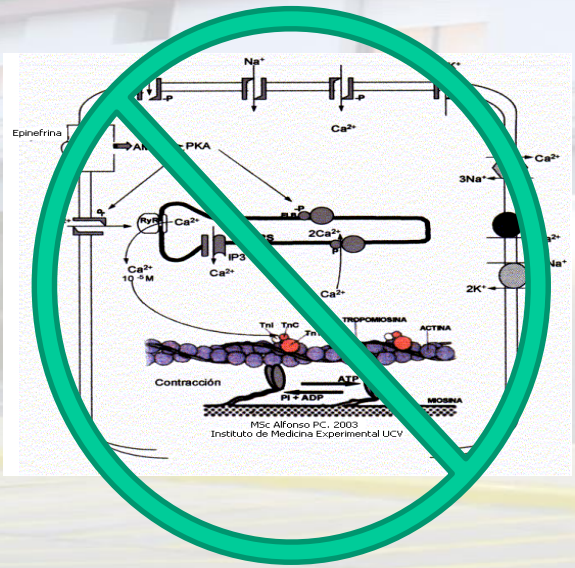


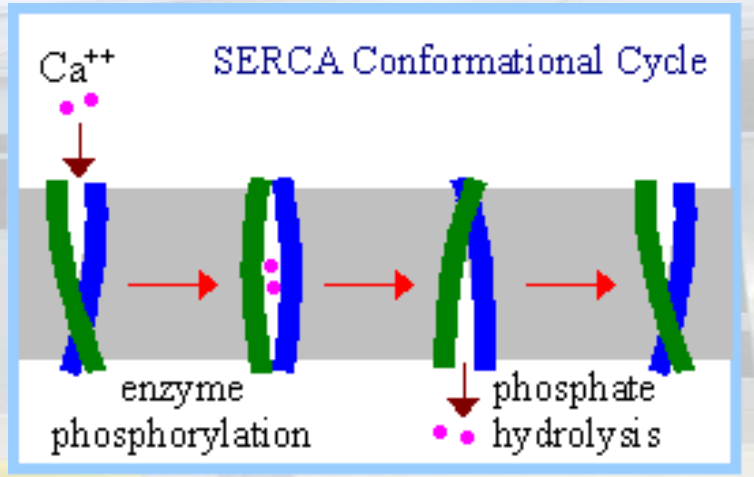
Images courtesy of ABPI


Ca 2+
hiperpolarización
Canal de Ca 2+
Canal de K+
K+
b
Ca 2+ = relajación
Ca 2+ = contracción
a
K+
Canal de Ca 2+
Canal de K+
Ca 2+
despolarización

Bloqueantes Cálcicos reducen el Calcio citoplasmático

- Reducción de su ingreso extra celular
- Aumento de su bombeo al circuito sarcoplasmico





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¿Como modifican el potencial de acción?

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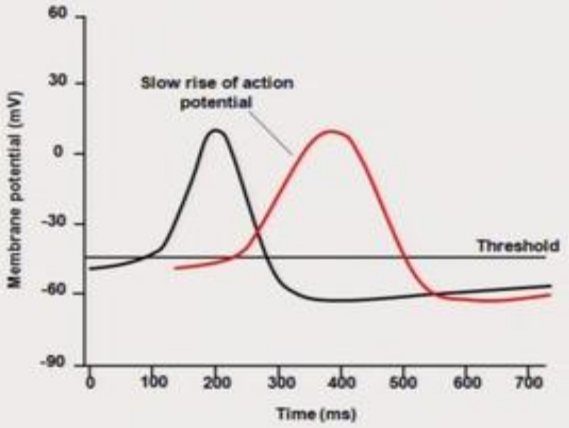
Class IV Antiarrhythmics

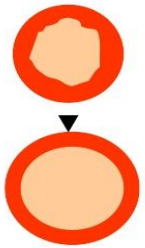
Ca^{2+} channel blockers



Bloqueadores de los canales de calcio

Acentuada reducción de la corriente de Calcio
En canales de calcio tipo L

Músculo liso



RELAJACION

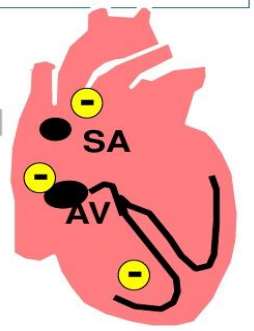
Nifedipino

Corazón

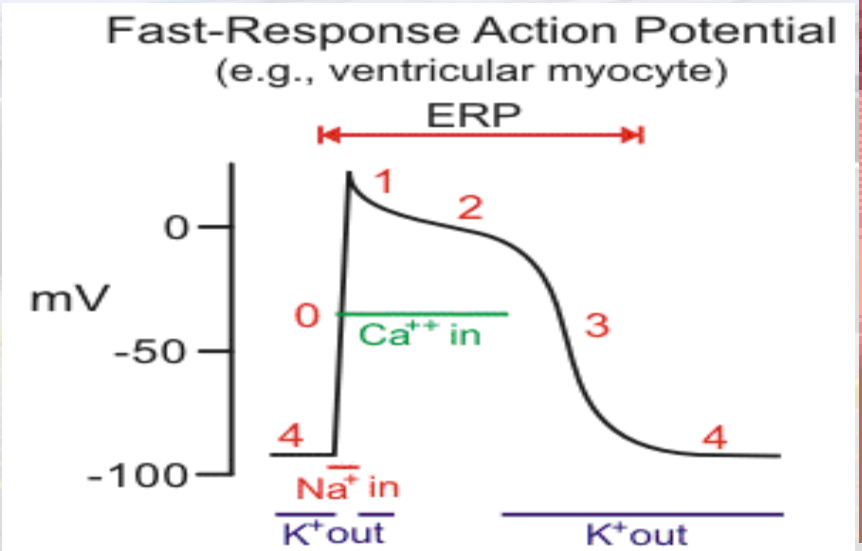
Contractibilidad

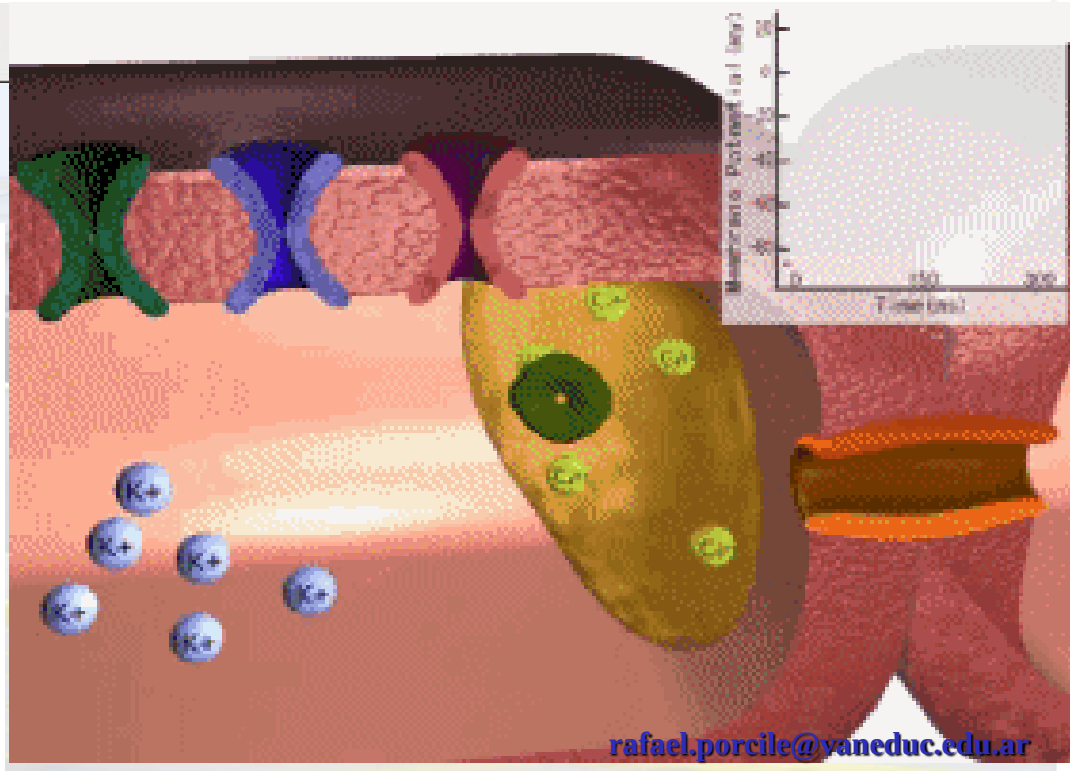
Frecuencia del NSA

Velocidad de Conducción del NAV



Verapamilo
Diltiacem





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Tipos de calcio antagonistas

NO DIHIDROPIRIDINICOS

- Verapamilo (fenilalkilaminas)
- Diltiazem (benzotiacepinas)

DIHIDROPIRIDINICOS

- NIFEDIPINO
- AMLIDIPINO
- NIMIDIPINO
- NICARDIPINA
- FELODOPINA
- ISRADIPINA
- NITRANDIPINA

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dihidropiridinicos

- Disminución eventos cardiovasculares, sin evidencia de sangrado, cáncer o enfermedad coronaria
- Disminución de eventos stroke en comparación a otros antihipertensivos
- No efecto sobre los lípidos
- No efecto sobre homeostasis glucosa
- Combinación con IECA: tiene buen perfil de seguridad
- No efecto sobre electrolitos

