MERTE SUBITE E INSUFICIENCA CARDÍACA

Rafael Porcile

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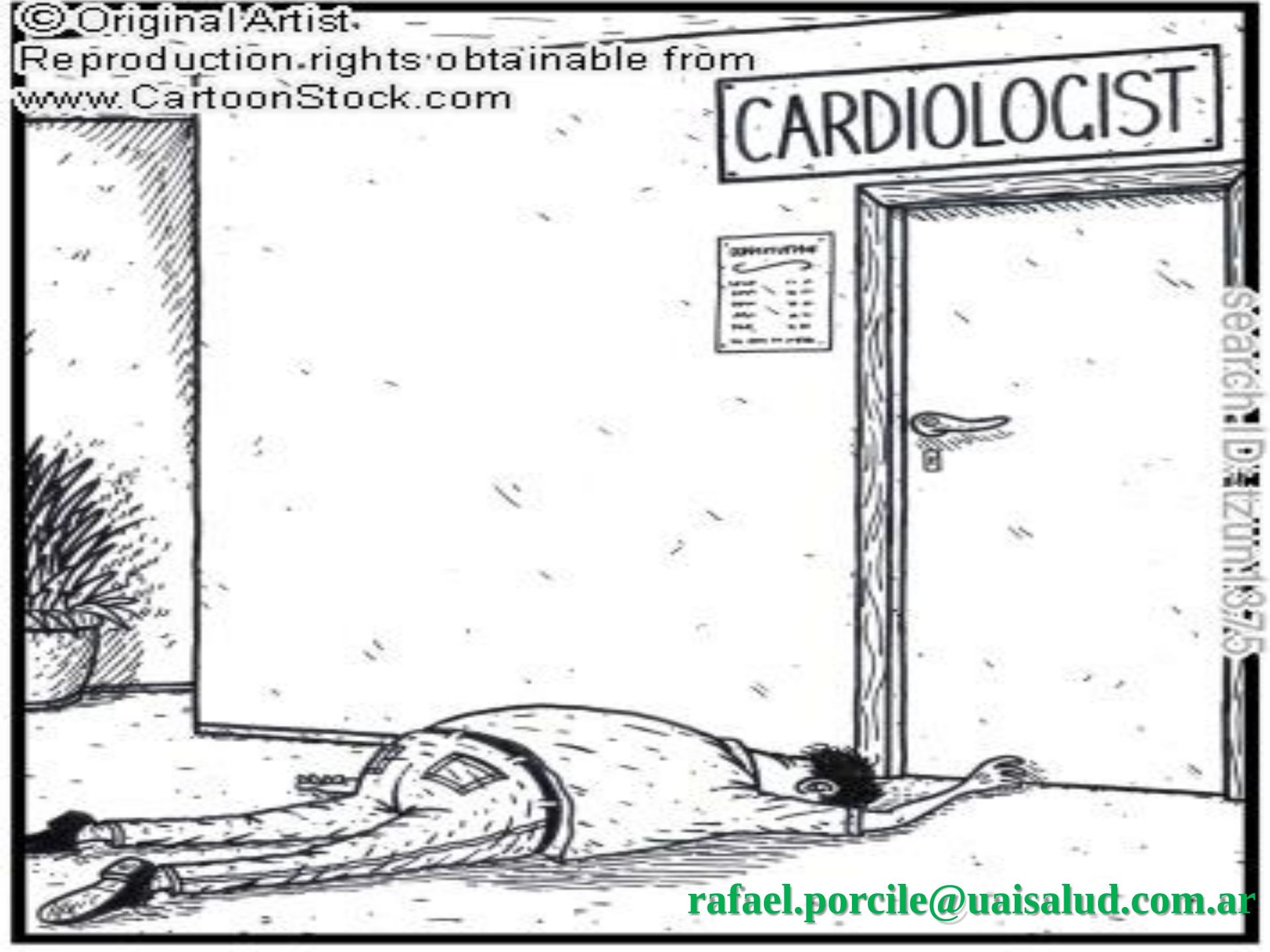

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Muerte súbita

- ✓ **Muerte súbita**: "*Muerte ocurrida por causas naturales dentro de la primera hora tres del inicio de los síntomas*"

- ✓ **Muerte súbita cardíaca :** "*Muerte ocurrida por causas naturales debida a causa cardíaca dentro de la primera hora tras el inicio de los síntomas. La enfermedad cardíaca preexistente podía ser o no conocida pero, en cualquier caso, el tiempo y modo de muerte es inesperado*"

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Muerte súbita no cardíaca

- ✓ Embolismo pulmonar masivo
- ✓ Disección o rotura aórtica o pulmonar
- ✓ ACV masivo
- ✓ Rotura aneurisma de seno de Valsalva

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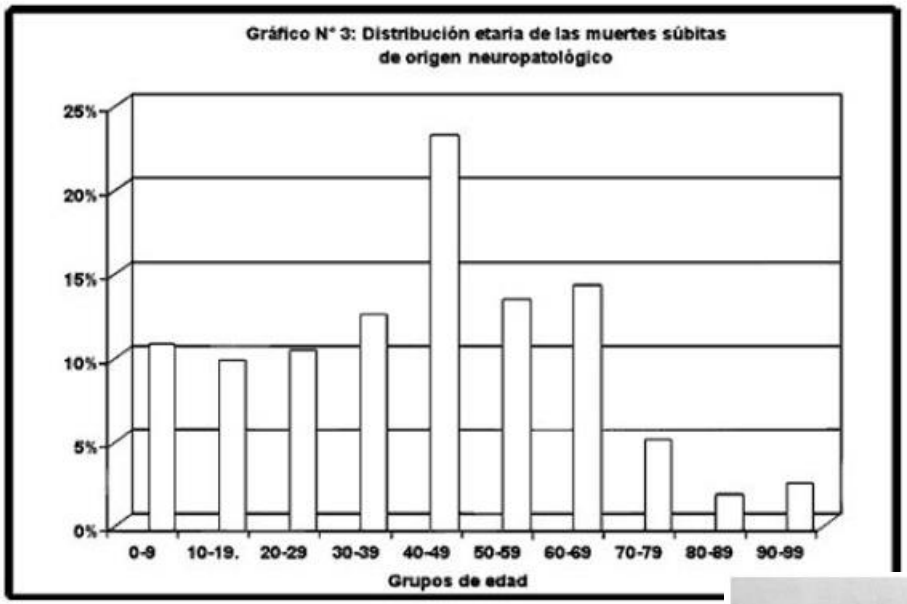
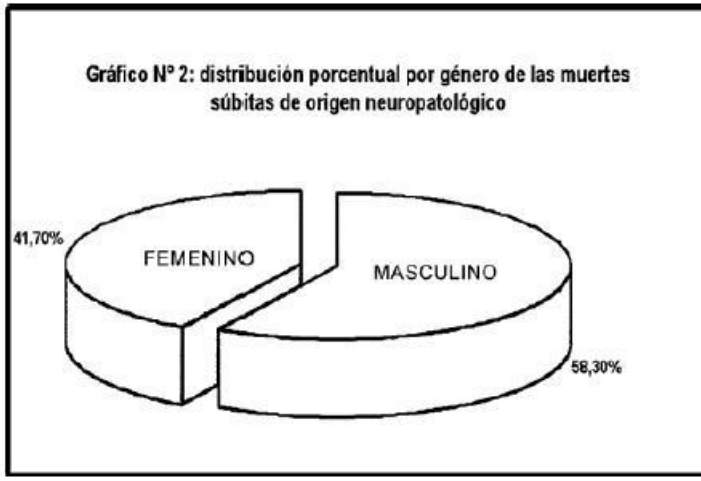


Fuente: Cuadro Nº 4



Fuente: Cuadro Nº 3

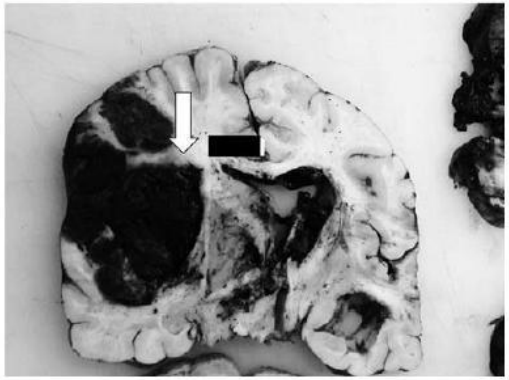
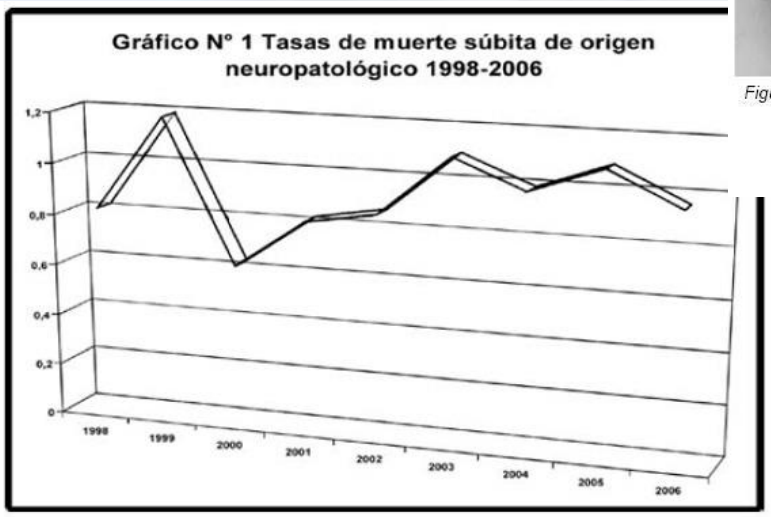
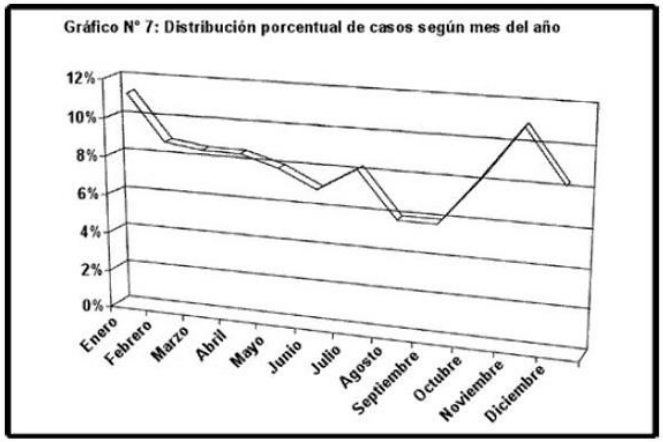


Figura 5: *Hematoma intraparenquimatoso de origen hipertensivo*
Imagen cortesía del Dr. Raúl Bonilla Montero, neuropatólogo del Departamento de Medicina Legal – OIJ.



Fuente: Cuadro Nº 2



Uncommon causes

Cardiomyopathy

Risk factors for coronary atherosclerosis: older age, male sex, hyperlipidemia, smoking, hypertension, diabetes

Coronary atherosclerosis

Genetic factors, hypertension

Genetic factors, infection, others

<5%

~10–15%

~80%

Primary electrical and genetic ion-channel abnormalities, valvular or congenital heart disease, other causes

Hypertrophic cardiomyopathy

Dilated cardiomyopathy

Chronic myocardial scar caused by infarction

Acute plaque destabilization: rupture, fissure, hemorrhage, thrombosis

Triggers of cardiac arrest:
transient ischemia, hemodynamic fluctuations, neurocardiovascular influences, environmental factors

Sudden Death

Typical sequence of electrical events:

Sinus rhythm

Ventricular tachycardia

Ventricular fibrillation

Asystole

PREVALENCIA MS

- ✓ **Evidencia de aterosclerosis coronaria en 65%**
- ✓ **La mayor parte se considera MS arrítmica**
- ✓ **El parámetro mas fidedigno de MSC en IC es el deterioro de la FEY**
- ✓ **En la población general, la incidencia anual de muerte súbita está en torno al O,1-0,2% anual.**
- ✓ **En grupos de muy alto riesgo, la incidencia anual de muerte súbita puede ser superior al 20-30%**

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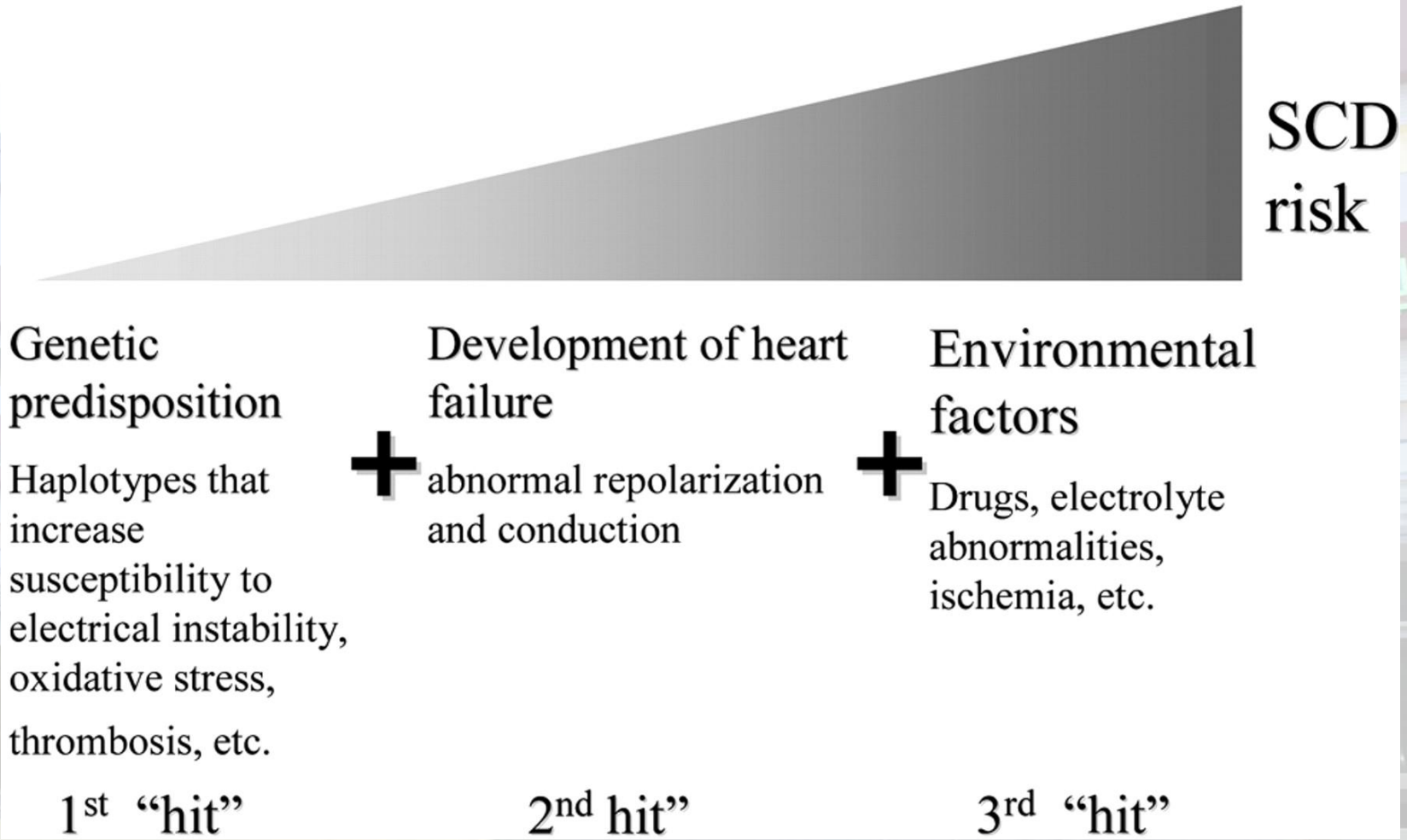
Multi-hit hypothesis of the development of SCD. Heart failure serves to enhance the risk by the associated alterations in the myocardial substrate and increasing the frequency/intensity of triggers of malignant arrhythmias.



Tomaselli G F , and Zipes D P Circulation Research 2004;95:754-763

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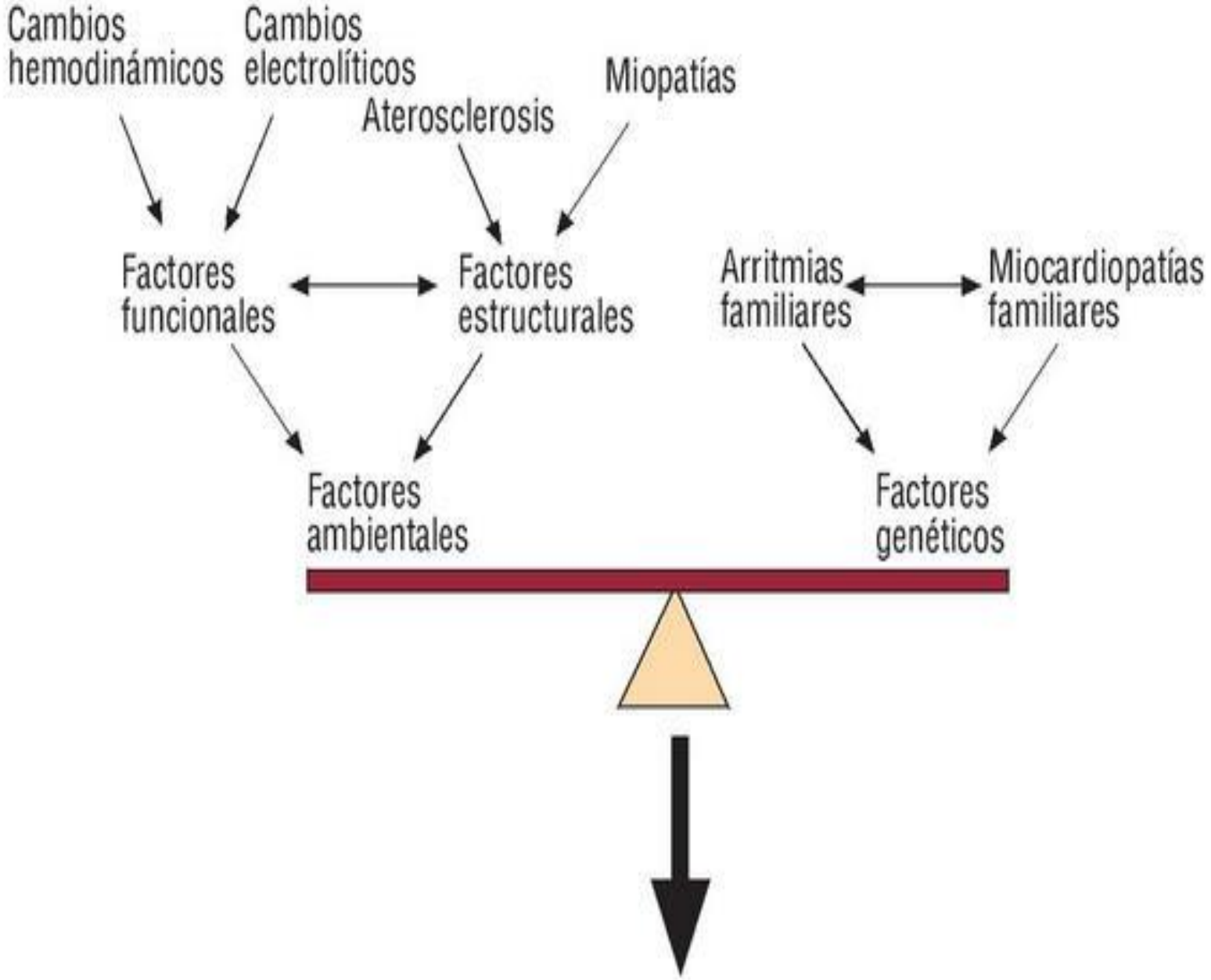
Factores de inestabilidad


Cambios hemodinámicos
Cambios electrolíticos
Aterosclerosis
Miopatías
Factores funcionales
Factores estructurales
Arritmias familiares
Miocardiopatías familiares
Factores ambientales
Factores genéticos

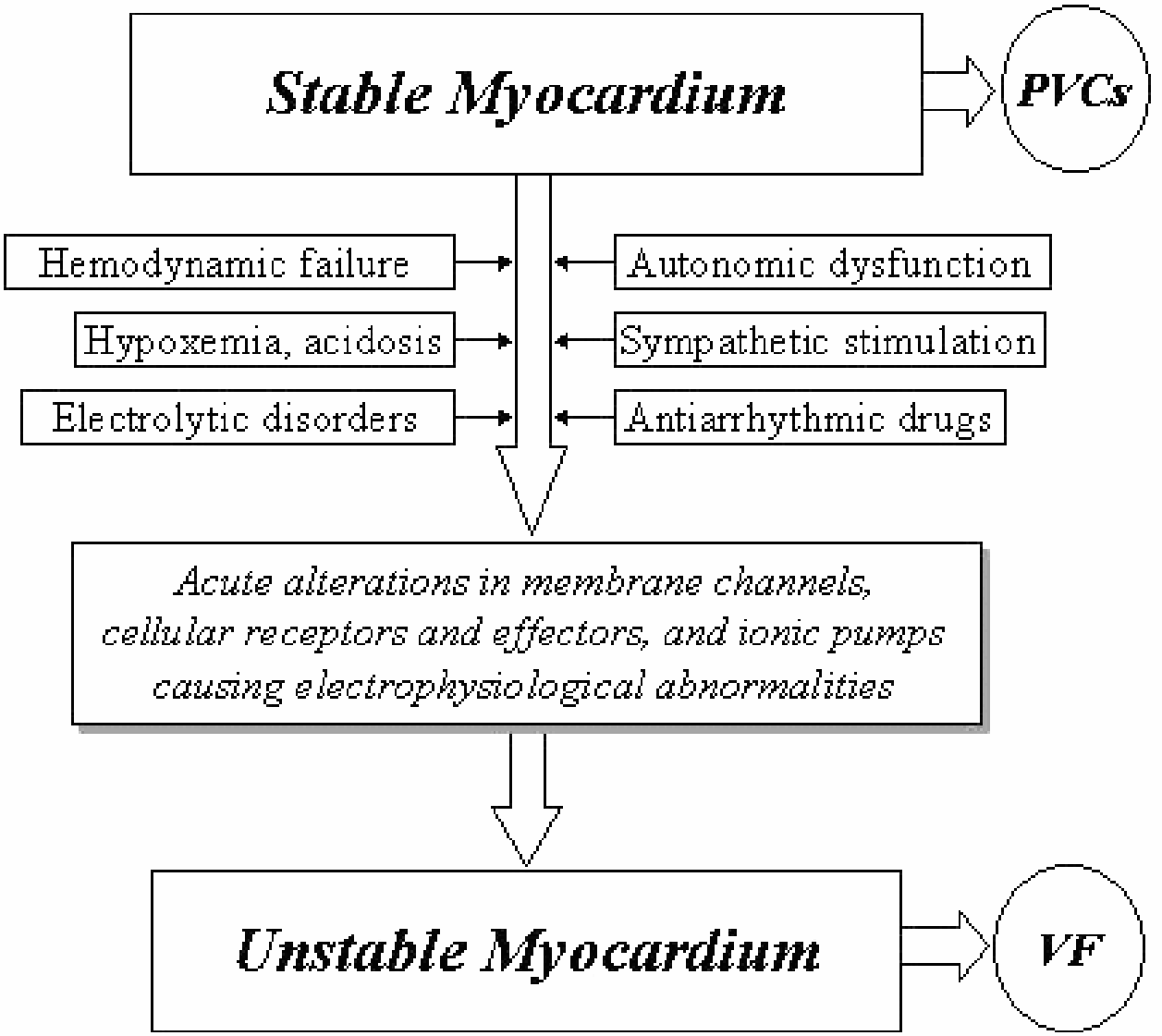


Fig. I – Instability of structurally abnormal myocardium through the interaction of different functional modulators, resulting in ventricular fibrillation. PVCs – premature ventricular contractions; VF – ventricular fibrillation

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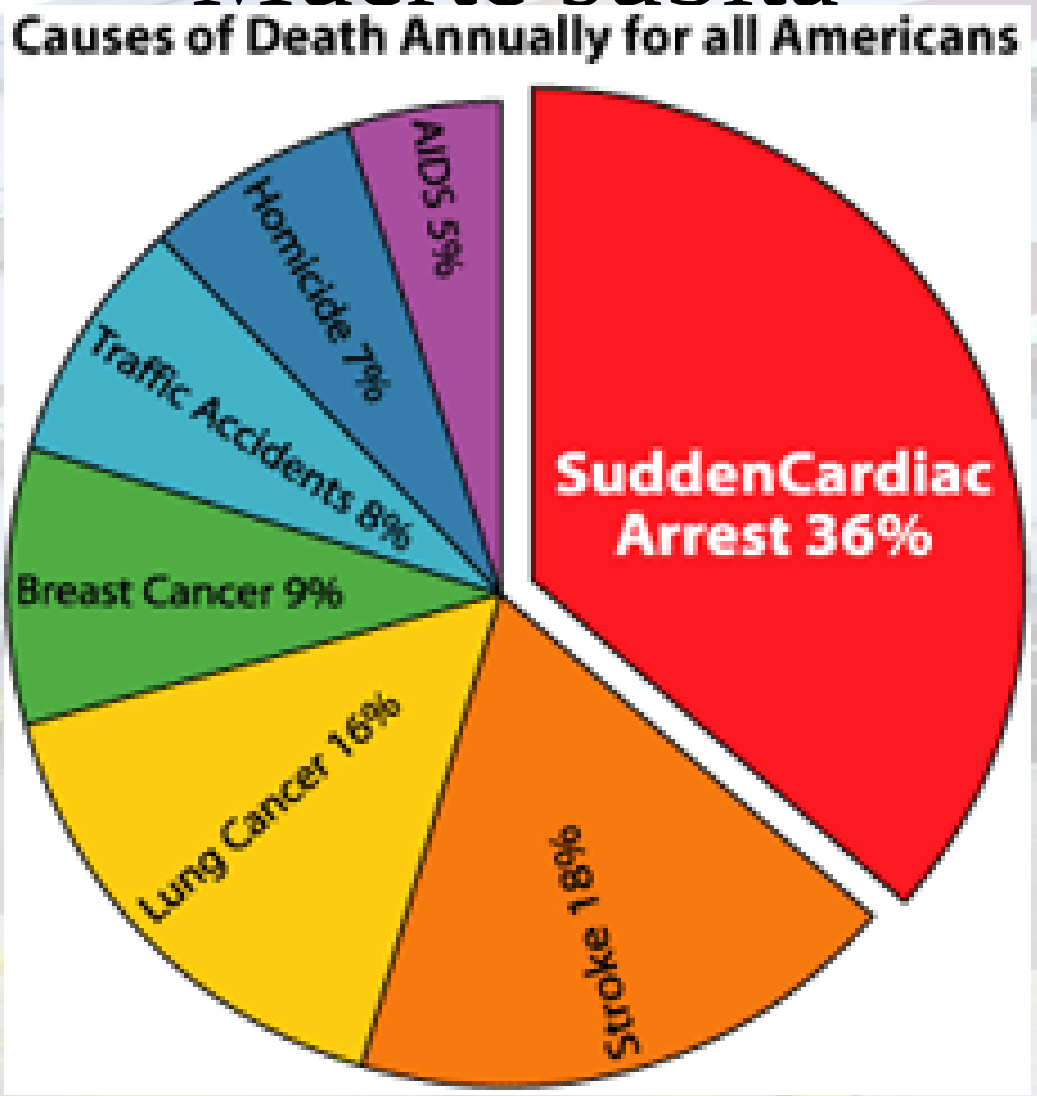
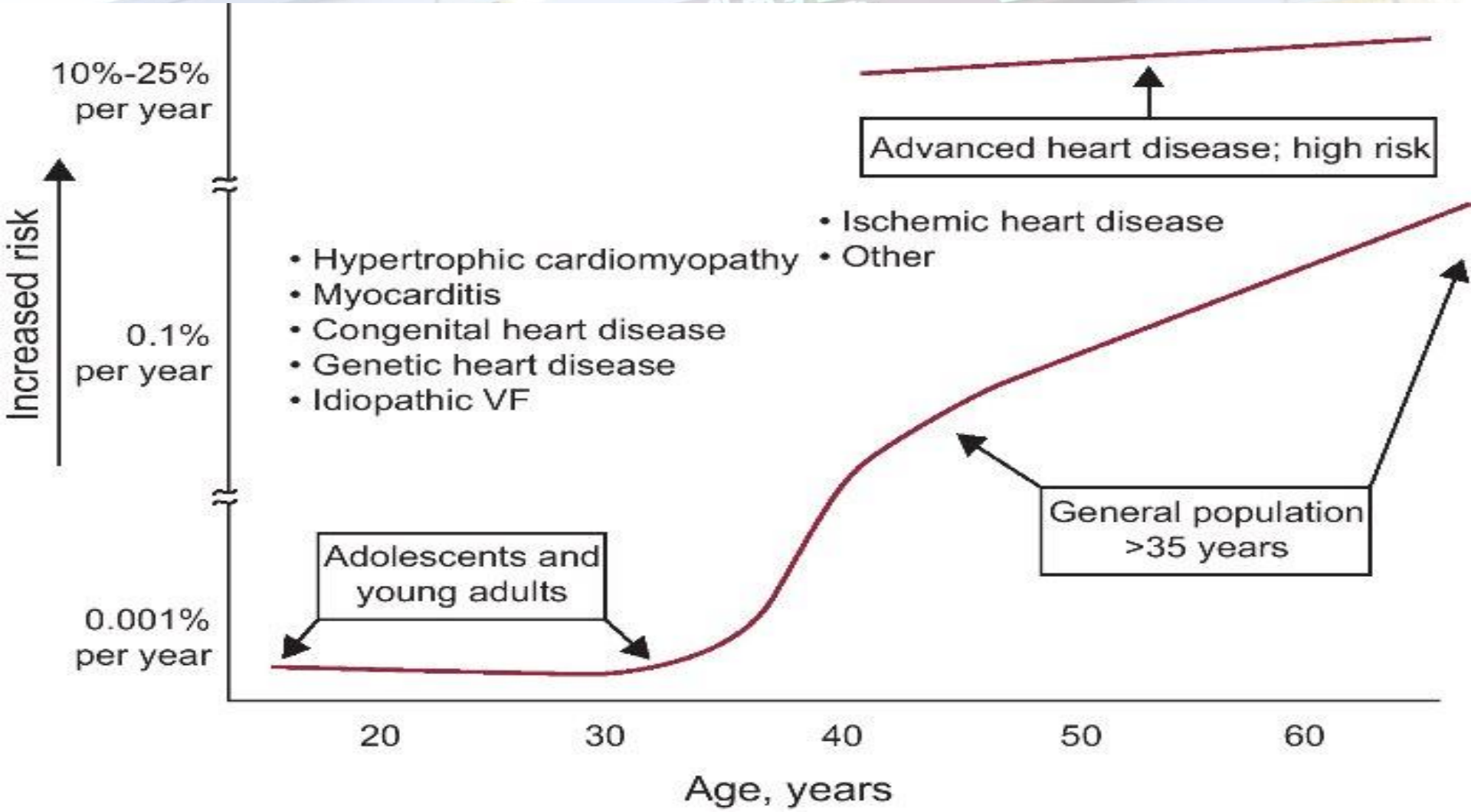
- **Major predictors:**
  - ventricular dysfunction
  - nonsustained ventricular tachycardia* on Holter monitoring/ETT
  - sustained ventricular tachycardia
  - resuscitation from cardiac arrest
  - severe bradyarrhythmia (SND, advanced AV block)
  - syncope
- **Less important predictors:**
  - late potentials (signal averaged ECG)
  - presyncope
- **Variables with no prognostic value:**
  - isolated ventricular extrasystole (Holter)
  - isolated RBBB
  - induction of polymorphic VT or VF on PVS
- **Variables to be investigated:**
  - heart rate variability
  - QT dispersion

Muerte súbita



EDAD Y MUERTE SUBITA



MS en subgrupos poblacionales

The New England Journal of Medicine

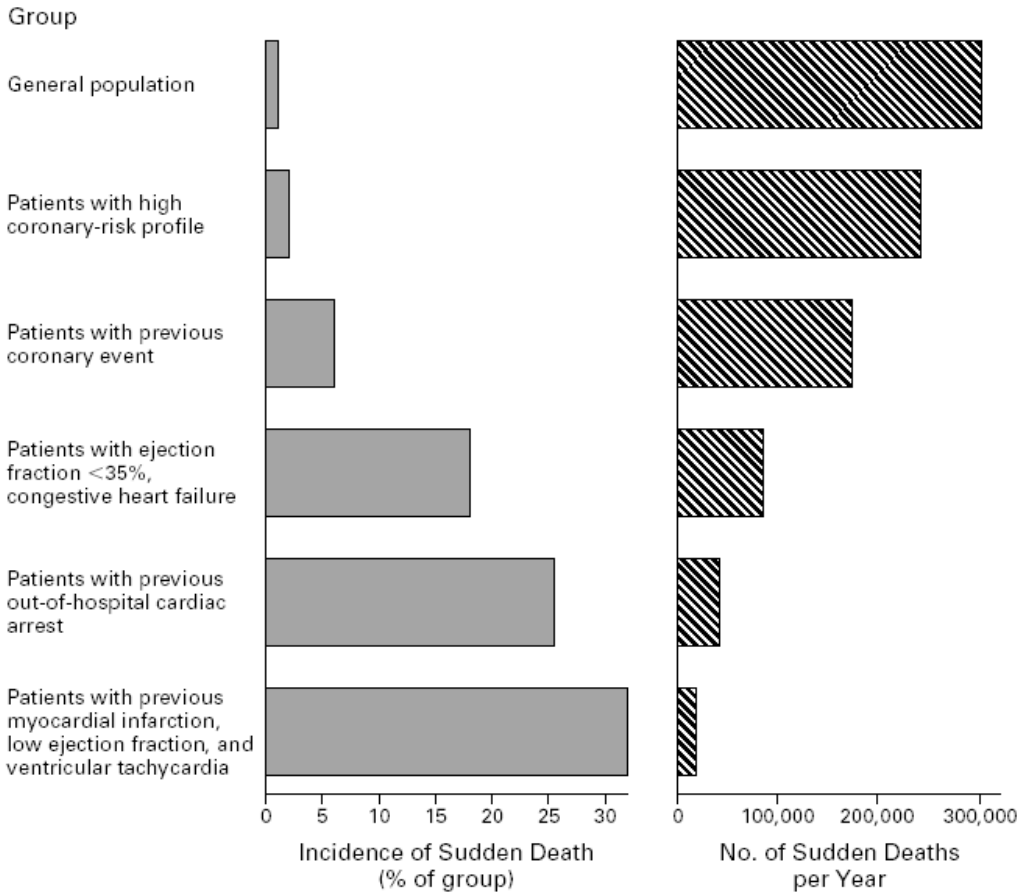
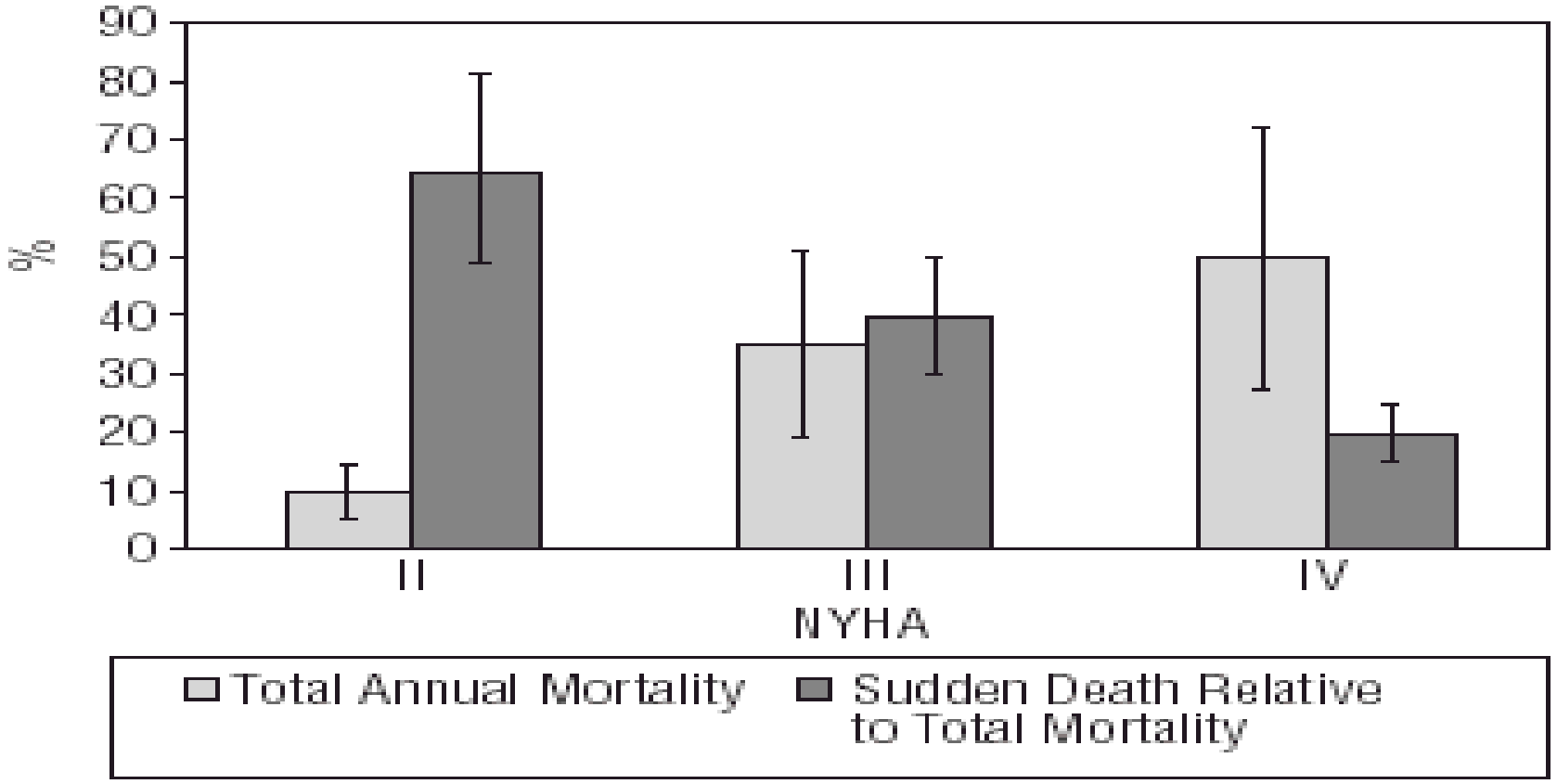


Figure 1. The Incidence of Sudden Death in Specific Populations and the Annual Numbers of Sudden Deaths in Those Populations. Most of the deaths occur in the larger, lower-risk subgroups. Modified from Myerburg et al.[10] with the permission of the publisher.

Muerte súbita en insuficiencia cardíaca según clase funcional



MUERTE SUBITA EN DEPORTISTAS

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Una patología que afecta a uno de cada 700.000 deportistas

La prevalencia entre los atletas es un tercio menor que en la población común.

Los exámenes previenen 95% de los casos

EL CASO DE PIERMARIO MOROSINI CONMOVIÓ AL MUNDO EN 2012

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Antonio Puerta

Lugar y fecha de nacimiento:
Sevilla, 26-11-1984

Altura y peso:
1,83 m. y 74 kg.