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ANTAGONISTAS DEL CALCIO

•Además de sus efectos antiarritmicos y antianginosos los bloqueadores de los canales del Ca++ producen Hipotensión arterial al dilatar las arteriolas (inhibe la entrada de Ca++ al músculo liso arterial)

•VERAPAMILO , DILTIACEM, NIFEDIPINO

•INDICACIONES : PROFILAXIS Y TRATAMIENTO DE ANGINA E HIPERTENSION

•CONTRAINDICACIONES : shock cardiogénico

•Nifedipino : contraindicado en estenosis aórtica

•Verapamilo y diltiacem : insuficiencia cardíaca , uso de b-bloqueantes

•EFECTOS ADVERSOS :

•Verapamilo, diltiacem : hipotensión , bradicardia , ICC, estreñimiento

•Nifedipino : hipotensión , taquicardia, edema periférico , rubefacción , mareo

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VERAPAMILO

- Calcio antagonista; indicado para el tratamiento de taquiarritmias supraventriculares, que incluyen:
  - taquicardias paroxísticas supraventriculares, incluyendo las asociadas con las vías accesorias (WPW).
  - Control temporal de la frecuencia ventricular rápida en fibrilación auricular o aleteo

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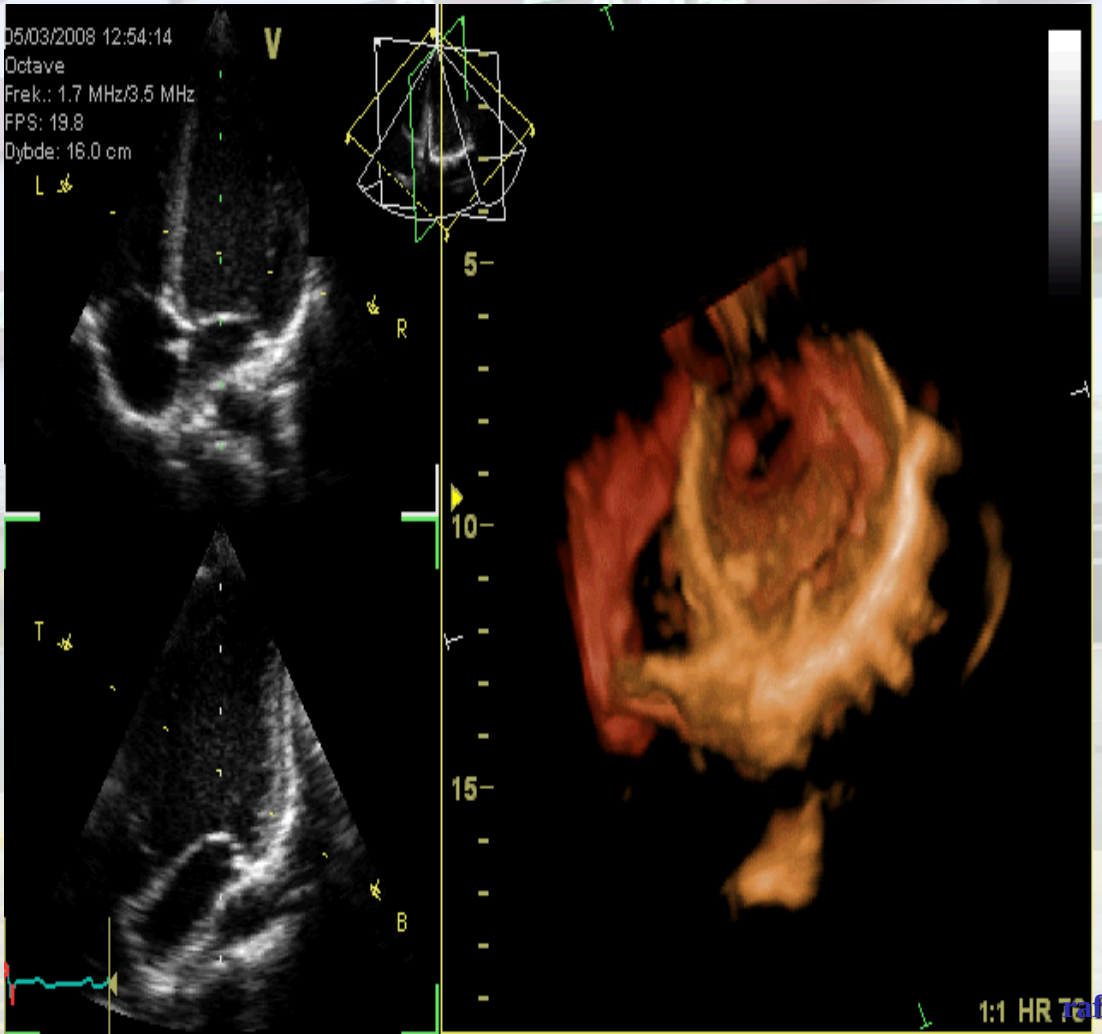
DIGOXINA



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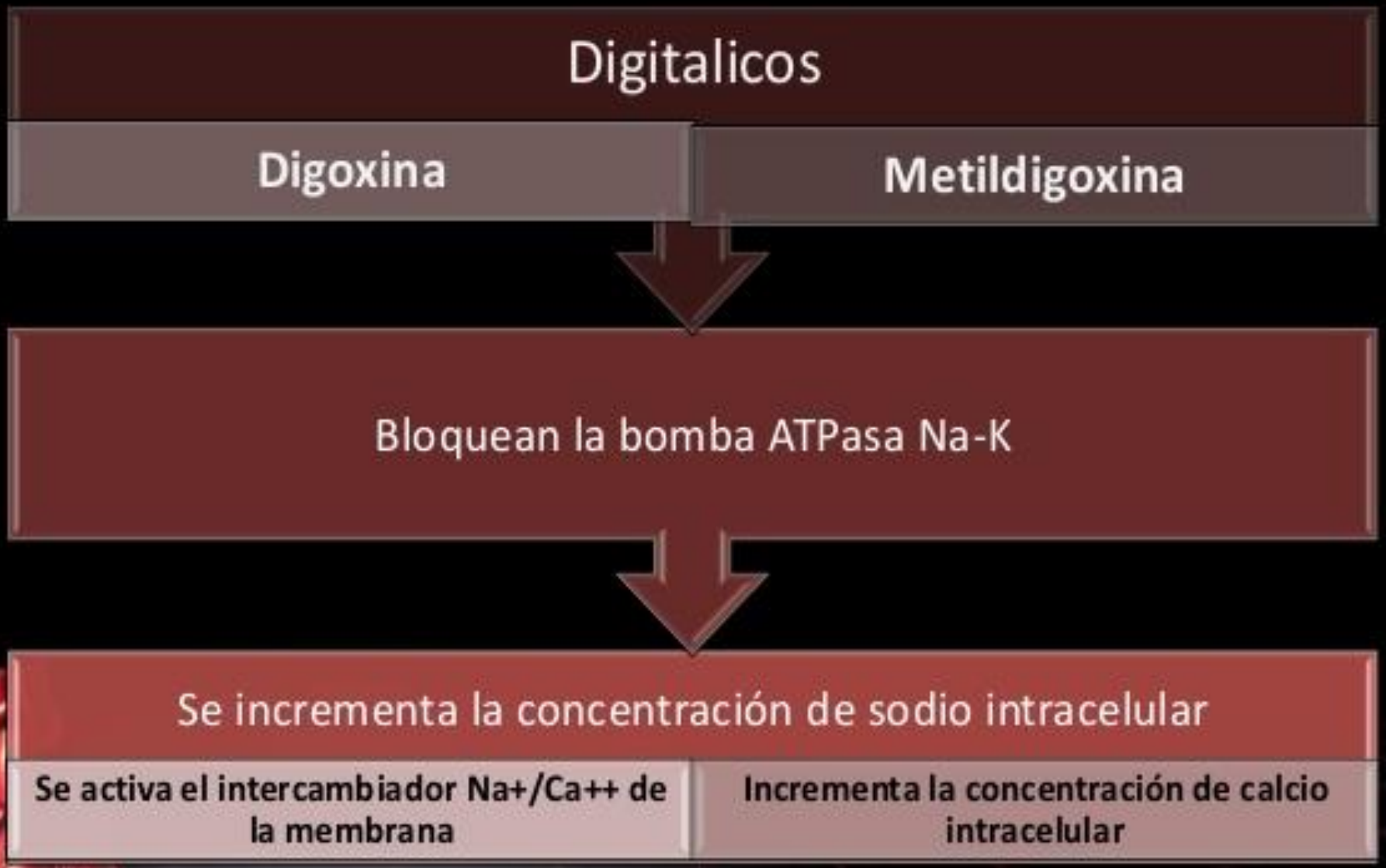