Internacional:
Una vez (07-10-2006)

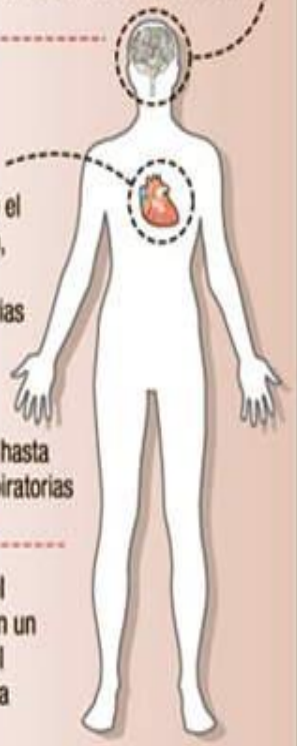
En las filas del Sevilla, Puerta conquistó **dos Copas de la UEFA** (2006 y 2007), **una Copa del Rey** (2007), **una Supercopa de Europa** (2006) y **una Supercopa de España** (2007)

UN DESENLACE TRÁGICO

1. Durante el partido ante el Getafe del pasado sábado, Puerta se desvaneció y, posteriormente, sufrió varias arritmias ventriculares, debidas a una displasia arritmogénica de origen genético, que provocaron hasta cinco paradas cardiorrespiratorias

2. El prolongado paro cardiaco causó 'sufrimiento' cerebral, con necrosis del tejido nervioso

3. Los graves daños en el cerebro desembocaron en un fallo multiorgánico y en el fallecimiento del futbolista

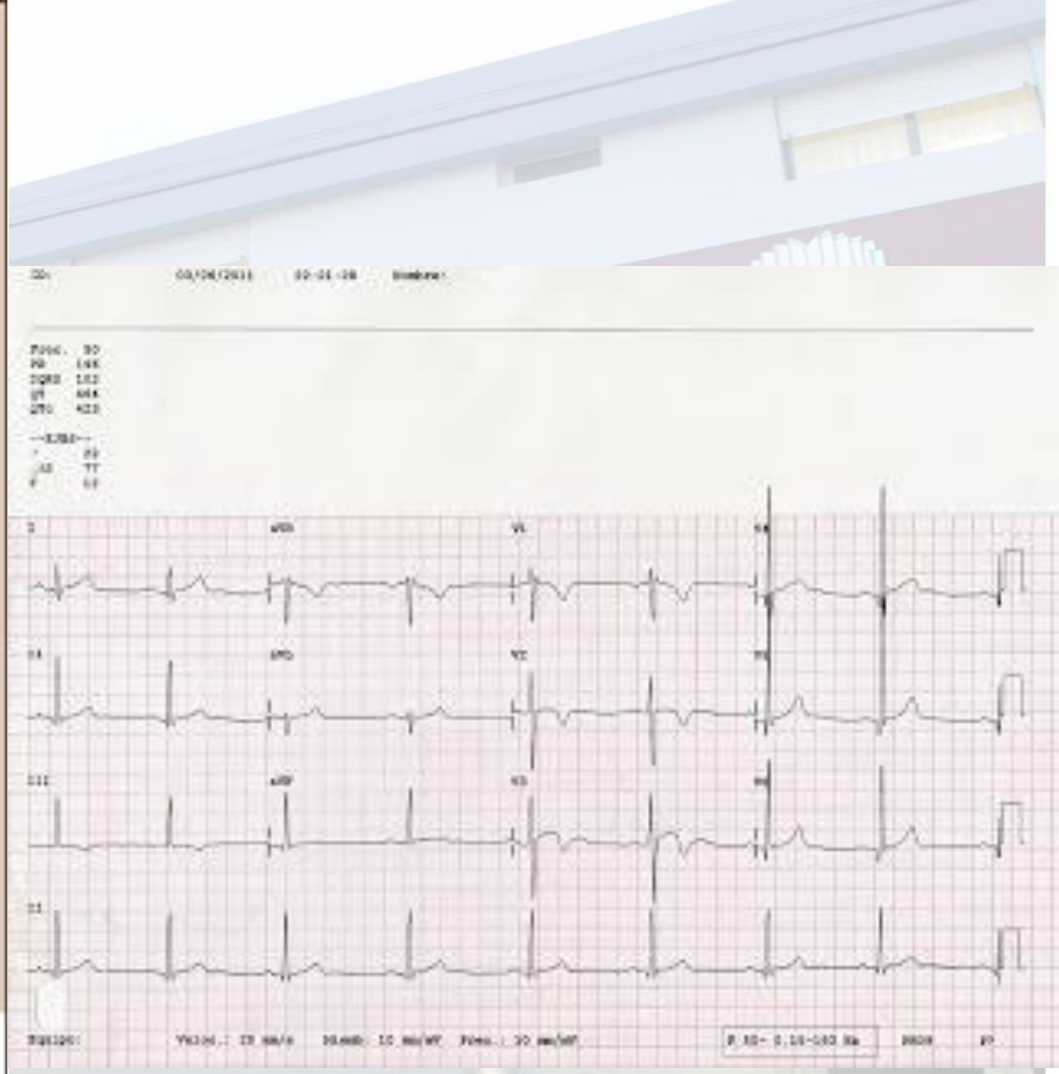


Trayectoria
(siempre en el Sevilla)

	Liga		Copa		Comp. europeas	
Temporada	Partidos	Goles	Partidos	Goles	Partidos	Goles
2003-04	1	0	0	0	–	–
2004-05	7	1	3	0	0	0
2005-06	17	2	0	0	12	3
2006-07	29	2	7	0	10	0
2007-08	1	0	0	0	0	0

Fuente: L'Equipe/Agencias/Elaboración propia

GRAFÍA



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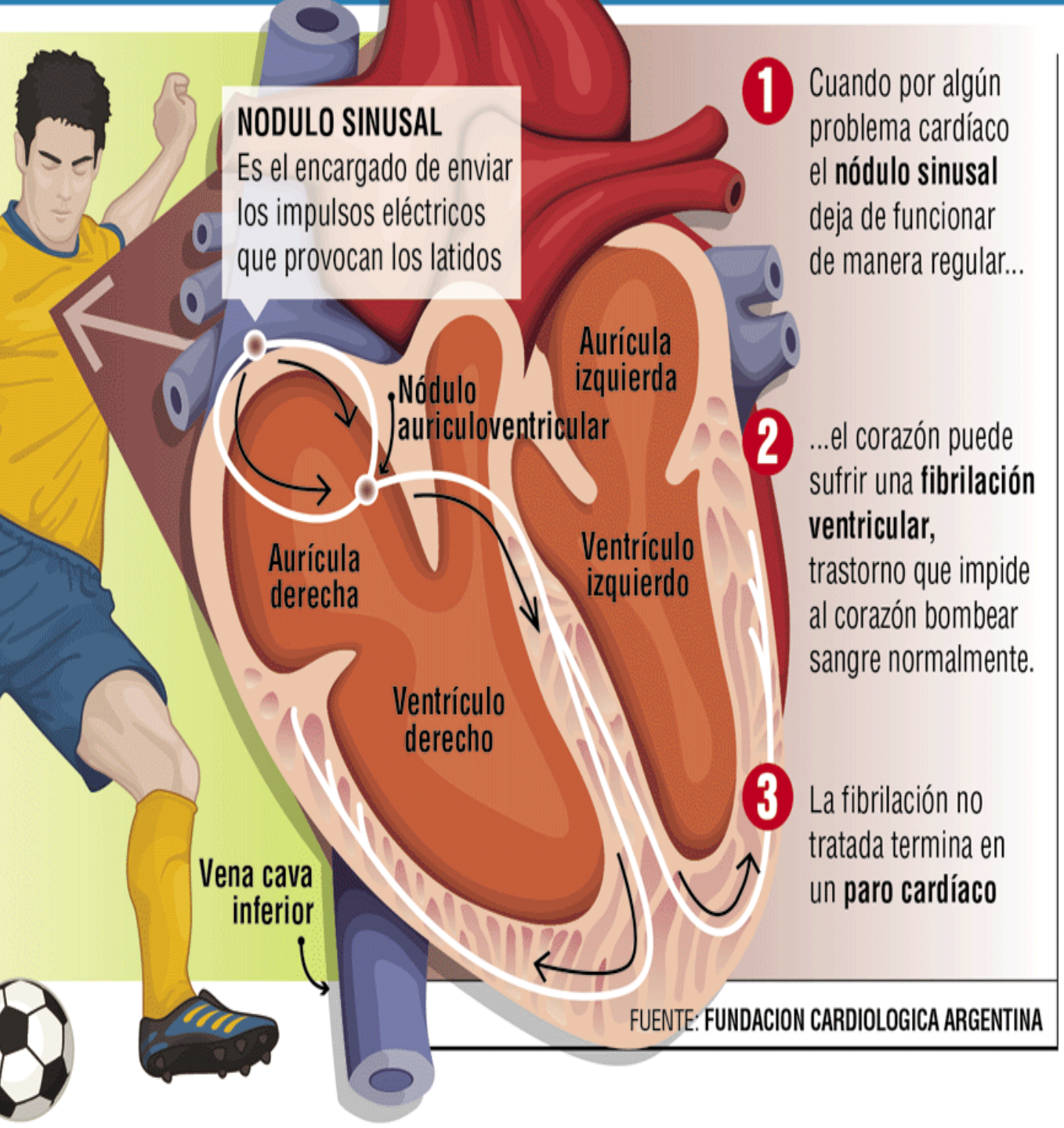


1 Cuando por algún problema cardíaco el **nódulo sinusal** deja de funcionar de manera regular...

2 ...el corazón puede sufrir una **fibrilación ventricular,** trastorno que impide al corazón bombear sangre normalmente.

3 La fibrilación no tratada termina en un **paro cardíaco**

FUENTE: **FUNDACION CARDIOLOGICA ARGENTINA**

CAUSAS

EN LOS MENORES DE 35 AÑOS

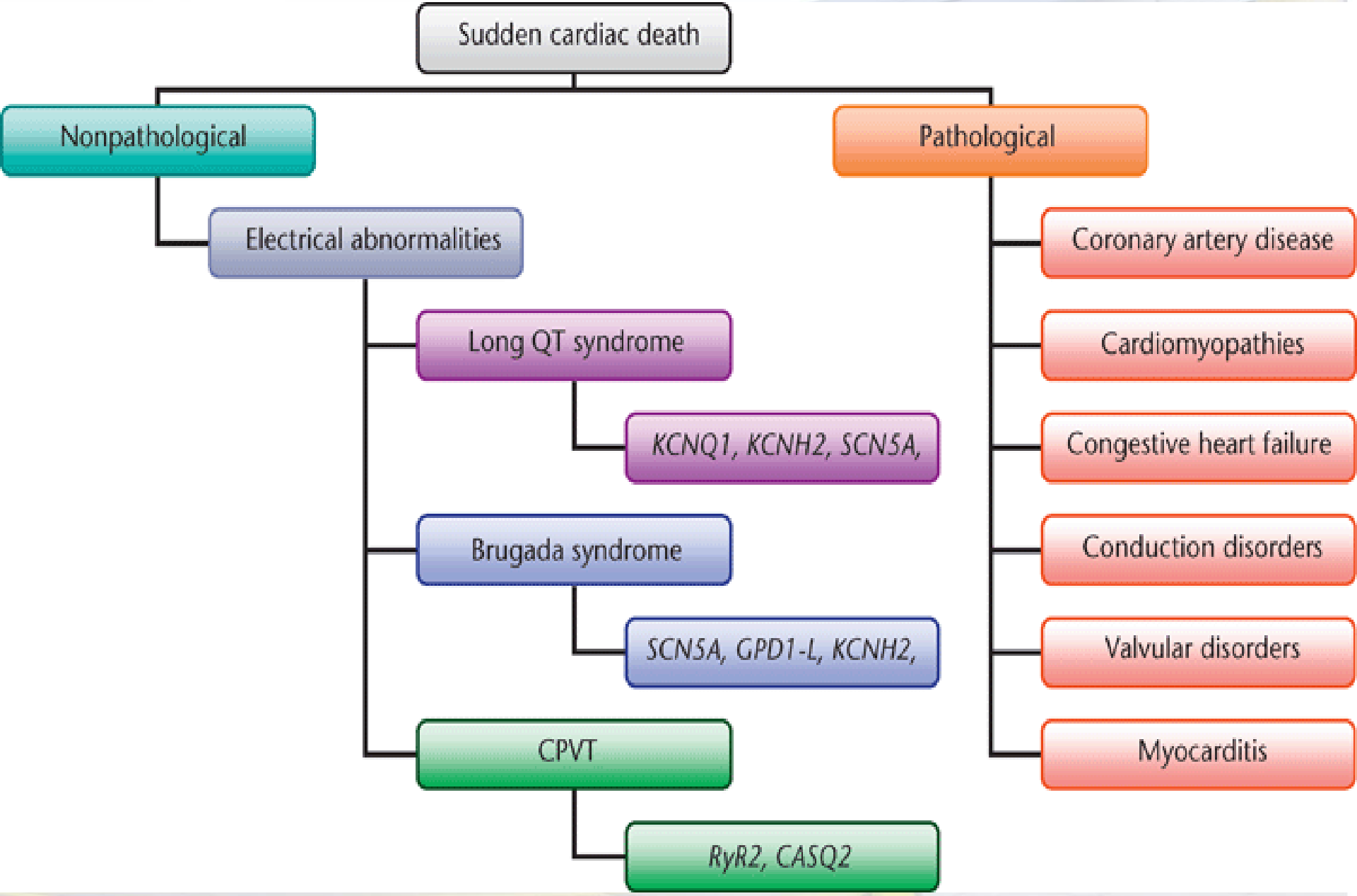
Mayormente es consecuencia de una enfermedad coronaria congénita

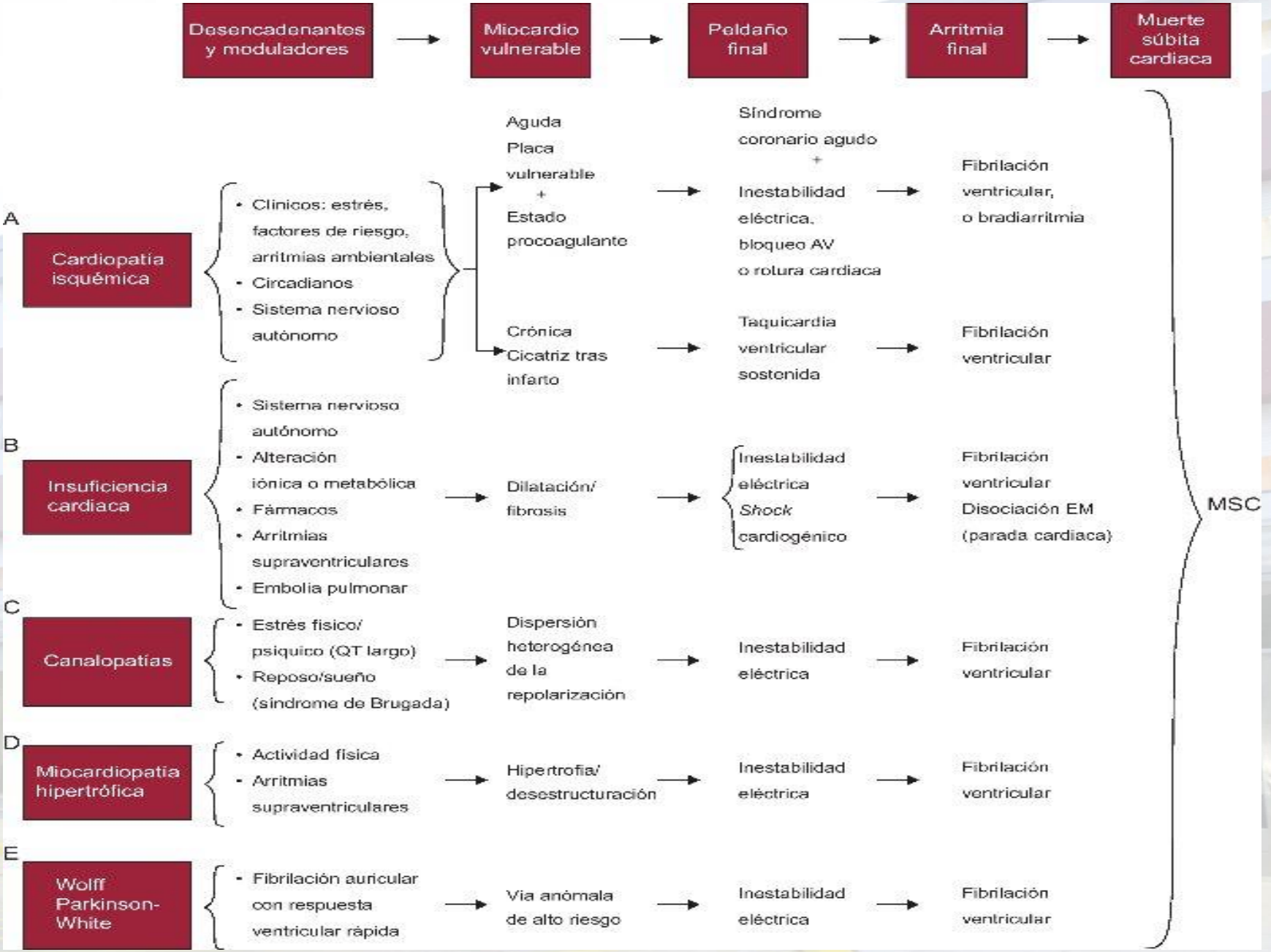
Miocardopatía hipertrófica	**36 %**
Anomalías coronarias congénitas	19 %
Hipertrofia idiopática ventrícular izq.	10 %
Coronaria descend. anterior en túnel	5 %
Ruptura de aorta	5 %
Estenosis aórtica	4 %
Otras	21 %

EN LOS MAYORES DE 35 AÑOS

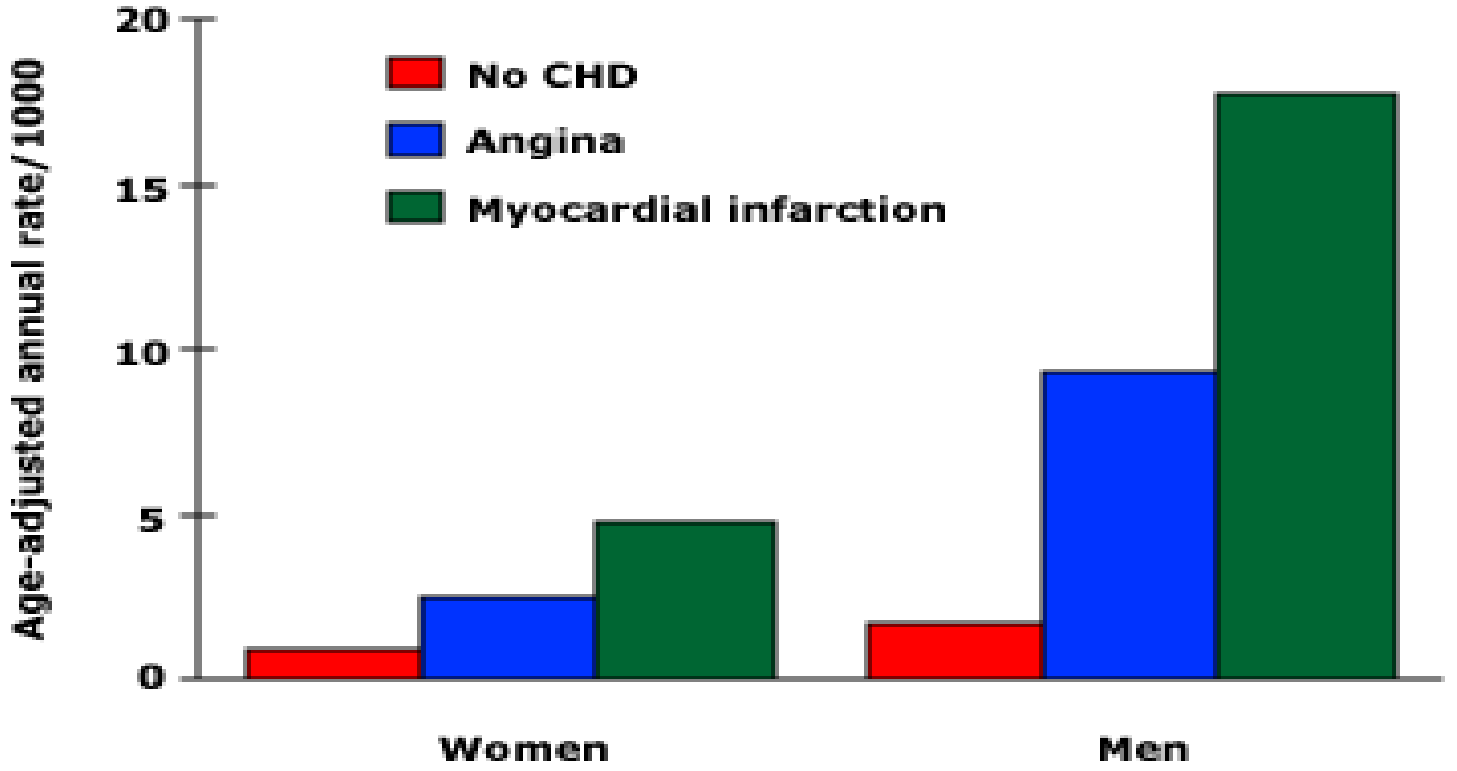
Ocurre generalmente por una enfermedad coronaria, producto de malos hábitos

Ateroesclerosis coronaria	**85 %**
Enfermedad valvular	7 %
Enfermedades no cardíacas	3 %
Arritmias	3 %
Miocardiopatía hipertrófica	2 %


Sudden cardiac death
Nonpathological
Pathological
Electrical abnormalities
Long QT syndrome
KCNQ1, KCNH2, SCN5A,
Brugada syndrome
SCN5A, GPD1-L, KCNH2,
CPVT
RyR2, CASQ2
Coronary artery disease
Cardiomyopathies
Congestive heart failure
Conduction disorders
Valvular disorders
Myocarditis


Desencadenantes y moduladores
Miocardio vulnerable
Peldaño final
Arritmia final
Muerte súbita cardiaca
A
Cardiopatía isquémica
• Clínicos: estrés, factores de riesgo, arritmias ambientales
• Circadianos
• Sistema nervioso autónomo
Aguda
Placa vulnerable
+
Estado procoagulante
Síndrome coronario agudo
+
Inestabilidad eléctrica, bloqueo AV o rotura cardiaca
Fibrilación ventricular, o bradiarritmia
Crónica
Cicatriz tras infarto
Taquicardia ventricular sostenida
Fibrilación ventricular
B
Insuficiencia cardiaca
• Sistema nervioso autónomo
• Alteración iónica o metabólica
• Fármacos
• Arritmias supraventriculares
• Embolia pulmonar
Dilatación/ fibrosis
Inestabilidad eléctrica
Shock cardiogénico
Fibrilación ventricular
Disociación EM (parada cardiaca)
C
Canalopatías
• Estrés físico/ psíquico (QT largo)
• Reposo/sueño (síndrome de Brugada)
Dispersión heterogénea de la repolarización
Inestabilidad eléctrica
Fibrilación ventricular
D
Miocardiopatía hipertrófica
• Actividad física
• Arritmias supraventriculares
Hipertrofia/ desestructuración
Inestabilidad eléctrica
Fibrilación ventricular
E
Wolff Parkinson-White
• Fibrilación auricular con respuesta ventricular rápida
Vía anómala de alto riesgo
Inestabilidad eléctrica
Fibrilación ventricular
MSC

Muerte súbita y miocardiopatias isquemico necrotica



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Miocardiopatia Chagasica

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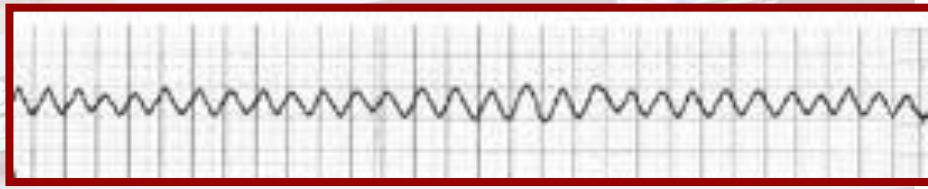
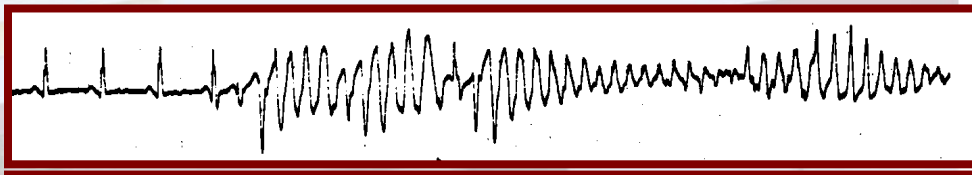
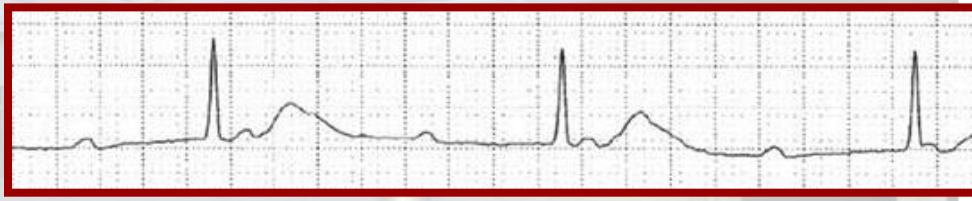
Muerte Súbita - Ritmos

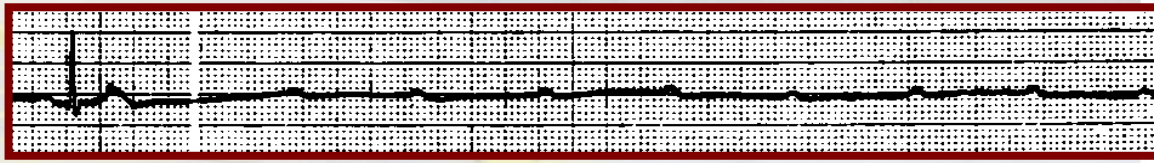
- ✓ Taquiarritmias
  - -**Fibrilación ventricular (FV)**
  - -**Taquicardia ventricular (TV)**
    - TVPS
    - TVMS
- ✓ Bradiarritmias
  - -Asistolia
  - **-Bloqueo AV completo**
- ✓ Disociación electromecánica

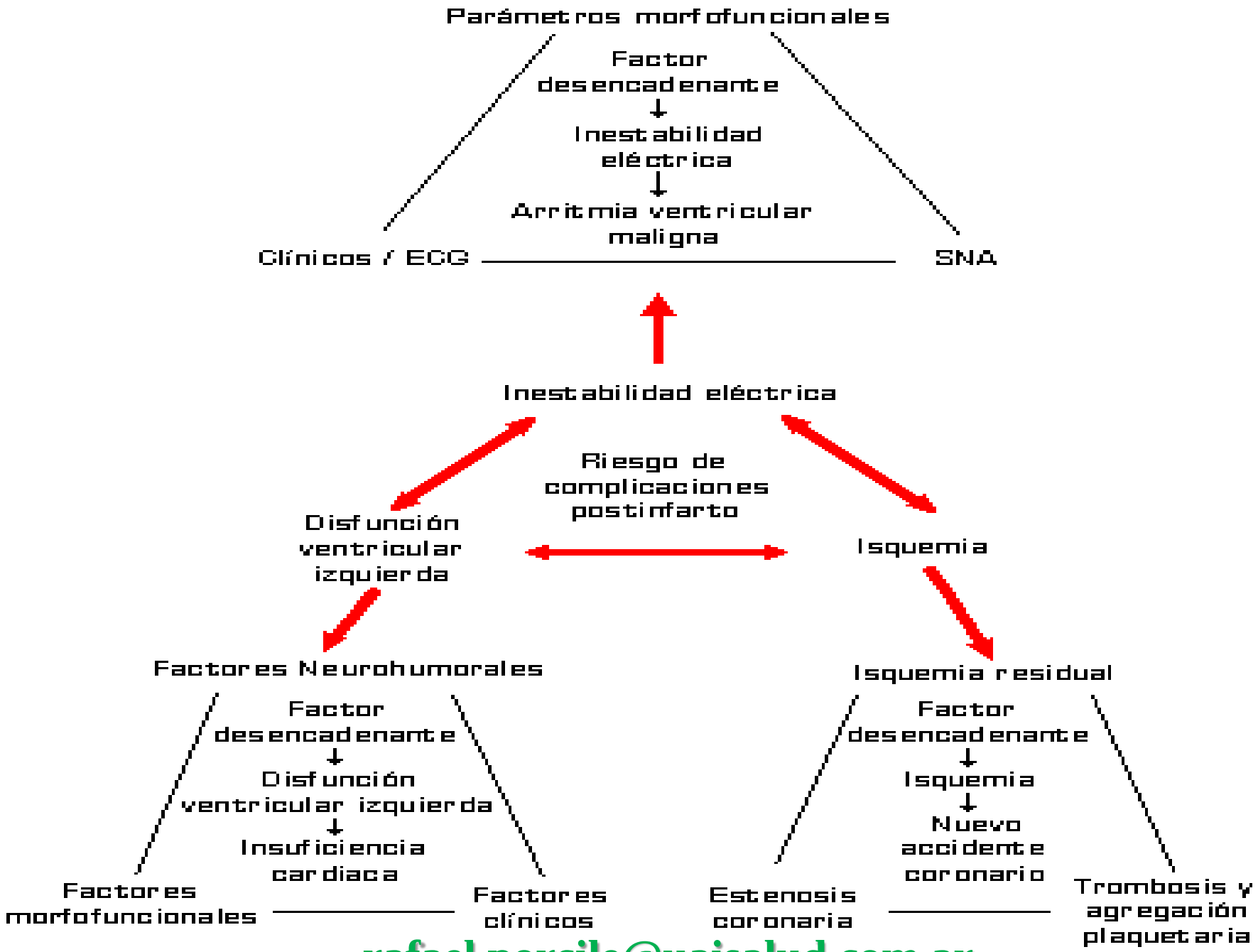
(AESP)











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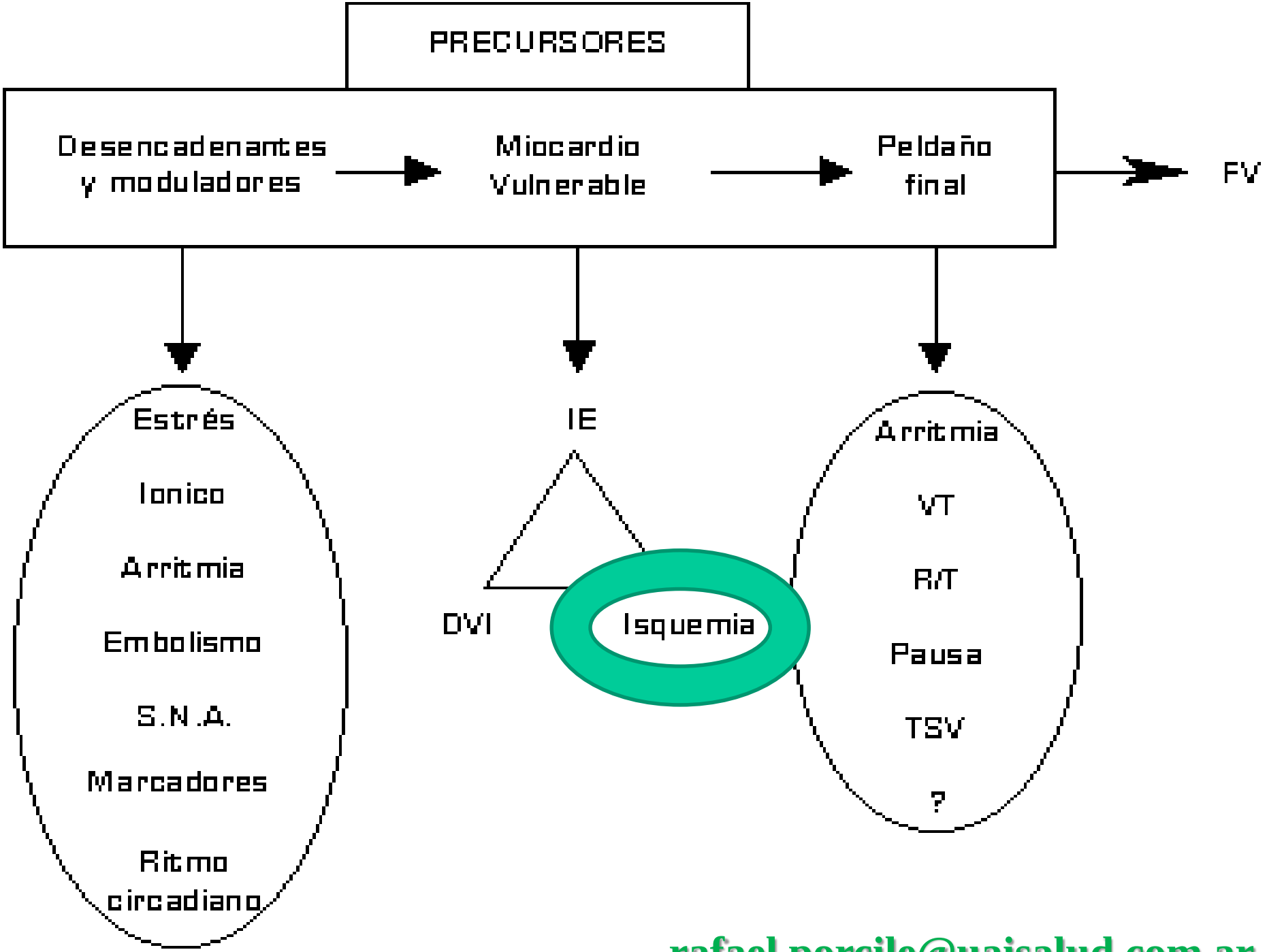

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MUERTE SUBITA

ISQUEMIA

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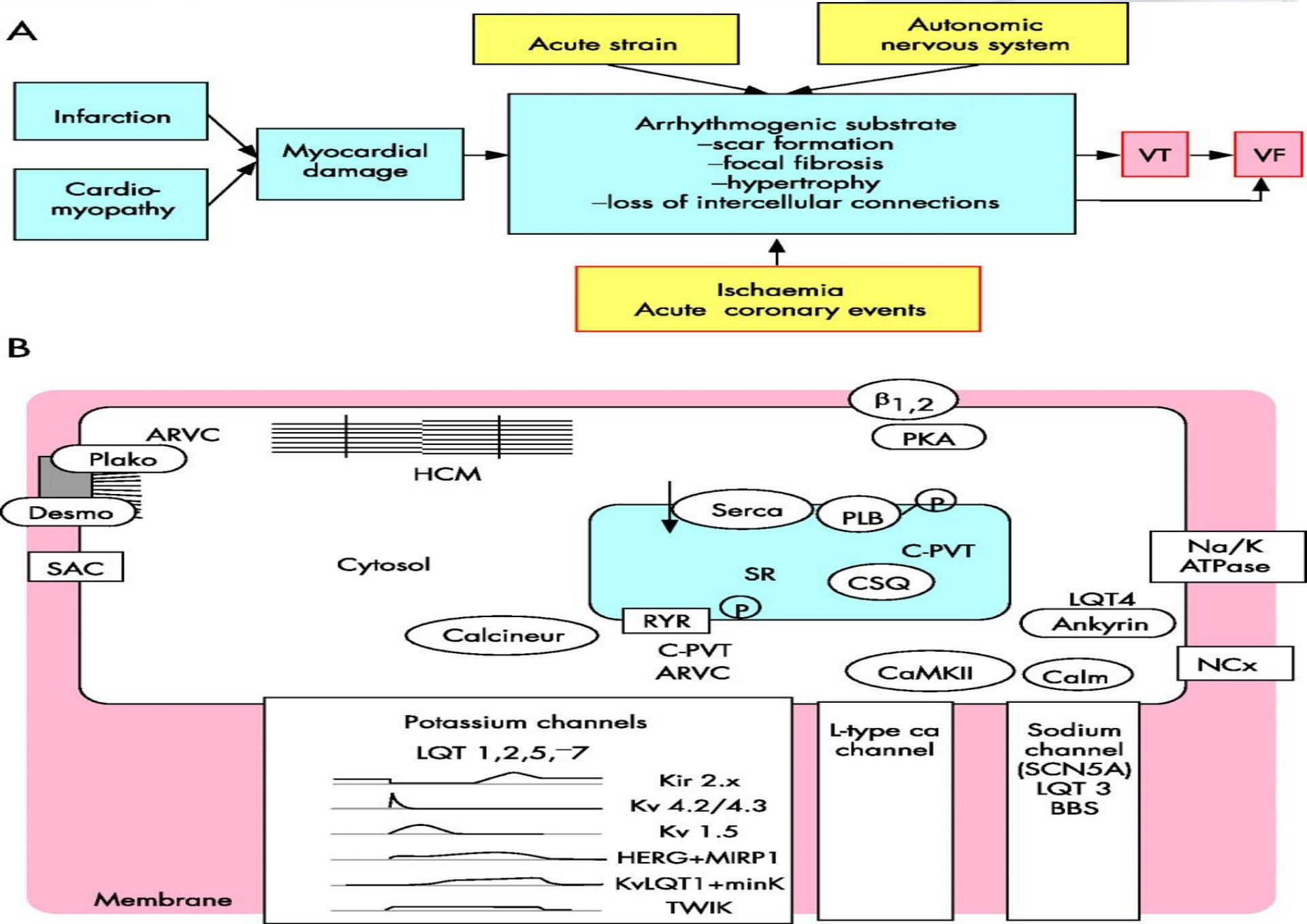

A
Acute strain
Autonomic nervous system
Infarction
Cardio-myopathy
Myocardial damage
Arrhythmogenic substrate
–scar formation
–focal fibrosis
–hypertrophy
–loss of intercellular connections
VT
VF
Ischaemia
Acute coronary events
B
β1,2
PKA
ARVC
Plako
HCM
Desmo
SAC
Cytosol
Serca
PLB
P
C-PVT
SR
CSQ
P
RYR
Calcineur
C-PVT
ARVC
Na/K ATPase
LQT4
Ankyrin
NCx
CaMKII
Calm
Potassium channels
LQT 1,2,5,–7
Kir 2.x
Kv 4.2/4.3
Kv 1.5
HERG+MIRP1
KvLQT1+minK
TWIK
L-type ca channel
Sodium channel (SCN5A)
LQT 3
BBS
Membrane

The heart mainly produces ATP through oxidative pathways

Glucose oxidation

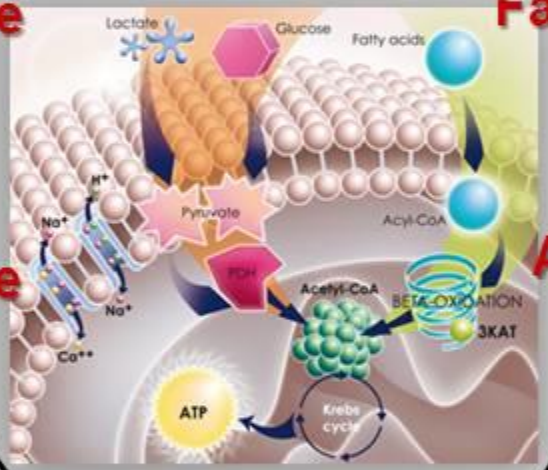
- Provides 10% to 40% of energy.
- More 0_2 efficient pathway.
- ATP/0_2=3

Fatty Acid β-oxidation

- Provides 60% to 90% of energy.
- Requires more 0_2 than glucose.
- ATP/0_2=2.6

Glucose

Fatty acids



Pyruvate

Acyl coA

Acetyl coA

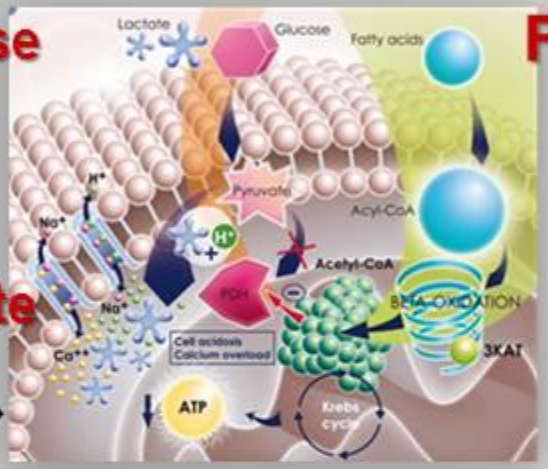
Energy (ATP)

Cardiac disease is closely linked to impairments in cardiac energy metabolism

Glucose

Fatty acids

↑ Fatty acid oxidation



↑ Anaerobic glycolysis

Pyruvate

Acyl coA

Acetyl coA

Cell acidosis
Calcium overload

Cell damage

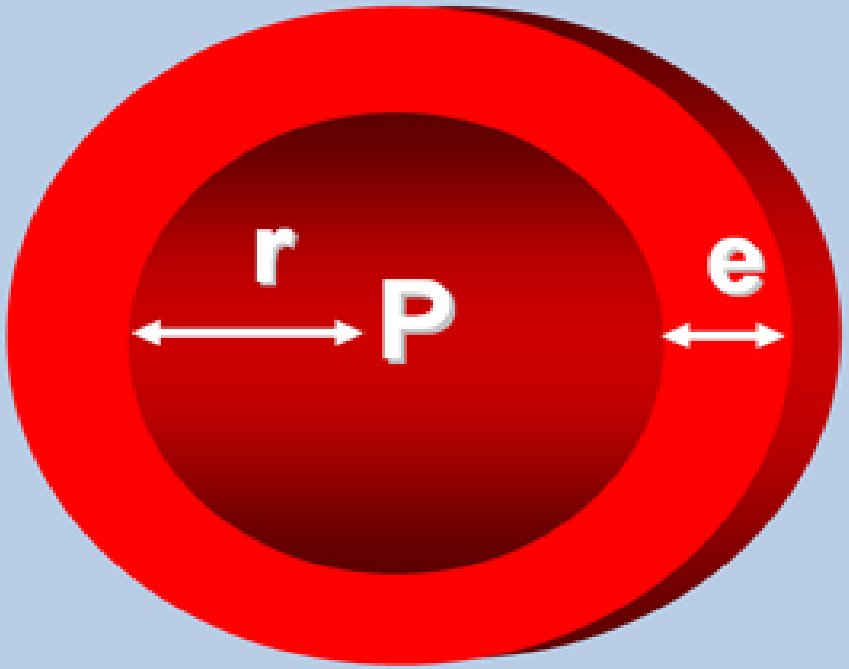
• Increase need of ATP for homeostasis.

Energy (ATP)

Contractile dysfunction

TENSIONPARIETAL= POSCARGA= **CONSUMO DE OXIGENO**

$$T_{pared} = \frac{P \times r}{2e}$$



Ley de Laplace

cardiofamilia

STRESS PARIETAL

=

ISQUEMIA

$$S = \frac{P \times r}{2h}$$

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- **+ HIPOXIA**
- **+HIPERTROFIA**
- **+CONSUMO DE OXIGENO**

+HIPOXIA

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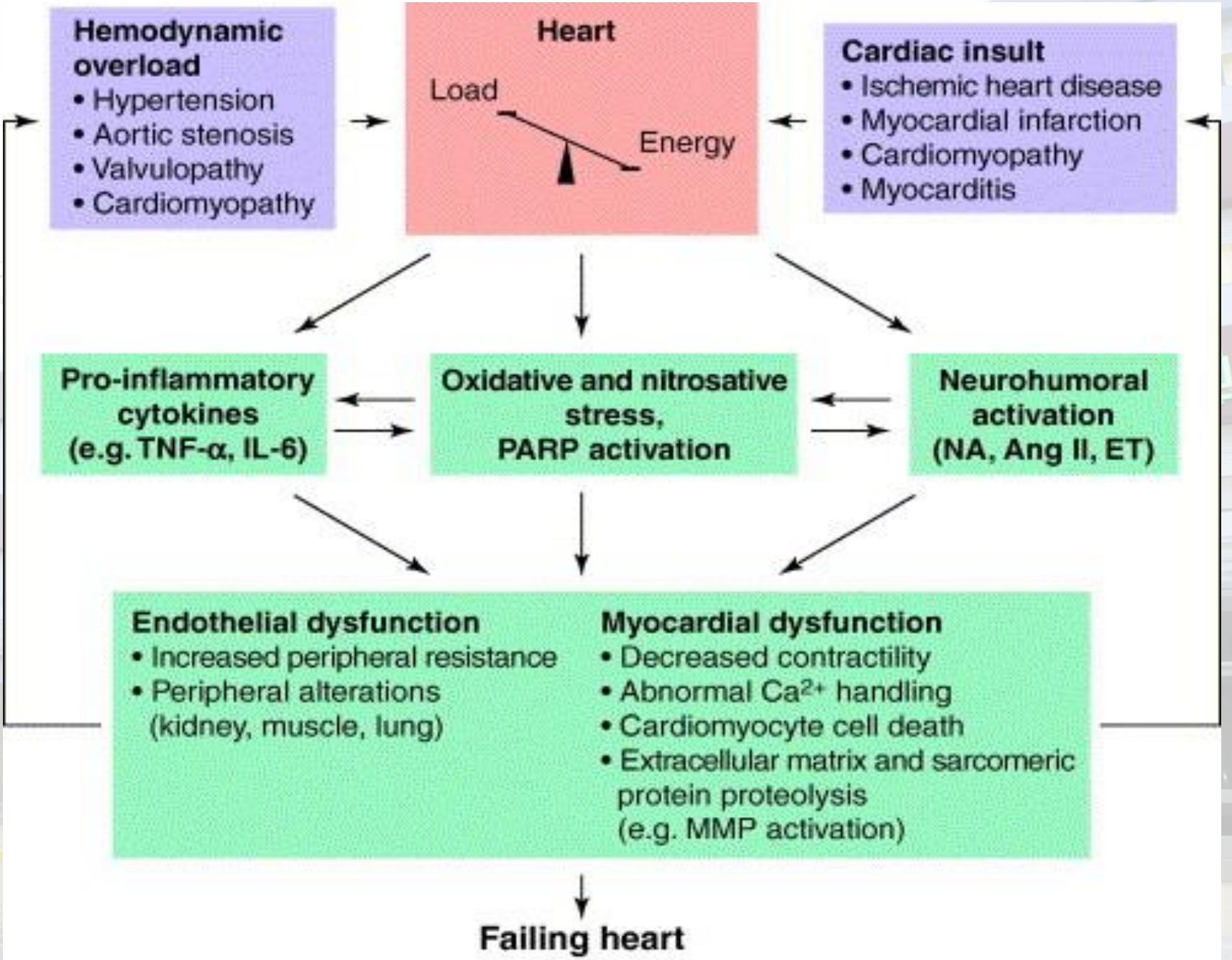
Hemodynamic overload
• Hypertension
• Aortic stenosis
• Valvulopathy
• Cardiomyopathy
Heart
Load
Energy
Cardiac insult
• Ischemic heart disease
• Myocardial infarction
• Cardiomyopathy
• Myocarditis
Pro-inflammatory cytokines (e.g. TNF-α, IL-6)
Oxidative and nitrosative stress, PARP activation
Neurohumoral activation (NA, Ang II, ET)
Endothelial dysfunction
• Increased peripheral resistance
• Peripheral alterations (kidney, muscle, lung)
Myocardial dysfunction
• Decreased contractility
• Abnormal Ca^{2+} handling
• Cardiomyocyte cell death
• Extracellular matrix and sarcomeric protein proteolysis (e.g. MMP activation)
Failing heart
TRENDS in Pharmacological Sciences

Evolución

- Mortalidad entre el 26 y 75 % a los 5 años
- **Muerte subita 30 % causa de muerte**
- **35 % muertes precedidas de un nuevo evento isquemico**
- 16 % de reiternacion anual
- Primera causa internacion mayores de 65 años

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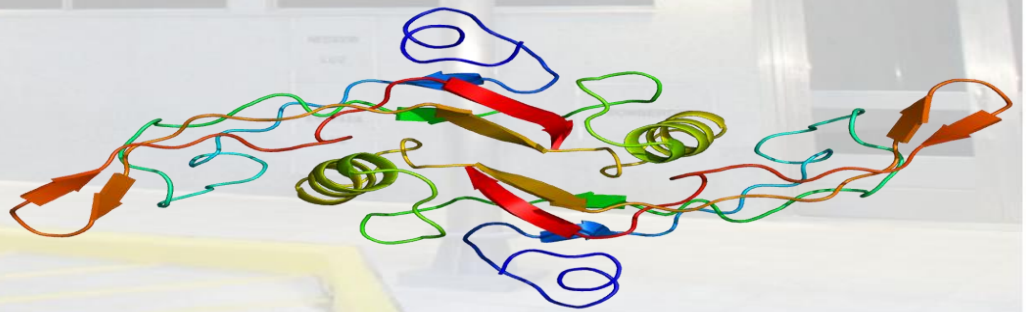
Transforming Growth Factor (TGF)-β

The extracellular concentration of TGF-β activity is primarily regulated by conversion of latent TGF-β to active TGF-β. Most tissues contain significant amounts of latent TGF-β; activation of only a small fraction of this latent TGF-β generates maximal cellular response



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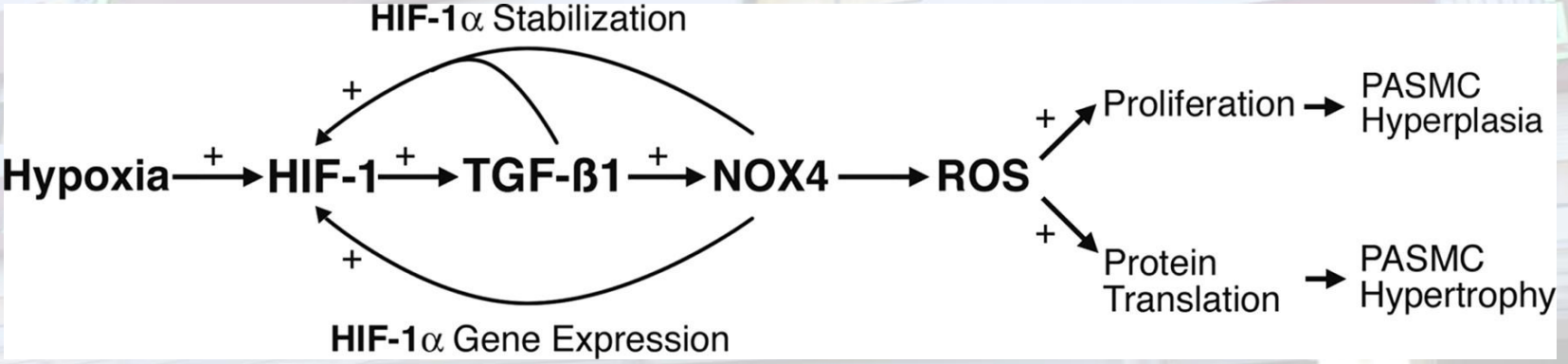
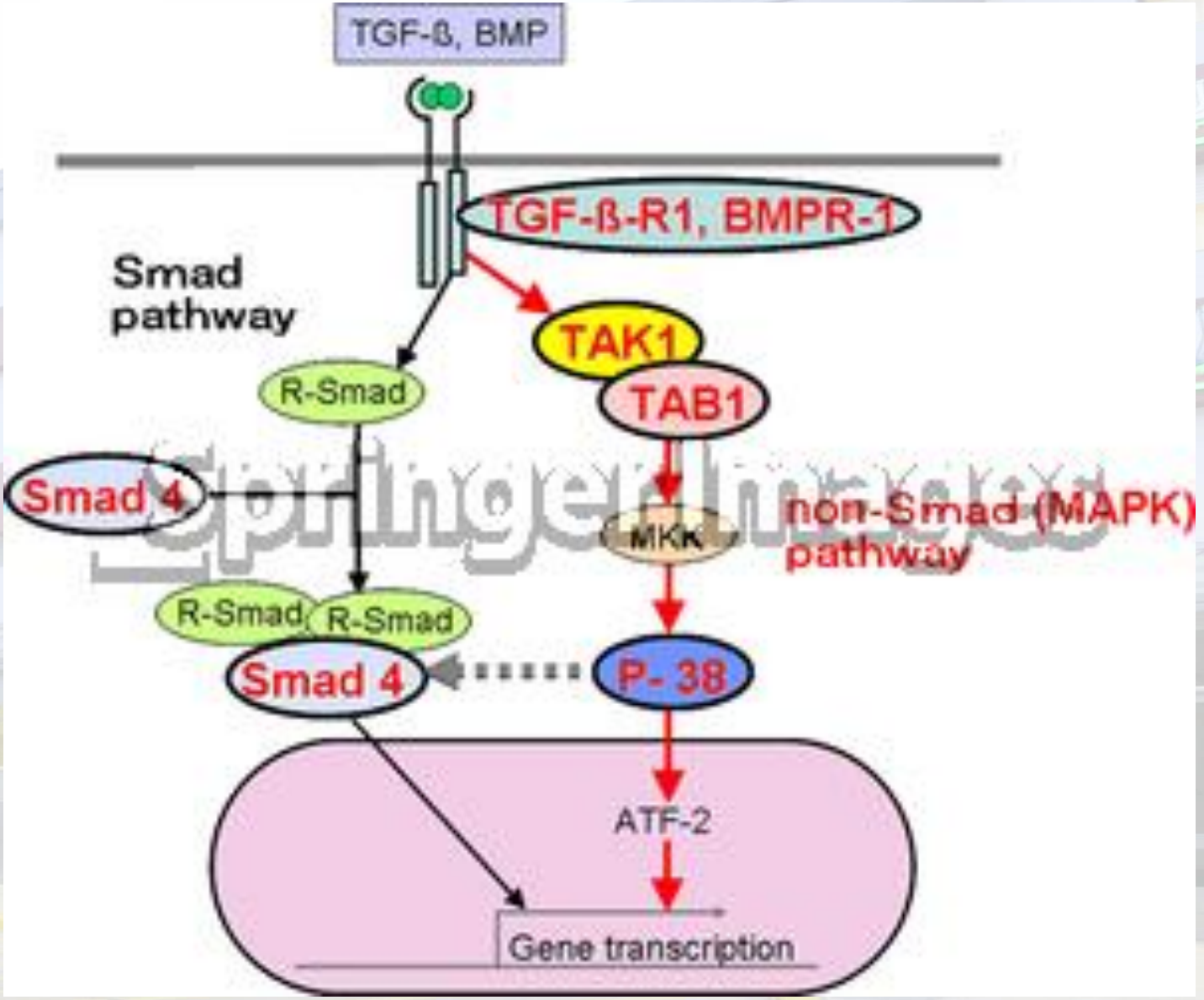
Schematic representation of the possible interplay of TGF-β1, HIF-1 and NOX4 the in pathogenesis of pulmonary smooth muscle hypertrophy and hyperplasia because of chronic hypoxia.



Sanders K A , and Hoidal J R Circulation Research 2007;101:224-226



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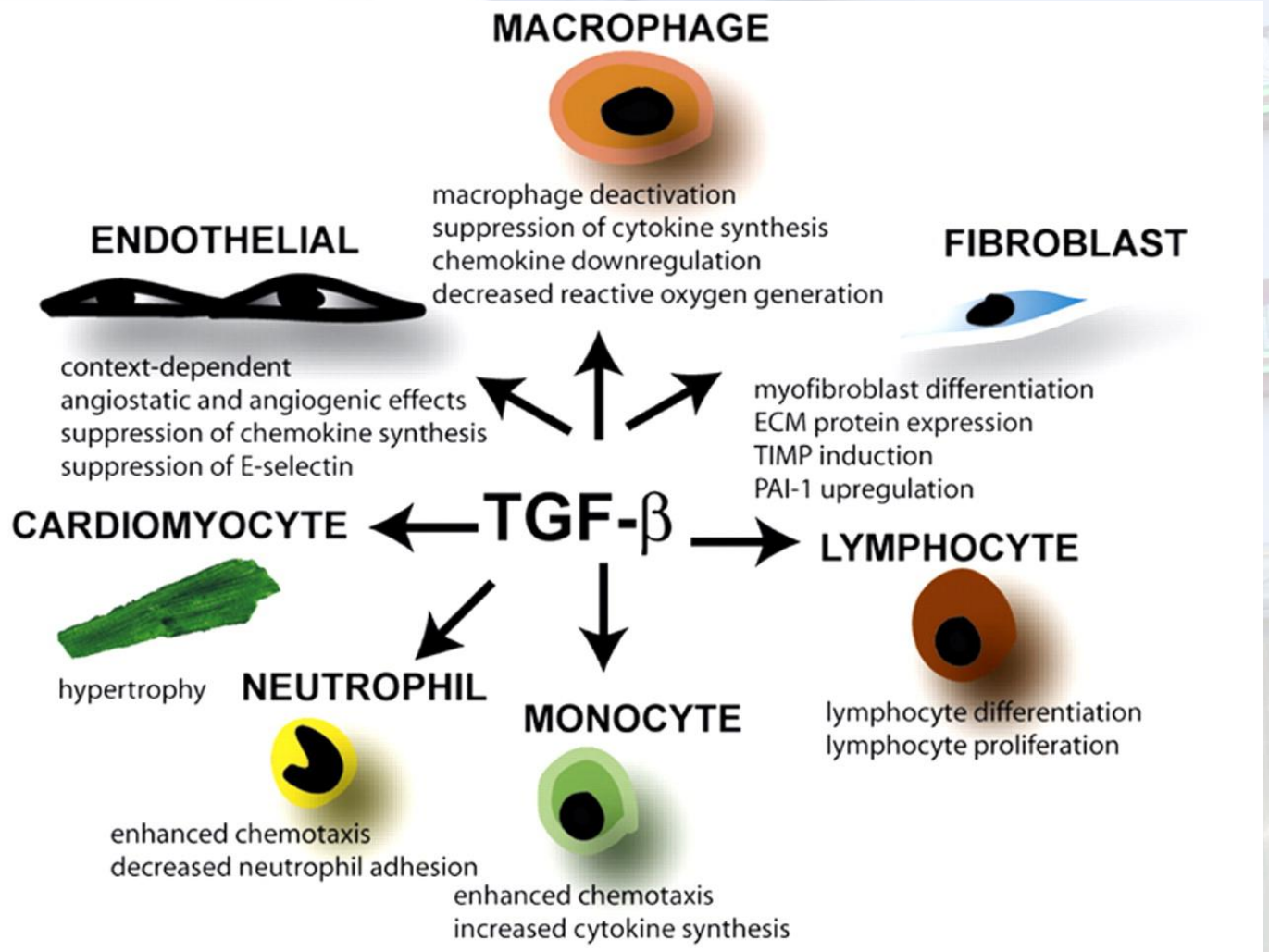
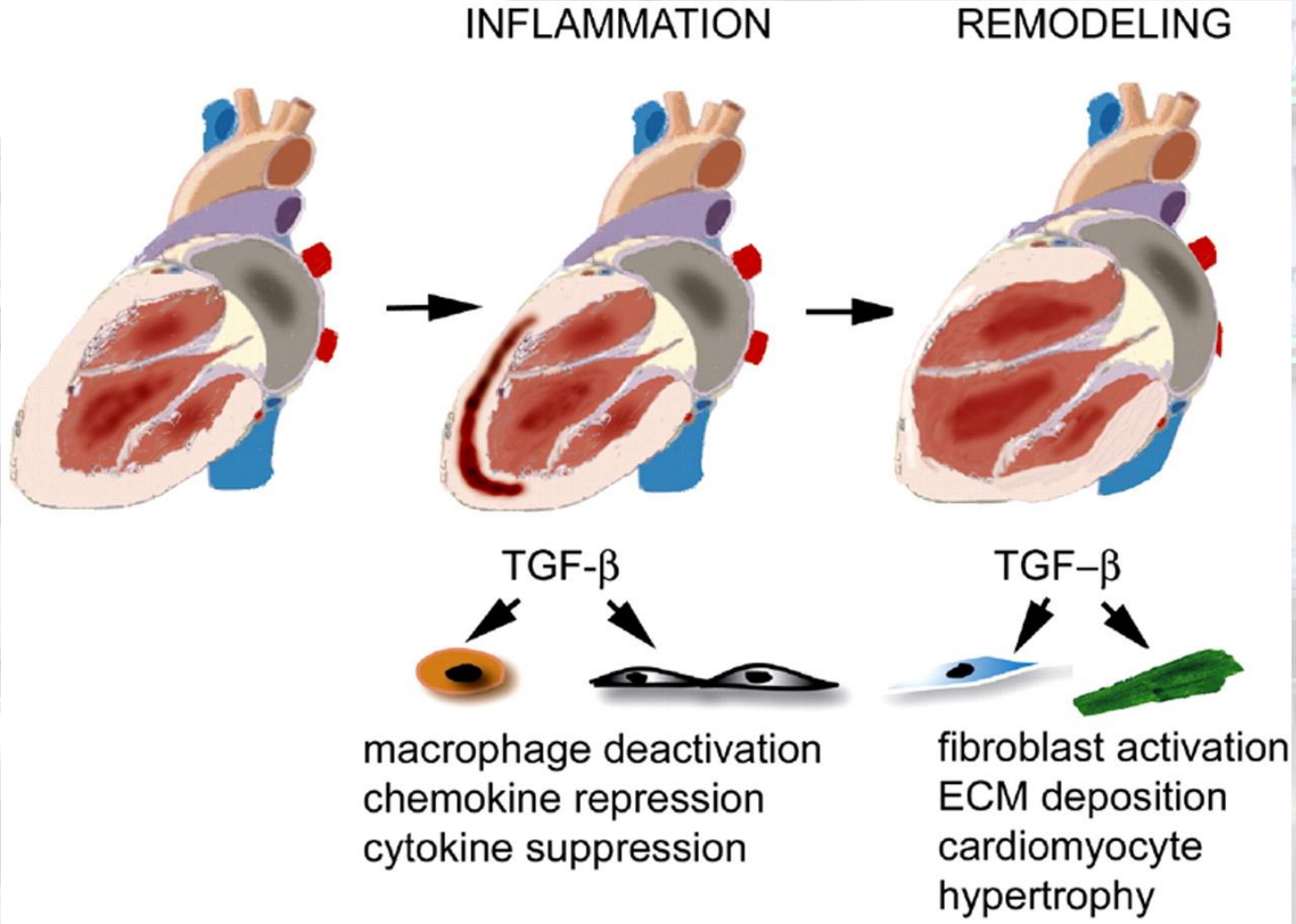
The diverse, multifunctional, and pleiotropic effects of TGF-β on cell types involved in infarct healing.



Bujak M , Frangogiannis N G Cardiovasc Res 2007;74:184-195

Cardiovascular Research

Role of TGF-β signaling in infarct healing and post-infarction remodeling.



Bujak M , Frangogiannis N G Cardiovasc Res 2007;74:184-195

Cardiovascular Research

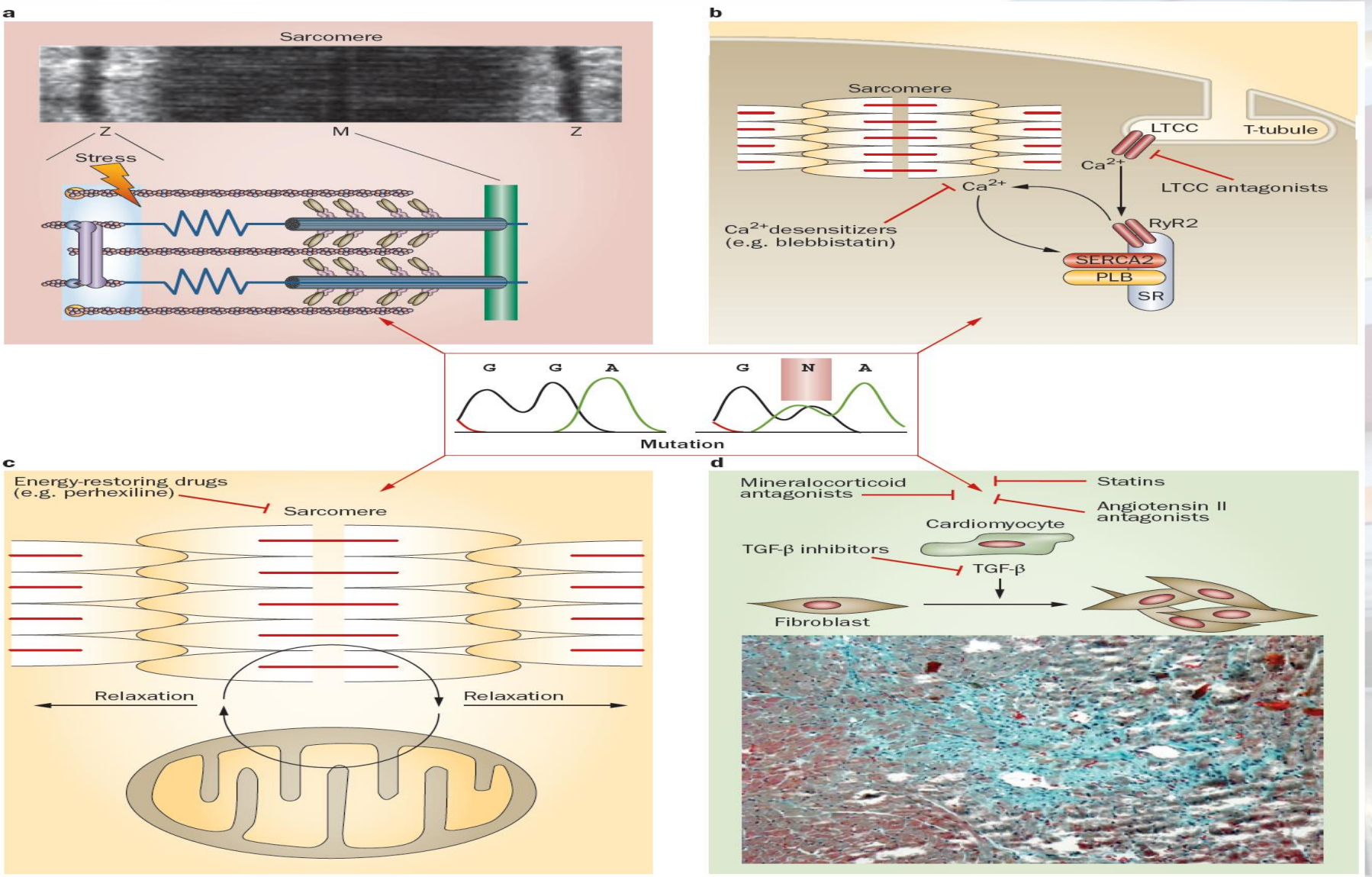


Figure 2 | Disease pathways of hypertrophic cardiomyopathy, and potential therapeutic interventions. Various signaling pathways and disease mechanisms can be activated as the result of a specific gene mutation. **a** | Disturbed biomechanical stress sensing. **b** | Impaired calcium cycling and sensitivity. **c** | Altered energy homeostasis. **d** | Increased fibrosis. These pathways should not be considered in isolation because they can act in concert (for example, metabolic deficits and impaired calcium cycling). Abbreviations: LTCC, voltage-dependent L-type calcium channel; PLB, cardiac phospholamban; RyR2, ryanodine receptor 2; SERCA2, sarcoplasmic/endoplasmic reticulum calcium ATPase 2; SR, sarcoplasmic reticulum; TGF-β, transforming growth factor β; T-tubule, transverse tubule.

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ISQUEMIA = M.S.

El Primer tratamiento para prevenir la muerte súbita no es el tratamiento para previenir de la muerte súbita

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REVACULARIZACIÓN COMPLETA

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Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators.. N Engl J Med 1997;337:1569-75

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CABG-Patch

Pacientes candidatos a CRM

- POP de CRM
- (2 grupos CDI versus control)
- pacientes con EC, candidatos a CRM con fey < 35% y ECG de señal promediada anormal.

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CABG-Patch

Pacientes candidatos a CRM

Absolute risk reduction Endpoint Events rate Absolute risk reduction (ARR) Studied treat. Control treat. All cause death 1,7%

La sobrevida no mejoro con el implante profiláctico de CDI en el momento de realizar la CRM en estos pacientes explicado probablemente por ser la revascularización lo que previene mas la MS.

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Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators.. N Engl J Med 1997;337:1569-75

- Absolute risk reduction Endpoint Events rate Absolute risk reduction (ARR) Studied treat. Control treat. All cause death 1,7%

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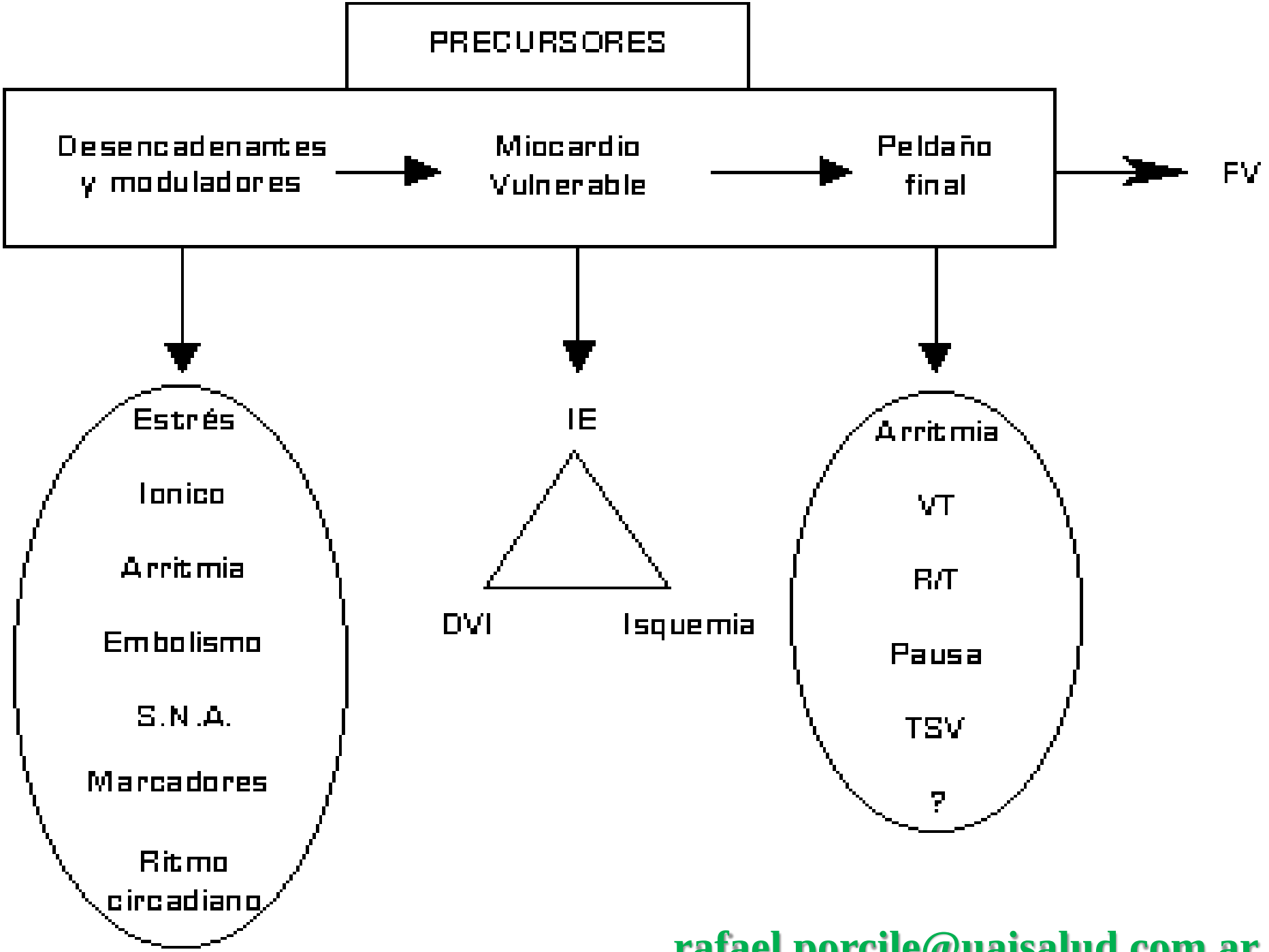

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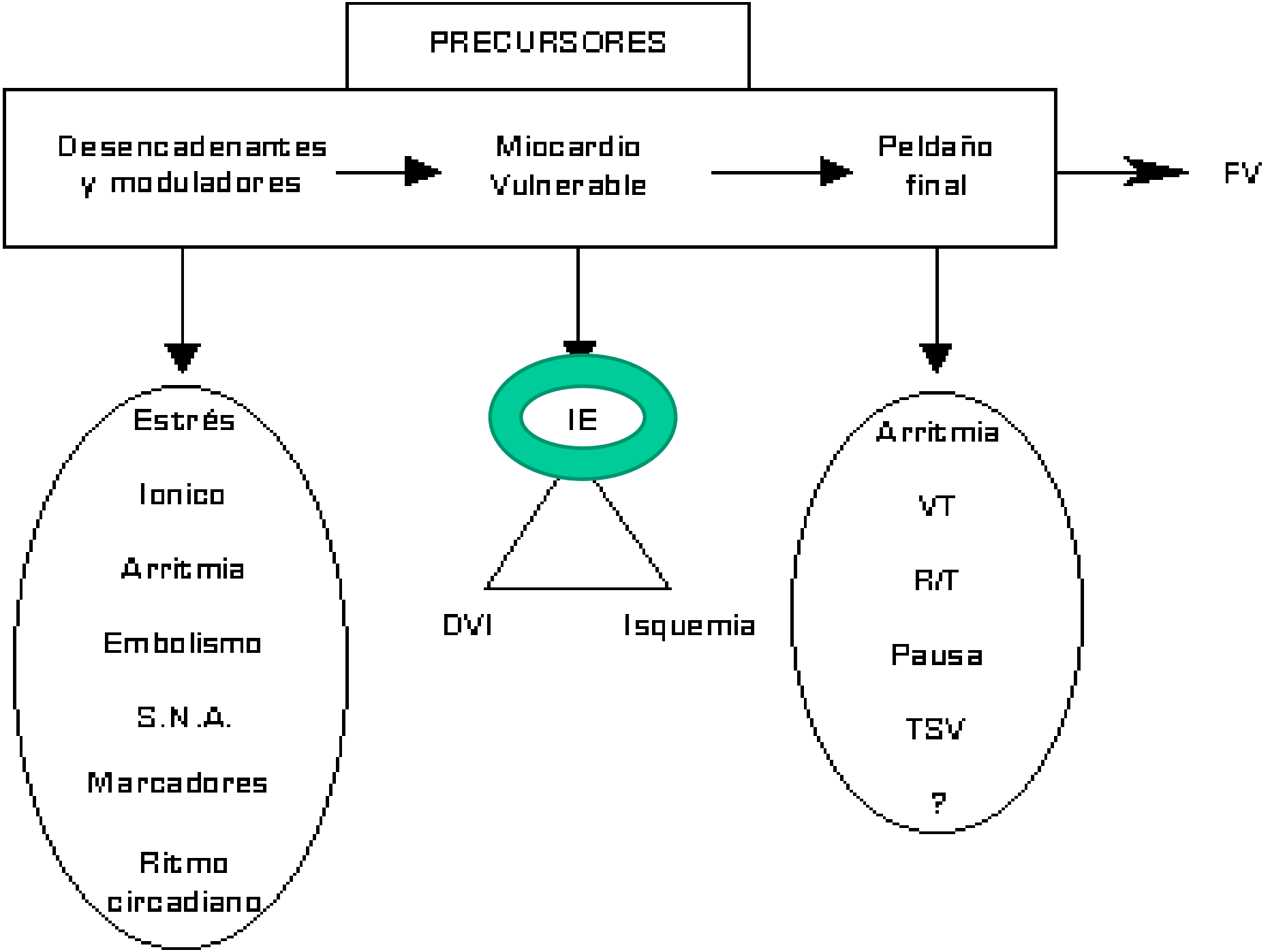

PRECURSORES
Desencadenantes y moduladores
Miocardio Vulnerable
Peldaño final
FV
Estrés
Iónico
Arritmia
Embolismo
S.N.A.
Marcadores
Ritmo circadiano
IE
DVI
Isquemia
Arritmia
VT
R/T
Pausa
TSV
?

MUERTE SUBITA

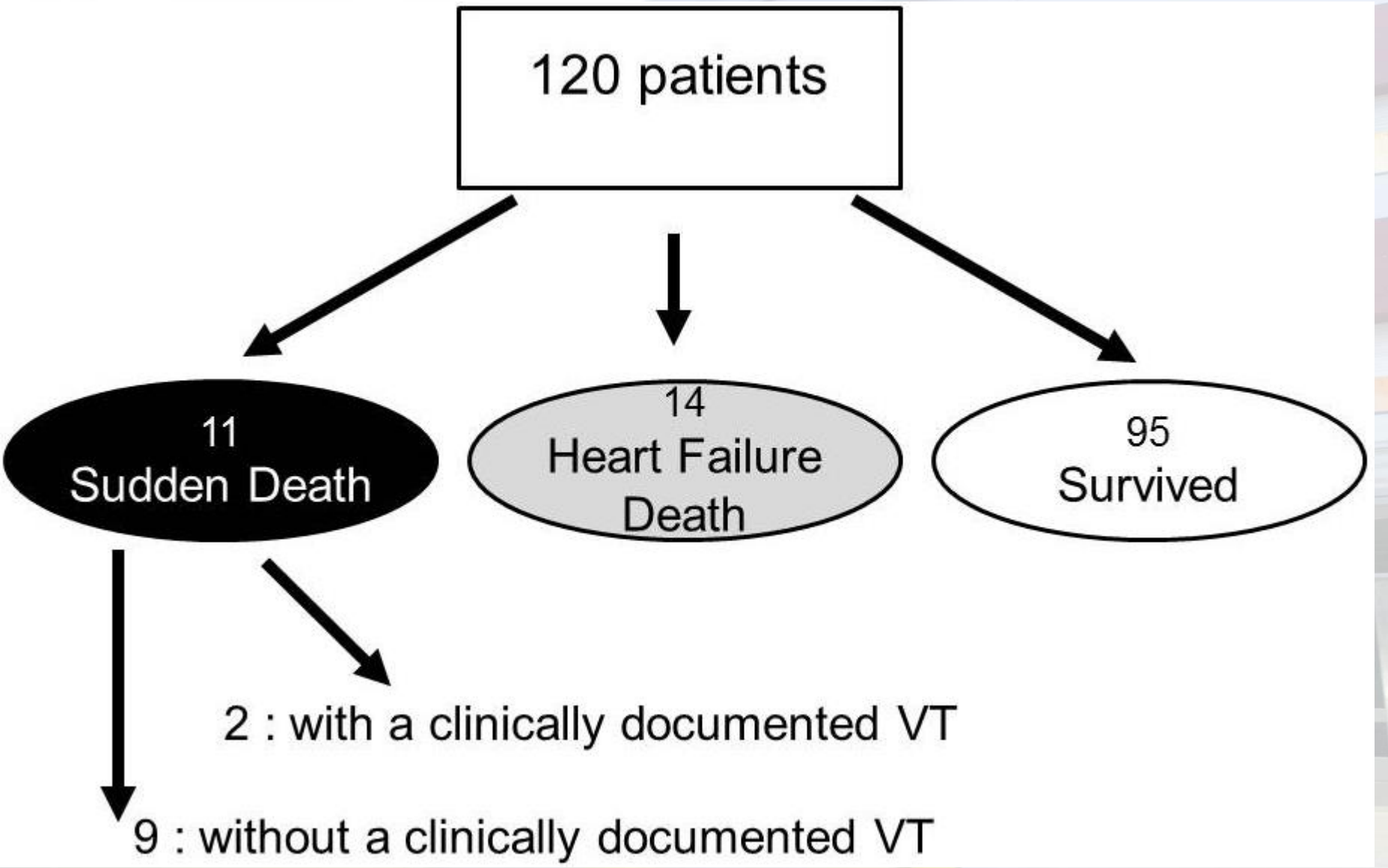
TONO ADRENERGICO

Risk Stratification of Sudden Cardiac Death by Evaluating Myocardial Sympathetic Nerve Activity Using Iodine-123 Metaiodobenzylguanidine Scintigraphy in Patients with Chronic Heart Failure and Dilated Cardiomyopathy

Yoshikazu Yazaki[1], Toshimasa Seki[1], Atsushi Izawa[2], Minoru Hongo[3] and Uichi Ikeda[1]

[School of Medicine, Matsumoto, Japan

[3] Department of Allied Health Science, Shinshu University School of Medicine, Matsumoto, Japan


120 patients
11
Sudden Death
14
Heart Failure
Death
95
Survived
2 : with a clinically documented VT
9 : without a clinically documented VT

We investigated the relationship between ^{123}I-MIBG findings and mode of death in patients with chronic heart failure. Sudden cardiac death in heart failure patients is closely associated with cardiac sympathetic nervous activity assessed by ^{123}I-MIBG scintigraphy. Our data, thus, confirm that **increased sympathetic tone in the myocardium play a harmful role on the progression of life-threatening ventricular tachyarrhythmias.** Assessment of cardiac sympathetic nervous activity using ^{123}I-MIBG may be helpful for the candidate selection of ICD in heart failure patients without sustained ventricular tachycardia

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Control Of Cardiac Function

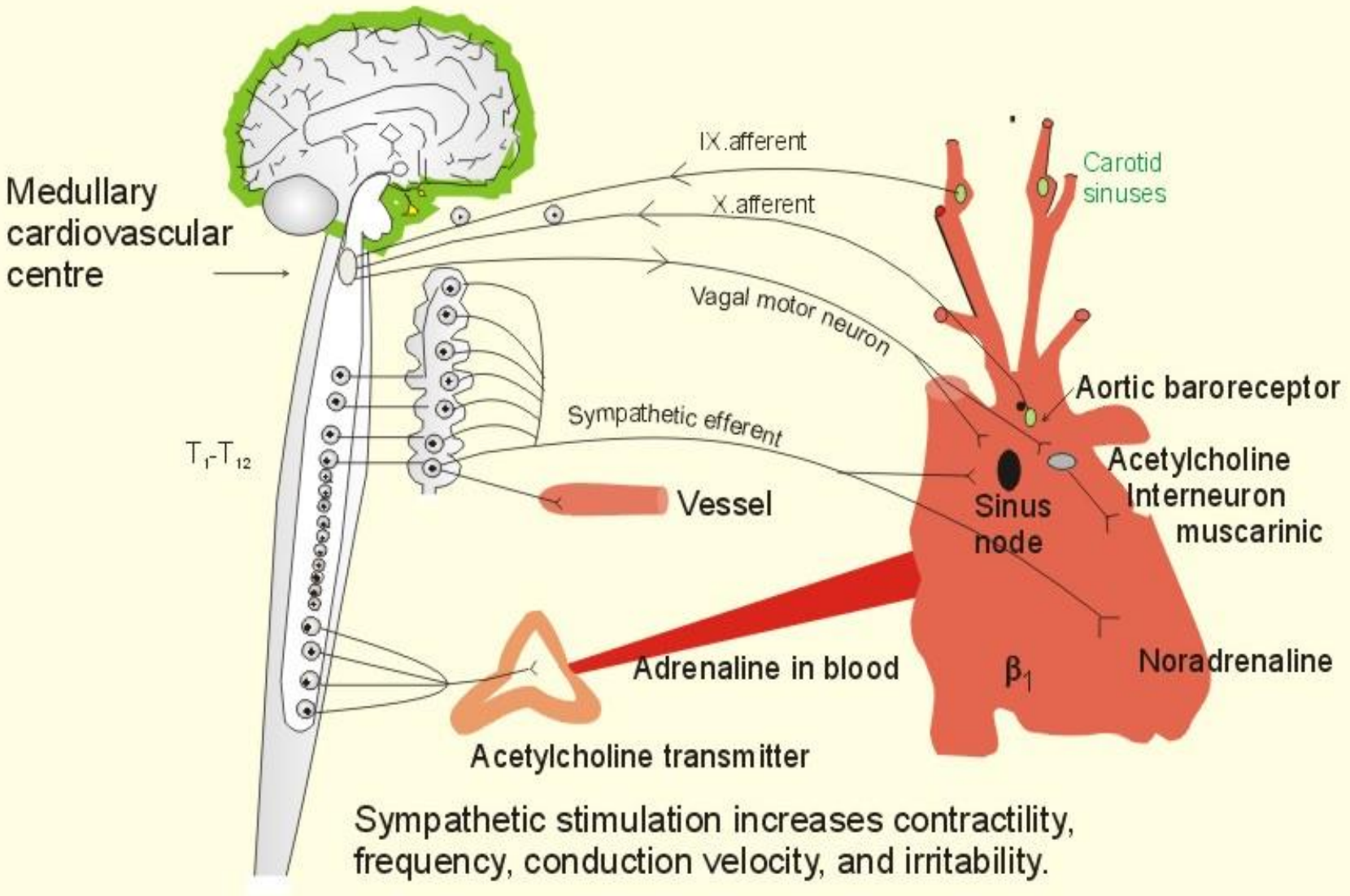
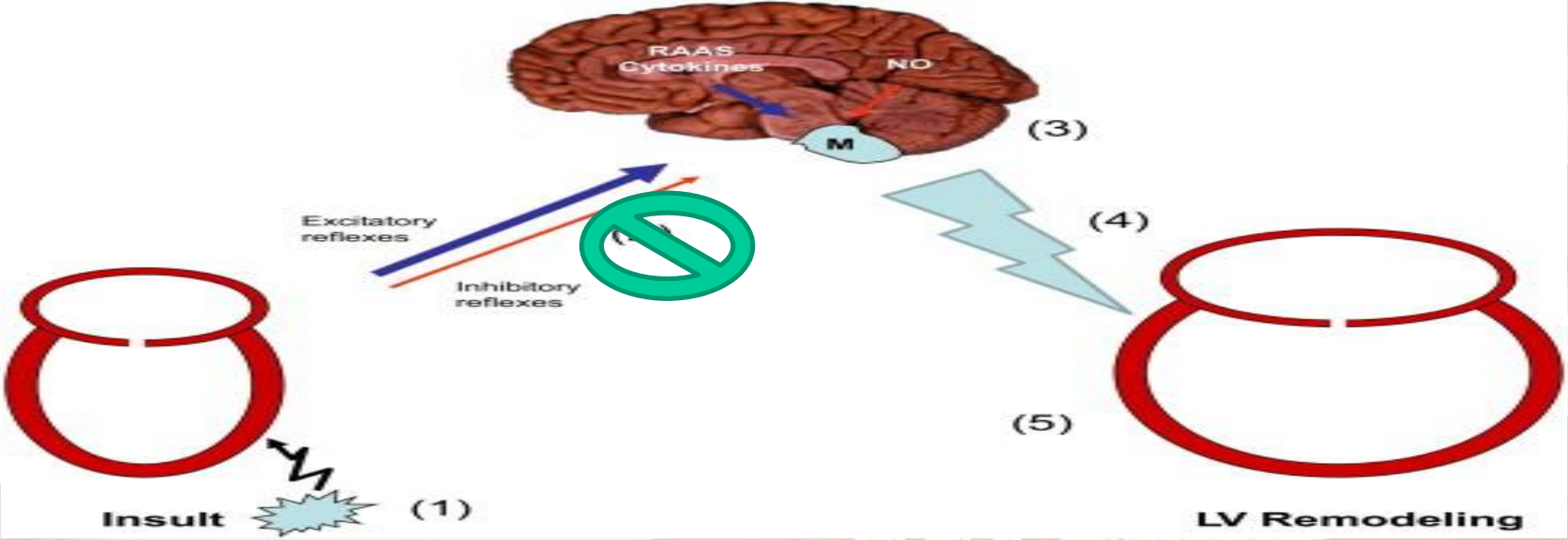


Fig. 11-1

KMc



(1) An insult causes cardiac dysfunction and decreases cardiac output.

(2) Attenuation of inhibitory sympathetic cardiovascular reflexes and augmentation of excitatory sympathetic cardiovascular reflexes is associated with increased sympathetic input in the central nervous system.

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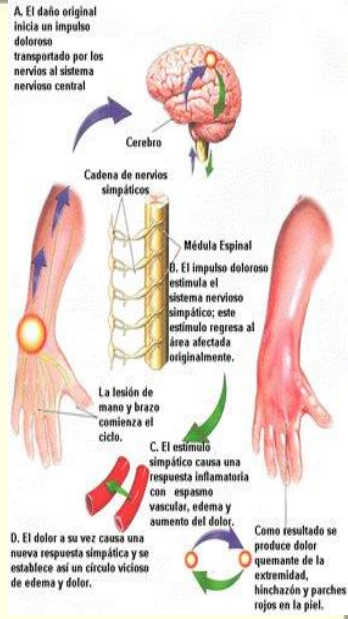
Control Of Cardiac Function



Medullary cardiovascular centre

IX.afferent

X.afferent

2

Vagal motor neuron

2

Sympathetic efferent

2

T_1-T_{12}

Vessel

Carotid sinuses

Aortic baroreceptor

Acetylcholine Interneuron muscarinic

Sinus node

Adrenaline in blood

β_1

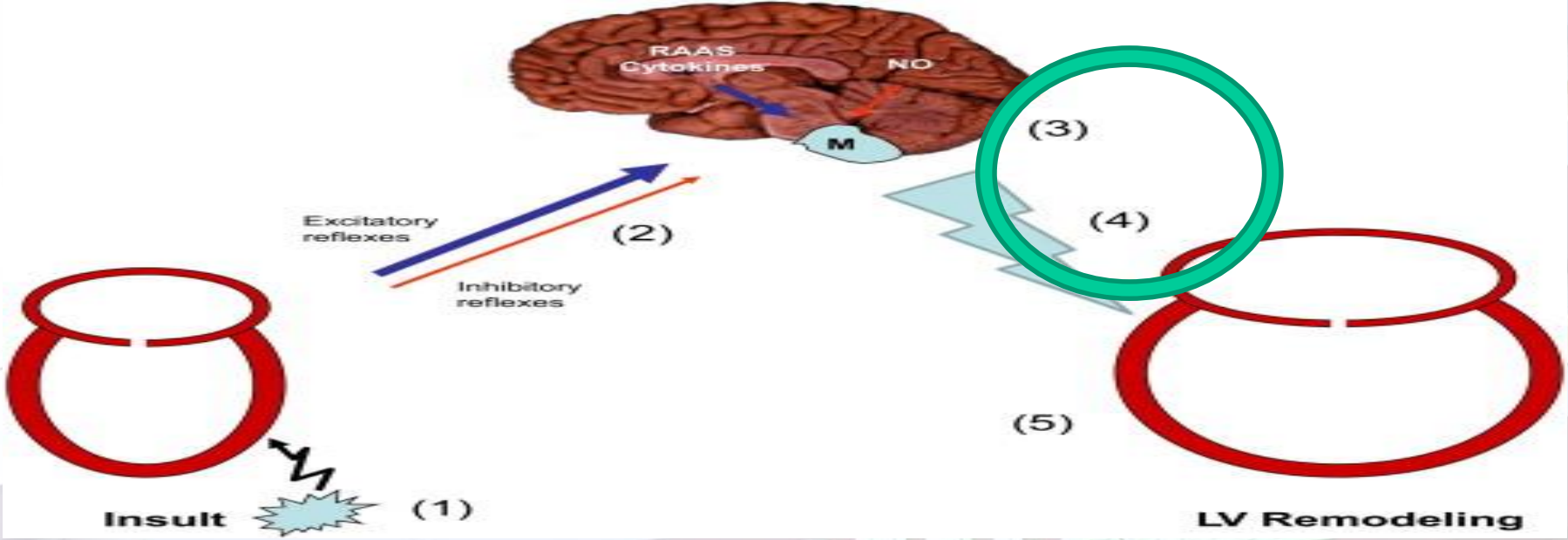
Noradrenaline

Acetylcholine transmitter

Sympathetic stimulation increases contractility, frequency, conduction velocity, and irritability.