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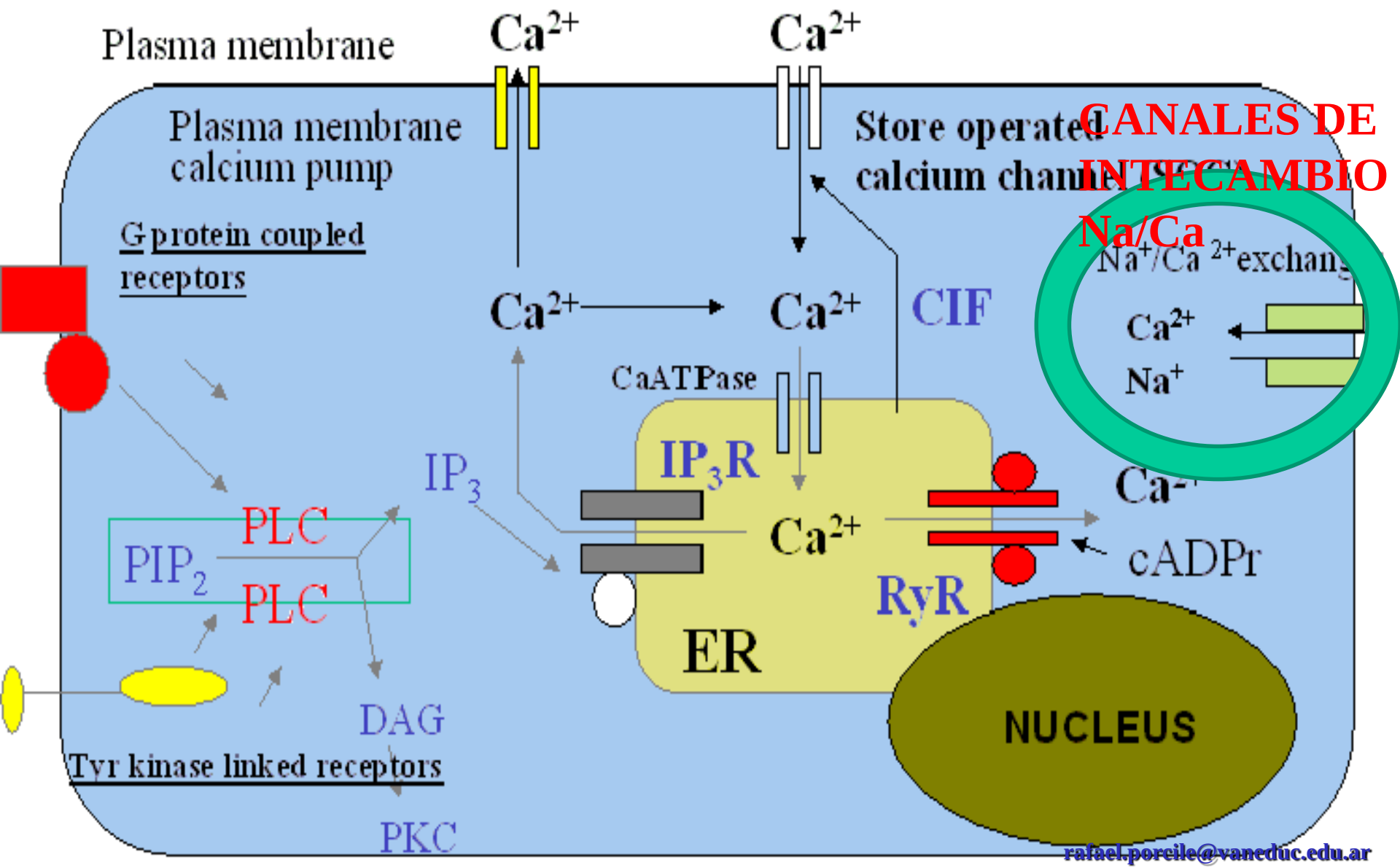
Calcium homeostasis



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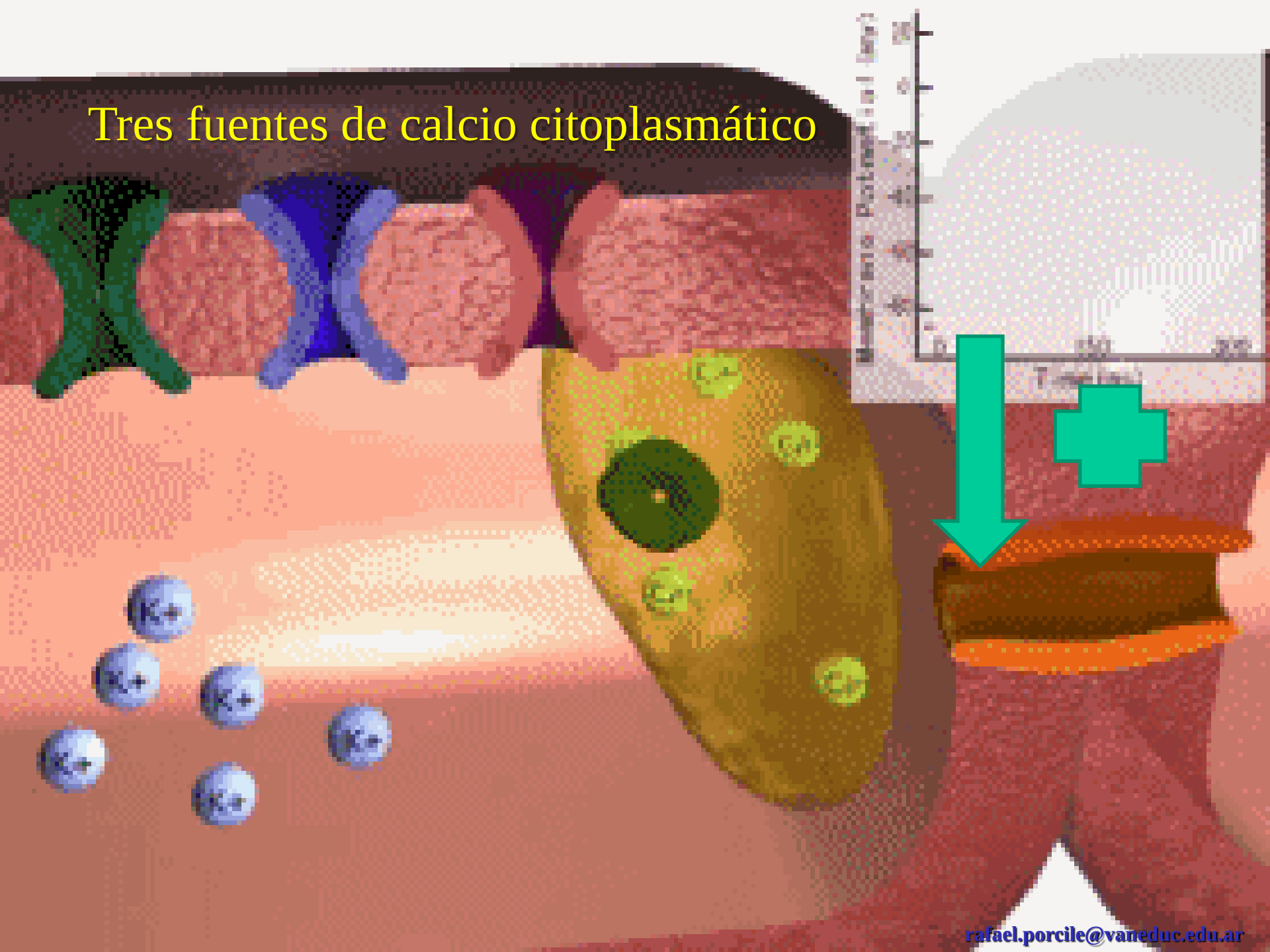
Tres fuentes de calcio citoplasmático



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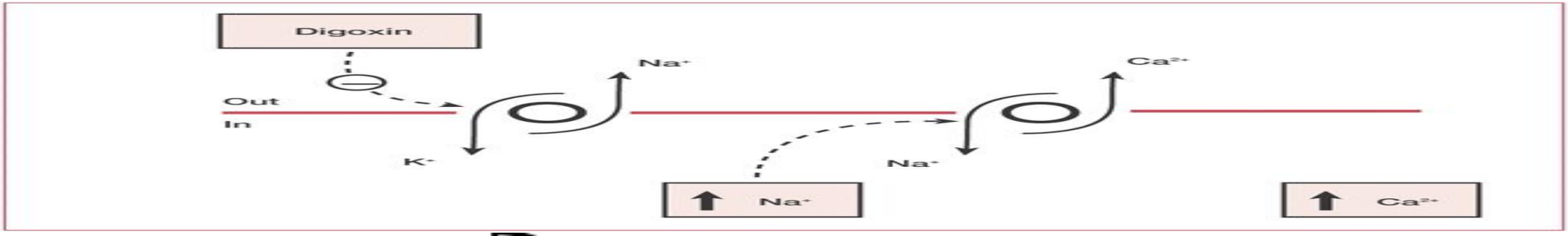
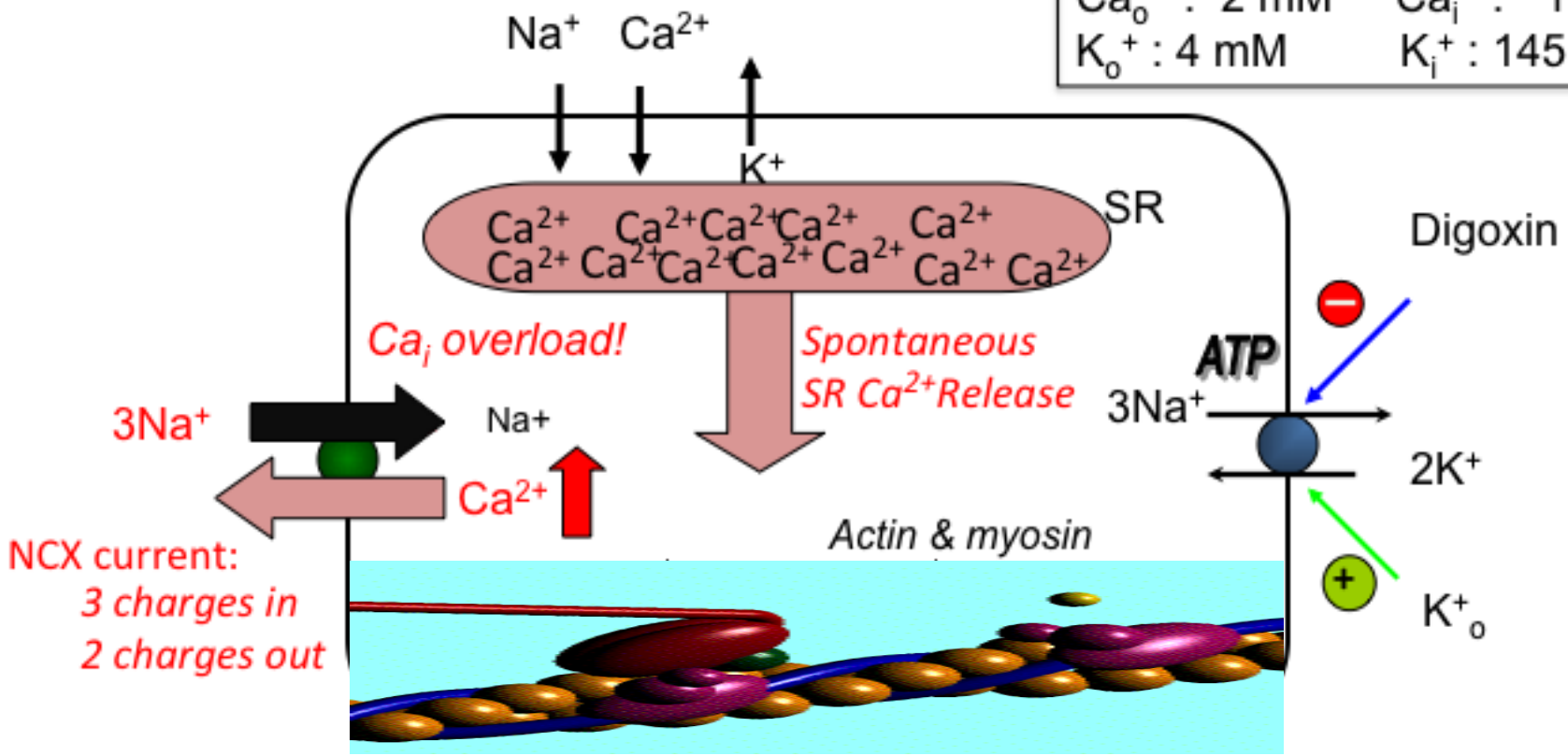


Na_o^+ : 140 mM Na_i^+ : 7 mM
Ca_o^{2+}: 2 mM Ca_i^{2+}: ~100 nM
K_o^+ : 4 mM K_i^+ : 145 mM



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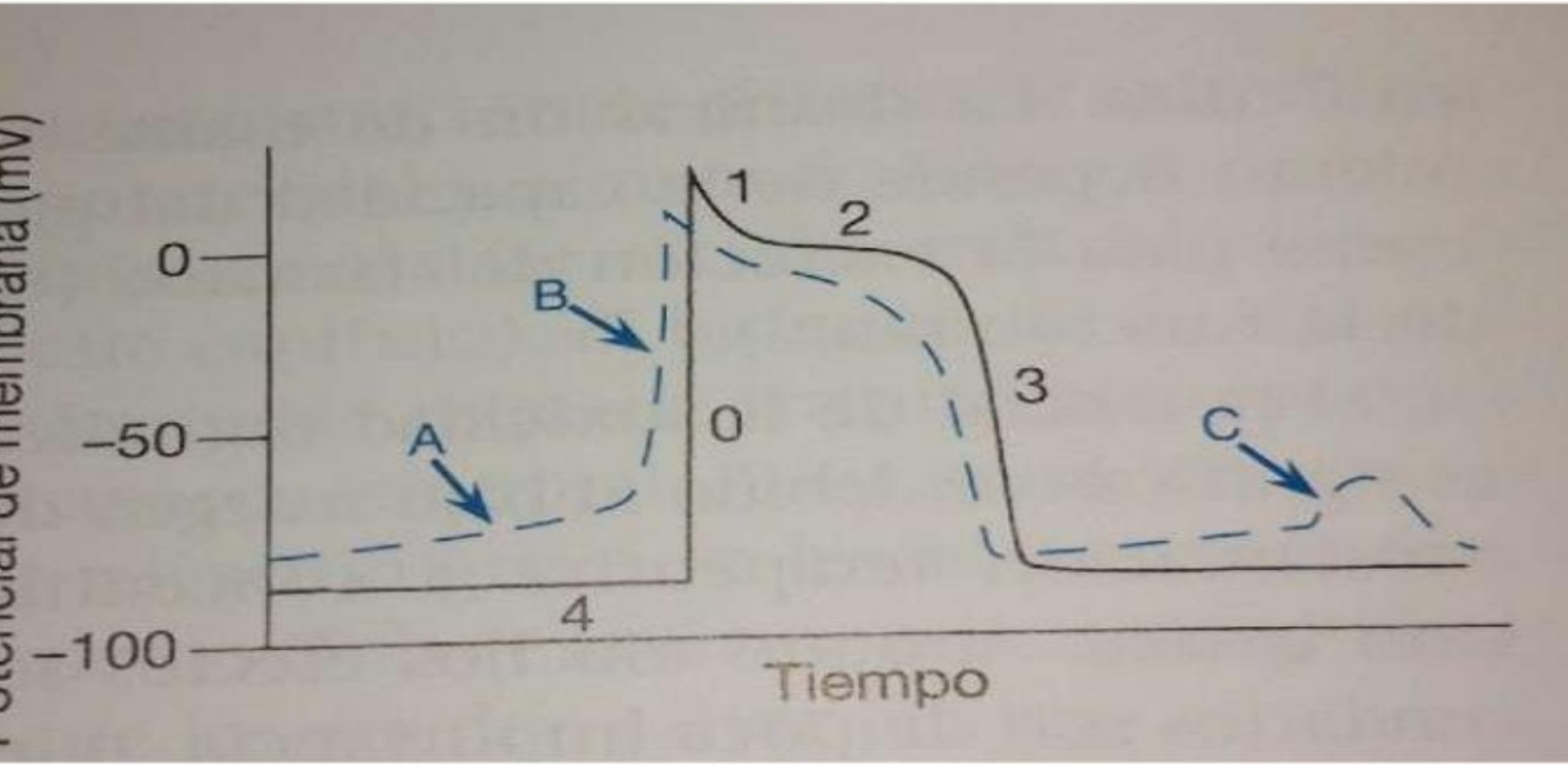
Digoxina



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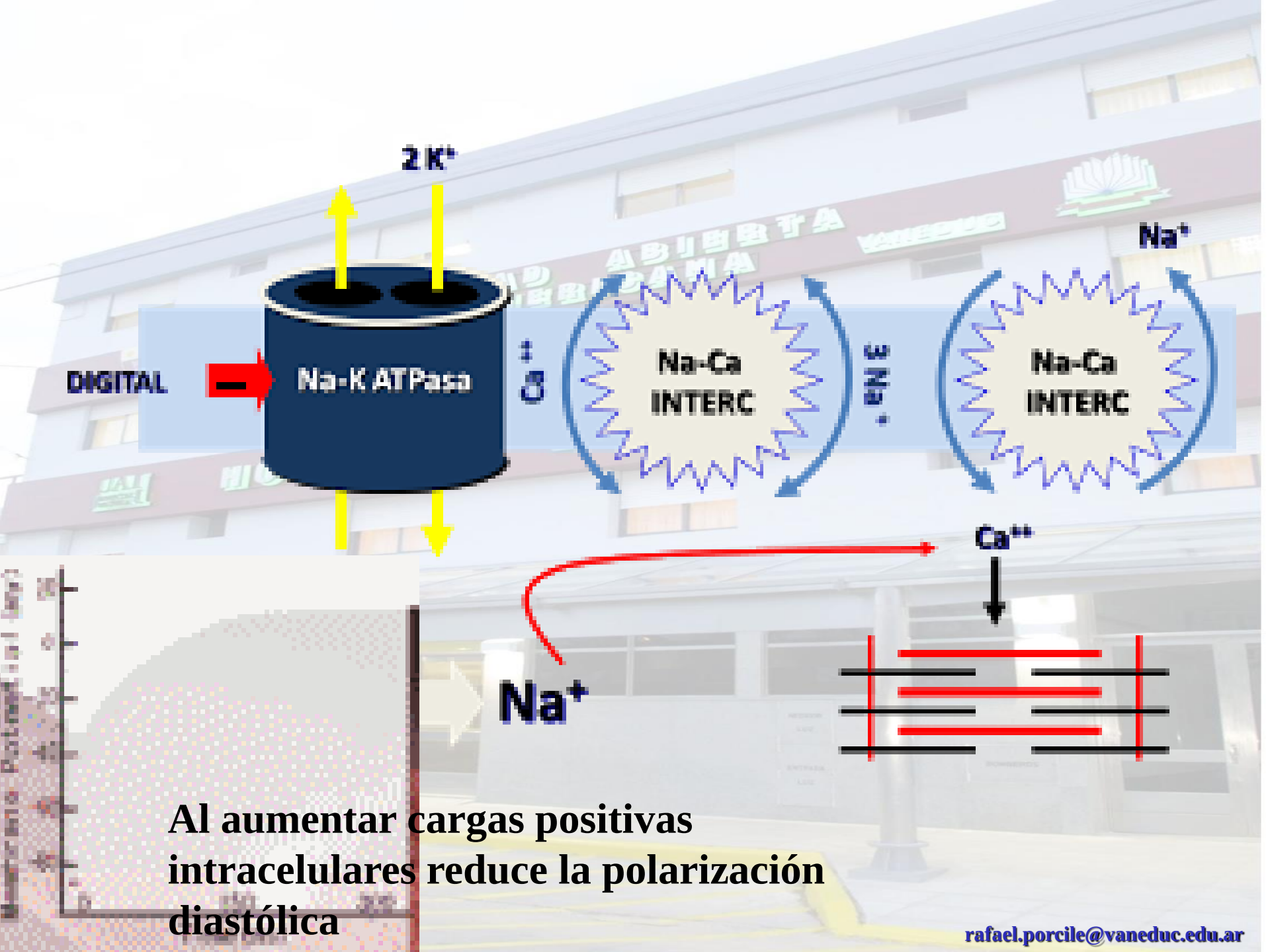
Digoxina