Fig. 11-1

KMc



3 and 4 Central facilitation of the augmented cardiovascular sympathetic afferent reflex mediated by an increase in angiotensin II and cytokines and a decrease in nitric oxide (NO) contributes to tonic increases in sympathetic output.

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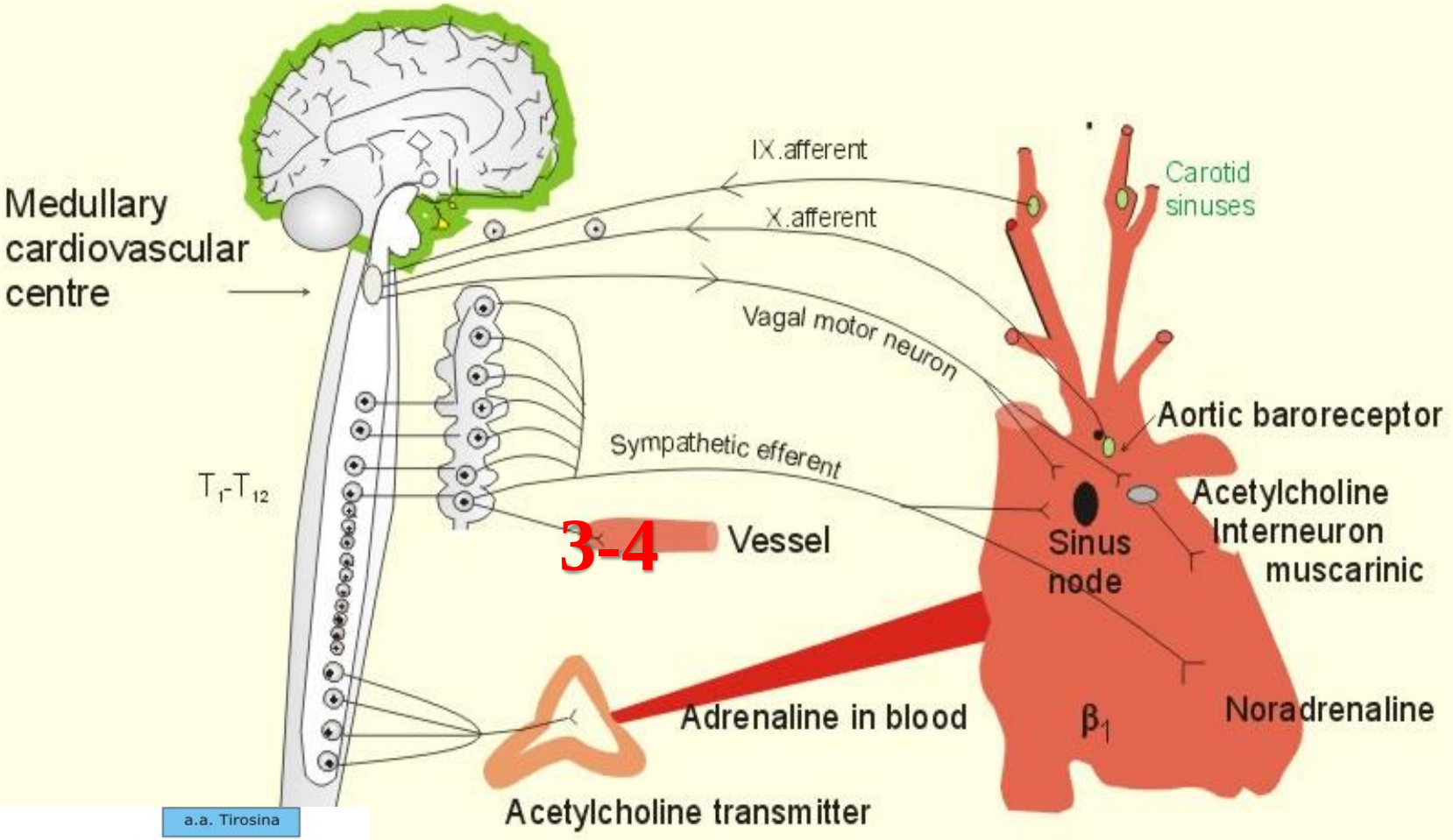
Control Of Cardiac Function



Sympathetic stimulation increases contractility, frequency, conduction velocity, and irritability.

KMc

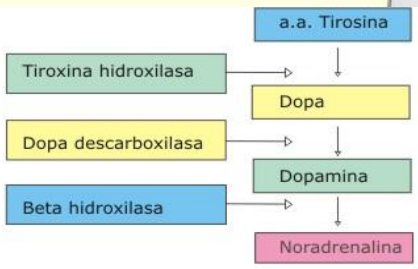
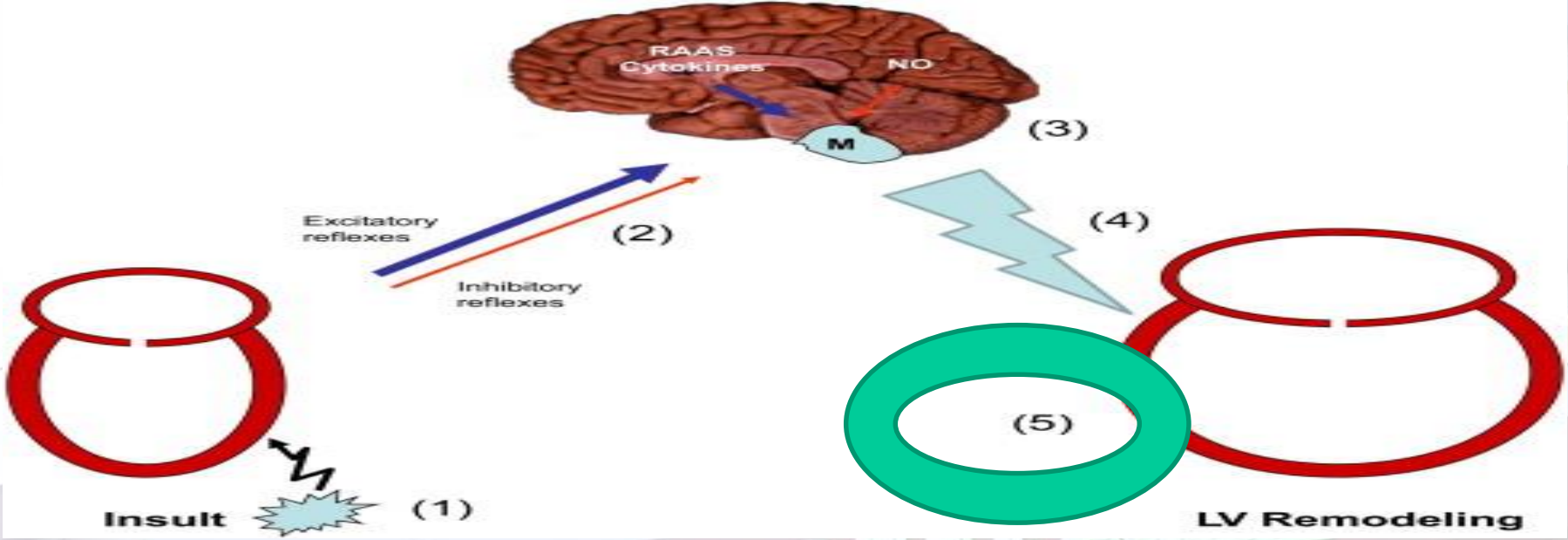


Fig. 3. Formación de la Noradrenalina.



(5) **The chronic increase in sympathetic output is associated with structural and functional changes in the cardiomyocytes and the interstitium leading to left ventricular (LV) dilation and systolic dysfunction (LV remodeling). m = medulla; RAAS = renin-angiotensin-aldosterone system.**

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Control Of Cardiac Function

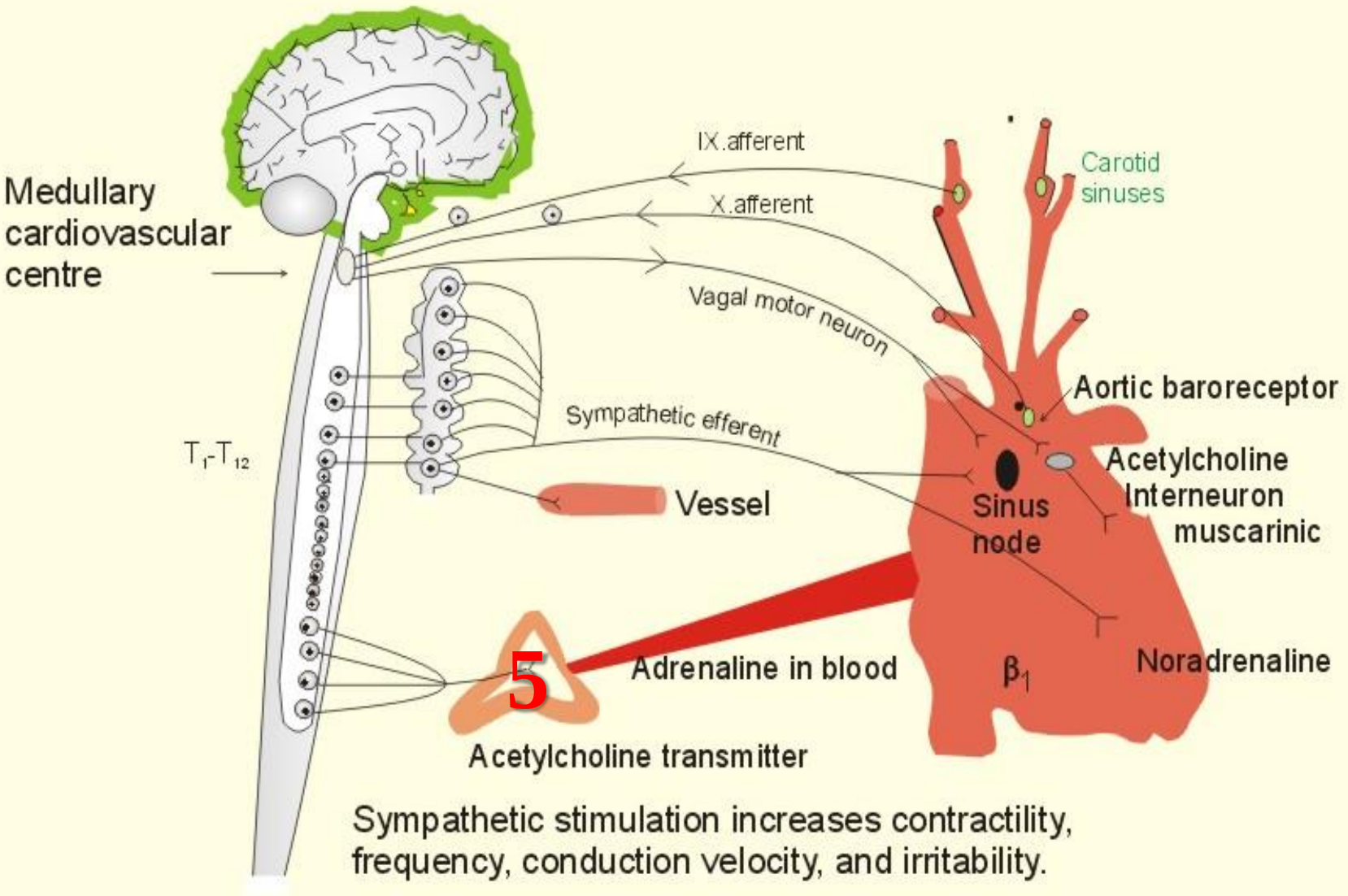
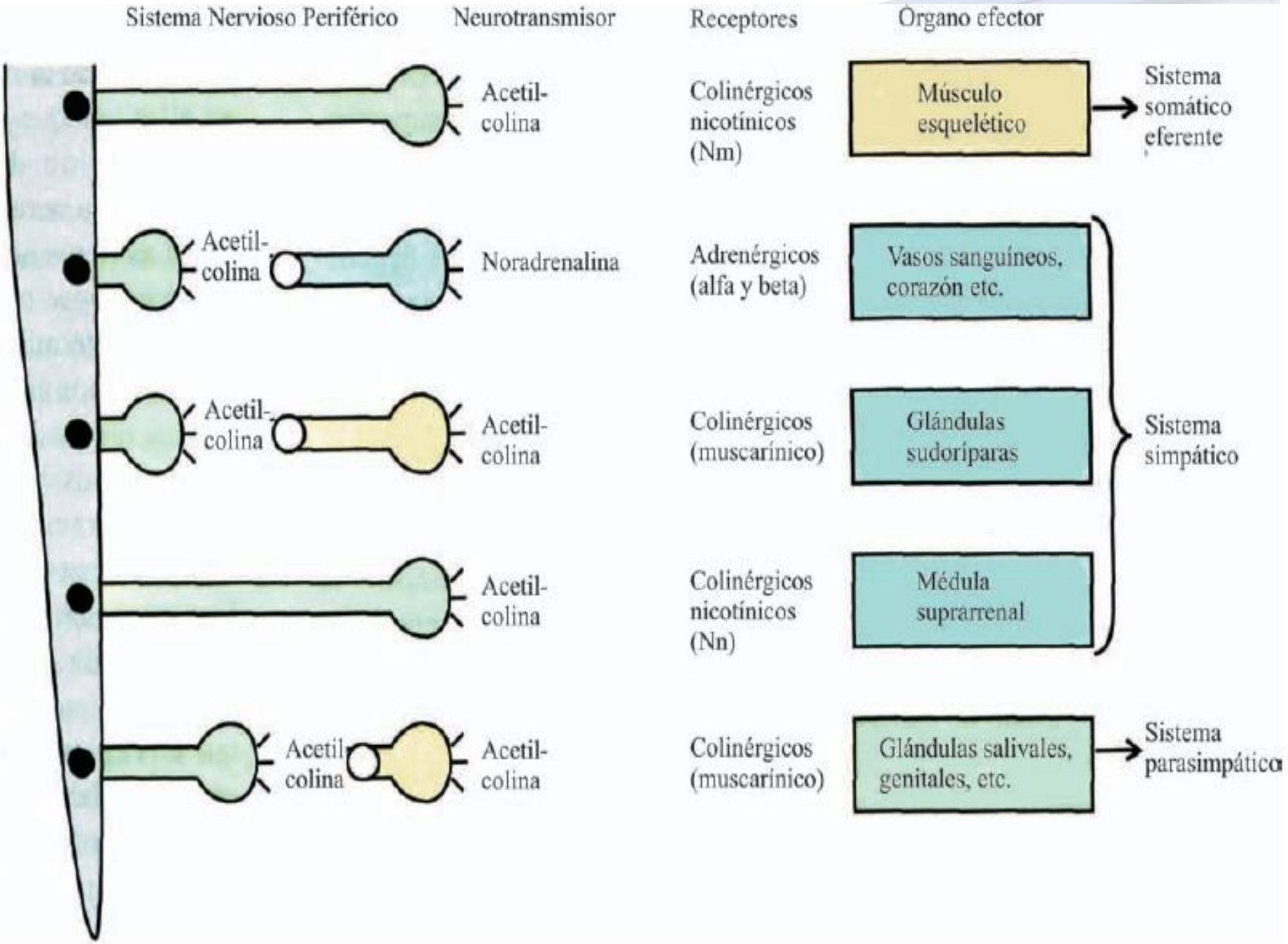


Fig. 11-1

KMc


Sistema Nervioso Periférico
Neurotransmisor
Receptores
Organo efector
Acetil-colina
Colinérgicos nicotínicos (Nm)
Músculo esquelético
Sistema somático eferente
Acetil-colina
Noradrenalina
Adrenérgicos (alfa y beta)
Vasos sanguíneos, corazón etc.
Acetil-colina
Acetil-colina
Colinérgicos (muscarínico)
Glándulas sudoríparas
Sistema simpático
Acetil-colina
Colinérgicos nicotínicos (Nn)
Médula suprarrenal
Acetil-colina
Acetil-colina
Colinérgicos (muscarínico)
Glándulas salivales, genitales, etc.
Sistema parasimpático

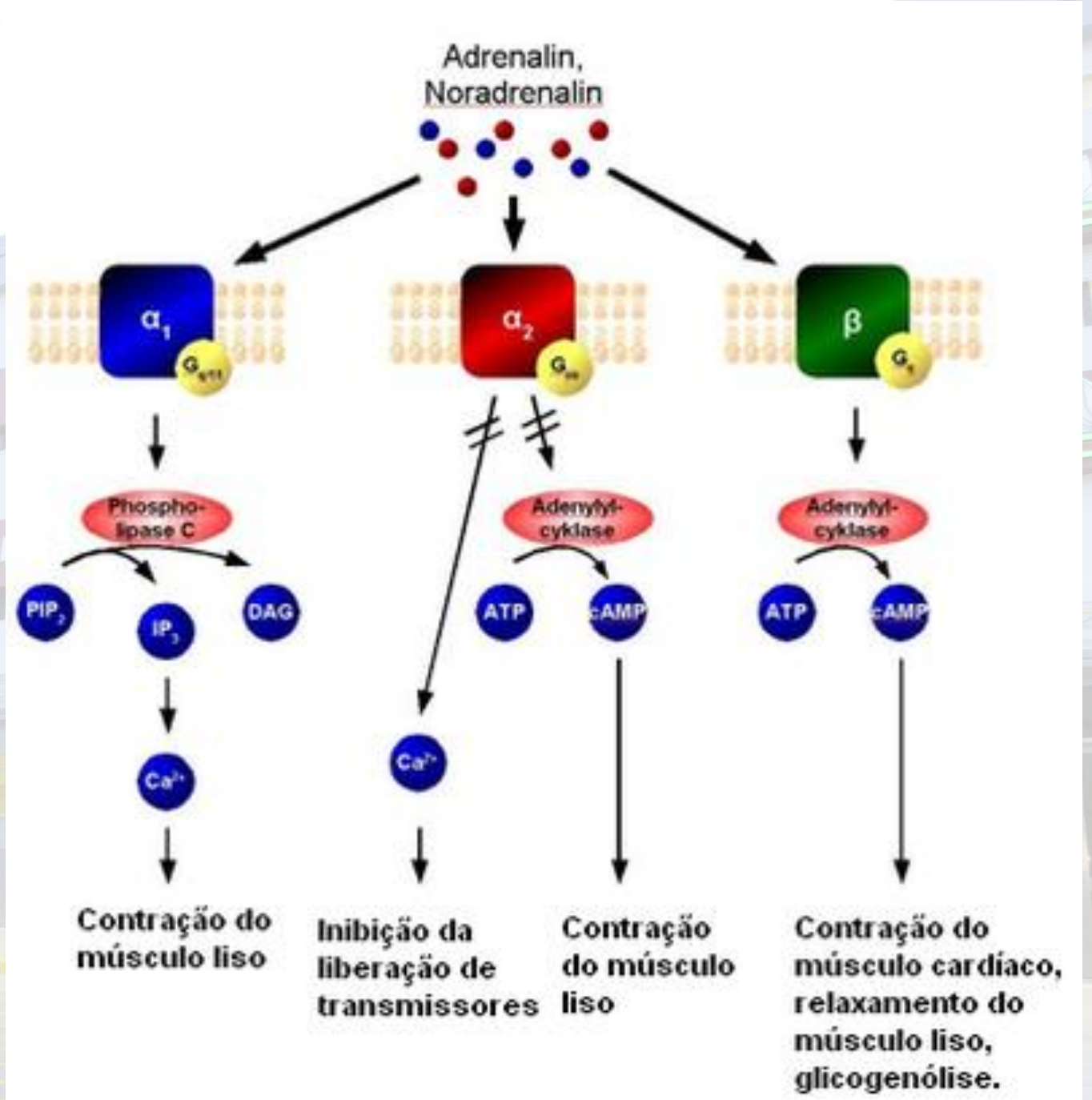

Adrenalin,
Noradrenalin
α1
α2
β
Phospho-
lipase C
Adenylyl-
cyklase
Adenylyl-
cyklase
PIP2
IP3
DAG
ATP
cAMP
ATP
cAMP
Ca2+
Ca2+
Kontrakce hladkého svalu
Inhibice uvolňování transmiterů
Kontrakce hladkého svalu
Kontrakce srdečního svalu, relaxace hladkého svalu, glykogenolýza.

TABLA 1. **Efectos mediados por receptores adrenérgicos β_1 y β_2**

Tejido	Receptor	Efecto
Corazón		
Nodo sinoauricular	β_1, β_2	Aumento de la frecuencia cardíaca
Nodo auriculoventricular	β_1, β_2	Aumento de la velocidad de la conducción
Aurículas	β_1, β_2	Aumento de la contractilidad
Ventrículos	β_1, β_2	Aumento de la contractilidad, de la velocidad de la conducción y de la automaticidad de los marcapasos idioventriculares
Arterias	β_2	Vasodilatación
Venas	β_2	Vasodilatación
Músculo esquelético	β_2	Vasodilatación, aumento de la contractilidad, glucogenólisis, captación de K^+
Hígado	β_2	Glucogenólisis y gluconeogénesis
Páncreas (células β)	β_2	Secreción de insulina y glucagón
Células grasas	β_1	Lipólisis
Bronquios	β_2	Broncodilatación
Riñón	β_1	Liberacion de renina
Vesícula y conductos	β_2	Relajación
Vejiga urinaria	β_2	Relajación
Útero	β_2	Relajación
Gastrointestinal	β_2	Relajación
Terminaciones nerviosas	β_2	Promueve la liberación de noradrenalina
Glándulas paratiroideas	β_1, β_2	Secreción de hormona paratiroidea
Glándula tiroides	β_2	Conversión de T4 → T3

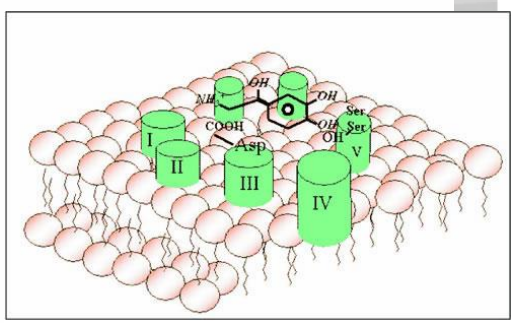
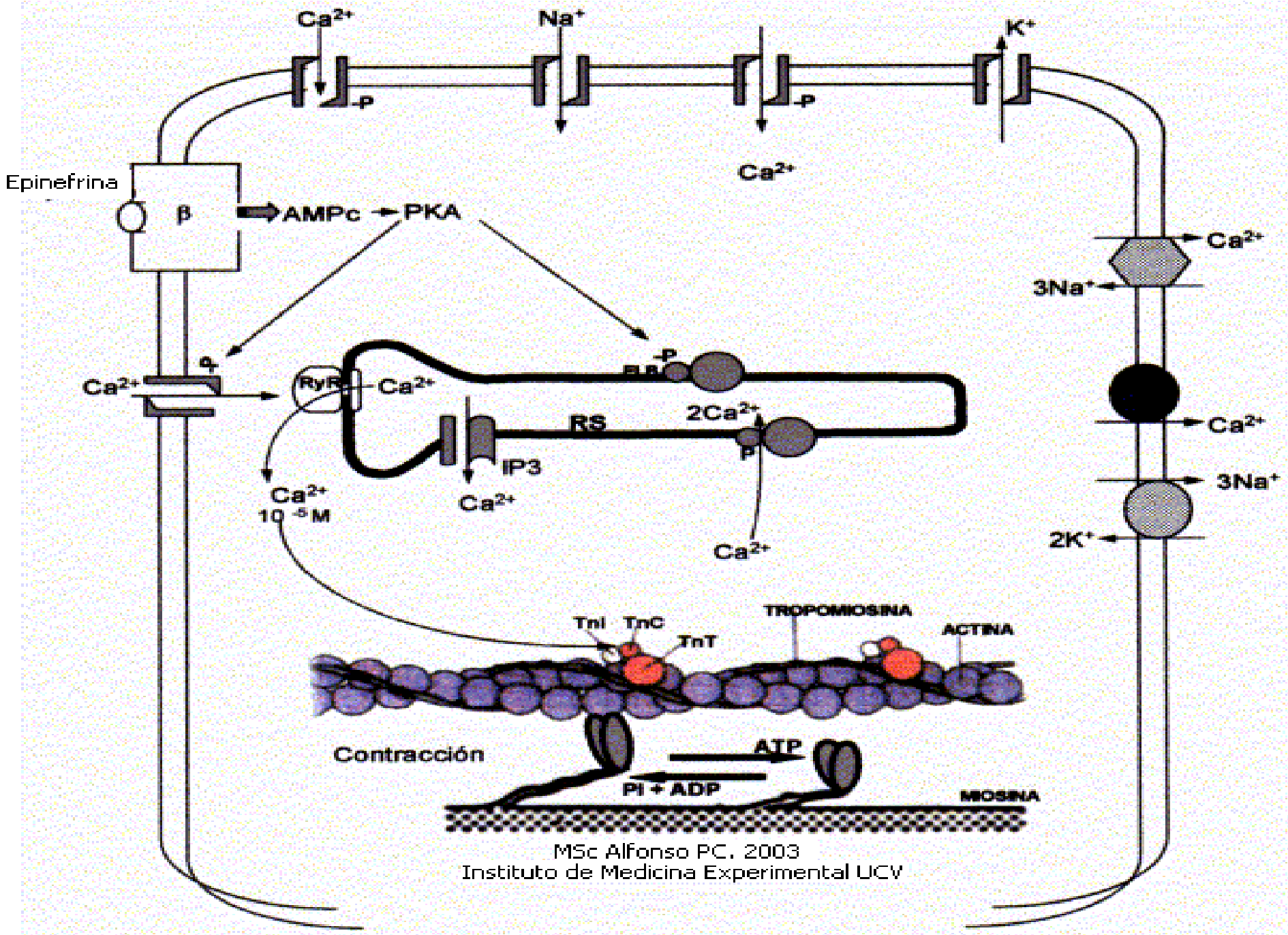


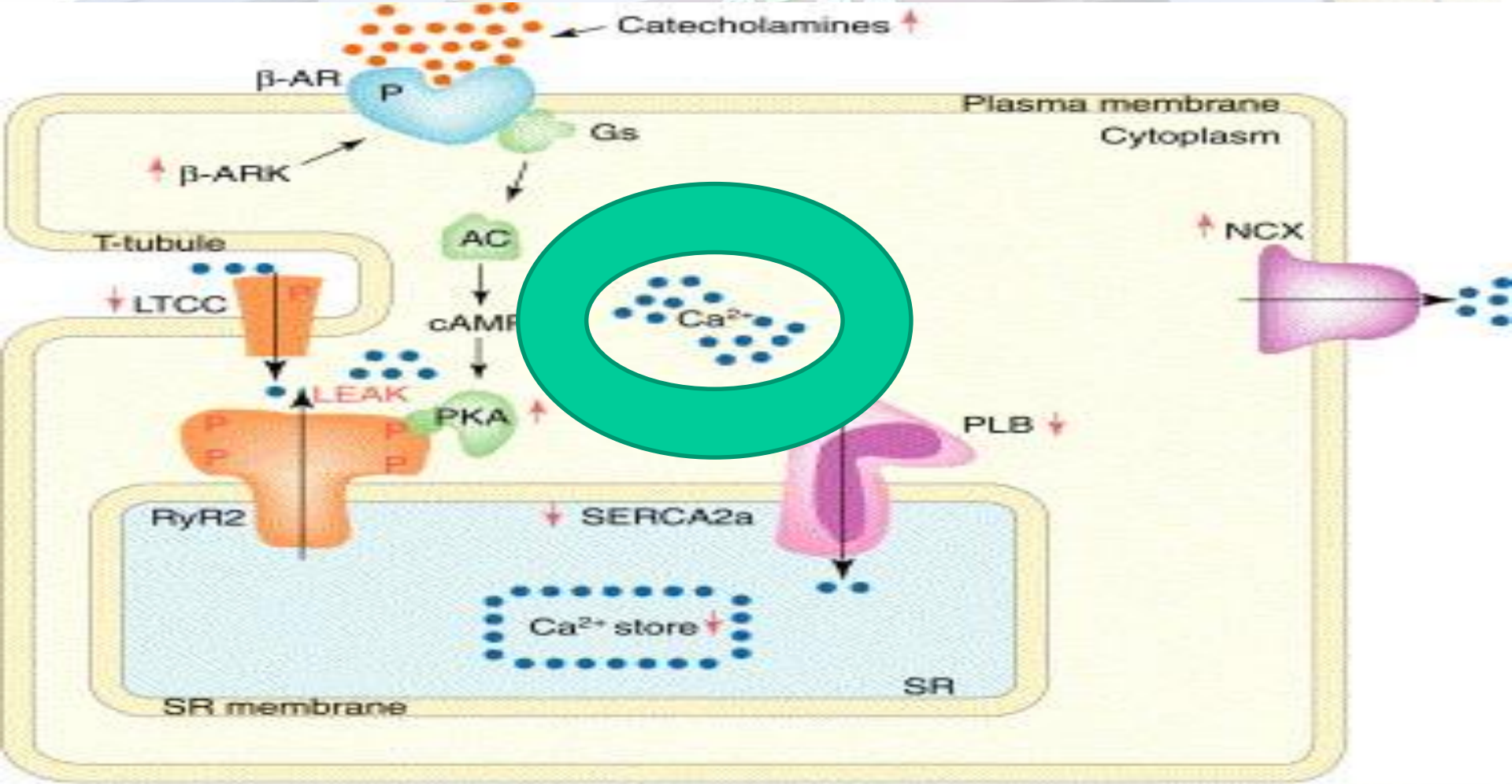
Figura 10. Estructura del receptor beta 2 adrenérgico. ADRB2 posee siete dominios transmembrana como es característico en la familia de receptores acoplada a proteína G.

Organo	Simpático	Parasimpático
Corazón	Aumento de la frecuencia cardiaca (beta 1y 2) Aumento de la fuerza de contracción (beta 1 y 2) Aumento de la velocidad de conducción	Disminución de la frecuencia cardiaca Disminución de la fuerza de contracción Disminución de la velocidad de conducción
Arterias	Contracción (alfa 1) Dilatación (beta 2)	Dilatación
Venas	Contracción (alfa 1) Dilatación (beta 2)	
Aparato Respiratorio	Broncodilatación (beta 2)	Broncoconstricción Aumento de secreción de glándulas bronquiales
Tracto Gastrointestinal	Disminución de la motilidad (beta 2) Contracción de esfinteres (alfa)	Aumento de la motilidad Relajación de esfinteres
Hígado	Glucogenolisis (beta 2 y alfa) Gluconeogénesis (beta 2 y alfa) Lipolisis (beta 2 y alfa)	Síntesis de Glucógeno
Riñón	Secreción de renina (beta 2)	
Vejiga	Relajación del detrusor (beta 2) Contracción de esfinteres (alfa)	Contracción del detrusor Relajación de esfinteres
Utero	Contracción de útero gestante (alfa) Relajación de útero gestante y no gestante (beta 2)	
Ojos	Dilatación pupilar (alfa)	Contracción pupilar Aumento de secreción de glándulas lagrimales
Glándulas Submandibular y Parótida	Secreción salival viscosa (alfa)	Secreción salival acuosa

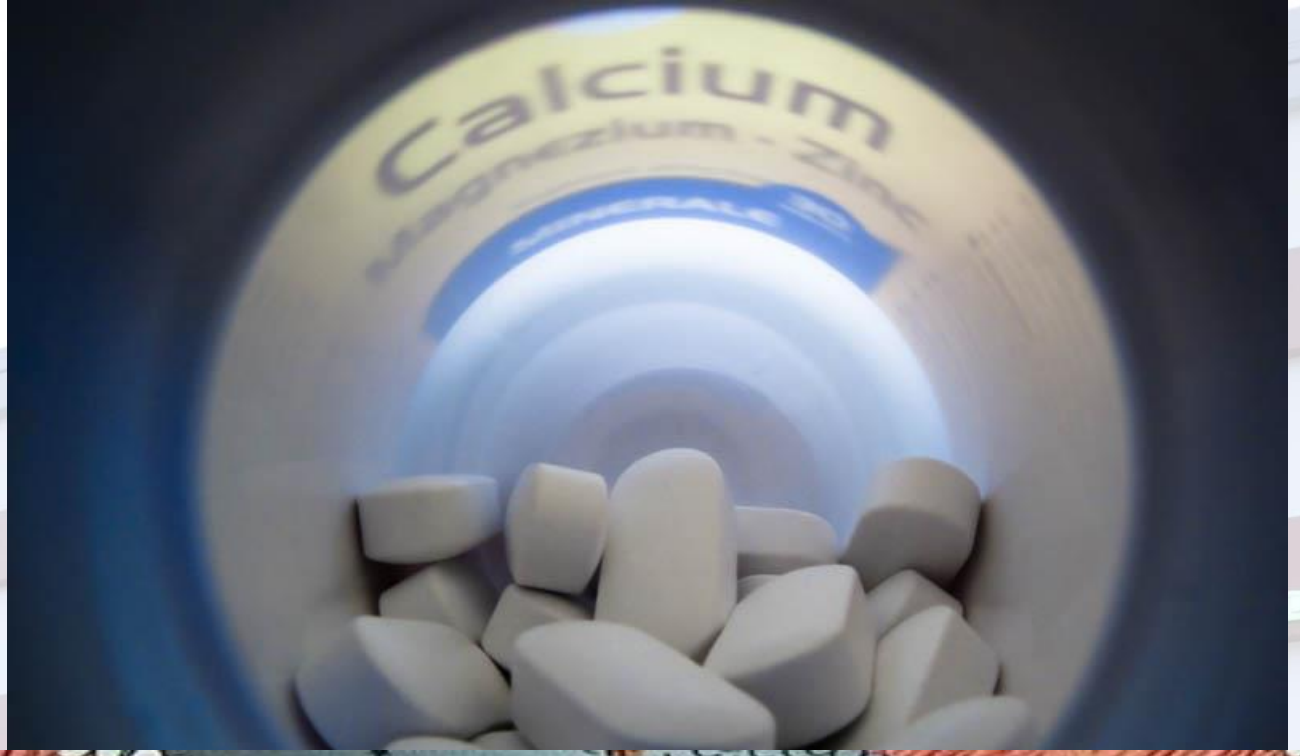


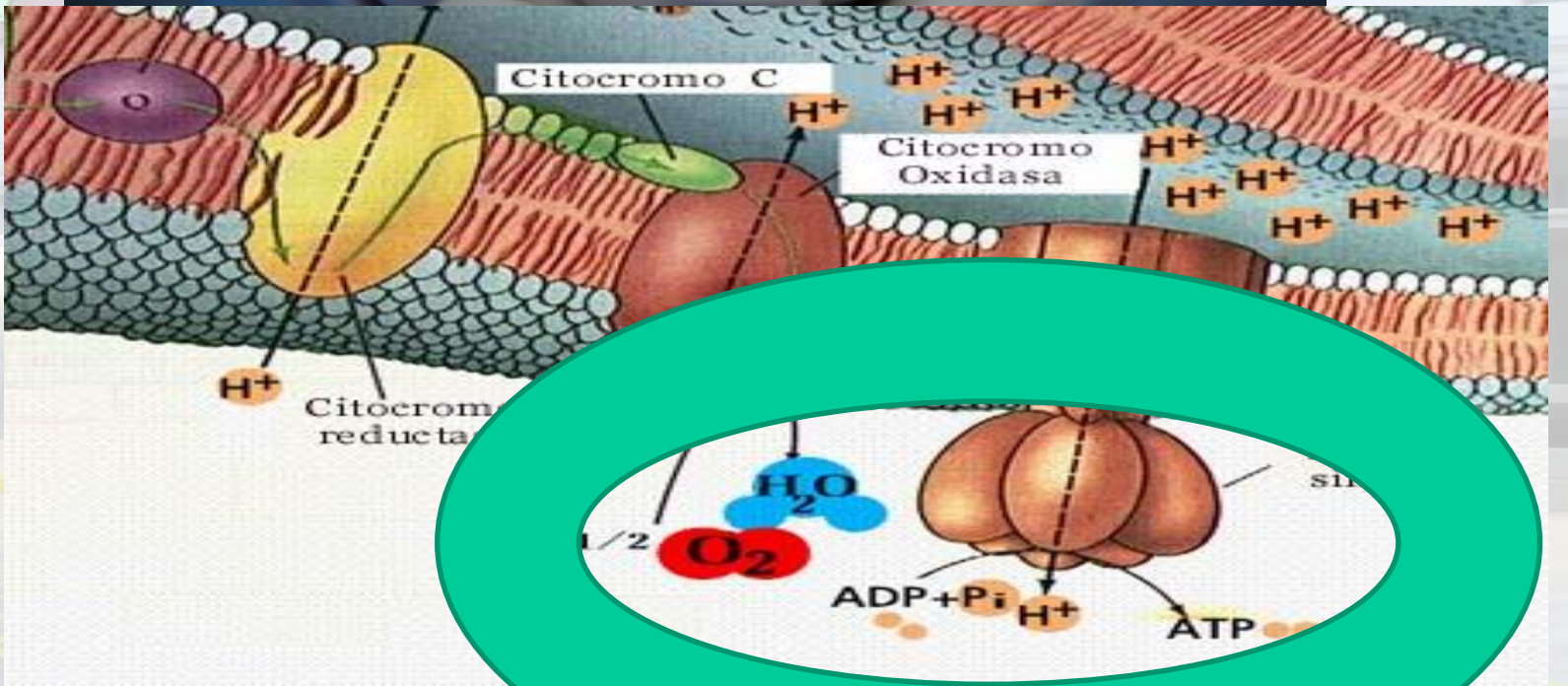
MSc Alfonso PC. 2003
Instituto de Medicina Experimental UCV

Efecto B1



Drug Discovery Today: Disease Mechanisms


Calcium


Citocromo C
Citocromo
Oxidasa
H+
Citocrom
reducta
H2O
O2
ADP+Pi
H+
ATP

AUMENTA EL CONSUMO DE OXIGENO

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STRESS PARIETAL

=

ISQUEMIA

$$S = \frac{P \times r}{2h}$$

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El Primer tratamiento para prevenir la muerte súbita no es el tratamiento para previenir de la muerte súbita

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REDUCCIÓN DE MS POR CONTROL DEL TONO ADRENERGICO

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β-Blocker Therapy in Heart Failure
Scientific Review

JoAnne Micale Foody, MD
Michael H. Farrell, MD
Harlan M. Krumholz, MD

JAMA®
The Journal of the American Medical Association

CIBIS II,[5] 1999		US Carvedilol,[8] 1996		COPERNICUS,[95] 2001		BEST,[96] 2001	
Placebo (n = 1224)	Bisoprolol (n = 1222)	Placebo (n = 398)	Carvedilol (n = 696)	Placebo (n = 1133)	Carvedilol (n = 1156)	Placebo (n = 1354)	Bucindolol (n = 1354)
61	61	58	58	63	63	60	60
80	80	76	77	80	79	77	79
25	25	22	23	20	20	23	23
0	0	0	0	0	0	0	0
0	0	52	54	0	0	0	0
83	83	44	44	0	0	92	92
17	17	3	3	100	100	8	8
1.25		3.125 or 6.35		3.125		3	
10		50-100		50		100 (<75 kg), 200 (≥75 kg)	
None		2 weeks		None		None	
Mortality		Mortality, exercise tolerance, quality of life, progression of disease		Mortality, combined death and hospitalization		Mortality	
17	12	8	3	19	11	33	30
34		65		35		10 (NS)	
Significant reduction in primary end point of all-cause mortality with bisoprolol. Greatest reduction in sudden death. No benefit in death from pump failure.		Significant reduction in all-cause mortality with carvedilol. Stopped early because of mortality benefit. No effect on exercise tolerance or quality of life.		Significant reduction in primary and secondary end points in patients with severe heart failure with carvedilol		No significant mortality benefit with bucindolol	

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CIBIS II,[5] 1999		Us
Placebo (n = 1224)	Bisoprolol (n = 1222)	Place (n = 3
61	61	58
80	80	76
25	25	22
0	0	C
0	0	52
83	83	44
17	17	3
1.25		
10		
Mortality		Mortality, of life,
17	12	8
34		
Significant reduction in primary end point of all-cause mortality with bisoprolol. Greatest reduction in sudden death. No benefit in death from pump failure.		Significant mortal Stopp mortal exerci

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999	US Carvedilol,[8] 1996		COPER
Bisoprolol (n = 1222)	Placebo (n = 398)	Carvedilol (n = 696)	Placebo (n = 1133)
61	58	58	63
80	76	77	80
25	22	23	20
0	0	0	0
0	52	54	0
83	44	44	0
17	3	3	100
	3.125 or 6.35		
	50-100		
ty	Mortality, exercise tolerance, quality of life, progression of disease		Mortality, cor hospitaliz
12	8	3	19
	65		
rimary end rtality with reduction in enefit in ilure.	Significant reduction in all-cause mortality with carvedilol. Stopped early because of mortality benefit. No effect on exercise tolerance or quality of life.		Significant redu and secon in patients failure with

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[8] 1996		COPERNICUS,[95] 2001		BEST,[9]
Carvedilol (n = 696)	Placebo (n = 1133)	Carvedilol (n = 1156)	Placebo (n = 1354)	
58	63	63	60	
77	80	79	77	
23	20	20	23	
0	0	0	0	
54	0	0	0	
44	0	0	92	
3	100	100	8	
35		3,125		
		50		100 (<1 200 (≥
		None		N
rance, quality of disease		Mortality, combined death and hospitalization		M
3	19	11	33	
		35		10 (
all-cause edilol. ause of o effect on or quality		Significant reduction in primary and secondary end points in patients with severe heart failure with carvedilol		No significant m with bucindo

Foody JA JAMA 2002

β-Blocker Therapy in Heart Failure

Scientific Review

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Michael H. Farrell, MD
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The Journal of the American Medical Association

CUS,[95] 2001	BEST,[96] 2001	
Carvedilol (n = 1156)	Placebo (n = 1354)	Bucindolol (n = 1354)
63	60	60
79	77	79
20	23	23
0	0	0
0	0	0
0	92	92
100	8	8
125	3	
0	100 (<75 kg), 200 (≥75 kg)	
one	None	
ned death and on	Mortality	
11	33	30
	10 (NS)	
on in primary y end points n severe heart rvedilol	No significant mortality benefit with bucindolol	

Foody JA JAMA 2002

Beta Bloqueantes

- Mejora fraccion eyección
- Reduce tasa reinternación
- Reduccion Mortalidad b1 b2
  - Carbedilol MAYOR RED MORT 17%
- Reduccion mortalidad en B 1 selectivos
  - Bisoprolol, Metoprolol