Fármaco	Biodisponibilidad	Metabolismo del primer paso	Vida media	Unión a proteinas	Volumen de distribución	pKa	Comienzo de acción (IV)	eliminación
Digoxina	75%	Si	36hrs	20 - 30%	6 - 7L/kg	7,15	5 – 30 min	Renal 80%

0,5 – 2 ng/ml

Indicaciones:

- ✓ ICC complicada pot fibrilación auricular
- ✓ ICC tto arritmias supraventriculares
- ✓ ICC sintomatica que no responde a IECA,ARAII, diureticos, β bloqueantes
- ✓ Taquicardias supraventriculares de reentrada



Al aumentar cargas positivas intracelulares reduce la polarización diastólica

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Farmacodinamia

- Bloquea la Bomba Na+/K+ ATPasa

  Se une a la subunidad α cuando está fosforilada

  Aumenta el Na+ intracelular, activando el intercambio con Ca++

- Aumenta tono vagal → contrarresta efecto adrenérgico de la ICC y disminuye FC.

Farmacodinamia

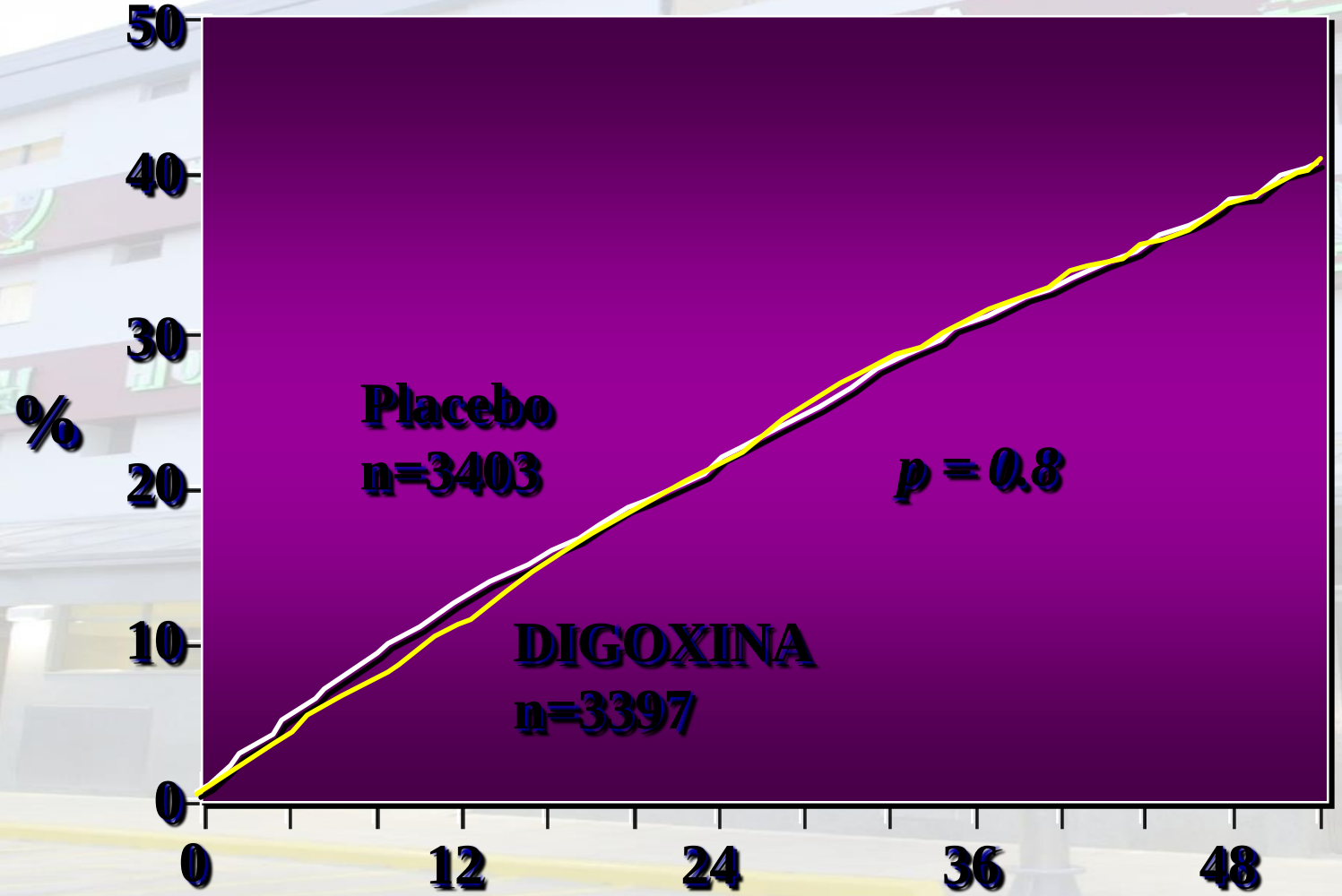
Farmacodinamia

- Efectos electrofisiológicos
  - Potencial de acción: acortan DPA.
  - Automatismo: disminuye. (aumenta en dosis tóxicas)
  - Período refractario: aumenta NAV.
  - Excitabilidad: aumenta. (disminuye en dosis tóxicas)

Farmacocinética

- Buena absorción VO (40 - 75%)
- Puede administrarse EV
- Efecto máximo 4 - 6 hs
- Vida media: 1 - 2 días
- Distribución lenta. UAP 25%
- Eliminación renal por FG y ST