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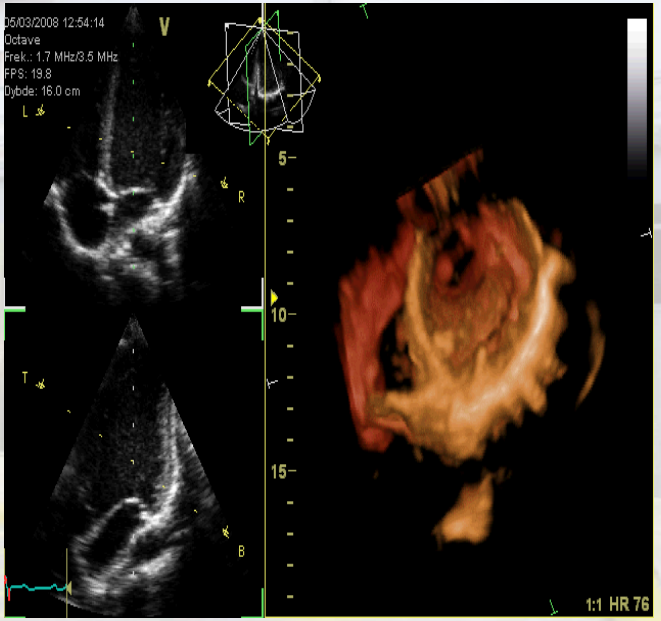
DIGOXINA



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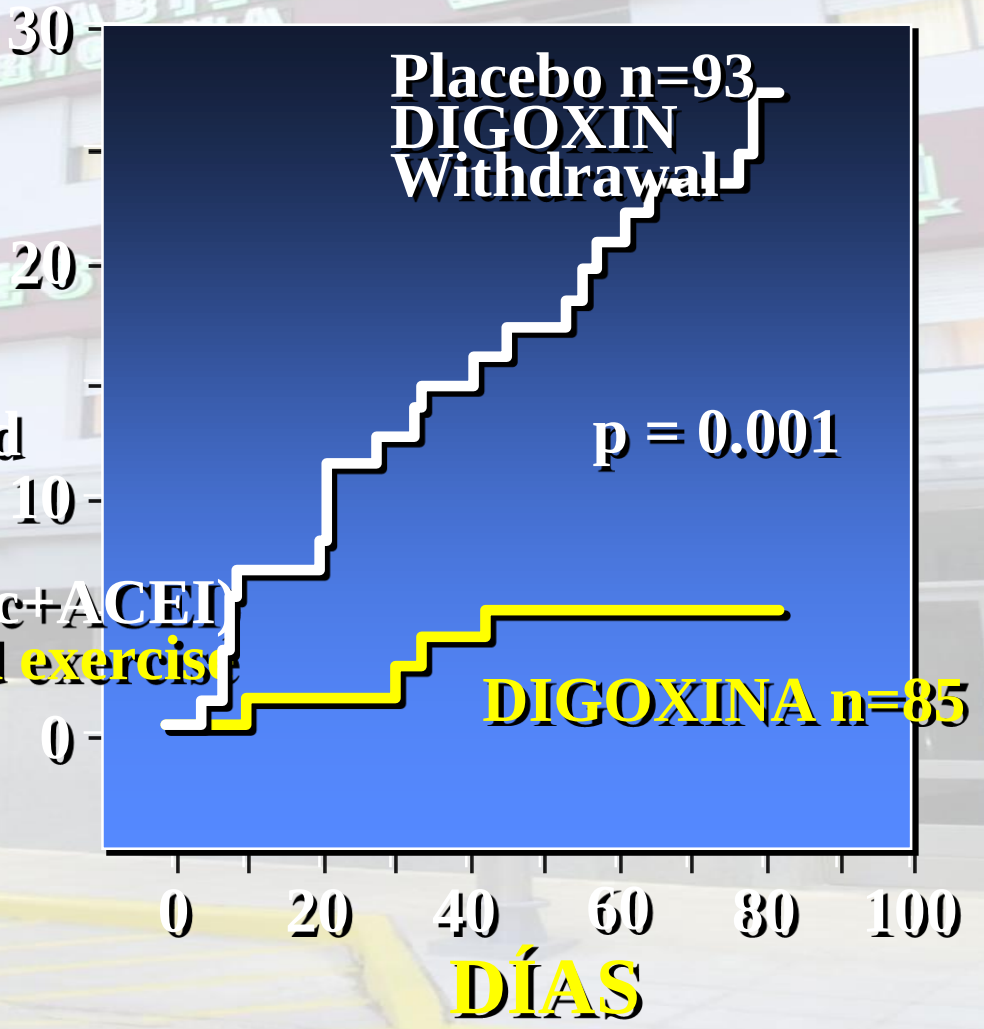
DIGOXINA
EFECTO SOBRE EVOLUCIÓN DE LA ICC

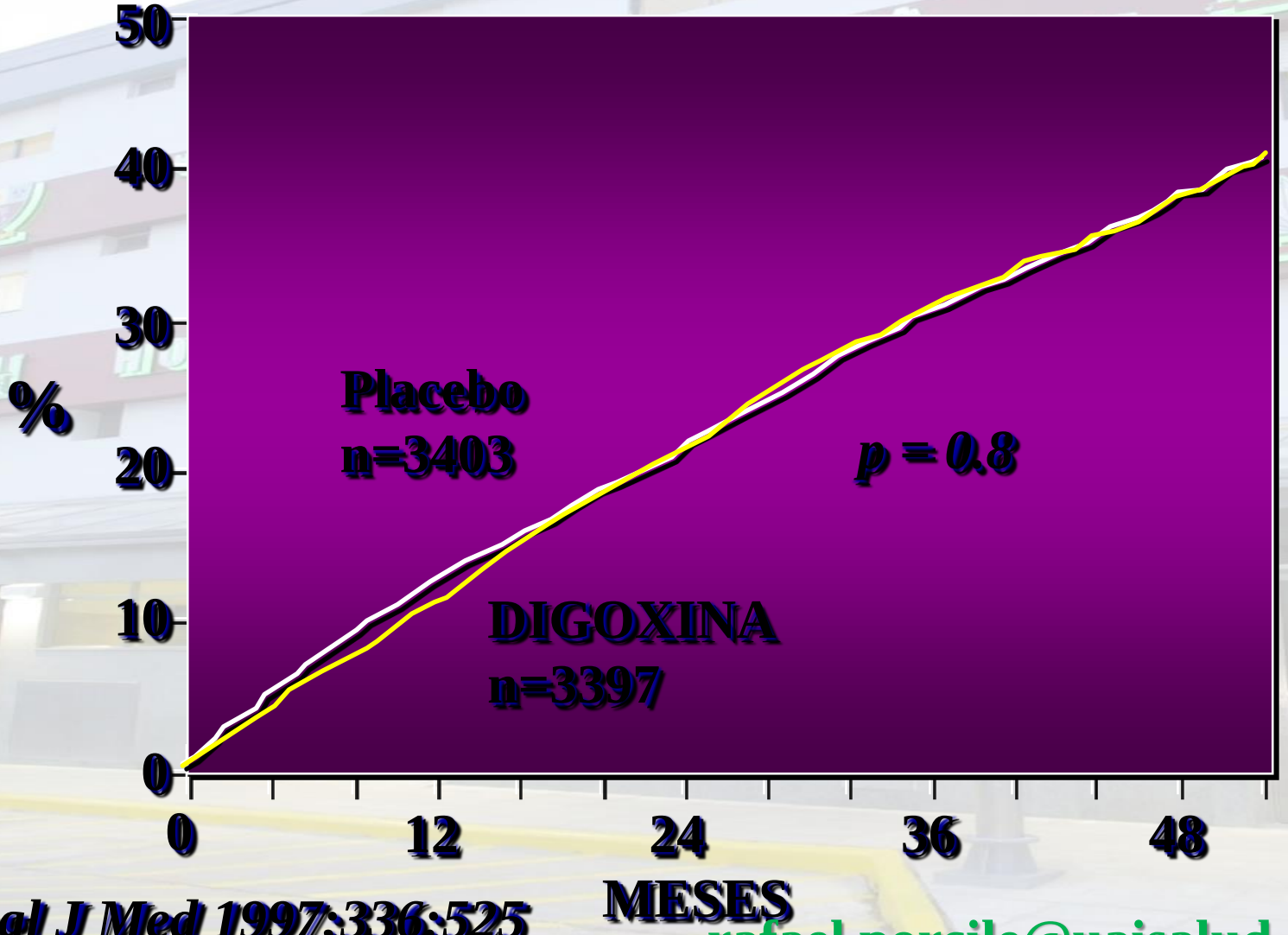
%
PROGRESIÓN



DIGOXIN: 0.125 - 0.5 mg /d
(0.7 - 2.0 ng/ml)
EF < 35%
Class I-III (digoxin+diuretic+ACEI)
Also significantly decreased exercise time and LVEF.

RADIANCE
N Engl J Med 1993;329:1

DIGOXINA Y MORTALIDAD EN ICC



DIG

N Engl J Med 1997;336:525

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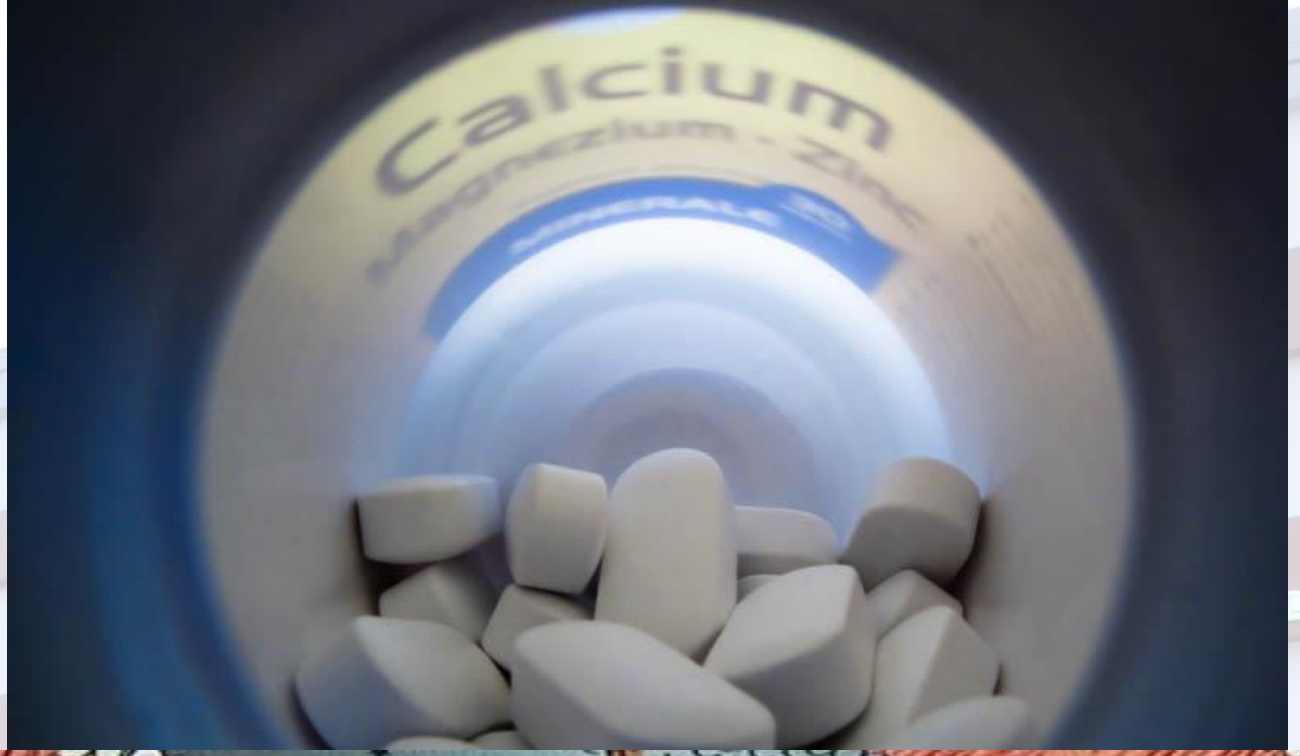
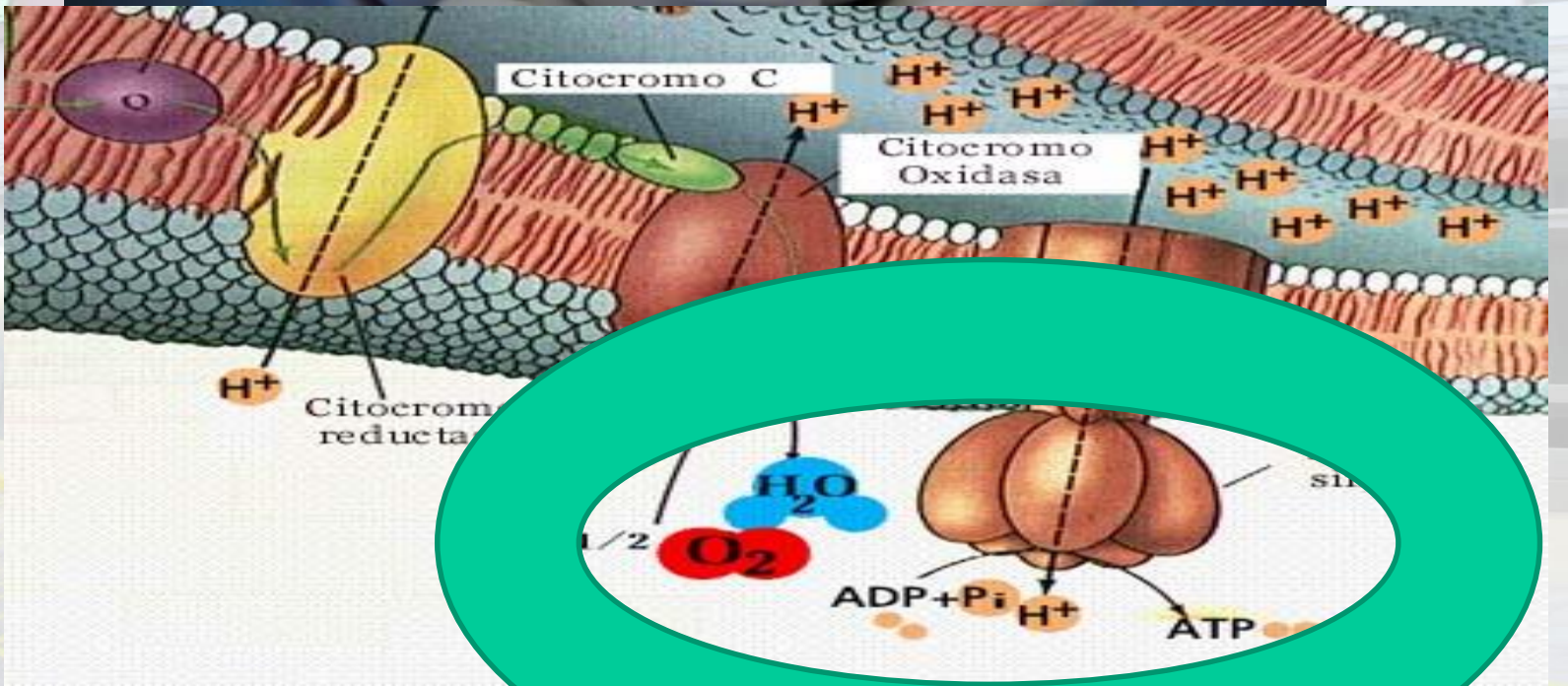
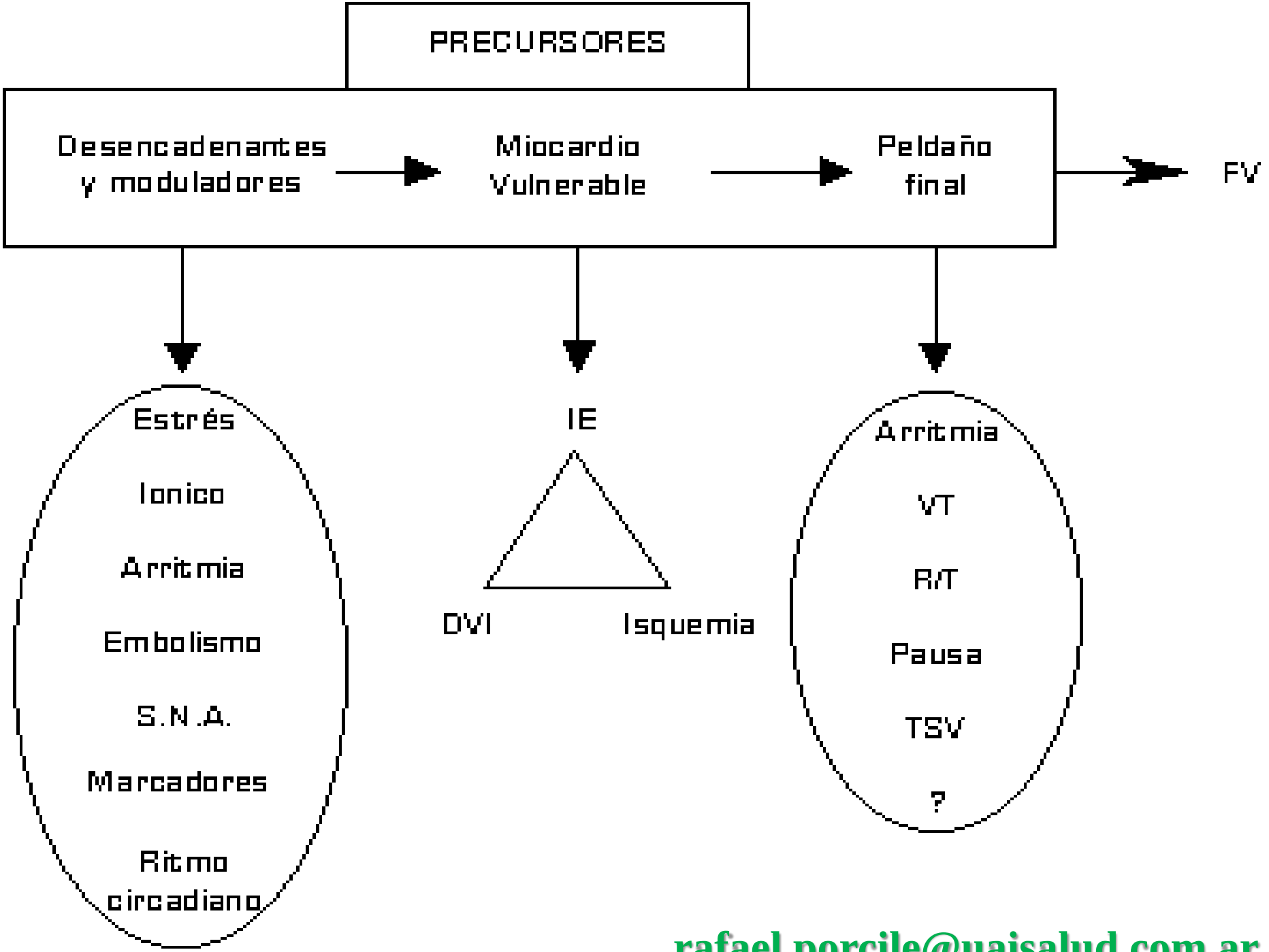
¿Por qué?

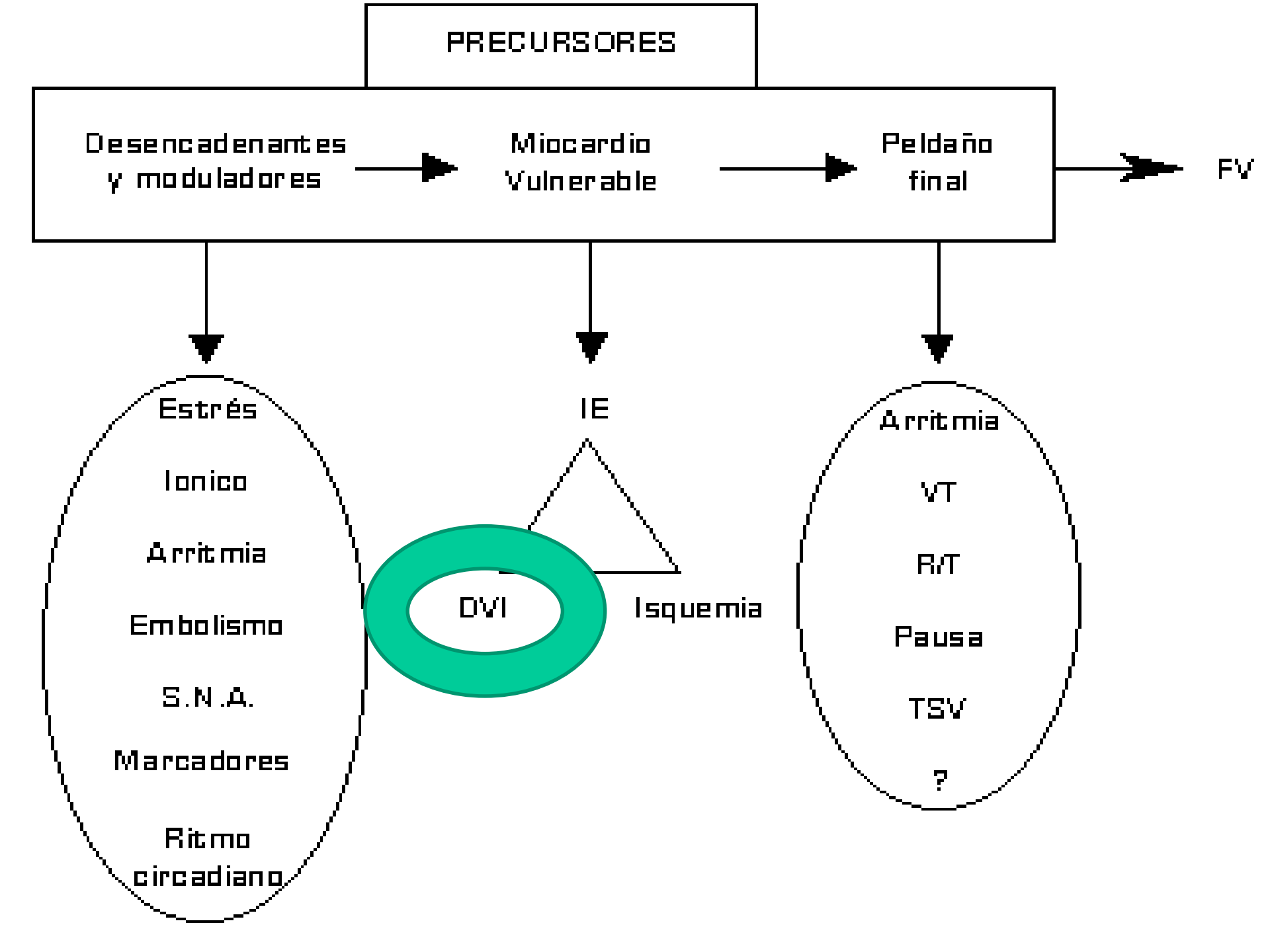

Calcium


Citocromo C
Citocromo
Oxidasa
H+
Citocrom
reducta
H2O
O2
ADP+Pi
H+
ATP


AUMENTA EL
CONSUMO DE
OXIGENO



rafael.porcile@uaisalud.com.ar


PRECURSORES
Desencadenantes y moduladores
Miocardio Vulnerable
Peldaño final
FV
Estrés
Iónico
Arritmia
Embolismo
S.N.A.
Marcadores
Ritmo circadiano
IE
DVI
Isquemia
Arritmia
VT
R/T
Pausa
TSV
?

FIBROSIS

+apoptosis

+hipertrofia

Remodelación

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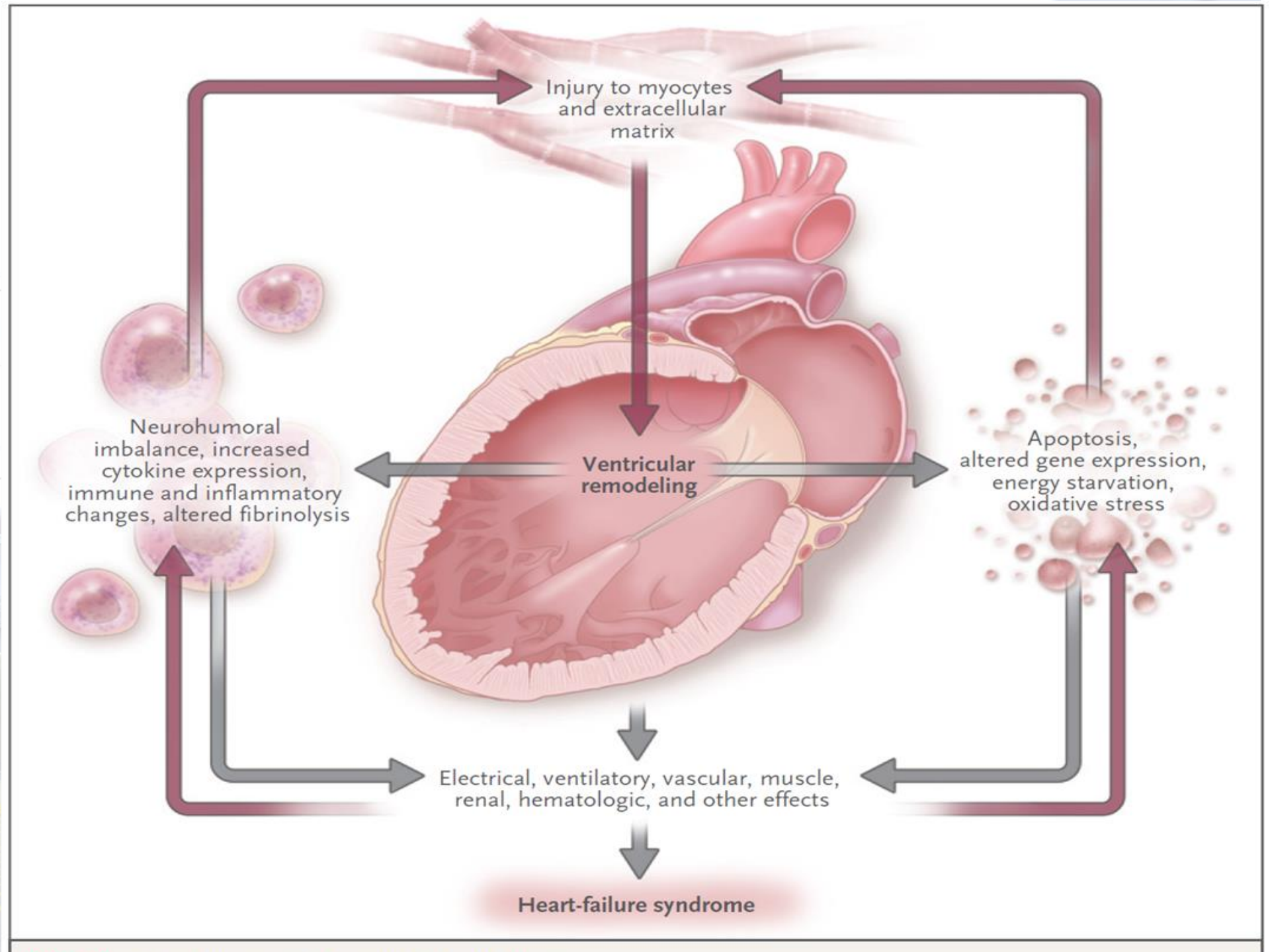
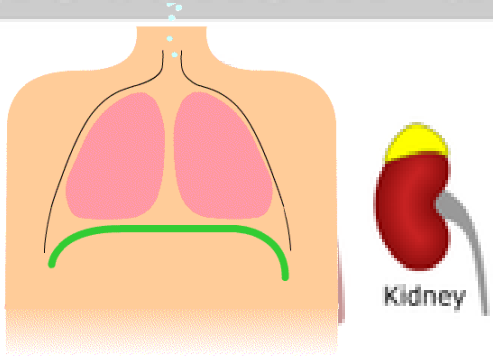

Injury to myocytes and extracellular matrix
Neurohumoral imbalance, increased cytokine expression, immune and inflammatory changes, altered fibrinolysis
Ventricular remodeling
Apoptosis, altered gene expression, energy starvation, oxidative stress
Electrical, ventilatory, vascular, muscle, renal, hematologic, and other effects
Heart-failure syndrome

Renin-angiotensin-aldosterone system



Liver

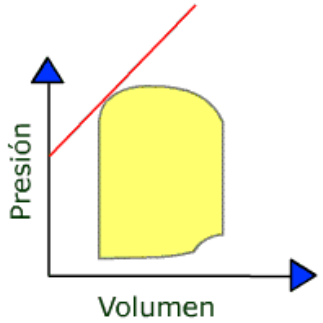
Surface of pulmonary and renal endothelium:
ACE

Angiotensinogen → Angiotensin I → Angiotensin II

Renin

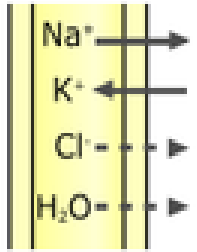
Decrease in renal perfusion (juxtaglomerular apparatus)

Kidney



Sympathetic activity

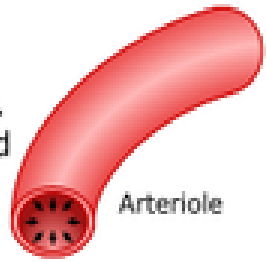
Tubular Na^+ Cl^- reabsorption and K^+ excretion. H_2O retention



Adrenal gland: cortex

Aldosterone secretion

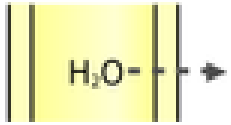
Arteriolar vasoconstriction. Increase in blood pressure



ADH secretion

Pituitary gland: posterior lobe

Collecting duct: H_2O absorption



INHIBIDORES DE LA ALDOSTERONA

ESPIRONOLACTONA ⇌ ALDOSTERONA

Competitive antagonist of the aldosterone receptor (myocardium, arterial walls, kidney)

- Retencion Na^+
- Retencion H_2O

→ **Edema**

- Excrecion K^+
- Excrecion Mg^{2+}

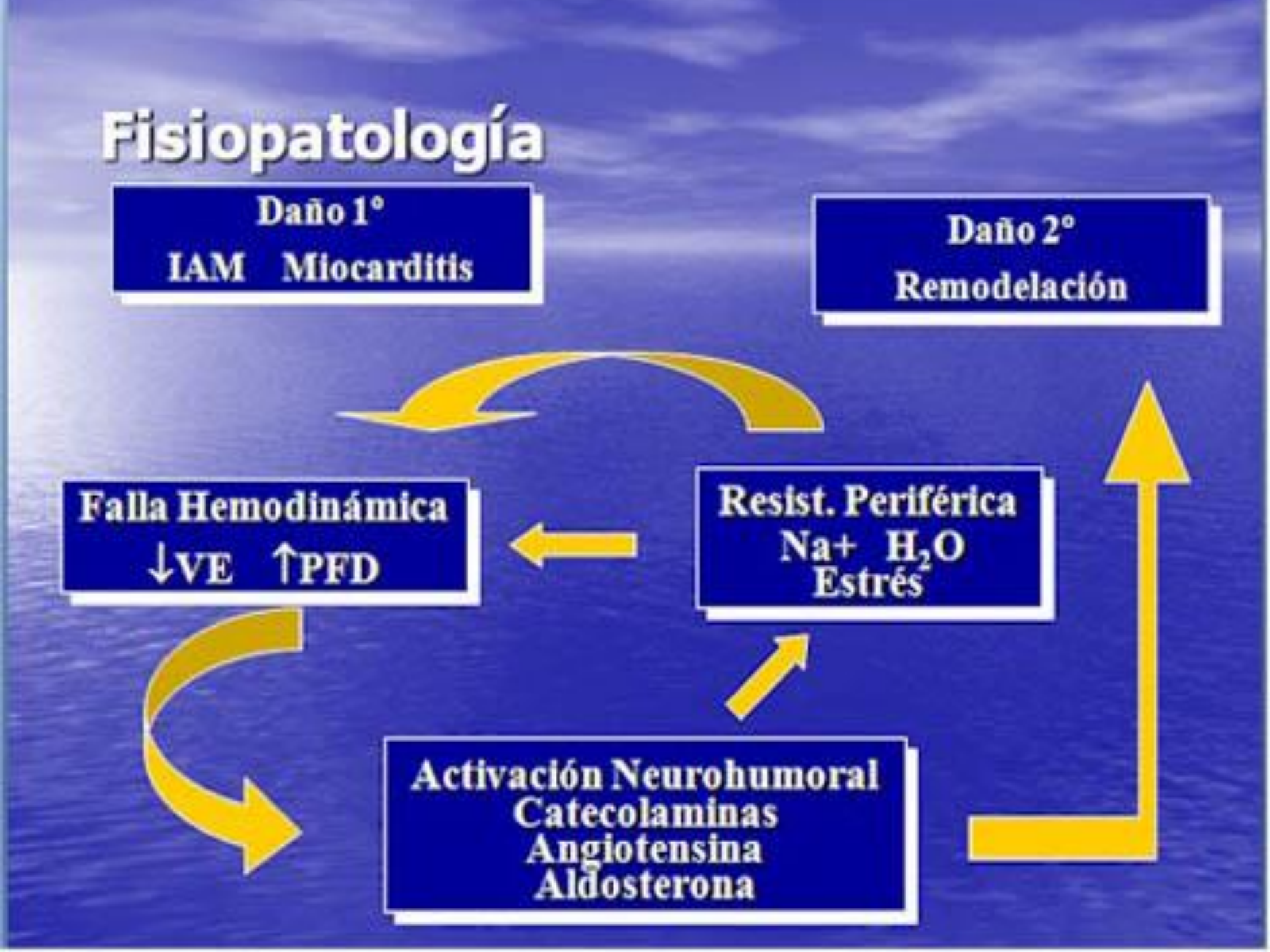
→ **Arritmias**

- Deposito de colageno

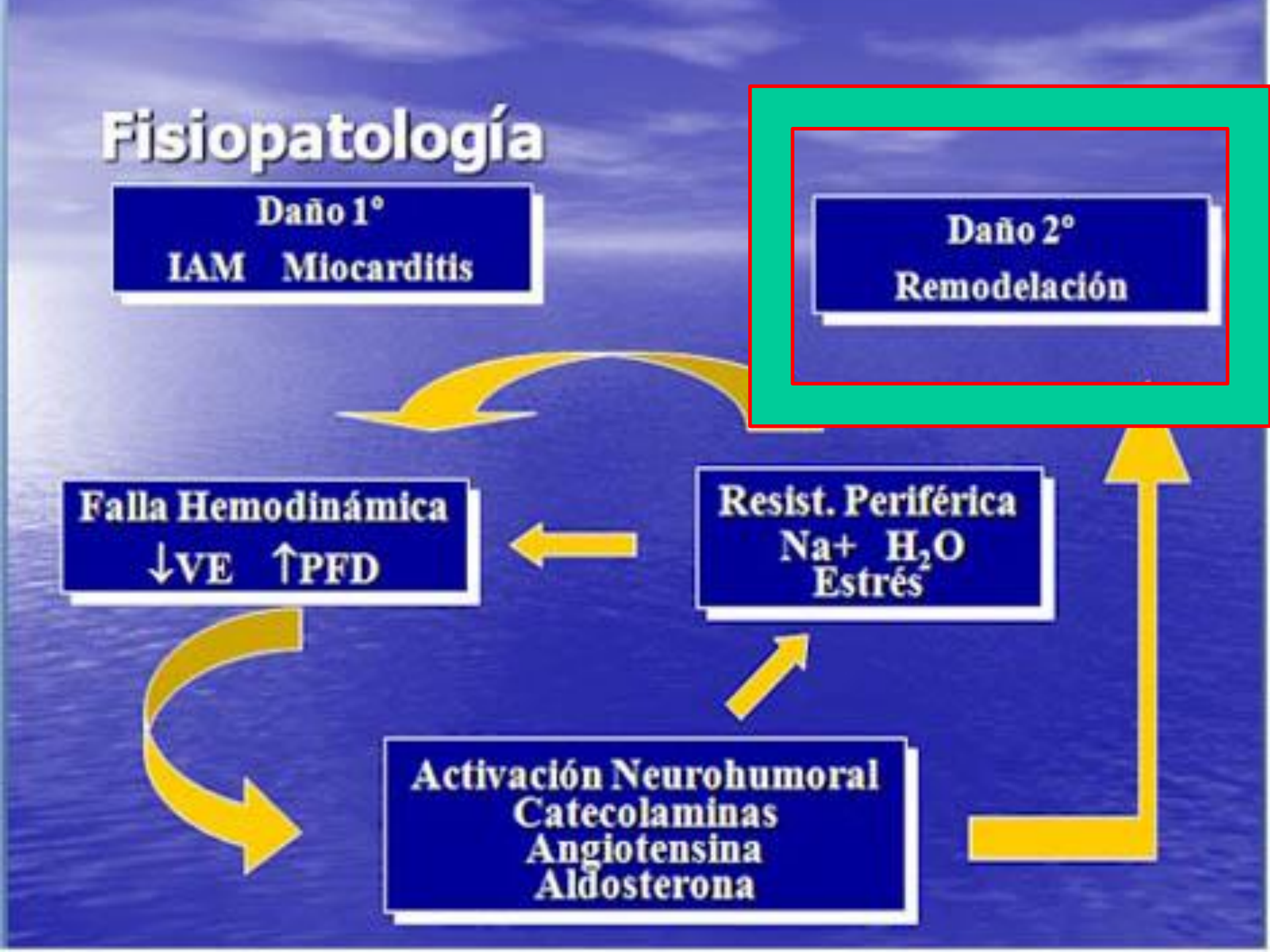
→ **Fibrosis**

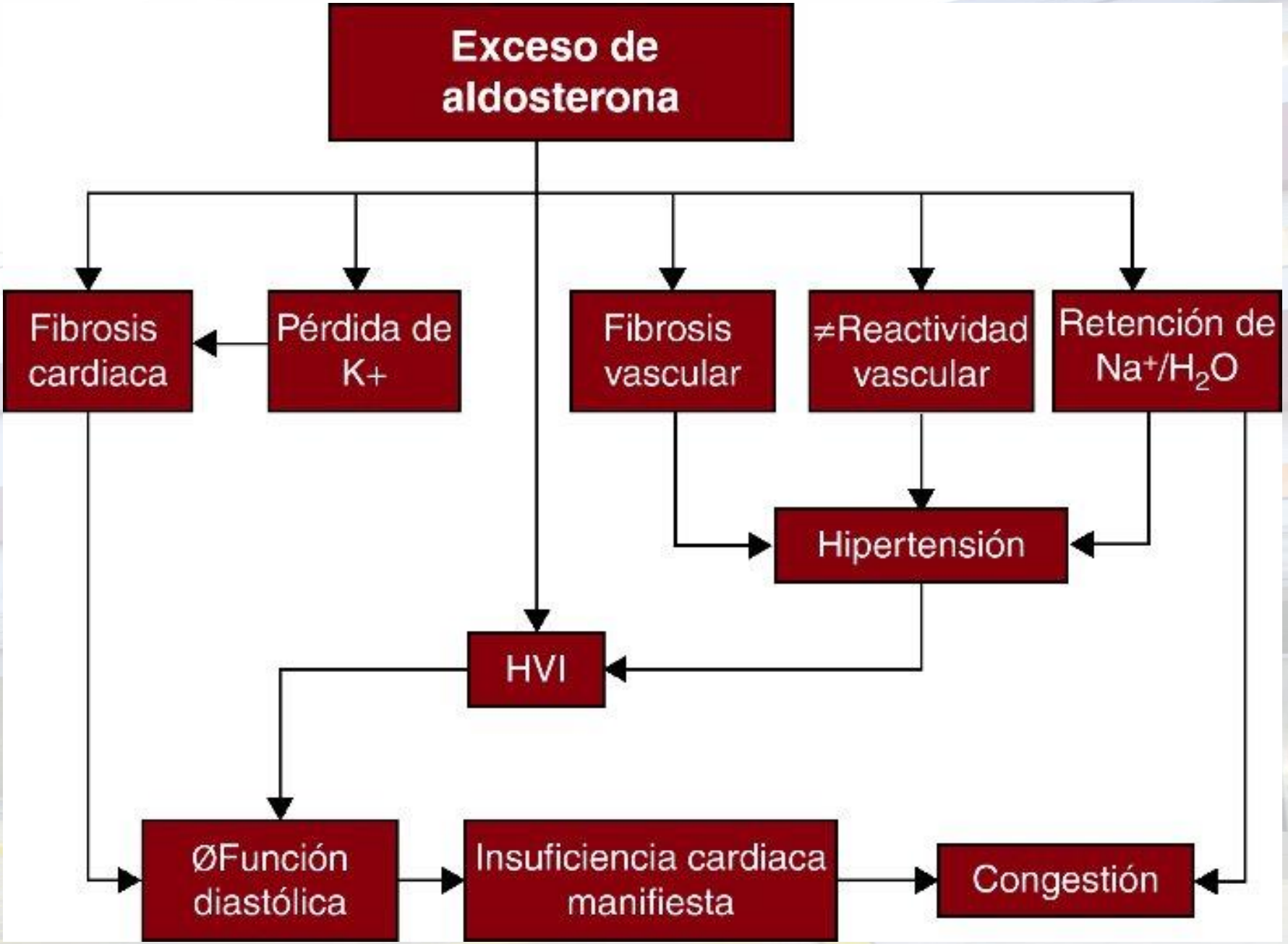
- miocardica
- vascular

Fisiopatología

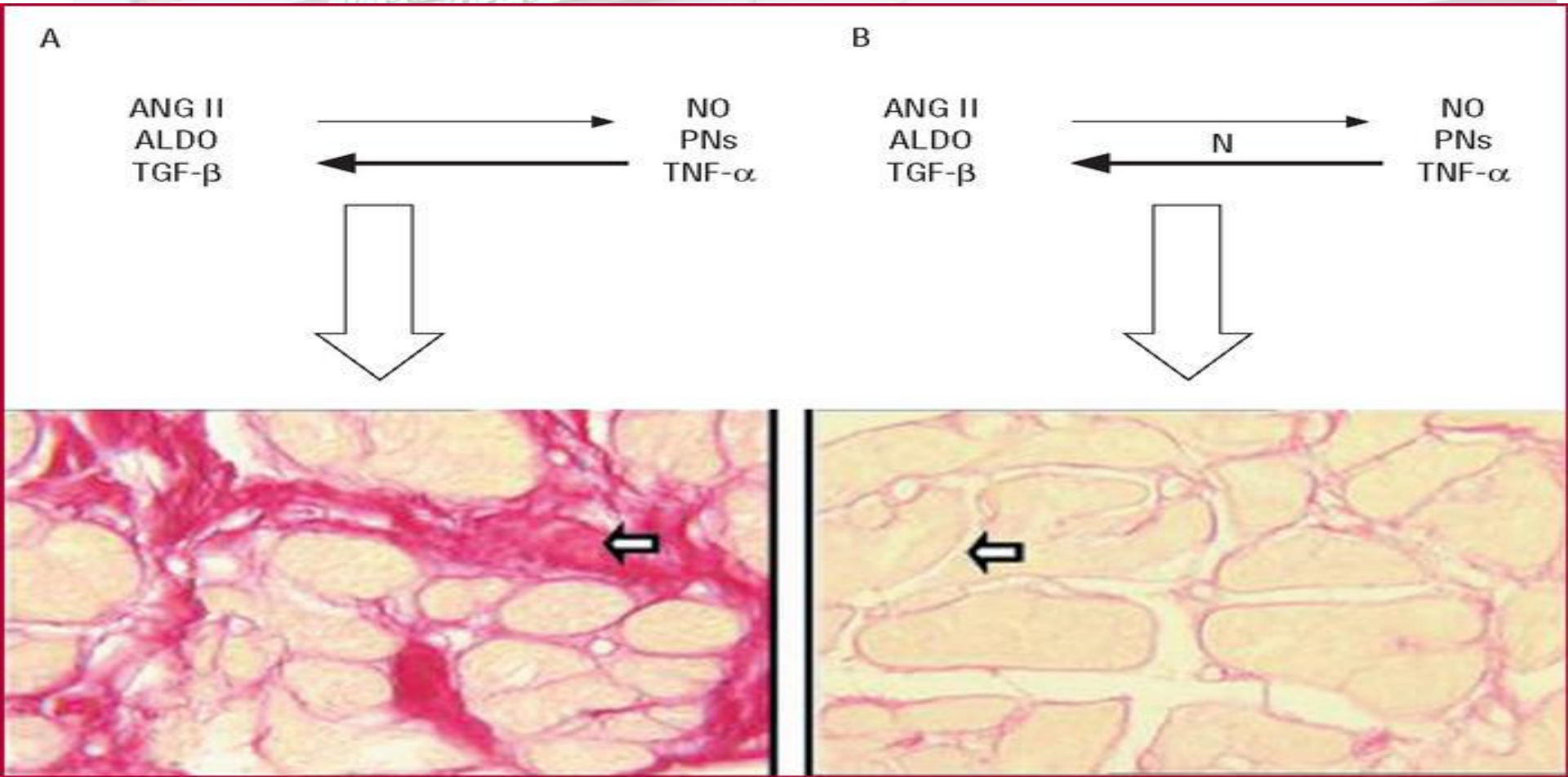


Fisiopatología

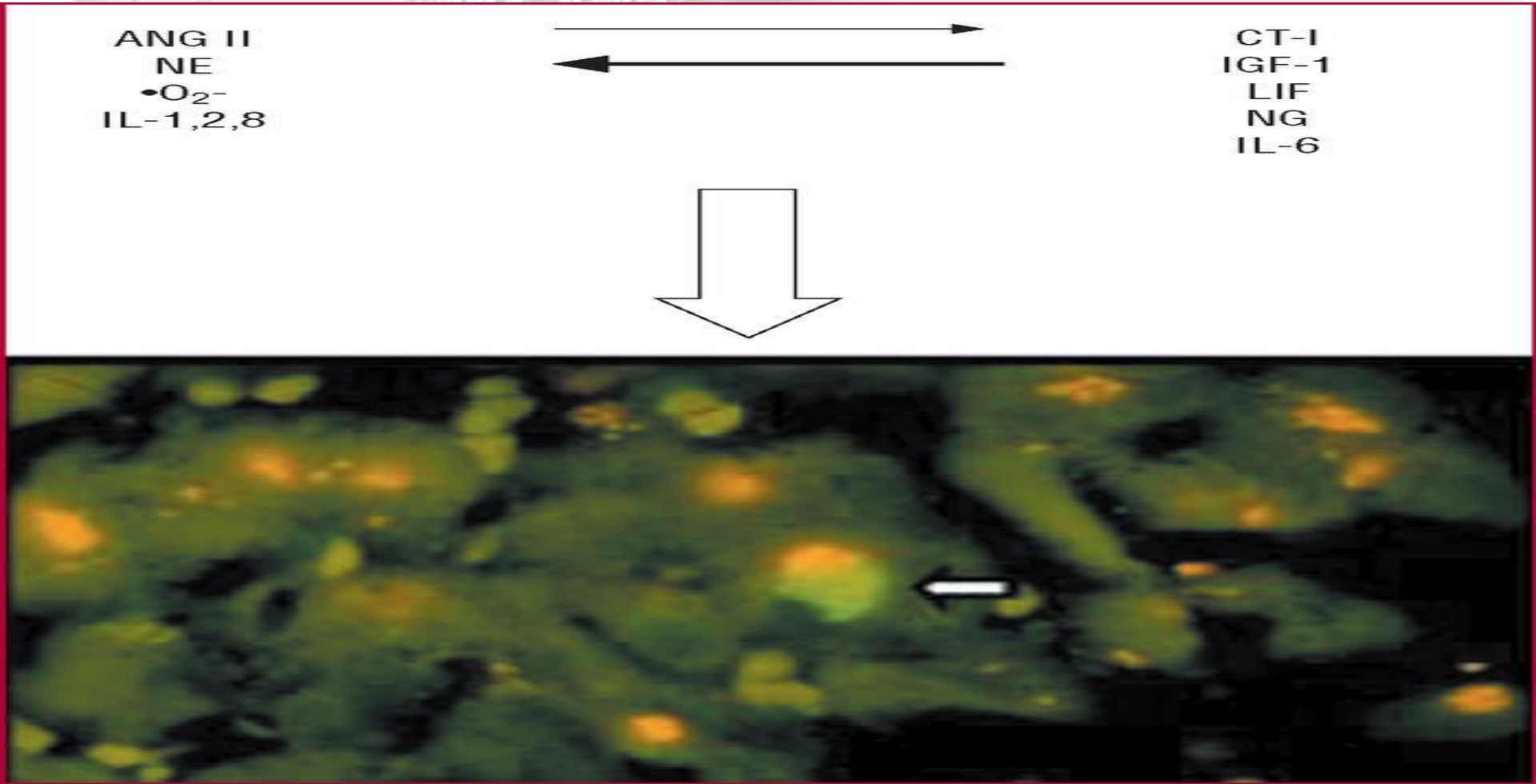


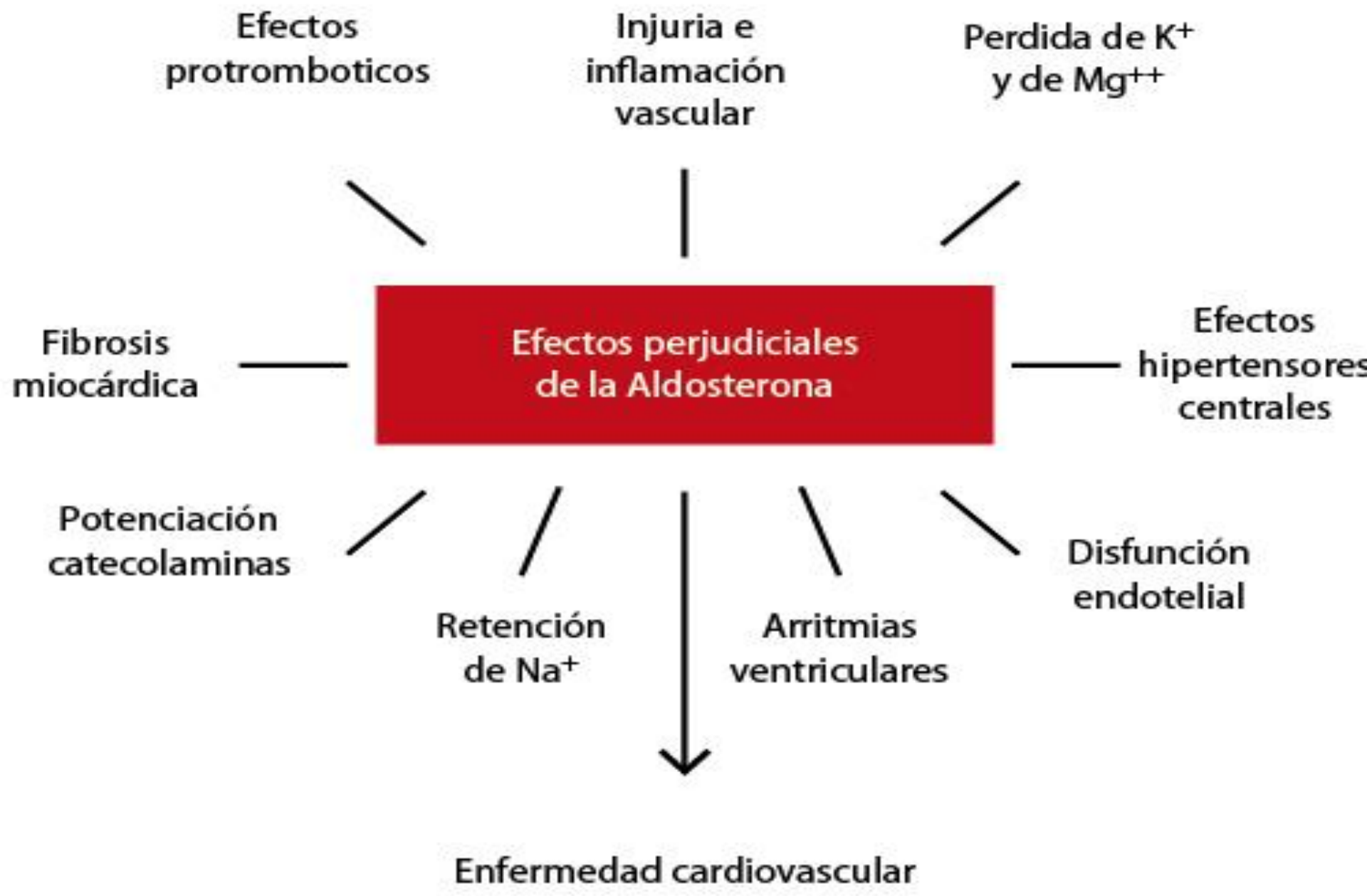

Exceso de aldosterona
Fibrosis cardiaca
Pérdida de K+
Fibrosis vascular
≠Reactividad vascular
Retención de Na^+/H_2O
Hipertensión
HVI
ØFunción diastólica
Insuficiencia cardiaca manifiesta
Congestión

Proliferación colágeno



APOPTOSIS




Efectos protrombóticos
Injuria e inflamación vascular
Perdida de K^+ y de Mg^{++}
Fibrosis miocárdica
Efectos perjudiciales de la Aldosterona
Efectos hipertensores centrales
Potenciación catecolaminas
Retención de Na^+
Arritmias ventriculares
Disfunción endotelial
Enfermedad cardiovascular

Interacciones crónicas Corazón - Riñón

Síndrome Cardiorrenal Crónico

IRC grado I-II
Tabaco, Obesidad HTA, DLP Inflamación crónica

IRC grado III-IV
Anemia, Tox. Urémicas Alt Ca y P Estado nutricional Sobrecarga H2O y Na Inflamación crónica

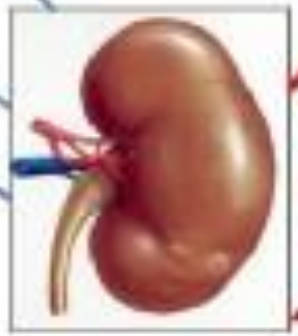
IRC grado V
Anemia, Malnutrición Alt Ca y P Calcif Tejidos Blandos, Sobrecarga H2O y Na, Resist Eritropoyetina Tox. Urémicas

Susceptibilidad
Factores genéticos, Factores de riesgo adquiridos, Bajo gasto cardiaco

Daño Renal
Bajo gasto Cardiaco, Inflamación subclínica Disfunción endotelial, Arterioesclerosis

Progresión del Daño Renal
Hipoperfusión crónica, aumento de las Resist Vasculares, Aumento de la PV
Embolismo

Hipoperfusión
Apoptosis



Síndrome Renal-Cardiaco Cronico

Periostinas e Integrinas

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Periostina y falla cardíaca

Periostina and Myocardial Repair, Regeneration, and Recovery

Gerald W. Dorn, II, M.D.
Center for Molecular Cardiovascular Research, University of Cincinnati, Cincinnati, USA.

N Engl J Med. 2007 Oct 11;357(15):1552-4

rafael.porcile@uaisalud.com.ar

La periostina normalmente es secretada por los fibroblastos cardíacos en respuesta a lesión del miocardio, y obra recíprocamente con los receptores de la integrina en las células diana para modular la remodelación celular de la matriz del corazón

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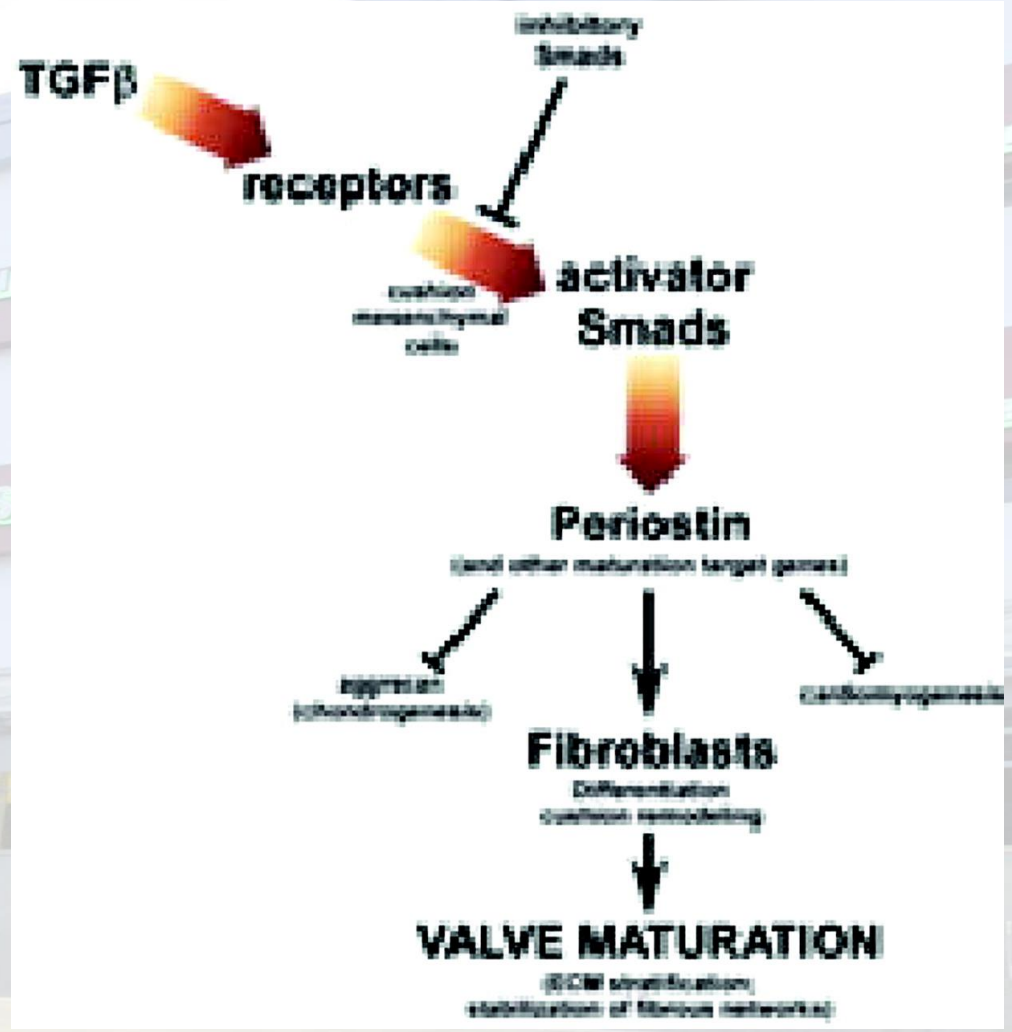
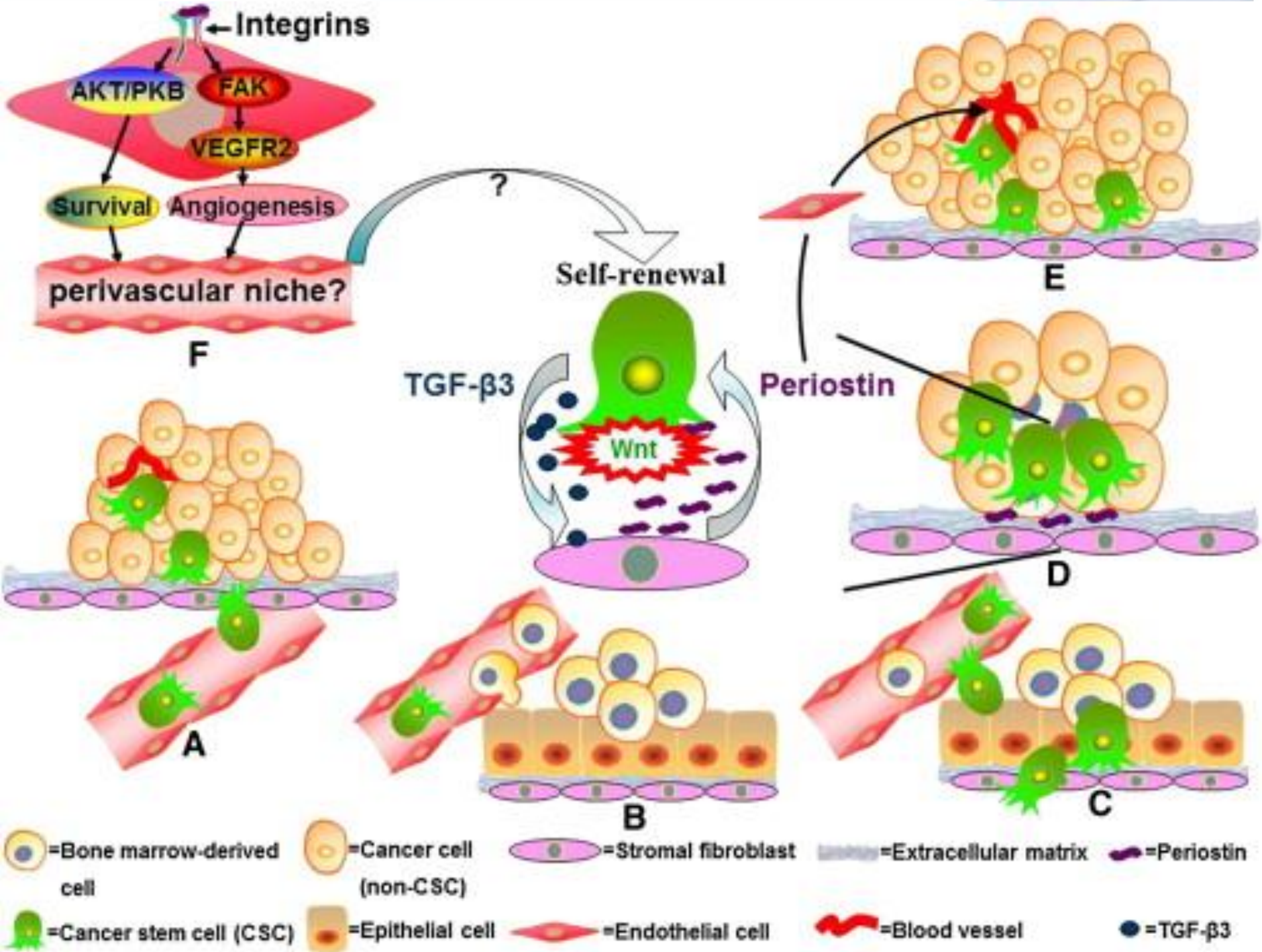
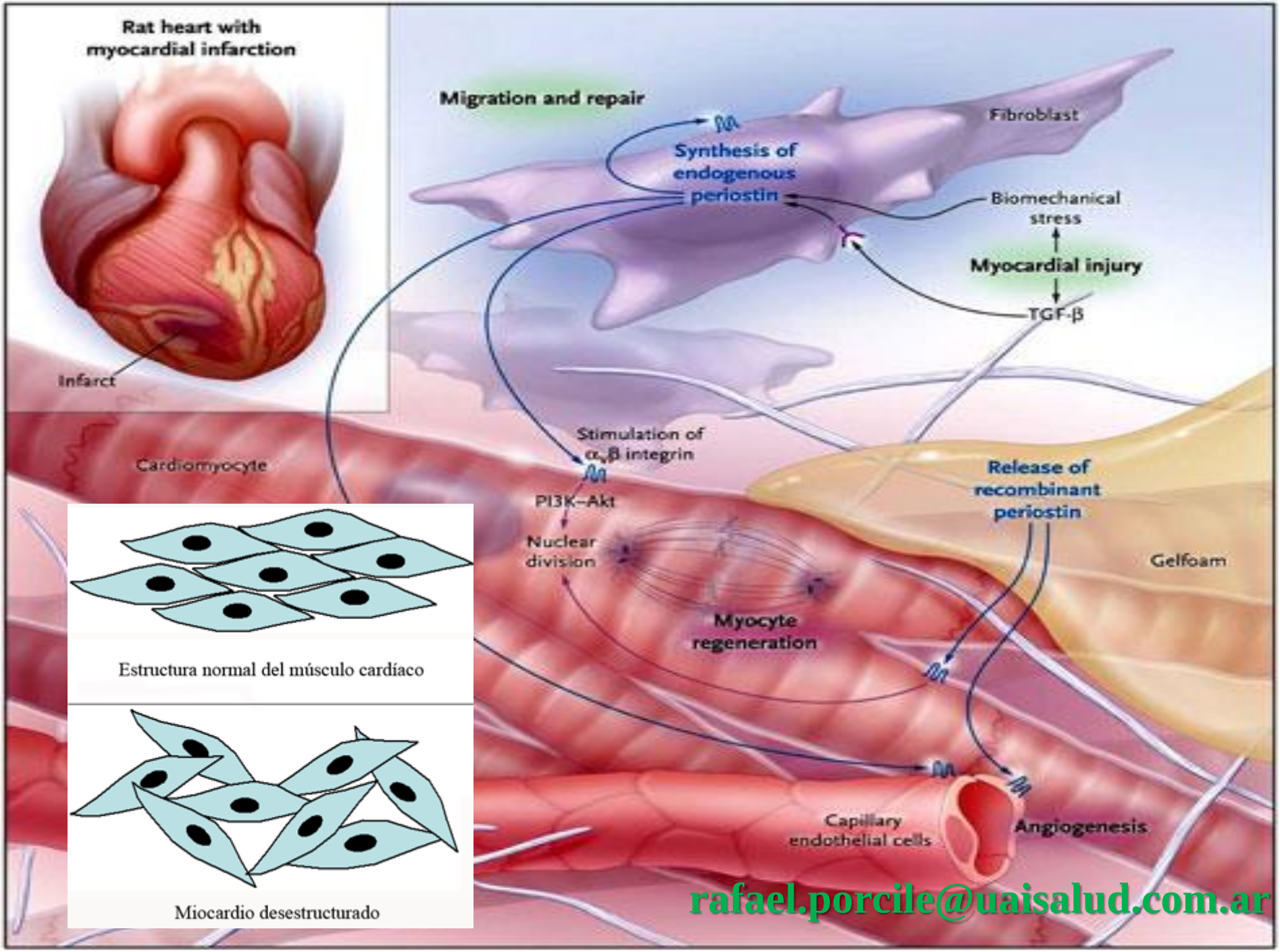
Figure 8. Diagram of the proposed function of periostin.



Snider P et al. Circulation Research. 2008;102:752-760


Integrins
AKT/PKB
FAK
VEGFR2
Survival
Angiogenesis
perivascular niche?
F
?
Self-renewal
TGF-β3
Wnt
Periostin
E
D
A
B
C
=Bone marrow-derived cell
=Cancer cell (non-CSC)
=Stromal fibroblast
=Extracellular matrix
=Periostin
=Cancer stem cell (CSC)
=Epithelial cell
=Endothelial cell
=Blood vessel
=TGF-β3



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Left ventricular periostin gene expression is associated with fibrogenesis in experimental renal insufficiency.

Nephrol Dial Transplant. 2012 Jan;27(1):115-22. doi: 10.1093/ndt/gfr279. Epub 2011 Jun 28.

Periostin is involved in fibrotic cardiac remodelling in CRI. The re-expression of periostin is localized to the fibrotic and inflammatory lesions and is most likely the consequence of elevated BP.

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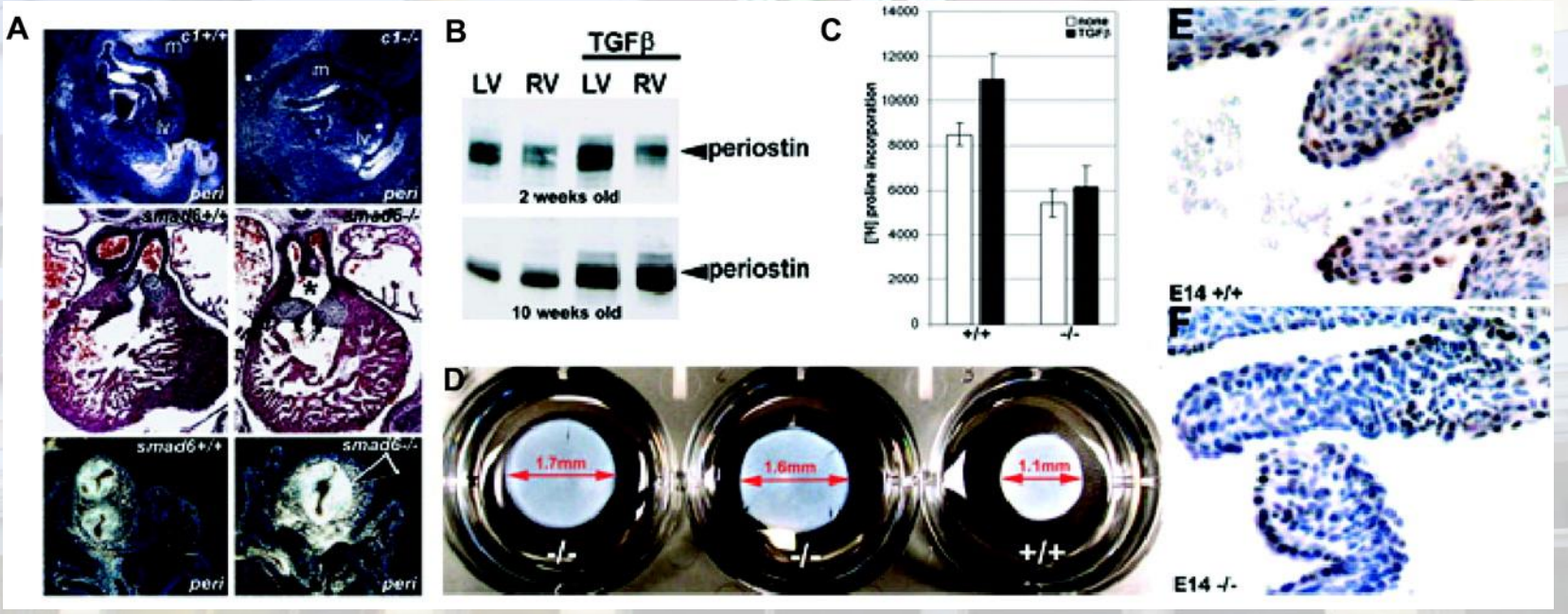
Figure 6. Periostin is responsive to TGFβ but can also mediate TGFβ responsiveness.



Snider P et al. Circulation Research. 2008;102:752-760

Integrinas.

Integrinas. Se trata de receptores glucoproteicos compuestos por dos subunidades, denominadas cadenas a y b. Como su nombre lo sugiere, facilitan la *integración* celular al medio circundante mediante la adhesión de diferentes células entre sí, y entre células y la matriz extracelular, pudiendo generar diversas señales intracelulares.

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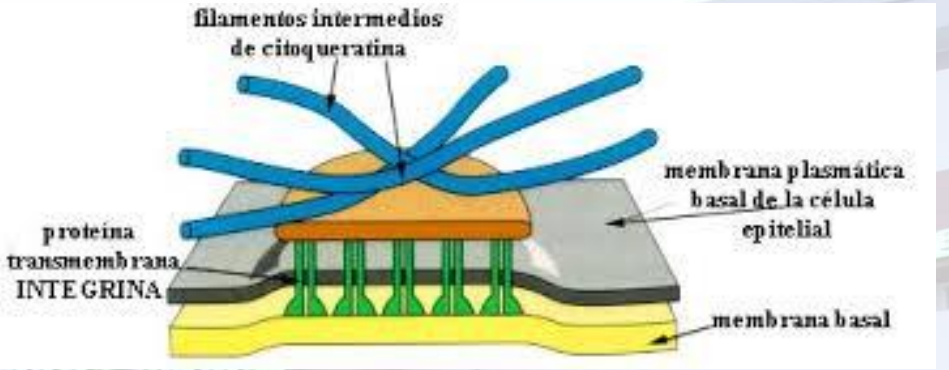
¿Que son las integrinas?

- Las integrinas son una superfamilia de proteínas integrales de membrana compuestas de cadenas de polipéptido que abrazan toda la membrana, posee una cadena α/ β unidas mediante enlaces no covalentes.

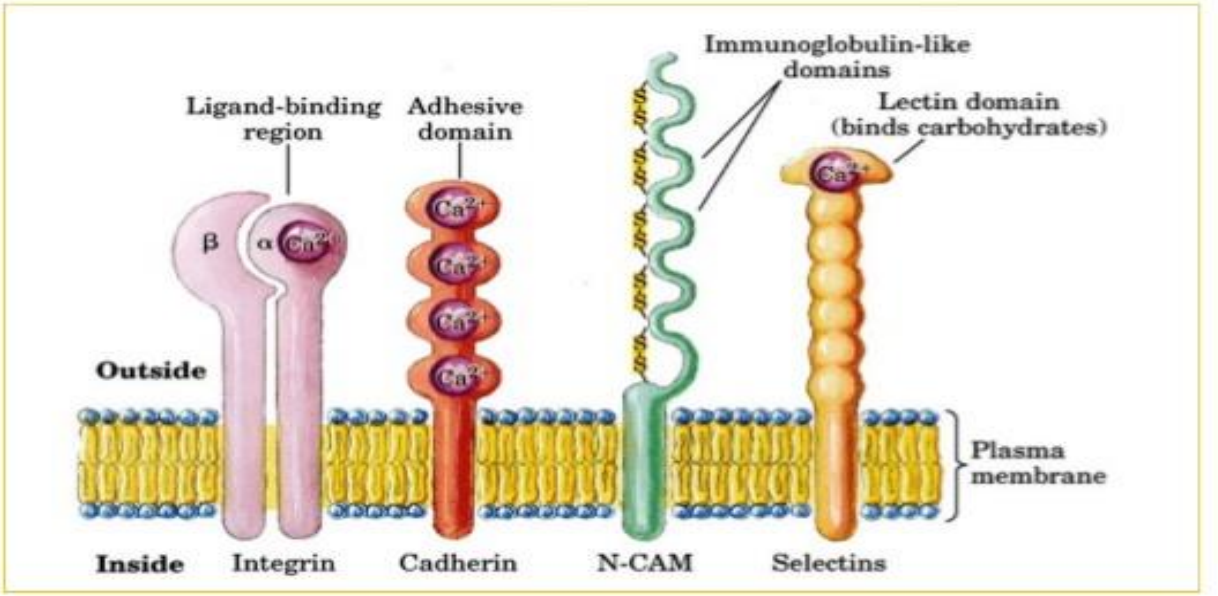
- Se conocen:
- La subunidad α 15 variables diferentes
- La subunidad β 8 variables diferentes

Ambas cadenas se combinan y crean 20 integrinas diferentes

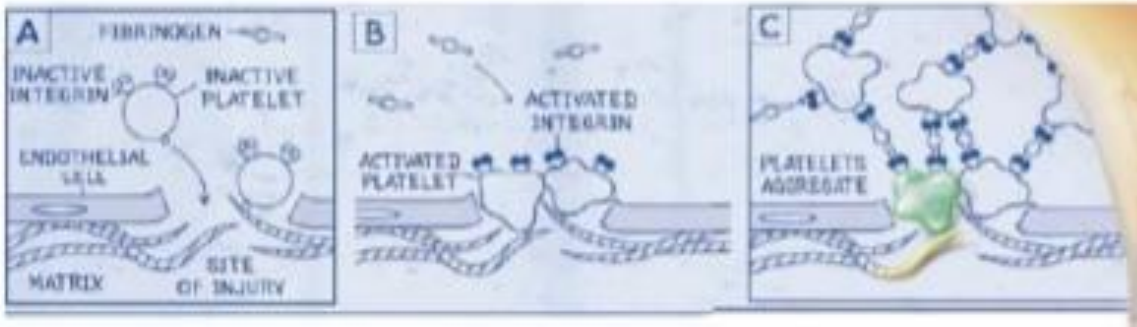
- Fundamentalmente son receptores de membrana, por la cara citoplasmática conectan con la trama superficial del *citoesqueleto*, concretamente con *actinas*. Por la cara externa conectan con proteínas como colágeno, *laminina* y *fibronectina*.

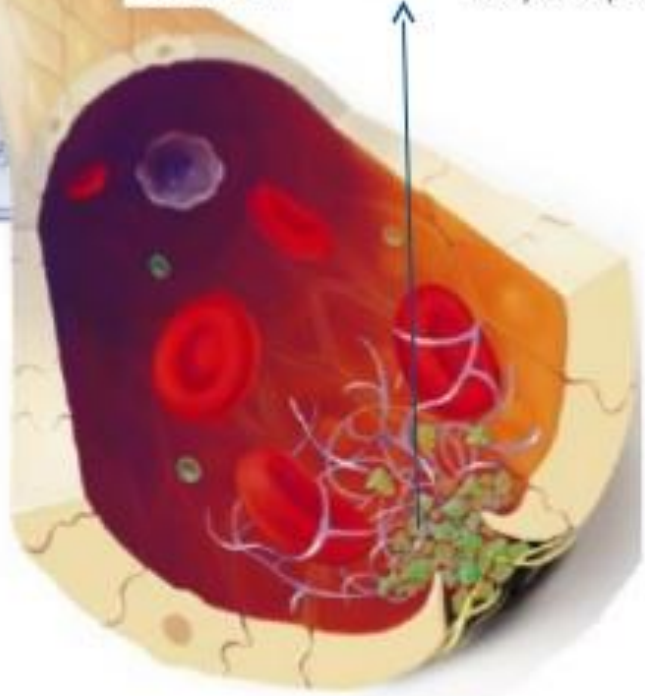


Las CAMs mas conocidas son:



Proceso de Coagulación

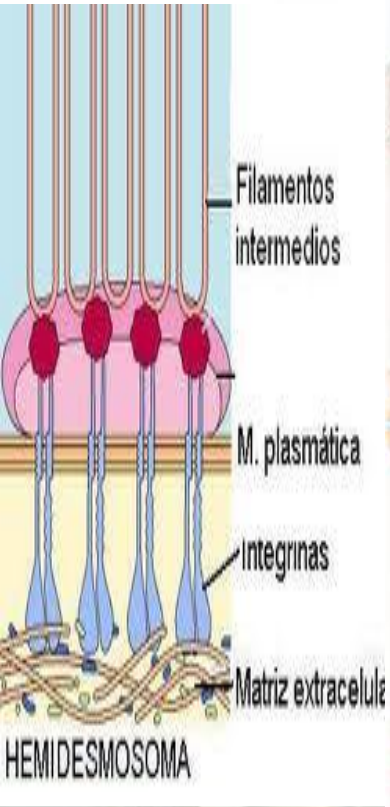




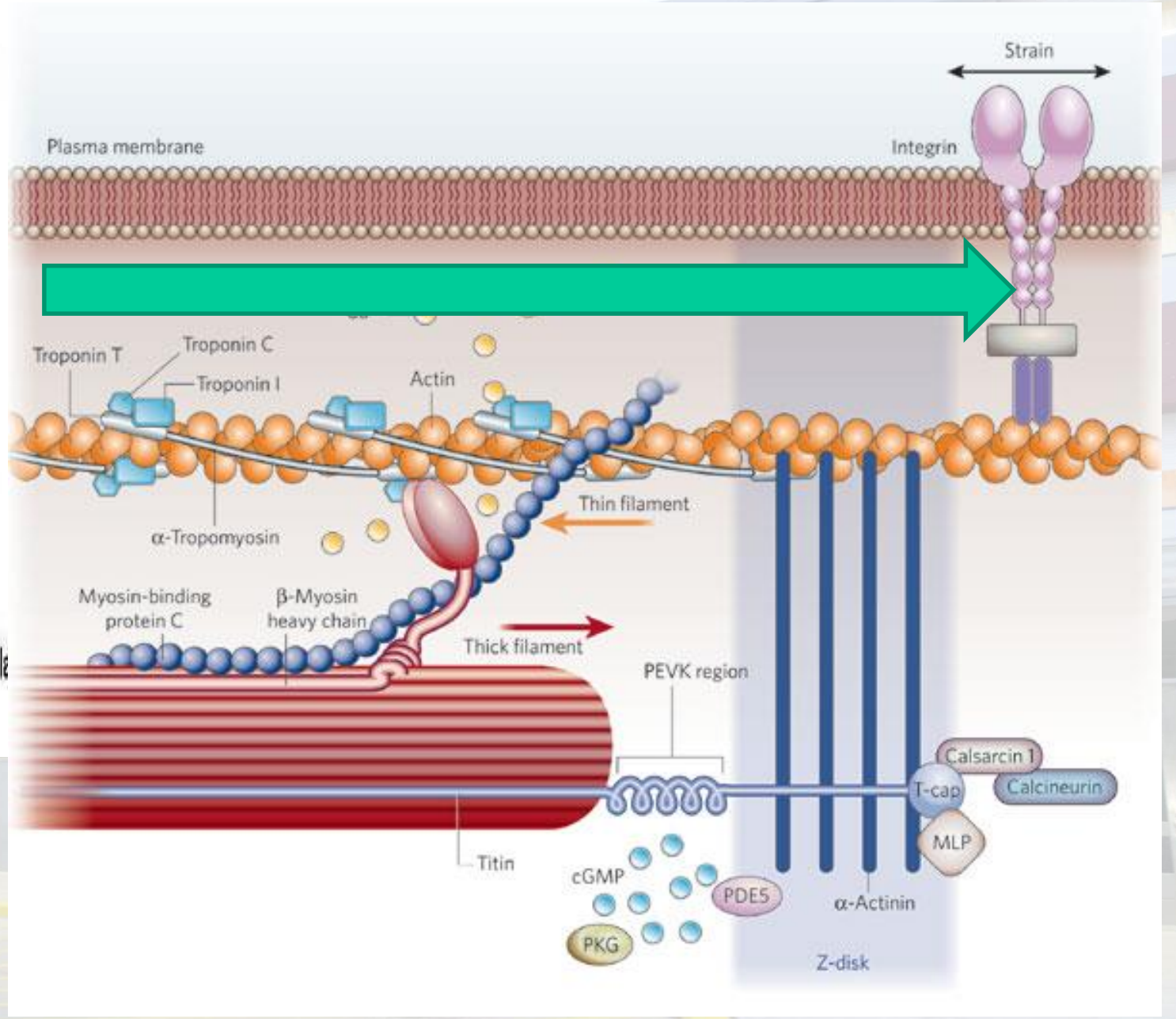
a) Se agregan plaquetas y se adhieren a la matriz epitelial del vaso sanguíneo.

b) El anclaje activa a la integrina αIIbβ3 que estaba inactiva

c) Esta activación provoca la unión de proteínas como el fibrinógeno, que tienden puentes con otras plaquetas. Se teje una red de células y fibras, para taponar la lesión e impedir una hemorragia.



HEMIDESMOSOMA



Temporal response and localization of integrins beta1 and beta3 in the heart after myocardial infarction: regulation by cytokines.

Sun M, Opavsky MA, Stewart DJ, et al. *Circulation.* 2003; 107: 1046-52.

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el proceso de remodelación secundario al infarto agudo del miocardio se halla estrechamente vinculado a la expresión de integrinas diferentes de las existentes en el tejido no injuriado, y que dicha variación condiciona en forma crítica los procesos de cicatrización, vascularización y muerte celular, con profundas consecuencias funcionales para el órgano dañado

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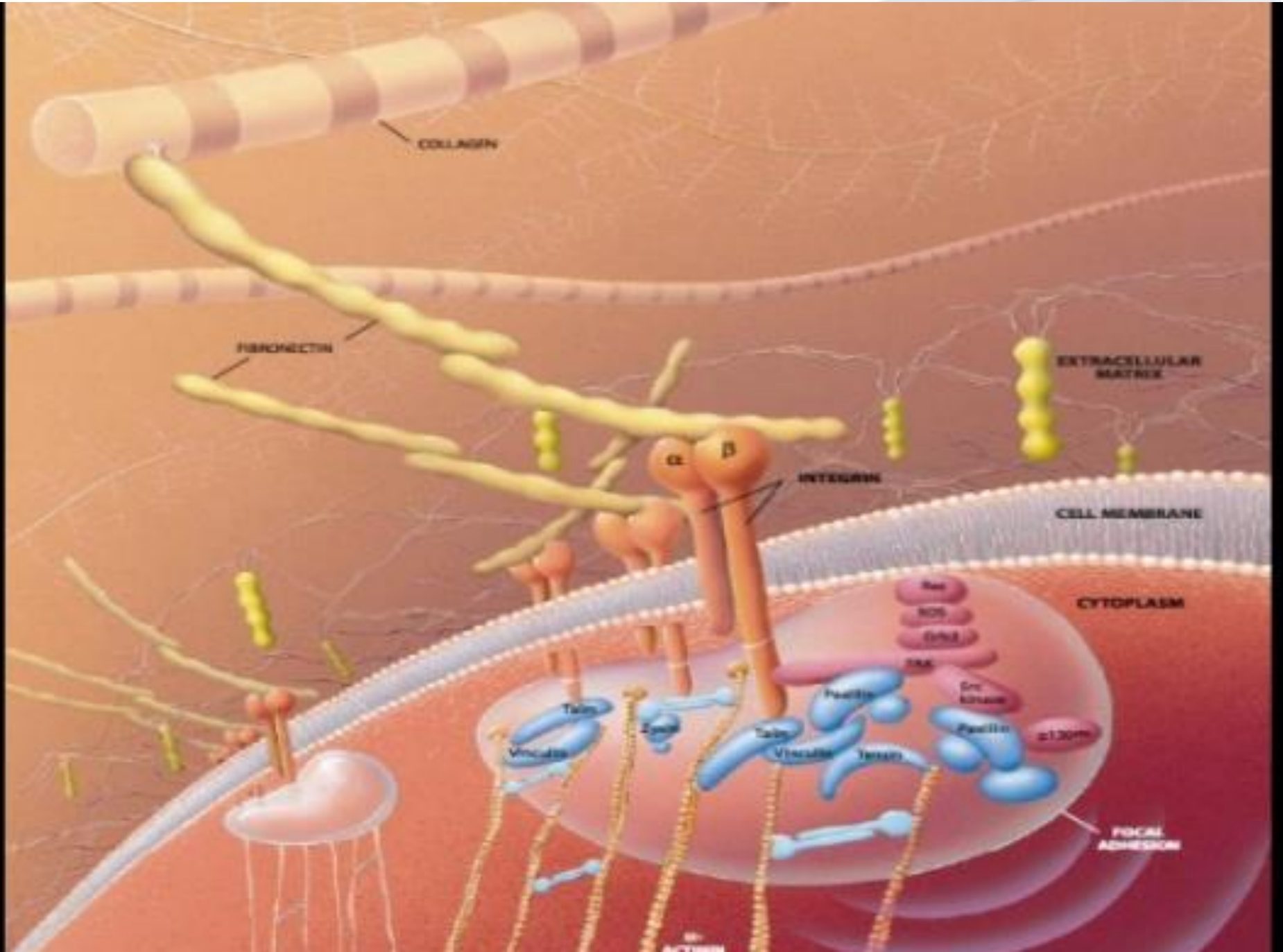
COLLAGEN
FIBRONECTIN
EXTRACELLULAR MATRIX
α
β
INTEGRIN
CELL MEMBRANE
CYTOPLASM
Talin
Vinculin
Talin
Vinculin
Tensin
FOCAL ADHESION

Integrin expression during reverse remodeling in the myocardium of heart failure patients

Cardiovasc Pathol. 2012 Jul-Aug;21(4):291-8. doi: 10.1016/j.carpath.2011.09.009. Epub 2011 Nov 18

These integrins are important for maintaining the architecture of the myocardial tissue and the mechanotransduction in the heart. Heart failure leads to various alterations in the myocardium, such as changes in morphology, and in expression of mRNAs, miRNAs, and proteins

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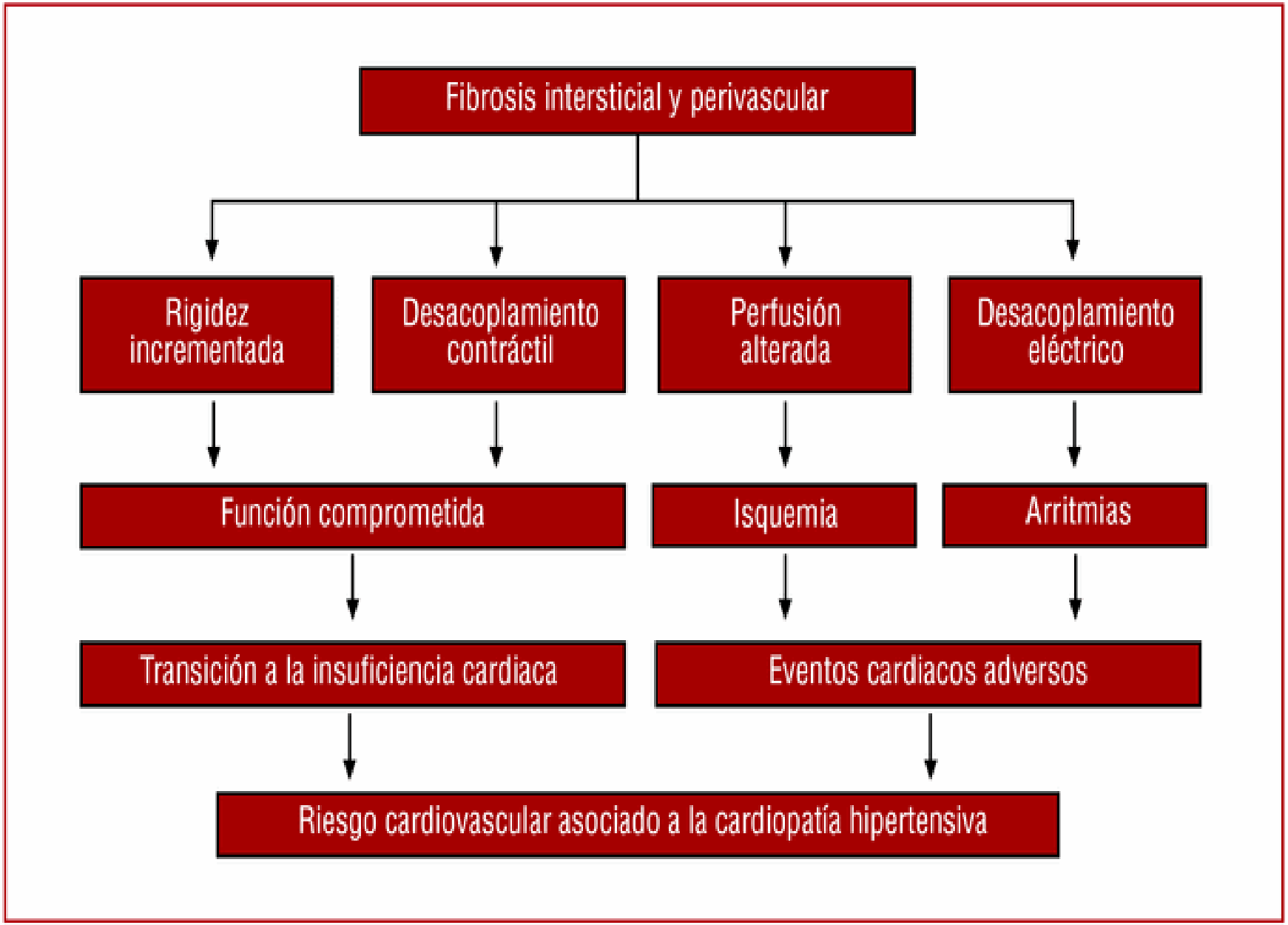

Fibrosis intersticial y perivascular
Rigidez incrementada
Desacoplamiento contráctil
Perfusión alterada
Desacoplamiento eléctrico
Función comprometida
Isquemia
Arritmias
Transición a la insuficiencia cardiaca
Eventos cardiacos adversos
Riesgo cardiovascular asociado a la cardiopatía hipertensiva

Sobrecarga crónica de volumen (I)

distensión mecánica de fibras miocárdicas

↳ cambios estructurales macro/microsc.