DIGOXINA Y MORTALIDAD EN ICC



DIG

N Engl J Med 1997;336:525

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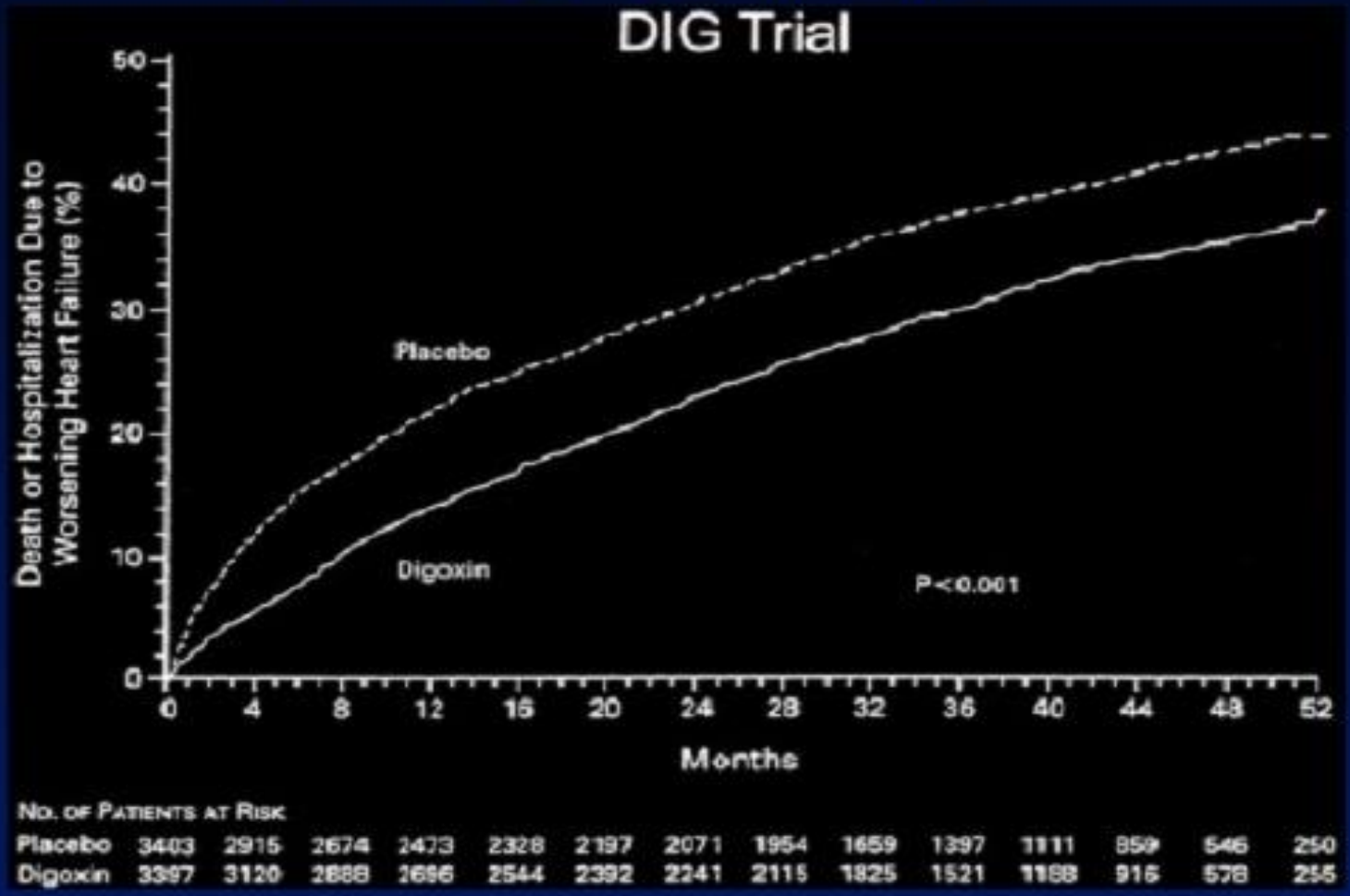
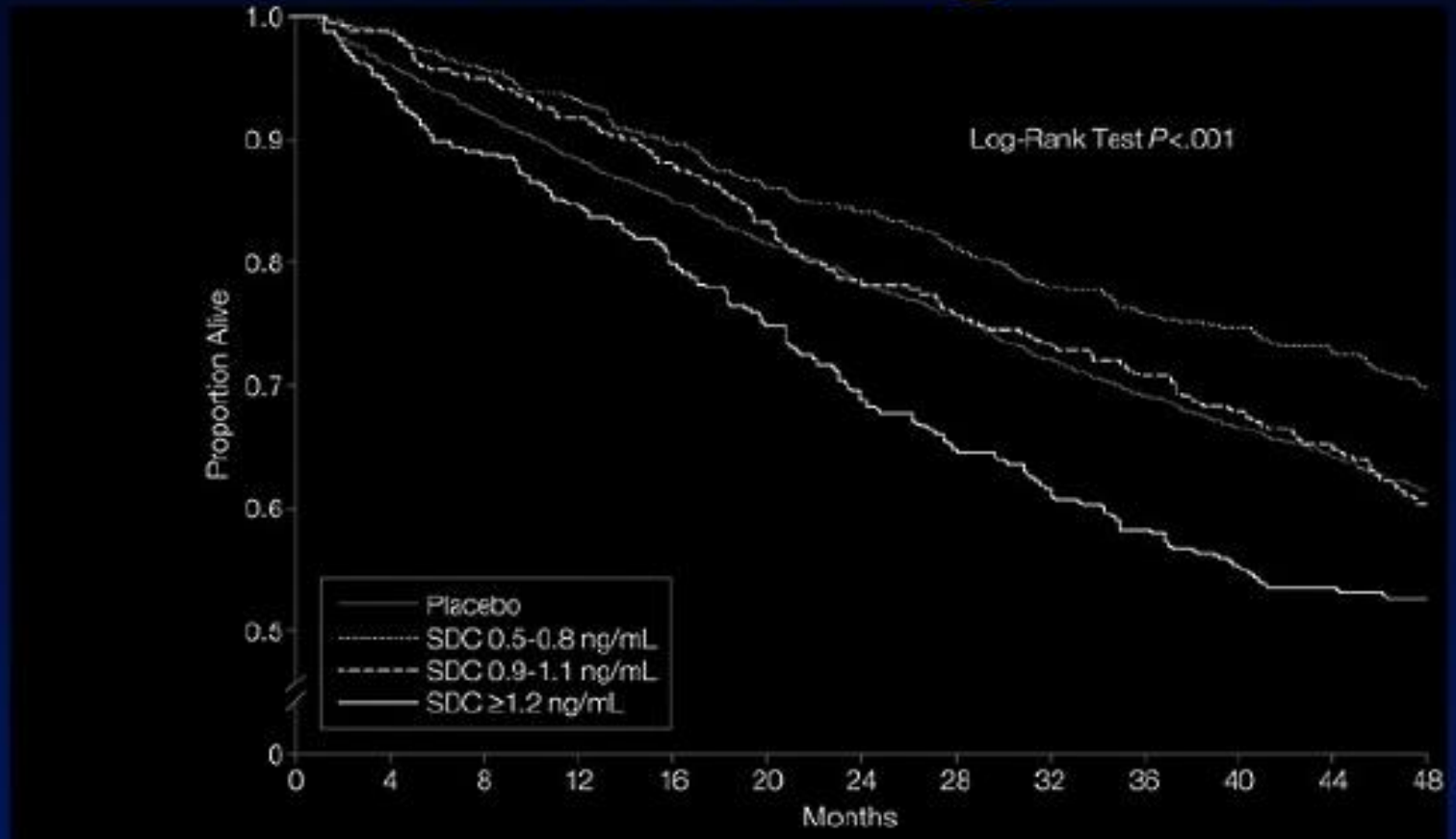
Pero Disminuye los Internamientos y Síntomas

Mortalidad y hospitalizaciones



DIG investigator group. *NEJM*. 1997; 336:525-533

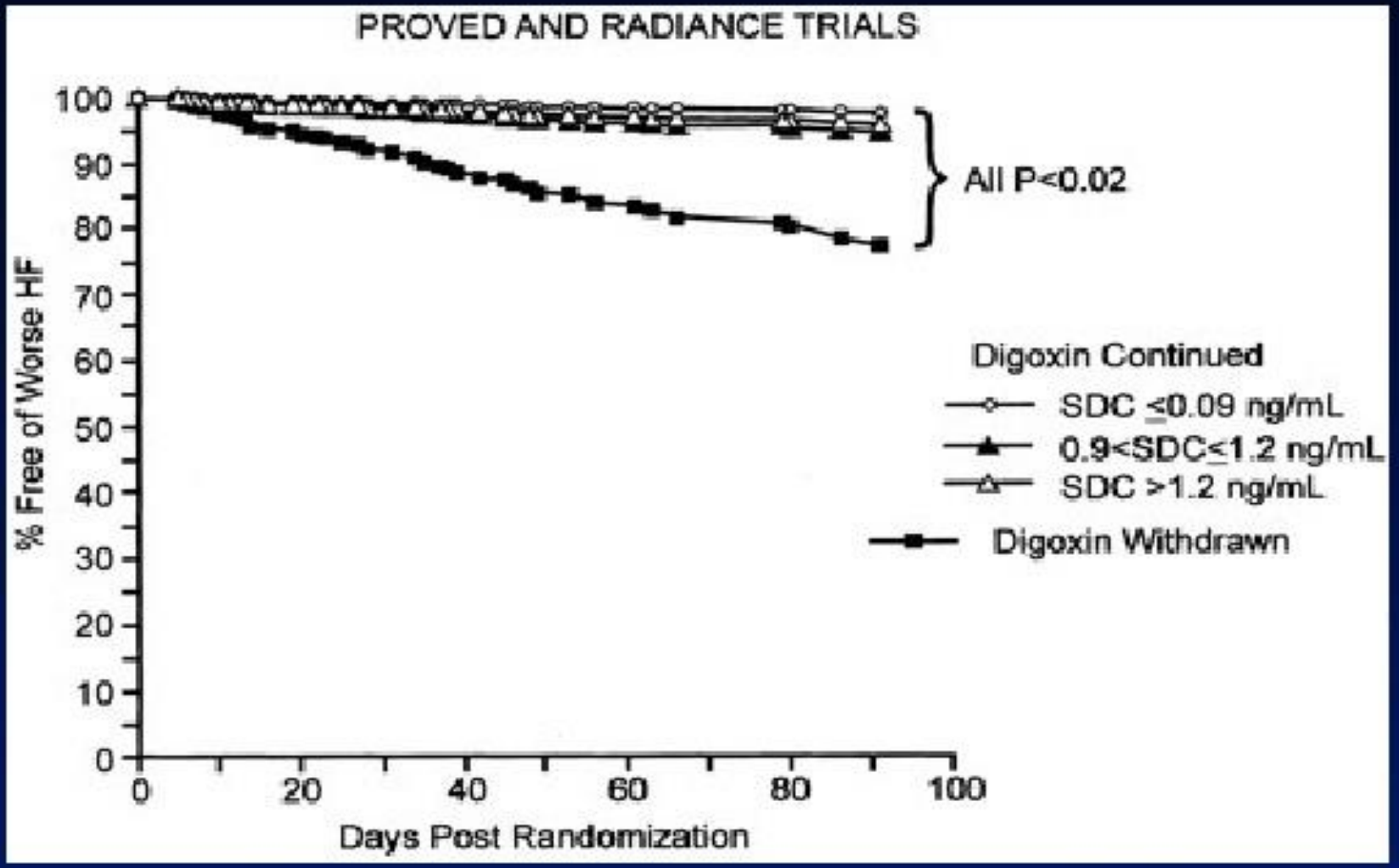
Mortalidad Depende de los Niveles de Digoxina



No. at Risk													
Placebo	2611	2514	2405	2302	2213	2117	2024	1948	1858	1625	1385	1111	852
SDC 0.5-0.8 ng/mL	572	566	549	533	512	490	477	459	441	427	419	361	290
SDC 0.9-1.1 ng/mL	322	319	306	295	282	267	250	240	232	225	211	180	138
SDC ≥1.2 ng/mL	277	262	246	234	221	206	187	177	166	159	150	133	116