↳ ↓ conexiones celulares & fibrosis

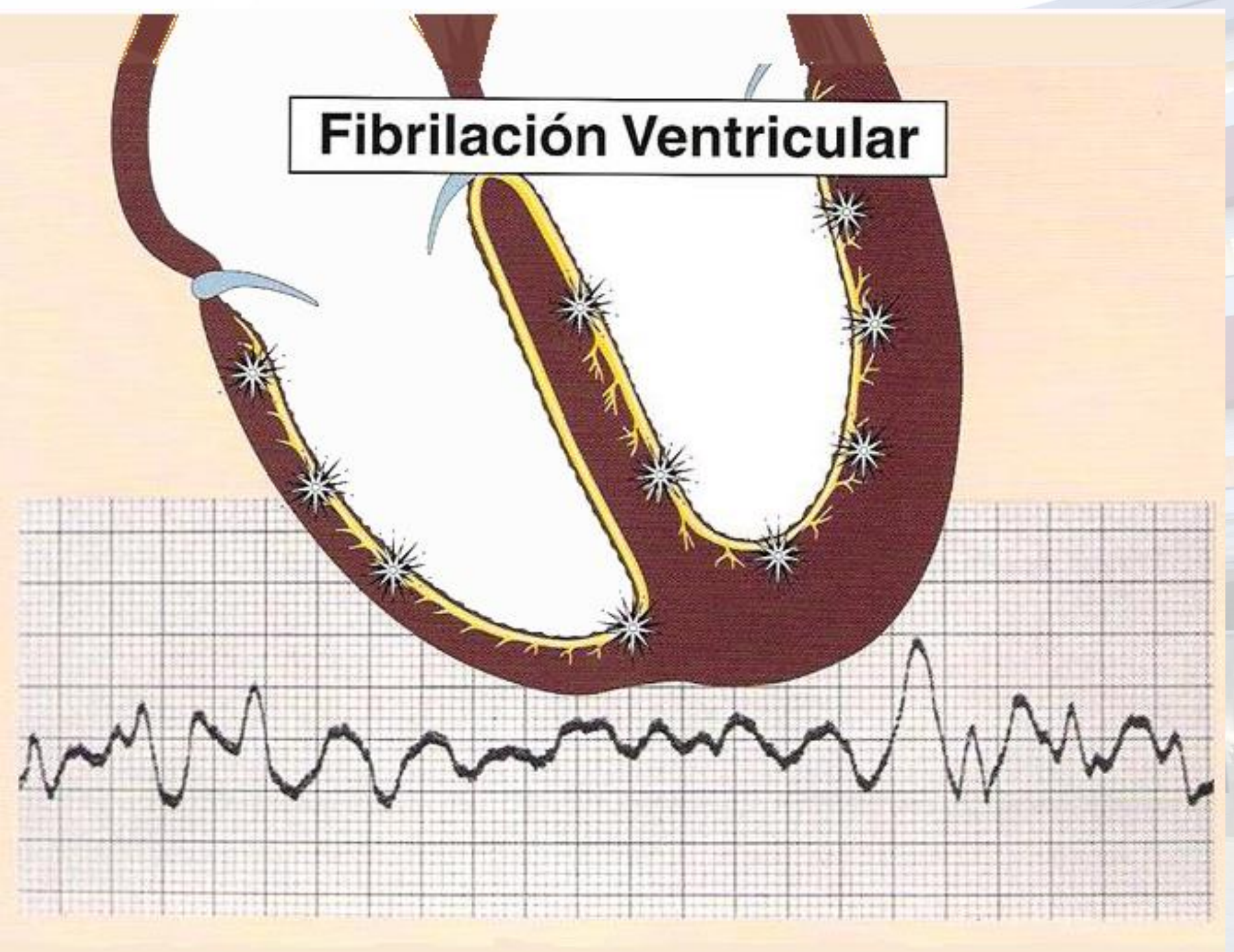
↳ ondas electr. no uniformes

↳ **REENTRADA**

↑ automatismo de fibras de Purkinje
automatismo anormal & "triggered activity"

Janse MJ Acta Cardiol 1992; 47: 93
Lab MJ. Circ Res 1978; 42: 519

AMB990313


Fibrilación Ventricular

FISIOPATOLOGIA

MUERTE SUBITA

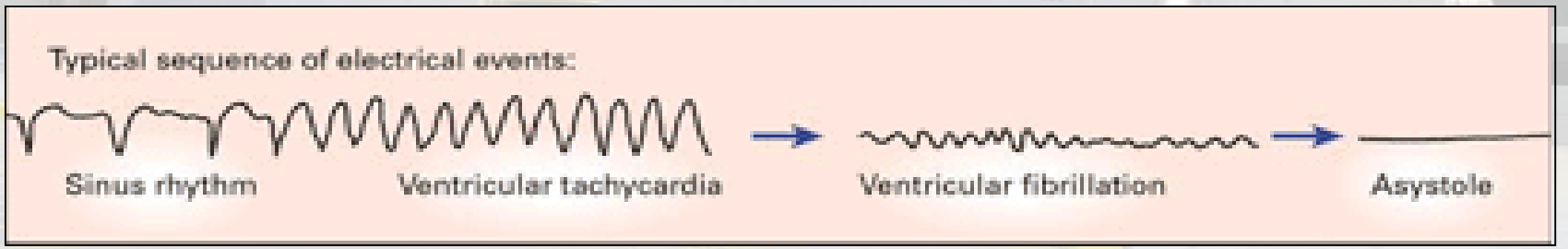
Cardiopatia subyacente (90 %)

+

Miocardio vulnerable(eléctricamente inestable)

+

Gatillo : isquemia,
trastornos hidroelectrolíticos,
trastornos EAB
drogas, fármacos, alcohol
catecolaminas,disautonomías



El Primer tratamiento para prevenir la muerte súbita no es el tratamiento para previenir de la muerte súbita

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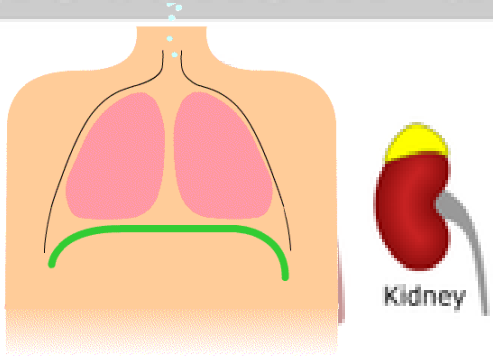
Renin-angiotensin-aldosterone system



Liver

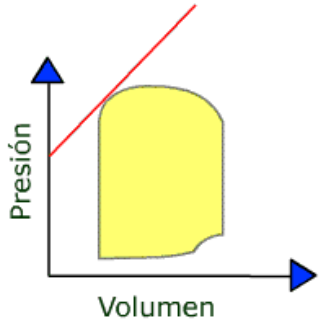
Surface of pulmonary and renal endothelium:
ACE

Angiotensinogen → Angiotensin I → Angiotensin II

Renin

Decrease in renal perfusion (juxtaglomerular apparatus)

Kidney



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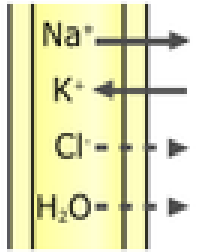
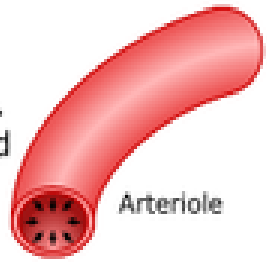


Adrenal gland: cortex

Aldosterone secretion

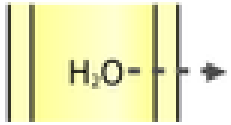
Arteriolar vasoconstriction. Increase in blood pressure



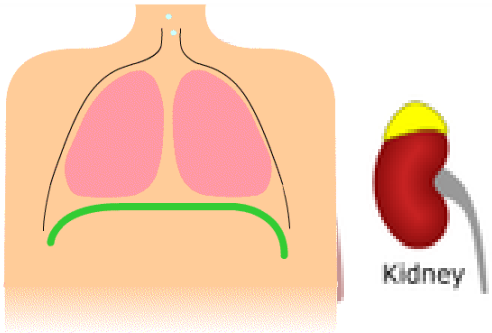
ADH secretion

Pituitary gland: posterior lobe

Collecting duct: H_2O absorption



Renin-angiotensin-aldosterone system



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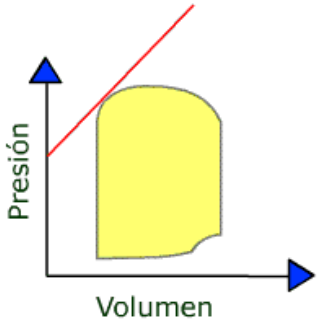
Decrease in renal perfusion (juxtaglomerular apparatus)

Kidney



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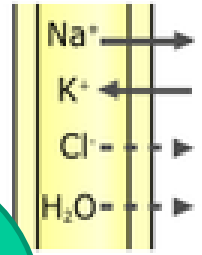

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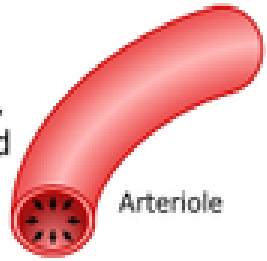

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ADH secretion

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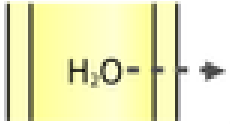


RALES 11% REDUCCIÓN MORTALIDAD

RALES: Randomized Aldactone Evaluation Study
- RESULTS continued -

Adverse events

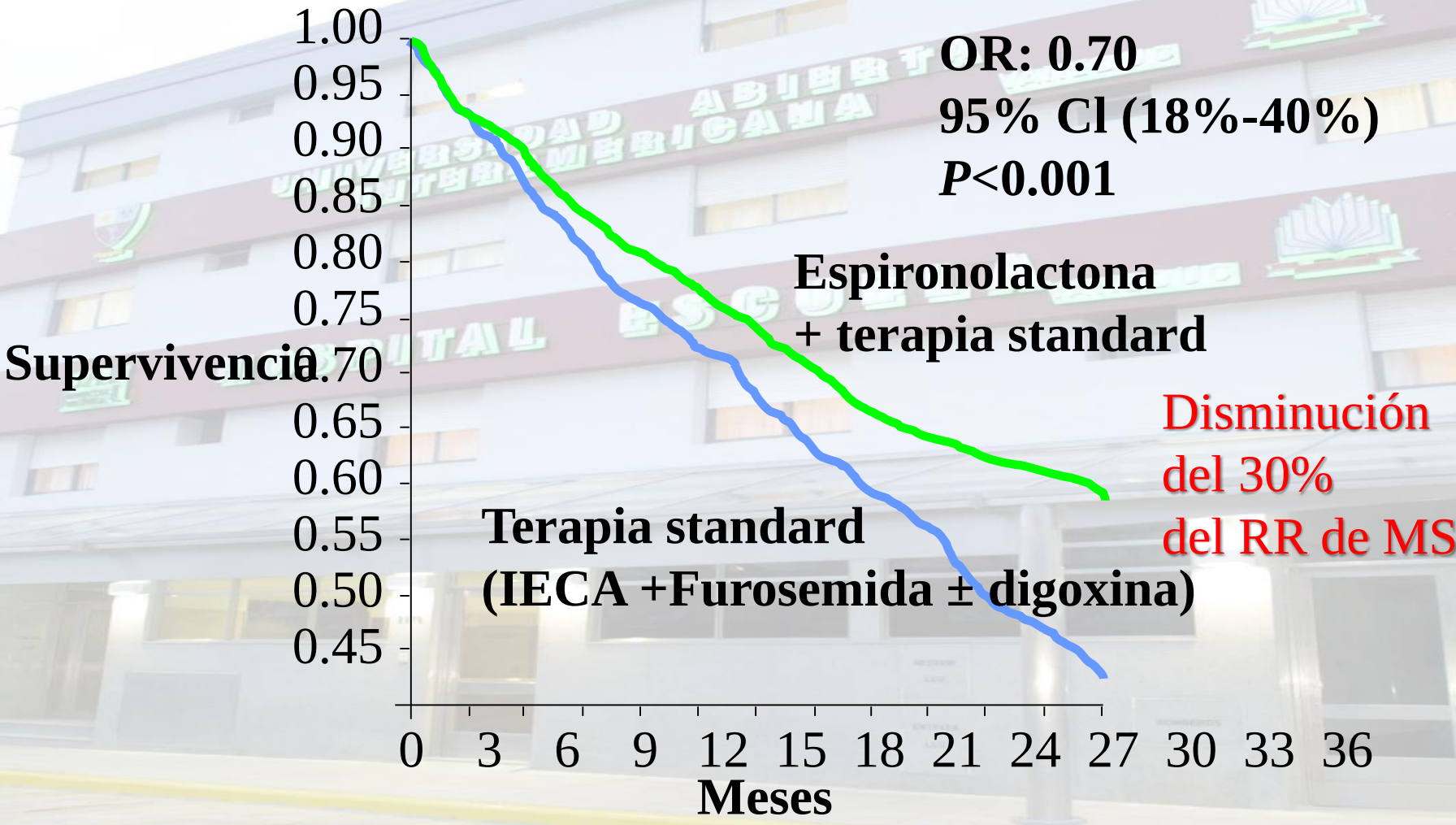
	Placebo n=841 No. (%)	Spironolactone n=822 No. (%)	P
Discontinuation because of adverse event	40 (5)	62 (8)	
Cardiovascular disorders	251 (30)	248 (30)	
Angina	83 (10)	103 (13)	
Heart failure	80 (10)	52 (6)	
Endocrine disorders*			
Gynecomastia in men	8 (1)	55 (9)	<0.001
Breast pain in men	1 (0.1)	10 (2)	0.006

*614 men in placebo group; 603 in spironolactone group.

Pitt et al. *N Eng J Med* 1999; **341**: 709–17.

InCirculation.net

RALES



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El Primer tratamiento para prevenir la muerte súbita no es el tratamiento de la muerte súbita

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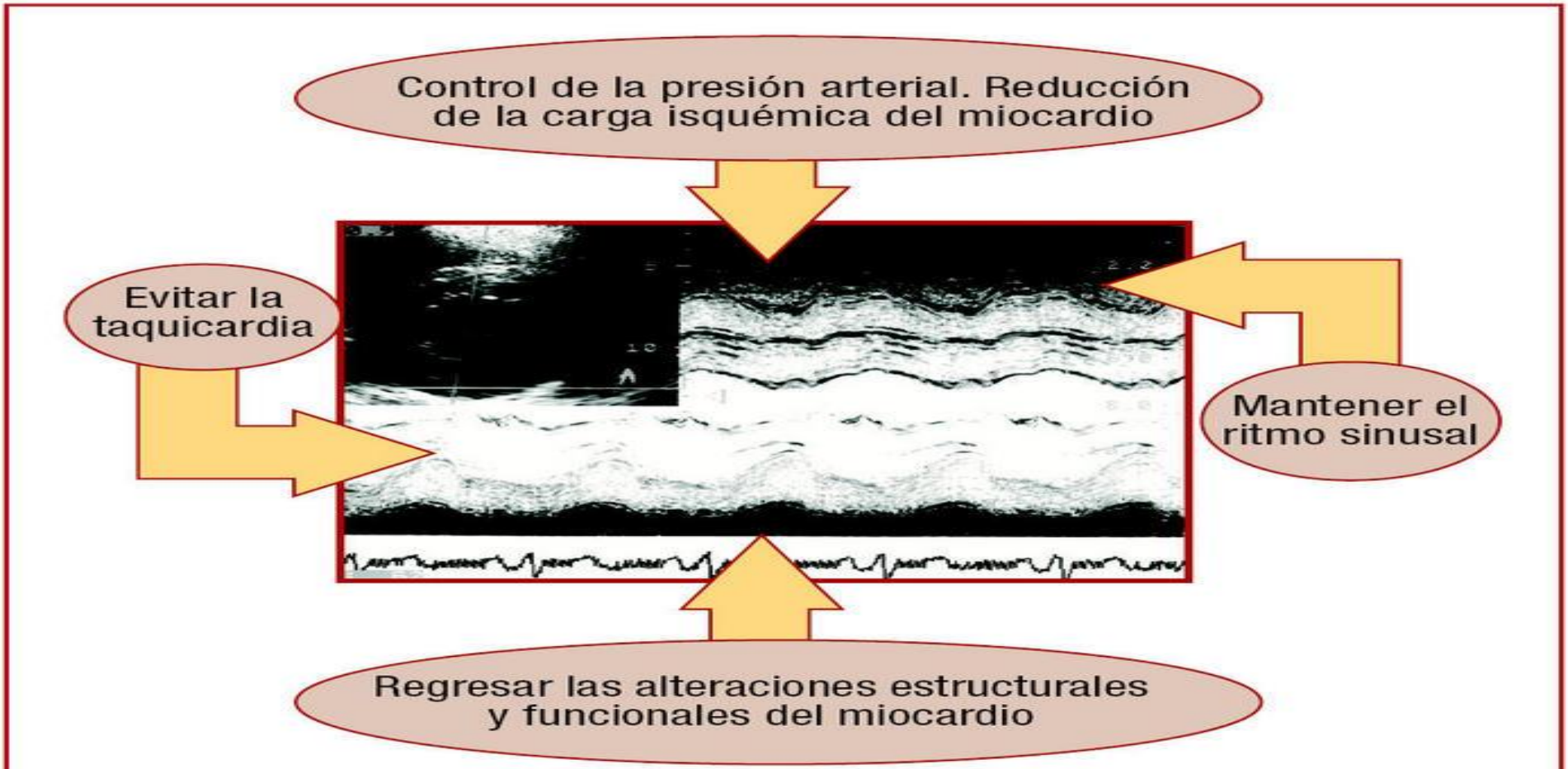
PREVENCION MUERTE SUBITA



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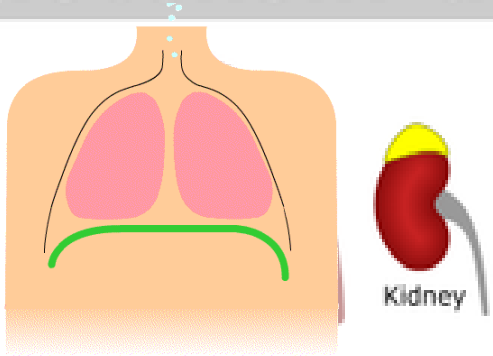

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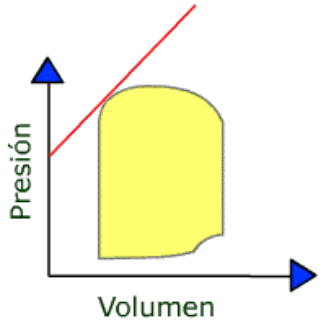

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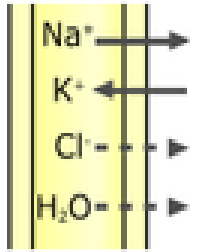

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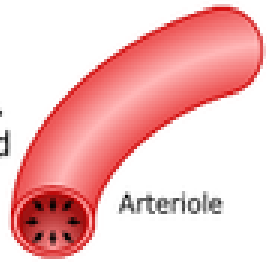

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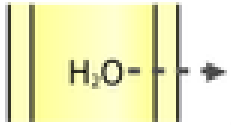

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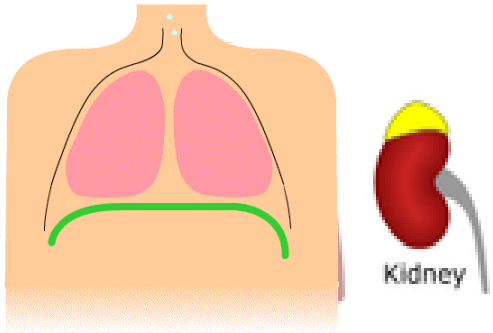

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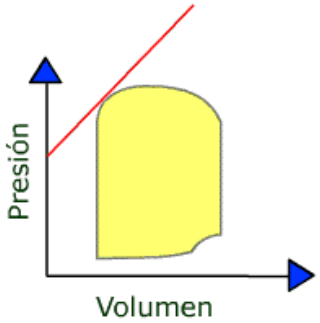

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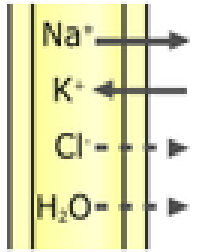

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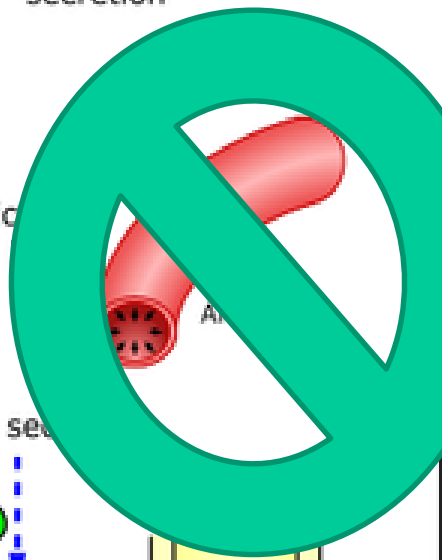

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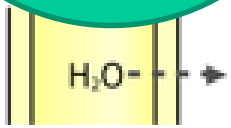

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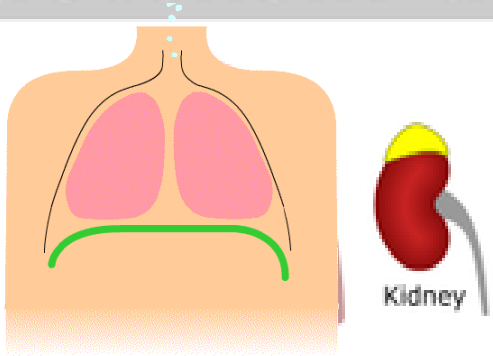

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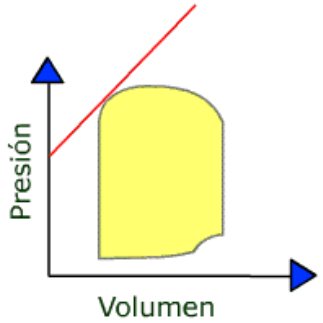

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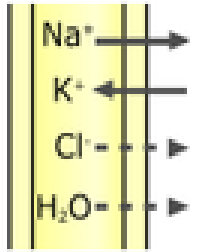

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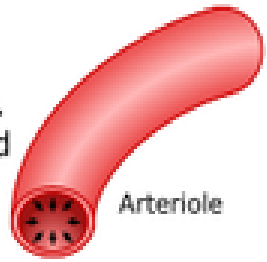

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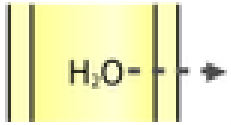

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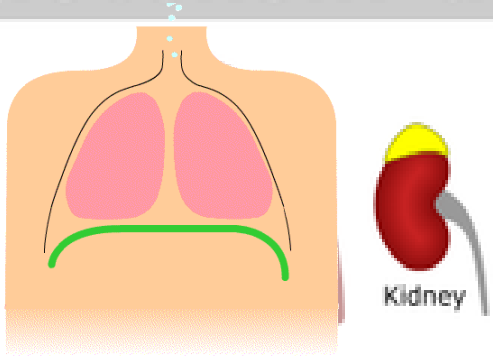

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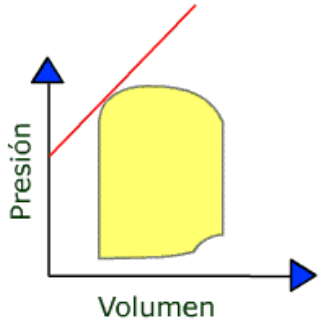

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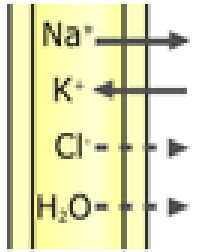

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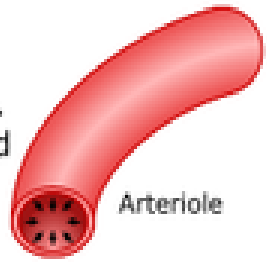

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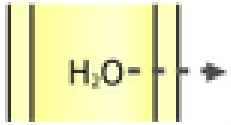

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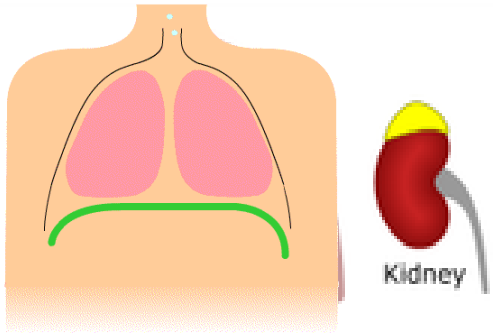

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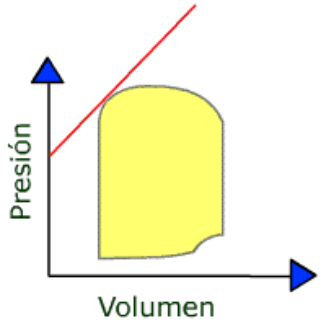

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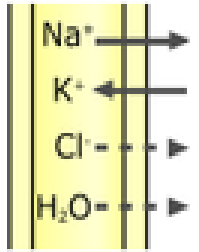

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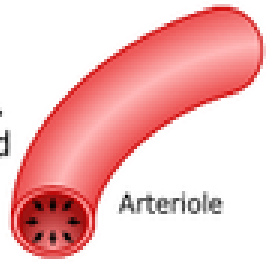

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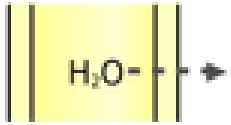

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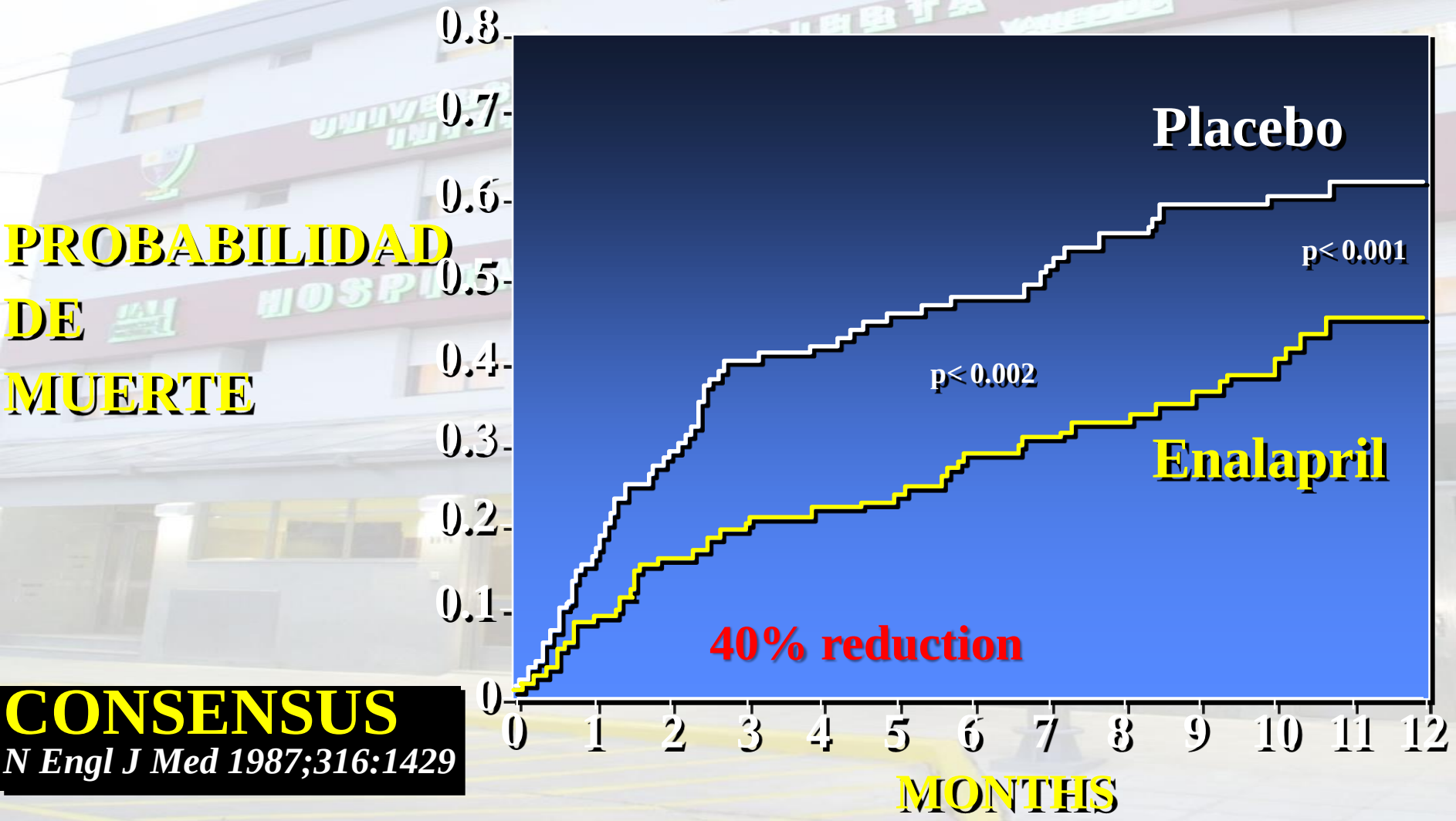
HOSPITAL UNIVERSITARIO

SOBREVIDA IECA



CONSENSUS
N Engl J Med 1987;316:1429

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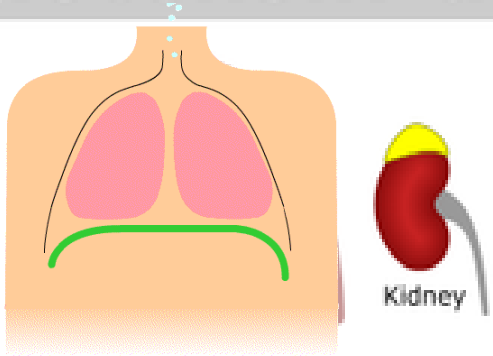

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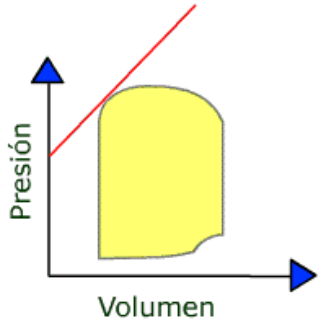

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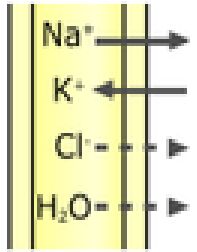

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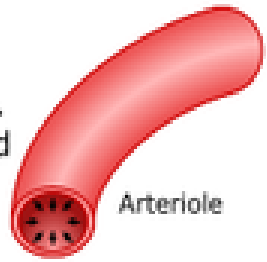

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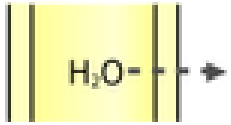

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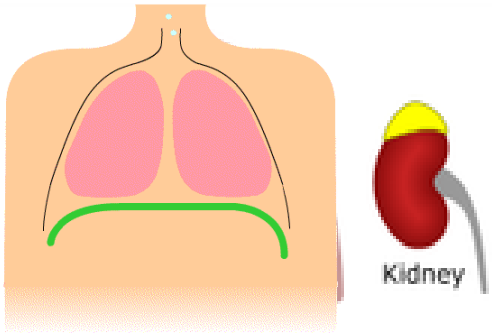

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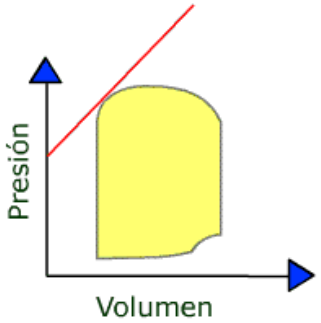

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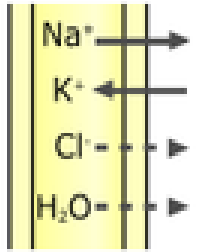

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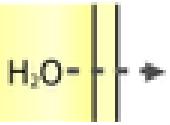

CONCEPTOS GENERALES

- NO MEJORAN , NI LLEGAN A IGUALAR LOS RESULTADOS DE LOS IECA

- RESERVADOS SOLO FRENTE A LA IMPOSIBILIDAD ABSOLUTA DE UTILIZAR IECA

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Tratamiento antiarritmico especifico en miocardiopatía dilatada

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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

Farmacos en prevención primaria

Antialdosterónicos

- *Espironolactona en el post IAM* (EPHESUS)
- *Eplerenone* en *Insuficiencia Cardíaca* (RALES)

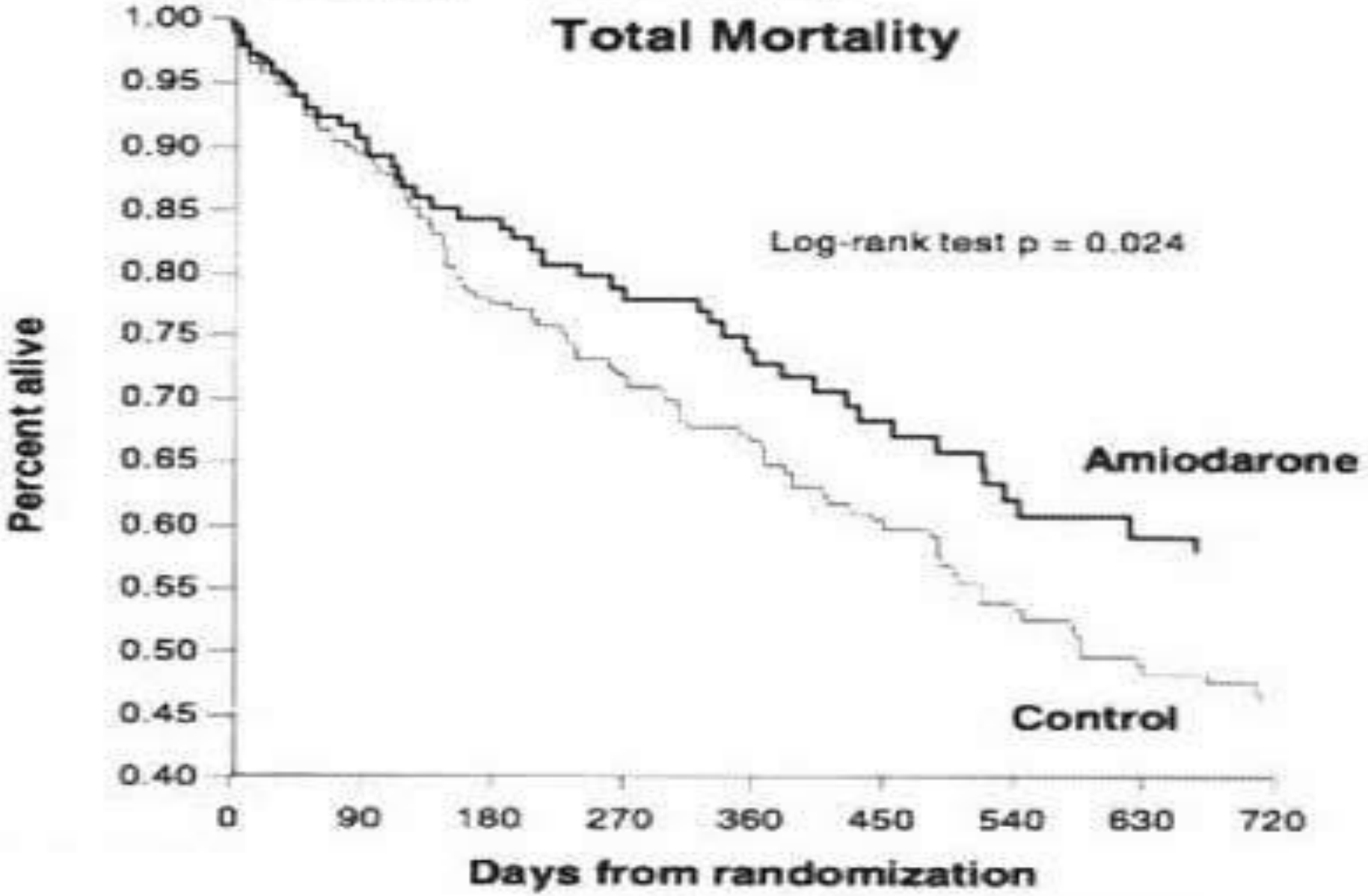
Evidenciaron reducción en la mortalidad y paralelamente de la MS.

Otros Antiarrítmicos

- *Estudio CAST I y II* (AA del grupo I)

detenidos prematuramente por **aumento de la mortalidad** momento desde el cual no se utilizan mas en prevención de la MS.

GESICA Results



Doval HC. Lancet. 1994;344:493-498.

Amiodarona

EMIAT (1997) (European Myocardial Infarction Amiodarone Trial)1486 p.Inclusión:5-21 días post IAM
Amiodarona vs. Placebo (50%) Fey< 41%.
.Total 103 vs. 102 ptes , Mort. Arrítmica :33 vs.50 ptes.(p=0.05).
Único Subgrupo beneficiado: FC > 90 lat. /min.