S S Rathore. *JAMA*. 2003;289:871-878

Digoxin Withdrawal Worsens HF, Independent of Dig Level



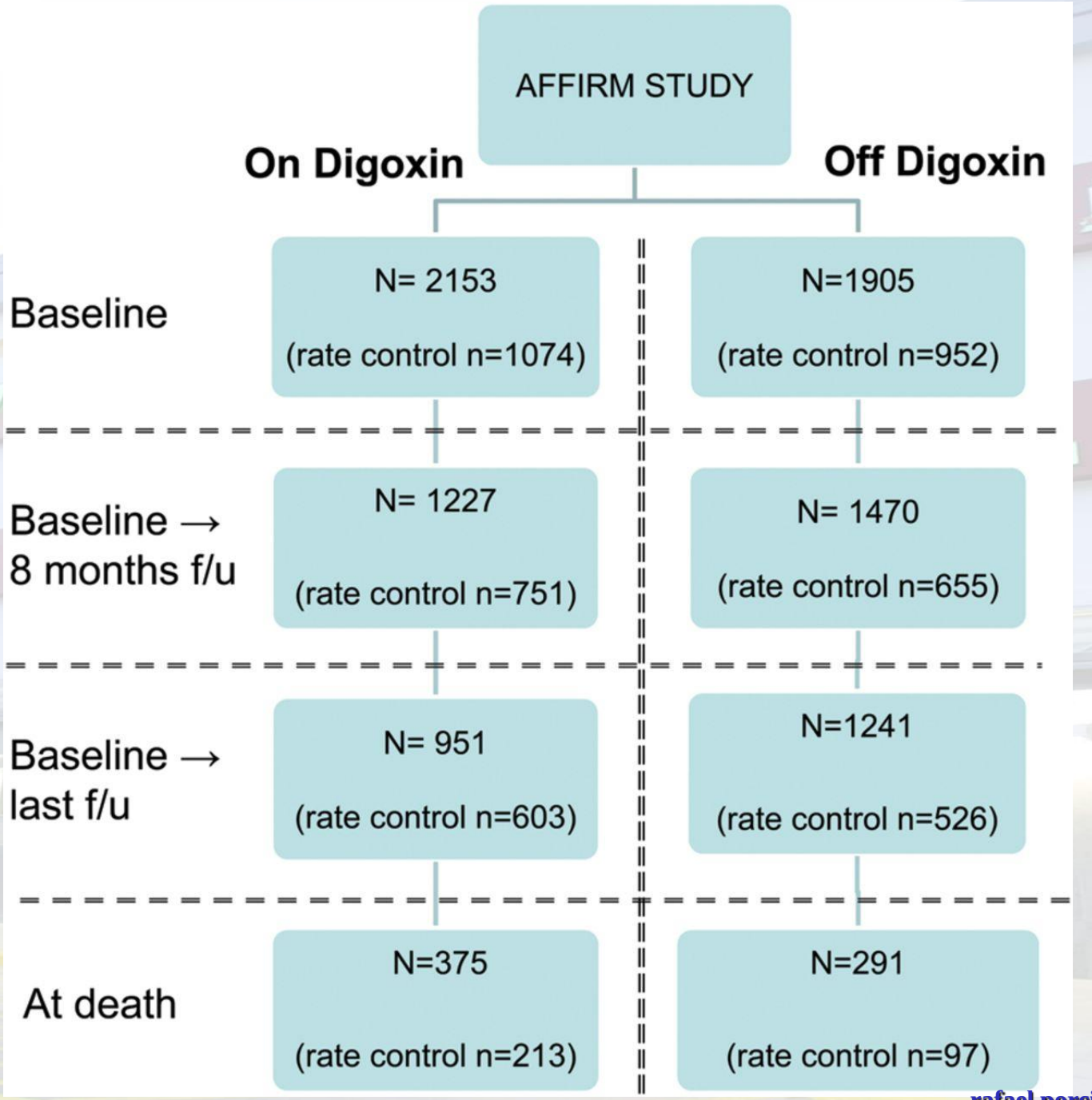
Adams K et al. *JACC*. 2002;39:946 –53

Metanalysis using RADIANCE and PROVED

Increased mortality among patients taking digoxin—analysis from the AFFIRM study

European Heart Journal (2013) 34, 1481–1488
doi:10.1093/eurheartj/ehs348

The AFFIRM trial randomized 4060 patients to rhythm control (2033 patients) vs. rate control (2027 patients).
The study included 1594 females representing 39.3% of the study cohort. Overall, 2816 patients (69.4%) received digoxin within 6 months of randomization and/or during the study.



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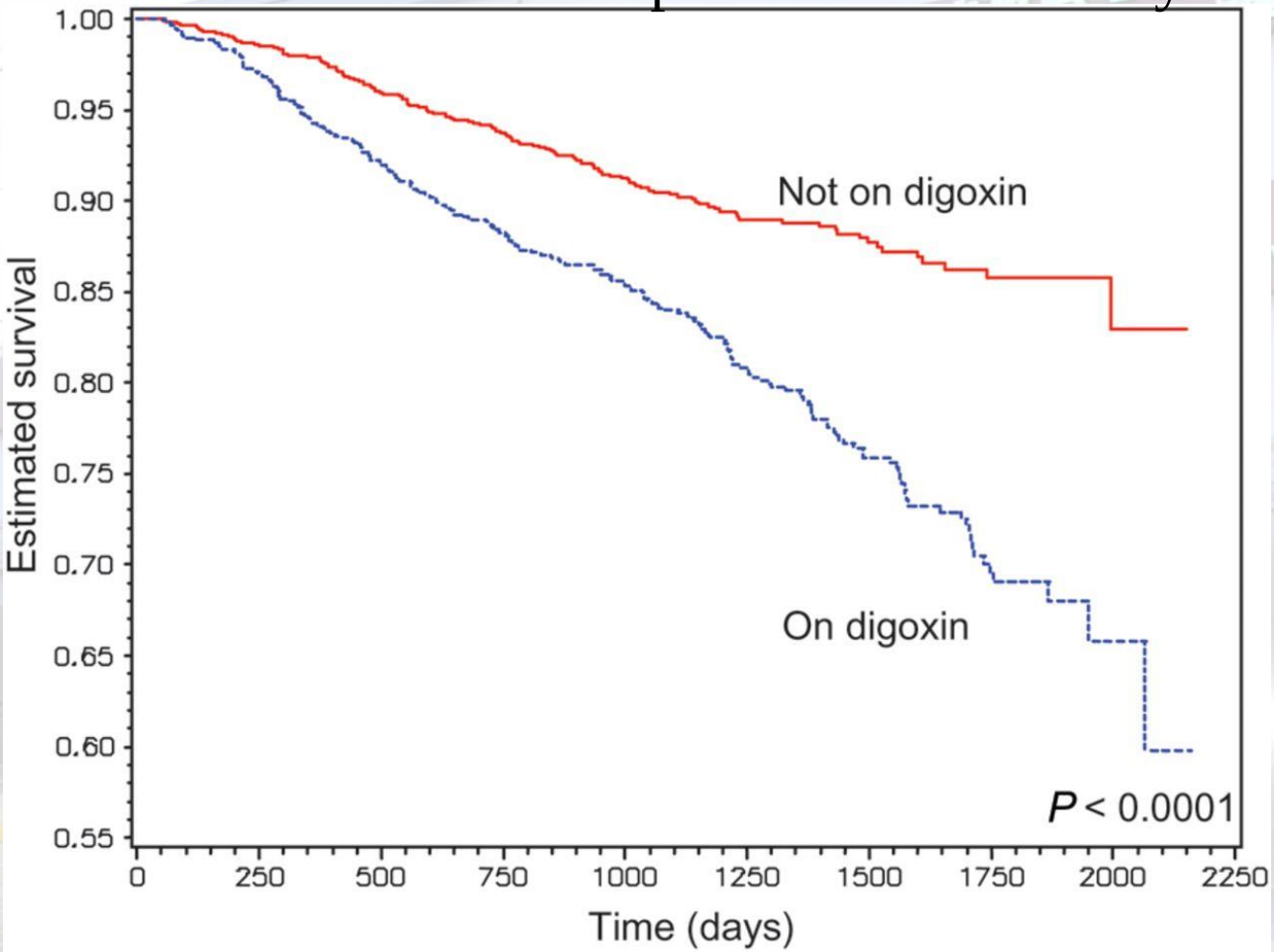
Kaplan–Meier curves for all-cause mortality based on digoxin use during the study. Shown are Kaplan–Meier curves for all-cause mortality in patients always or never on digoxin during the study. *P*-value for this comparison is <0.0001 by the likelihood ratio test.



European Heart Journal (2013) 34, 1481–1488
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Increased mortality among patients taking digoxin—analysis from the AFFIRM study

European Heart Journal (2013) 34, 1481–1488
doi:10.1093/eurheartj/ehs348

Digoxin was associated with a significant increase in all-cause mortality in patients with AF after correcting for clinical characteristics and comorbidities, regardless of gender or of the presence or absence of HF. These findings call into question the widespread use of digoxin in patients with AF

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¿Cuales pacientes son los que tienen mas probabilidad de morir bajo digoxina?

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Patients with no congestive heart failure and ejection fraction ≥40%

In patients with AF and no HF, digoxin was associated with a 37% increase in mortality.

This group represented more than half of all patients enrolled in AFFIRM.

These findings are consistent with previously published results from the **Registry of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) study.**[1][2]

The RIKS-HIA study examined 1-year outcomes of patients with AF, CHF, or both on digoxin by comparing them to a matched group of patients not receiving digoxin.

The 4426 patients with AF and no history of CHF taking digoxin had a significant increase in overall mortality (estimated relative risk 1.42, 95% CI 1.29–1.56) compared with 16 587 controls at discharge.

Among the 666 patients who died during the study, 375 (56.3%) received digoxin and 291 (43.7%) had no digoxin at the last follow-up visit before death. When comparing those two groups, **cardiac death with no evidence of ischaemia was a significantly more frequent cause of death among patients on digoxin** at the last follow-up visit (*n* = 139, 37.1% vs. *n* = 79, 27.1%, *P* = 0.007). There were no statistical differences for the following causes of death: cancer; pulmonary; and non-cardiovascular

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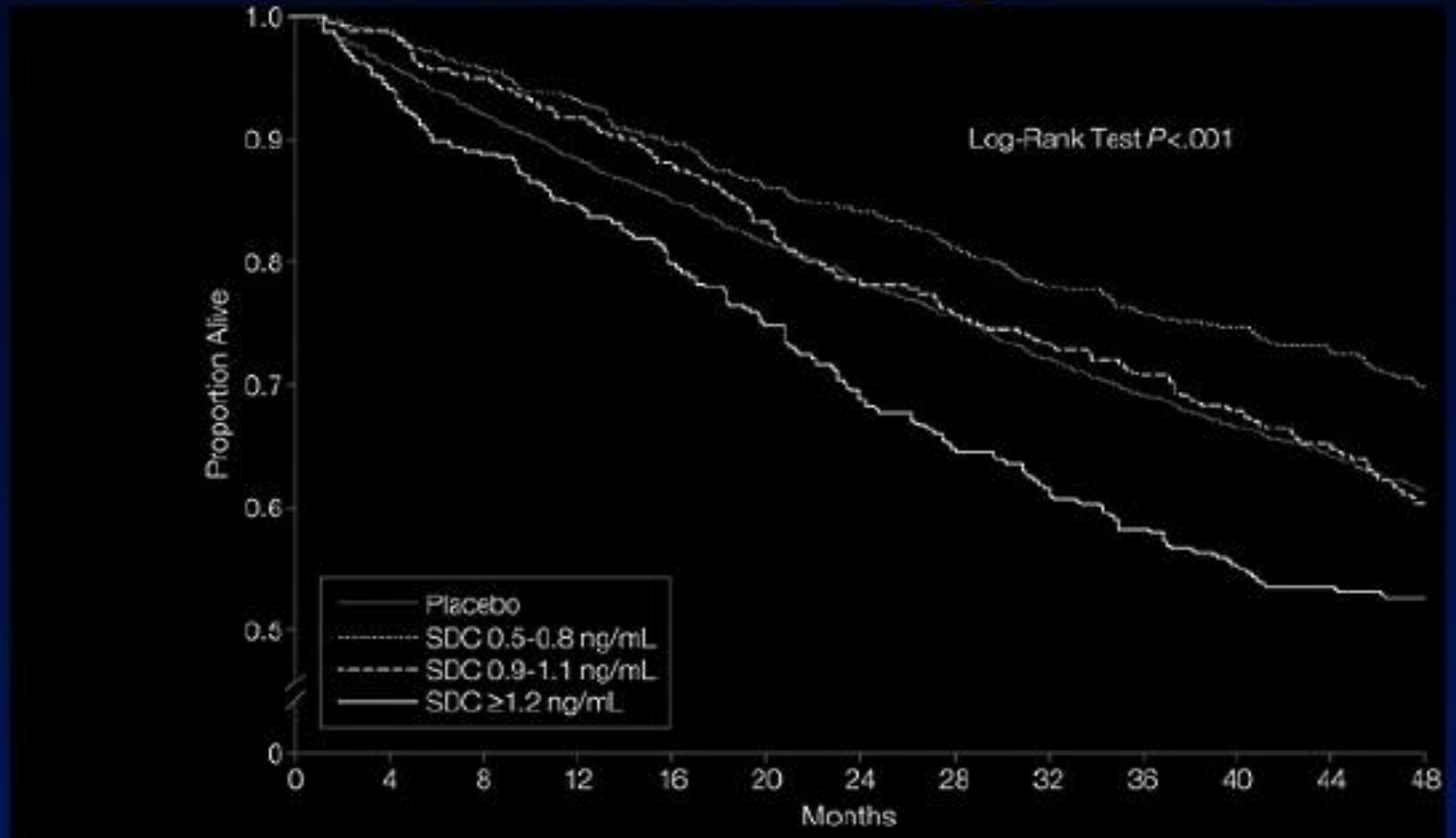
Mortalidad Depende de los Niveles de Digoxina



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SDC 0.5-0.8 ng/mL	572	566	549	533	512	490	477	459	441	427	419	361	290
SDC 0.9-1.1 ng/mL	322	319	306	295	282	267	250	240	232	225	211	180	138
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S S Rathore. *JAMA*. 2003;289:871-878

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Digoxin-associated mortality: a systematic review and meta-analysis of the literature

European Heart Journal
doi:10.1093/eurheartj/ehv143
2015

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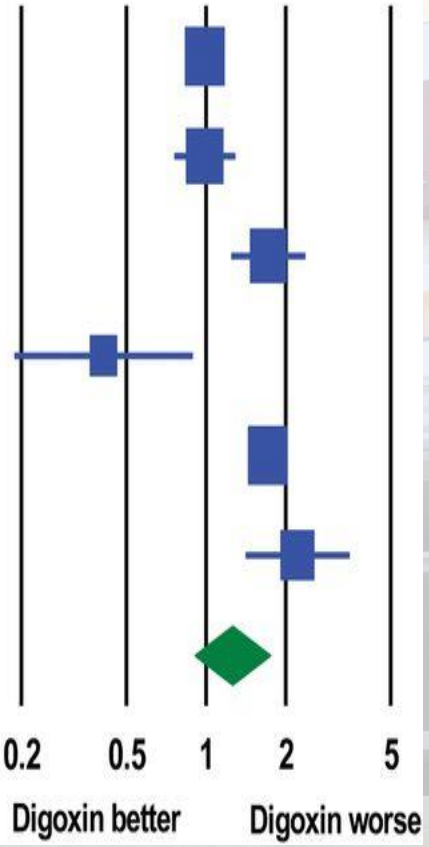
Sensitivity analysis of six studies which provided data on digoxin dosing.

Study	Patients	Digoxin dose (mg)	Statistics			
			Hazard ratio	95%	CI	p-Value
Garg (DIG), 1997	6800	0,244	0,99	0,91	1,07	0,81
Ahmed (DIG Ancillary), 2006	988	0,235	0,99	0,76	1,28	0,94
Freeman, 2013	2891	0,150	1,72	1,25	2,36	0,00
Mulder (RACE II), 2014	608	0,250	0,41	0,19	0,89	0,02
Freeman (ATRIA-CVRN), 2014	14787	0,164	1,71	1,52	1,93	0,00
Pastori, 2015	815	0,126	2,22	1,42	3,48	0,00
Total			**1,26**	**0,91**	**1,74**	**0,16**



Mate Vamos et al. Eur Heart J 2015;eurheartj.ehv143

European Heart Journal

This meta-analysis of the contemporary literature indicates that **digoxin therapy particularly without proper serum level control is associated with an increased mortality risk in patients with AF and with CHF.** Our sensitivity analysis, however, suggests negative effects of digoxin particularly in the AF population but somewhat less unfavourable effects in the CHF population. Coupled with the notion emphasized by Rathore *et al*.,[33] **this calls for randomized trials of dose-adjusted digoxin therapy at least in CHF patients**. Until such proper randomized controlled trials are being completed, digoxin should be used with great caution (including monitoring plasma levels), particularly when administered for rate control in AF.

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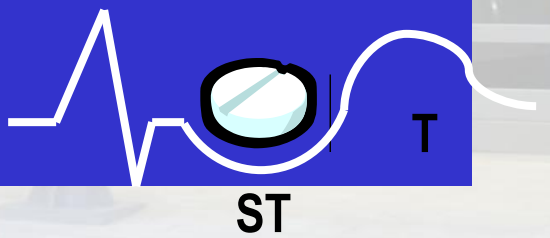
Digitalización

- Administración de Digoxina
- Rápida vs Lenta
- Ajuste de dosis en Insuficiencia Renal
- **Digoxinemia**: 1 a 1,5 ng/ml
- Muy bajo margen terapéutico
- **Impregnación digitálica**: infraST de concavidad superior (CUBETA DIGITALICA)



Intoxicación digitálica

MANIFESTACIONES CARDIACAS

- Bloqueo A-V 1° 2° grado
- Taquicardia supra ventricular con bloqueo
- Taquicardia auricular o de la unión
- Extrasístole ventricular monomorfa
- Taquicardia ventricular
- Fibrilación ventricular

Intoxicación digitálica

ECG

- Prolonga PR
- Acorta QT
- Infra ST
- Aplanamiento o inversión de T
- Bradicardia o Arritmia

Intoxicación digitálica

- Digestivas: N, V, D, Anorexia, perdida de peso
- SNC: parestesias, delirio, neuritis, confusión, depresión
- Oculares: escotomas, visión borrosa, colores

Intoxicación digitálica

FACTORES PREDISPONENTES

- **Hipokalemia!!!!!!!!!!!!!**
- Hipomagnesemia
- Hipercalcemia
- Alcalosis
- Hipoxemia
- Fallo renal
- Hipotiroidismo

Intoxicación digitálica

TRATAMIENTO

- Suspender la droga
- Potasio!!!!!!
- TV: Lidocaína
- Bradi / BAV: Atropina +- MCP transitorio
- Específico: AC ANTIDIGOXINA (Fab)
- Hemodiálisis