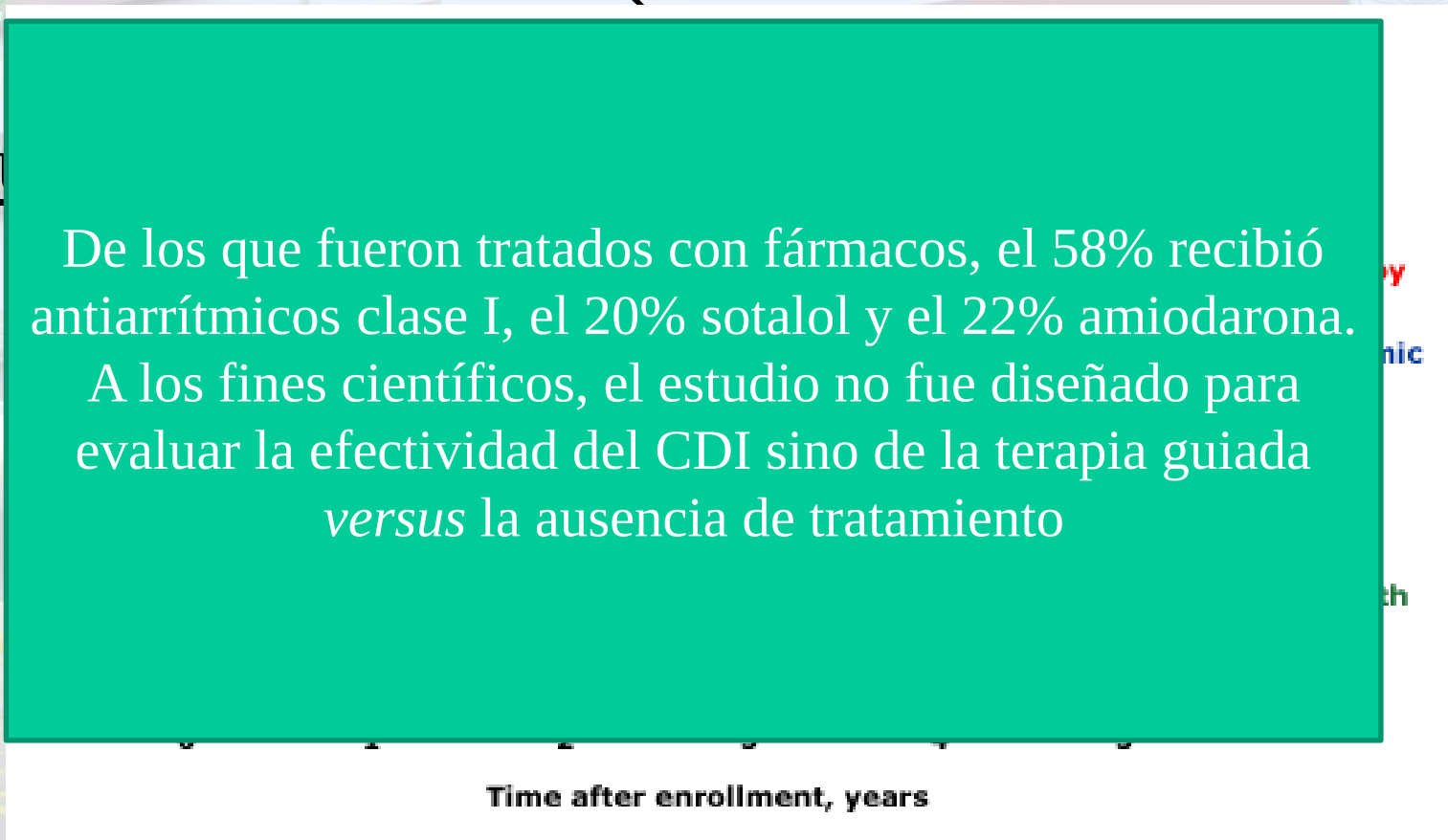
CAMIAT (1997) (Canadian Amiodarone Myocardial infarction Arrhytmia Trial) 1202 ptes.
6-45 días post IAM.
>10 EV y TVNS en Holter. Sgto 21 meses Mort. Arrítmica 15p vs. 31p Reducción de 48,5% con amiodarona.

rafael.porcile@uaisalud.com.ar

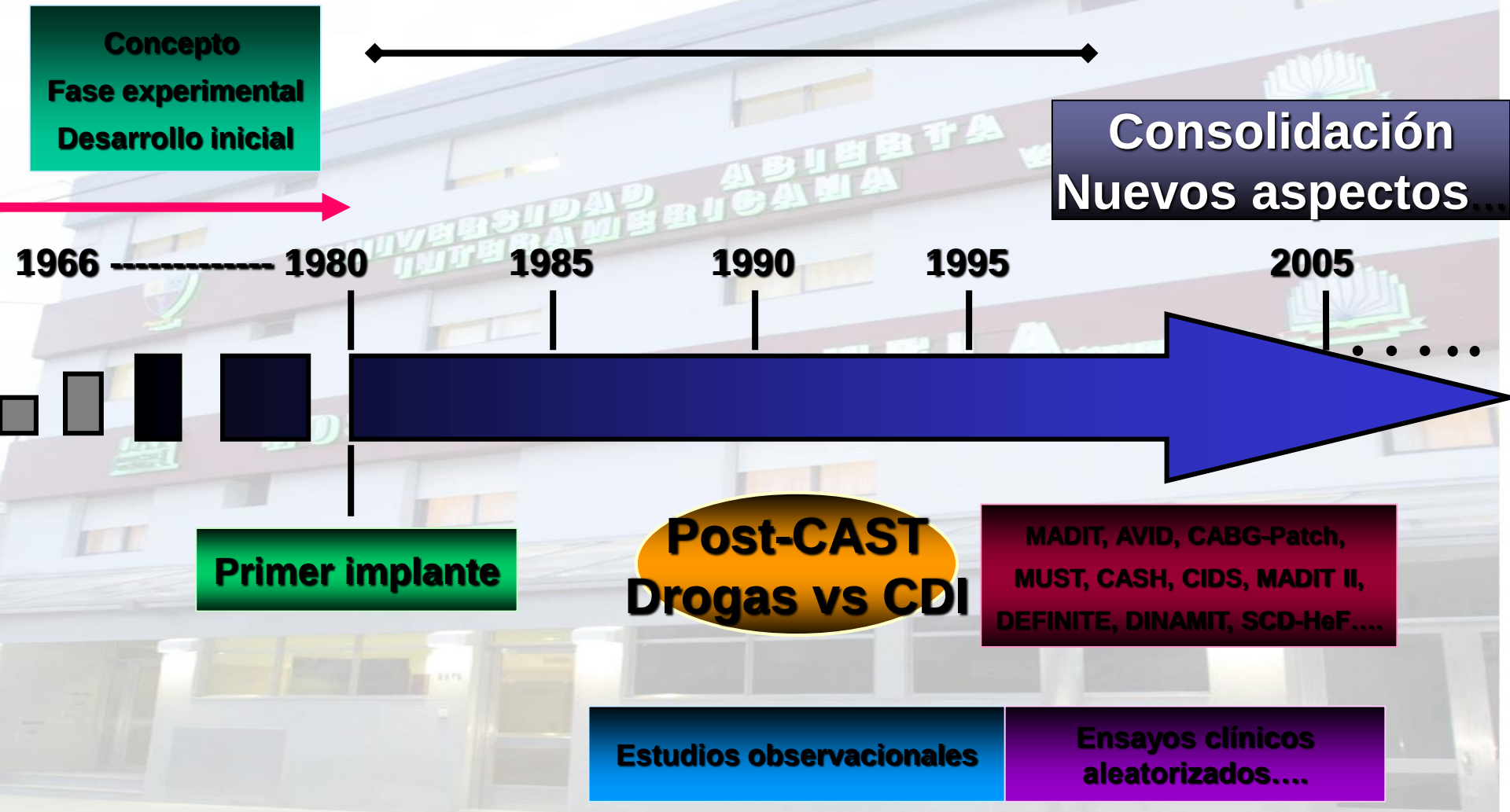
Prevention of sudden death in patients with coronary artery disease: the Multicenter Unsustained Tachycardia Trial (MUSTT

MU

De los que fueron tratados con fármacos, el 58% recibió antiarrítmicos clase I, el 20% sotalol y el 22% amiodarona. A los fines científicos, el estudio no fue diseñado para evaluar la efectividad del CDI sino de la terapia guiada *versus* la ausencia de tratamiento



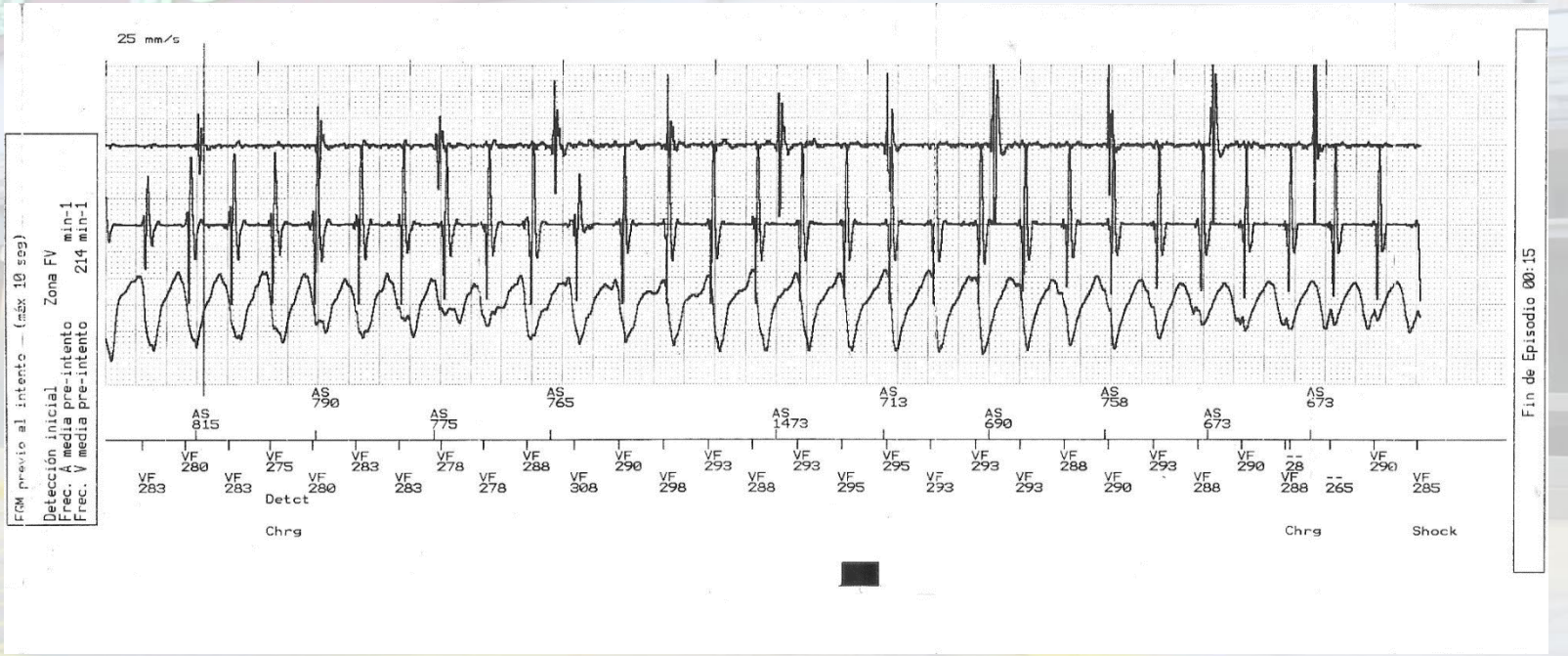
Historia



Modificado de: J Am Coll Cardiol 2009;54:747–63

CDI: mecanismo de acción

- Los CDI actuales pueden realizar marcapaseo antitaquicardia (inhibición por sobreestimulación), o CVE



The Multicenter Automatic Defibrillator Implantation Trial Investigators. MADIT- I

M

Se

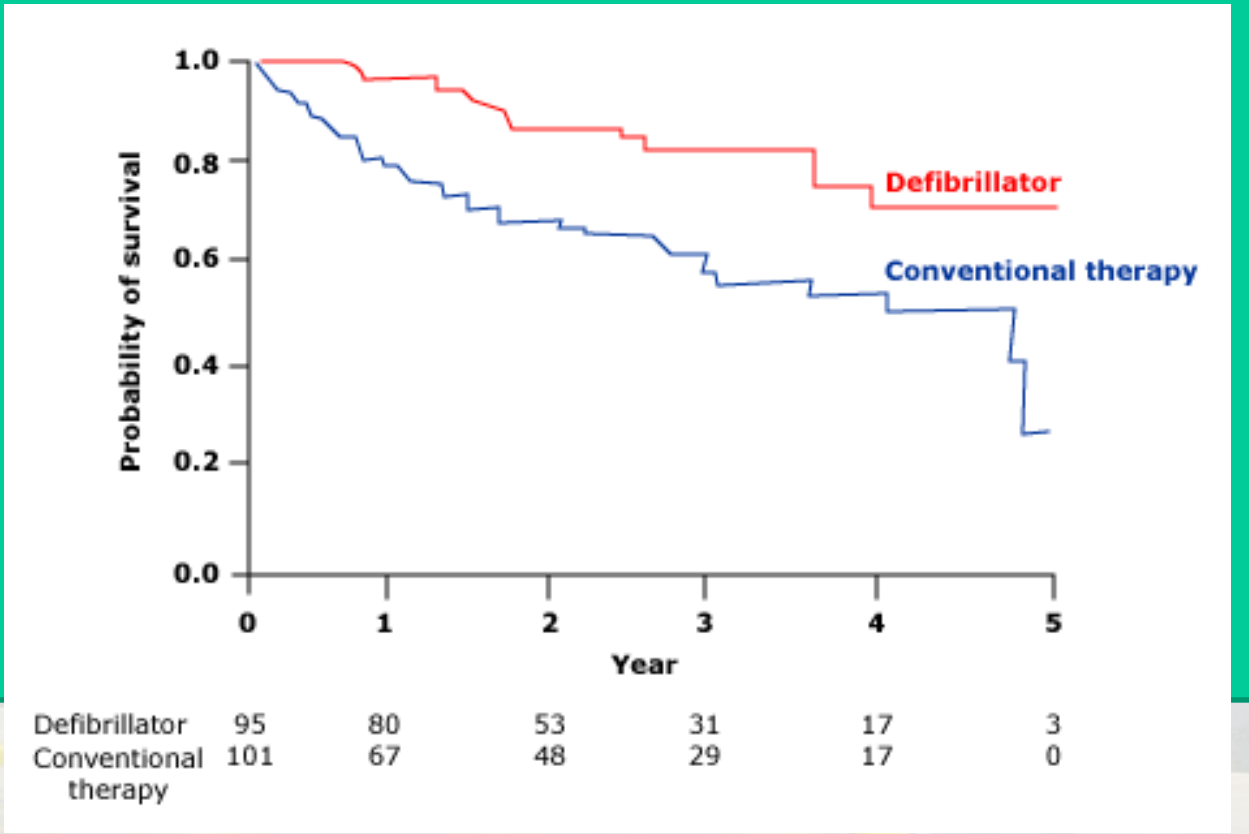
El 2

EVI

V

EV.

ón del

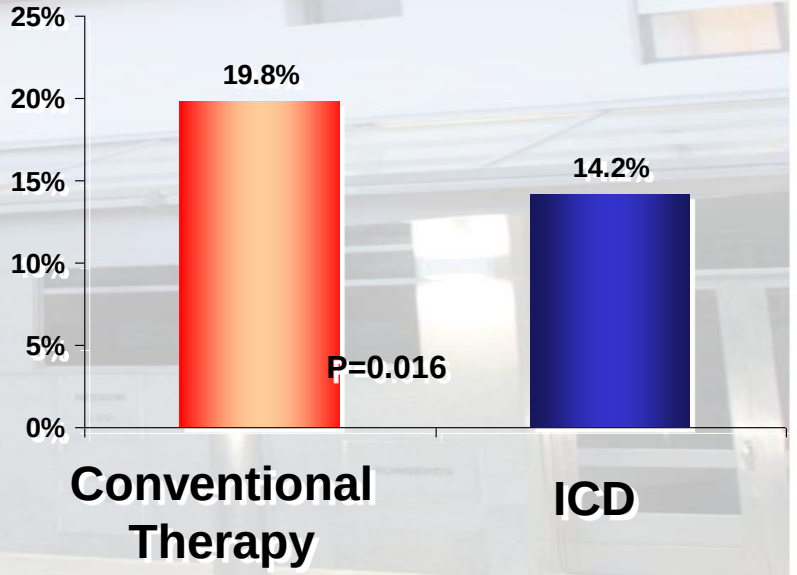


MADIT II

Incluyó 1232 pacientes con fracción de eyección ≤ 30% y antecedentes de IAM.
El 36% de ellos se encontraban en clase funcional I.

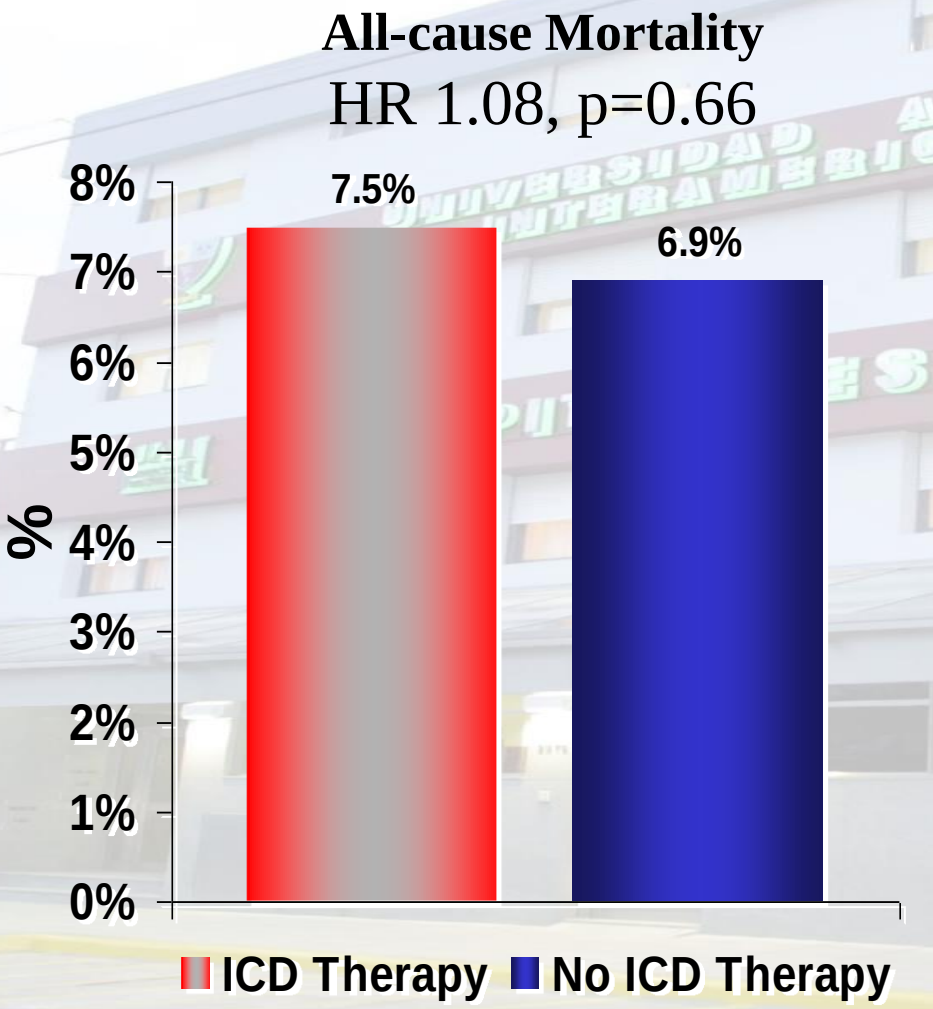
El seguimiento promedio fue de 20 meses y la mortalidad total se redujo del 19,8% en el grupo control al 14,2% en el grupo CDI (RRR 31%, IC95% 7 a 49%; p = 0,016).

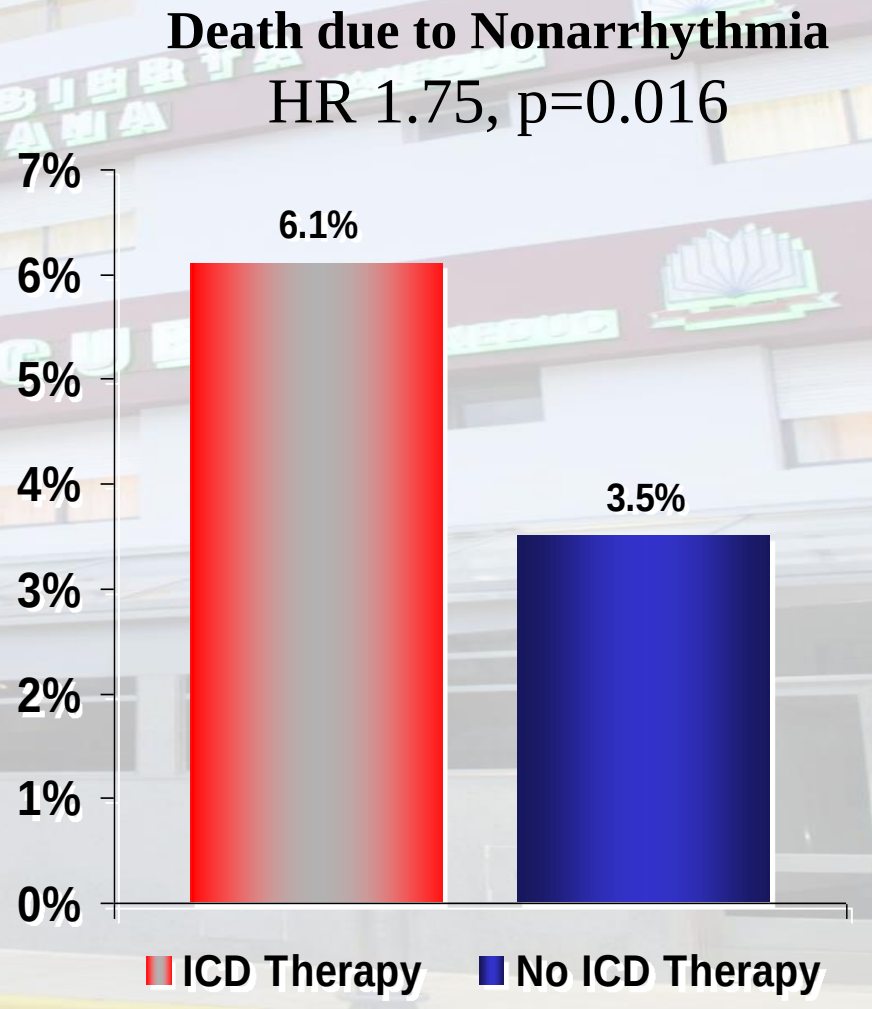
- Factores de riesgo independientes asociados con mayor mortalidad en grupo control:
  - edad > 72 años
  - FE < 25%
  - FA
  - CF III-IV
  - Cr > 1,4
  - QRS > 130ms

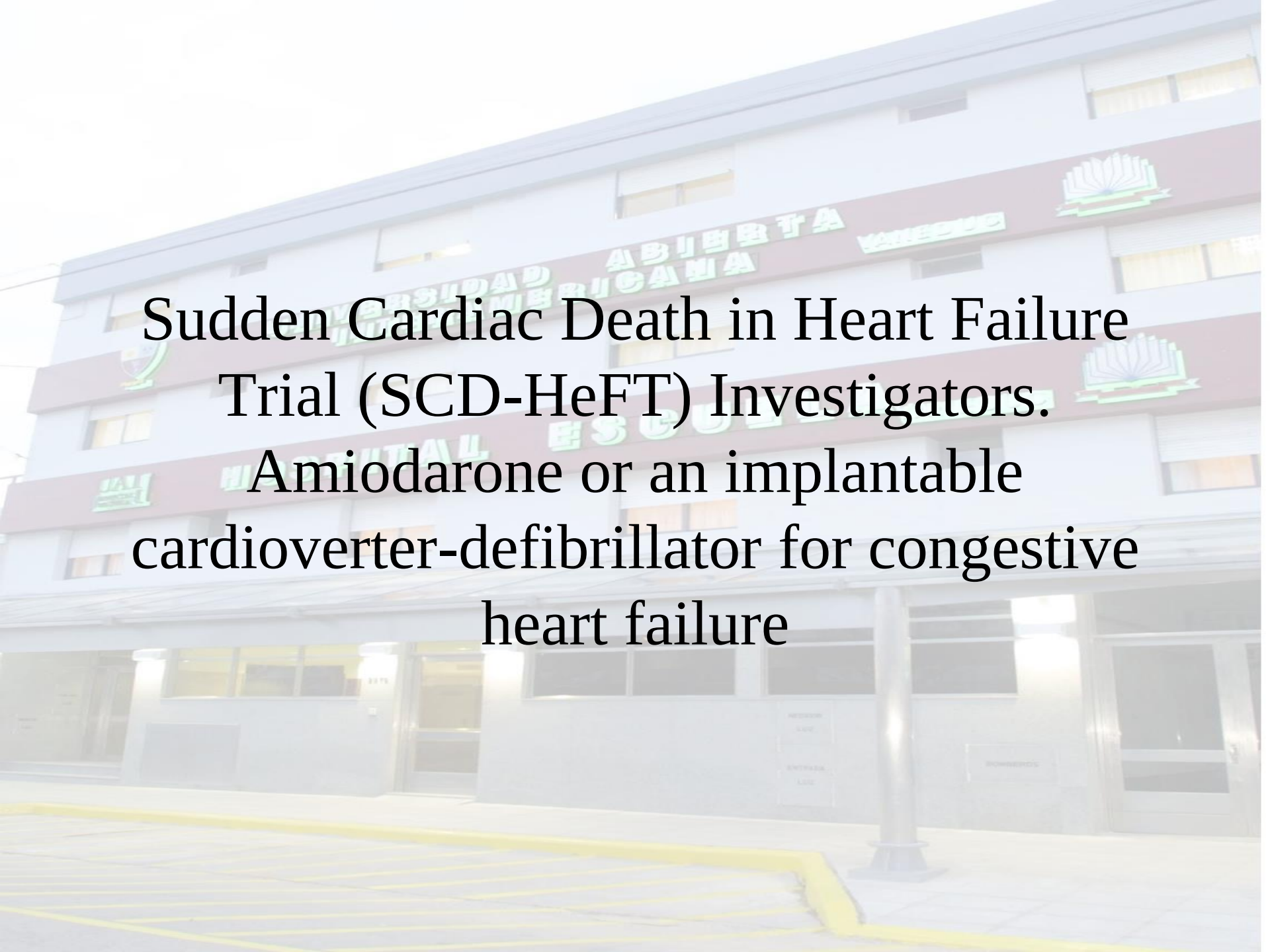


HR = 0.65

DINAMIT


All-cause Mortality
HR 1.08, p=0.66
8%
7%
6%
5%
4%
3%
2%
1%
0%
%
7.5%
6.9%
ICD Therapy
No ICD Therapy


Death due to Nonarrhythmia
HR 1.75, p=0.016
7%
6%
5%
4%
3%
2%
1%
0%
6.1%
3.5%
ICD Therapy
No ICD Therapy



Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure

SCD-HeFT

Comparó CDI *versus* amiodarona o placebo en 2521 pacientes con IC clase II-III y fracción de eyección ≤ 35%.
Seguimiento = 45 meses
El 70% = CF II
El 48% eran no isquémicos. (beneficio para Isquemicos y no Isquemicos)
La amiodarona no brindó beneficio y el uso del CDI redujo la mortalidad global del 29%

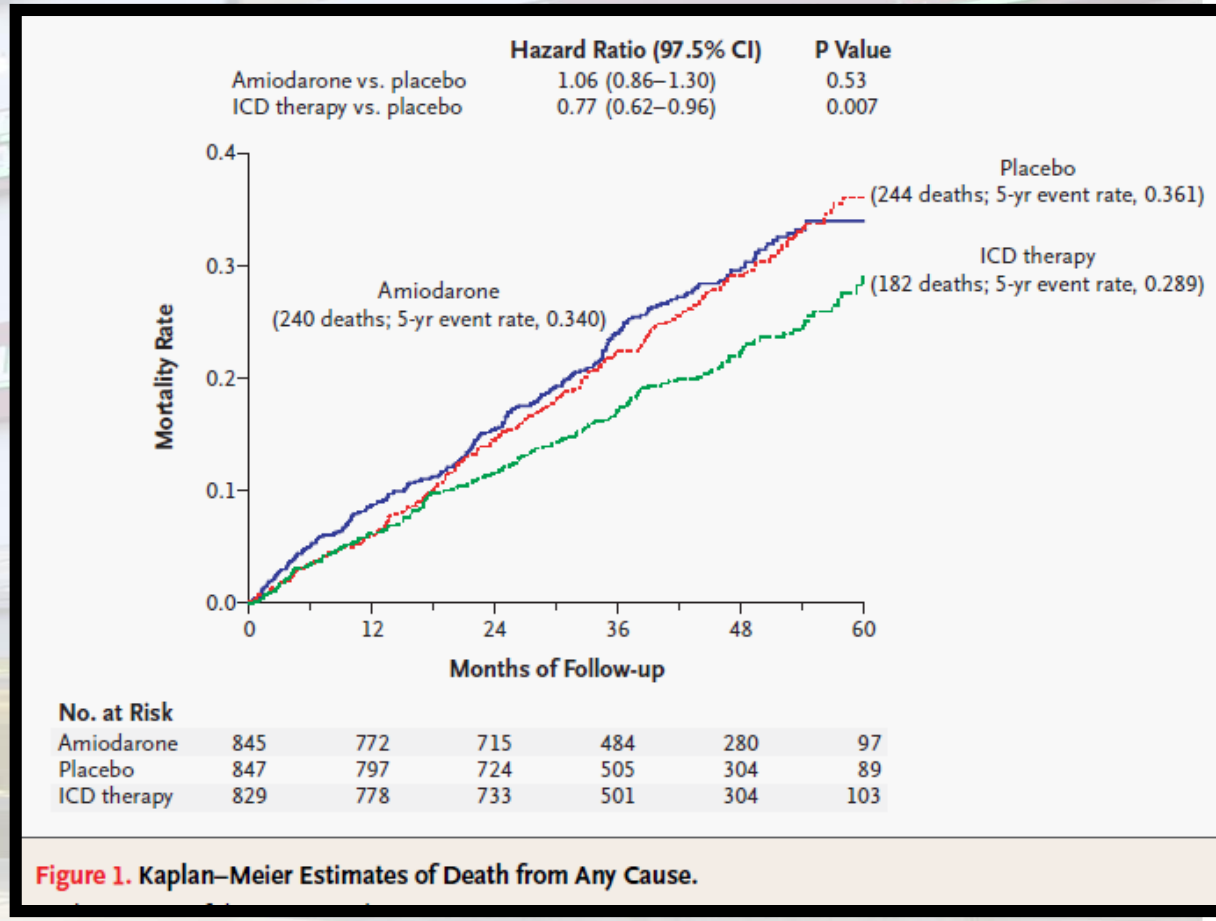


Figure 1. Kaplan–Meier Estimates of Death from Any Cause.

No hubo diferencias entre placebo y amioadarona, claro beneficio con CDI

Prevención secundaria

La evidencia muestra que el CDI en los pacientes que sobreviven a una MS o TV sintomática mejora la sobrevida reduciendo así el riesgo de nuevo episodio de MS y siendo superior al tratamiento antiarrítmico farmacológico.

Prevención secundaria

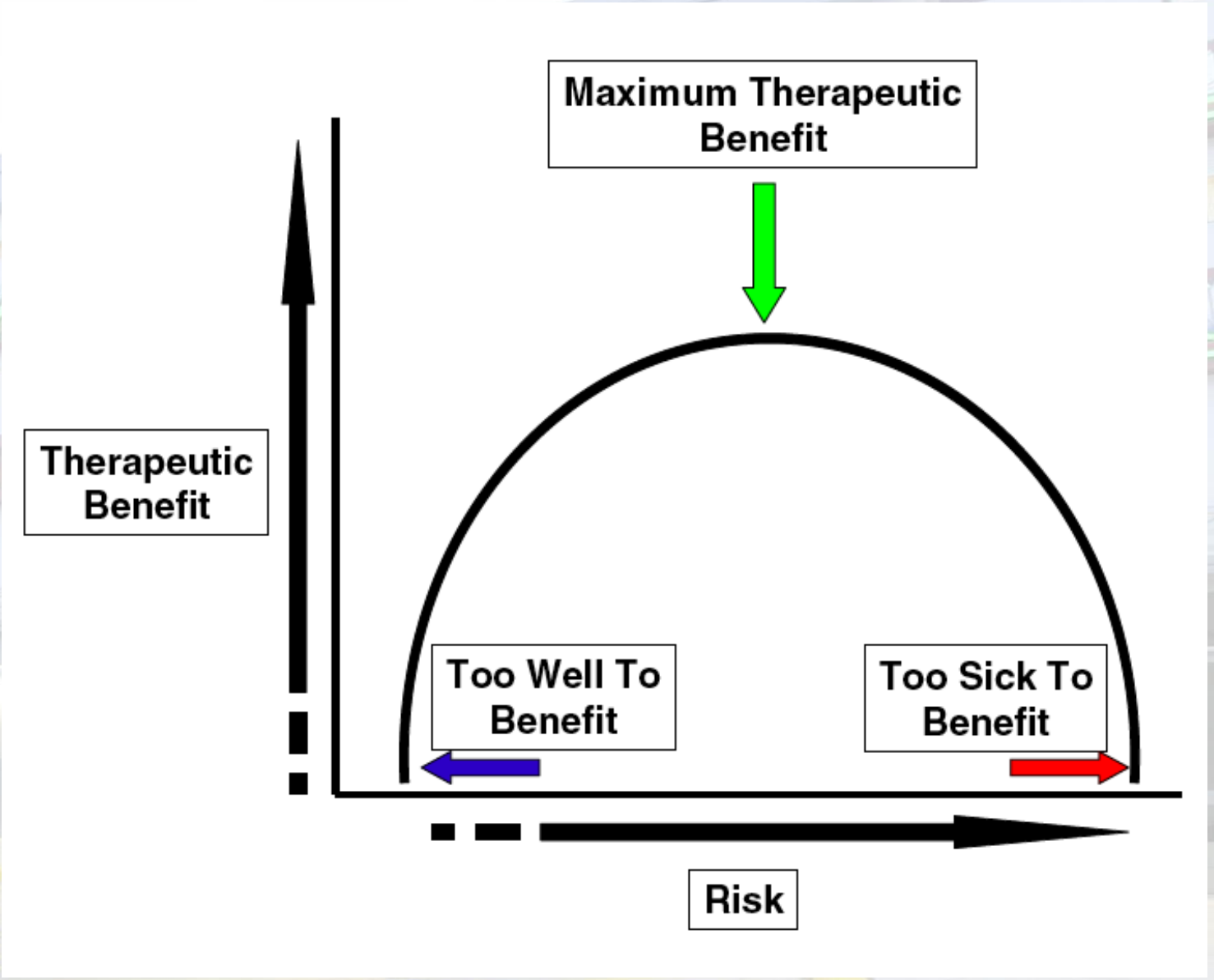
AVID

- Los 396 ptes con FEVI >35% no tuvieron mayor beneficio con el CDI.
- El grupo de 473 ptes con FEVI 20-34% mostraron una mejoría significativa.
- Los restantes 140 ptes con FEVI <20% presentaron una reducción no significativa.

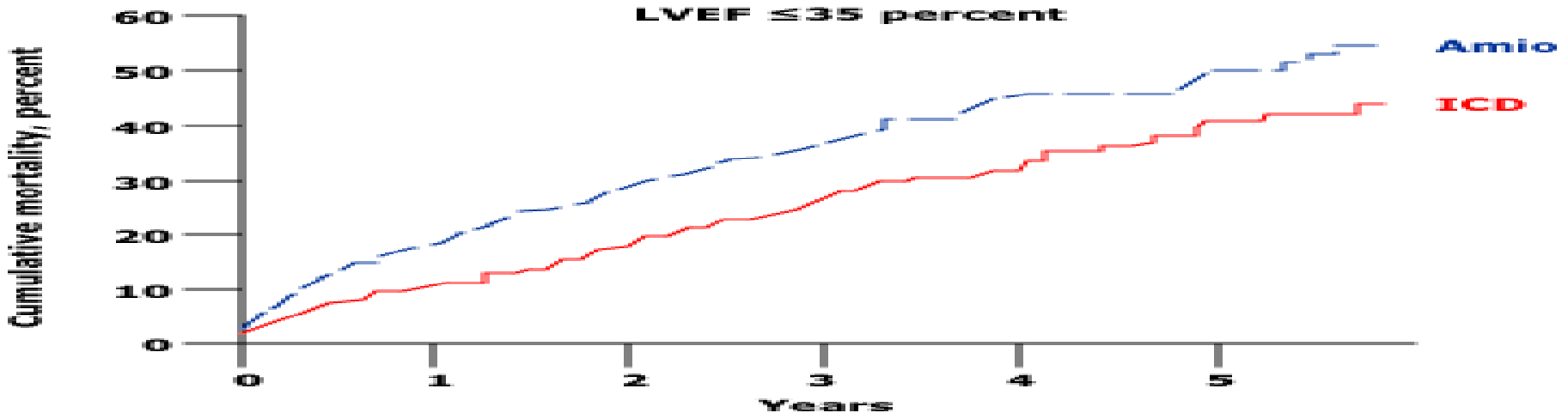
CIDS

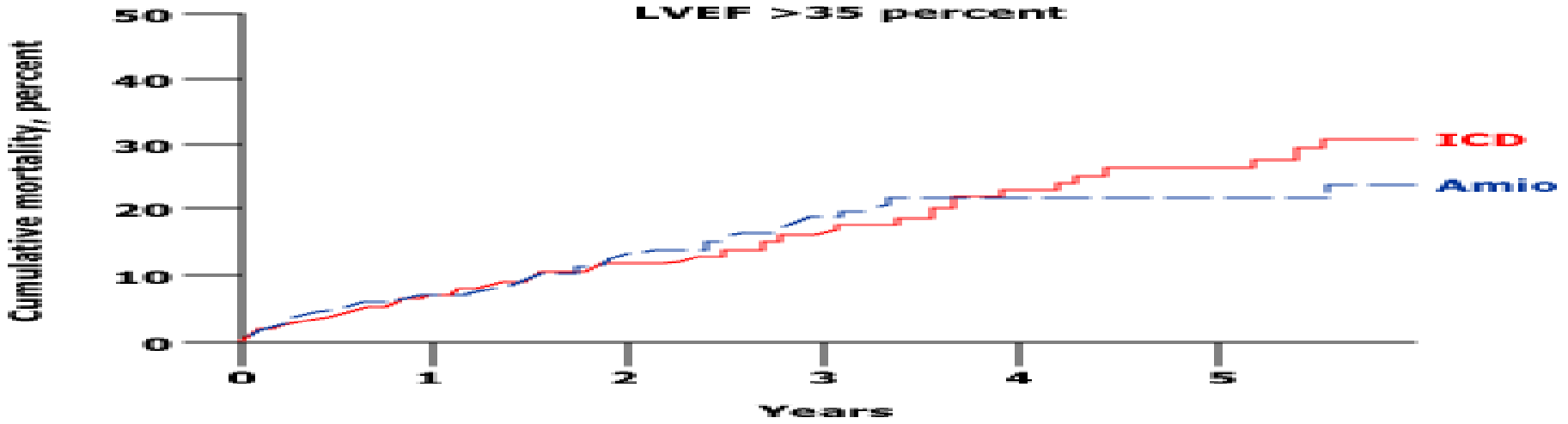
- Sin beneficio en el subgrupo sano.
- Reducción del 50% de la mortalidad en el subgrupo de alto riesgo (>70 años, FEVI <35% y CF III-IV)

Goldilock Effect



Meta-análisis





Selecting Patients with Heart Failure for Discussion About ICD As Primary Prevention of Sudden Death

☐ Does patient have Class IV symptoms (most patients hospitalized with HF)?

Yes → No ICD now. Re-evaluate for stability and risk after 1 month

☐ Does patient have risk profile for heart failure death during next year?

Factors to Consider, e.g.
High creat/BUN
Hypotension
ACEI/ARB intolerance
Low serum sodium
Very high serum BNP
Multiple HF hosps

Yes → High risk HF profile → No ICD

☐ Is prognosis for more than one year survival with good overall functional status limited by non-cardiac conditions?

Yes → No ICD

☐ Is patient within 40 days of myocardial infarction?

Yes → No ICD now. Re-evaluate after 3-6 mos of optimal Medical Rx

☐ Are there reversible factors for which treatment may improve LVEF?

Less than 3-6 months optimal med Rx
Prolonged tachycardia
Excess alcohol consumption
Medications that can exacerbate HF

Yes → No ICD now. Re-evaluate after 3-6 mos of optimal Medical Rx

If all answers "No": **Discuss risks and benefits of ICD** *in outpatient setting*

INDICACIONES

Pacientes con muerte subita abortada secundaria a FV o TV con descompensacion hemodinamica luego de excluir todas las causas reversibles ***(Clase I A)***

Pacientes con Sincope de causa desconocida y FV o TV con descompensacion hemodinamica inducidas en estudio electrofisiologico **(Clase I B)**

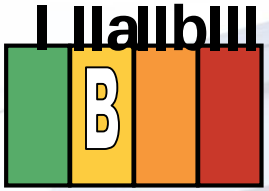
Pacientes con Fey < 35% por MCP isquemico necrotica despues de 40 dias de IAM y en CF II-III **(Clase I A)**

Pacientes con Fey < 30% por MCP isquemico necrotica despues de 40 dias de IAM y CF I **(Clase I A)**

MCPD no isquemica con Fey <35% y CF II-III y tto medico optimo **(Clase I B)**

TV no sostenida por IAM, Fey < 40% e induccion en EEF de FV/TV con descompensacion hemodinamica **(Clase I B)**

Stage B (cont.)



To prevent sudden death, placement of an ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are on appropriate medical therapy and have reasonable expectation of survival with a good functional status for more than 1 year.

Harm

Nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI.

Recommendations for Treatment of Stage B HF

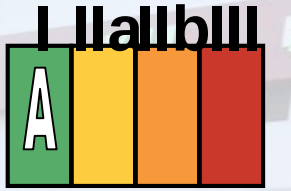
Recommendations	COR	LOE
In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF	I	A
In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF	I	B
In patients with MI, statins should be used to prevent HF	I	A
Blood pressure should be controlled to prevent symptomatic HF	I	A
ACE inhibitors should be used in all patients with a reduced EF to prevent HF	I	A
Beta blockers should be used in all patients with a reduced EF to prevent HF	I	C
An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on GDMT	IIa	B
Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF	III: Harm	C

Treatment of Stages A to D

Device Treatment for Stage C HF/EF

Device Therapy for Stage C HF*r*EF

ICD therapy is recommended for primary prevention of SCD to reduce total mortality in selected patients with nonischemic DCM or ischemic heart disease at least 40 days post-MI with LVEF of 35% or less, and NYHA class II or III symptoms on chronic GDMT, who have reasonable expectation of meaningful survival for more than 1 year.

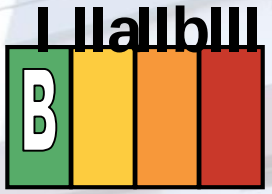


NYHA Class III/IV

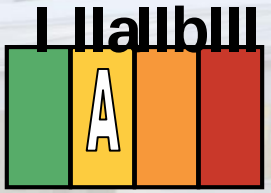
CRT is indicated for patients who have LVEF of 35% or less, sinus rhythm, left bundle-branch block (LBBB) with a QRS duration of 150 ms or greater, and NYHA class II, III, or ambulatory IV symptoms on GDMT.

NYHA Class II

Device Therapy for Stage C HF*r*EF (cont.)

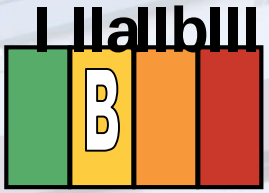


ICD therapy is recommended for primary prevention of SCD to reduce total mortality in selected patients at least 40 days post-MI with LVEF less than or equal to 30%, and NYHA class I symptoms while receiving GDMT, who have reasonable expectation of meaningful survival for more than 1 year.

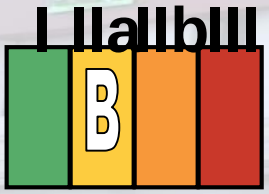


CRT can be useful for patients who have LVEF of 35% or less, sinus rhythm, a non-LBBB pattern with a QRS duration of 150 ms or greater, and NYHA class III/ambulatory class IV symptoms on GDMT.

Device Therapy for Stage C HF*r*EF (cont.)

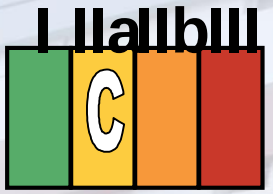


CRT can be useful for patients who have LVEF of 35% or less, sinus rhythm, LBBB with a QRS duration of 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT.



CRT can be useful in patients with AF and LVEF of 35% or less on GDMT if a) the patient requires ventricular pacing or otherwise meets CRT criteria and b) atrioventricular nodal ablation or pharmacological rate control will allow near 100% ventricular pacing with CRT.

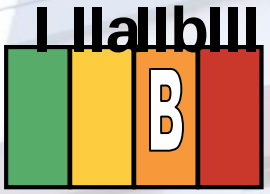
Device Therapy for Stage C HF*r*EF (cont.)



CRT can be useful for patients on GDMT who have LVEF of 35% or less, and are undergoing placement of a new or replacement device placement with anticipated requirement for significant (>40%) ventricular pacing.

The usefulness of implantation of an ICD is of uncertain benefit to prolong meaningful survival in patients with a high risk of nonsudden death as predicted by frequent hospitalizations, advanced frailty, or comorbidities such as systemic malignancy or severe renal dysfunction.

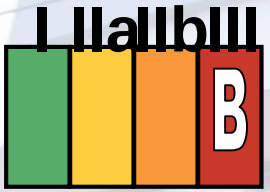
Device Therapy for Stage C HF*r*EF (cont.)



CRT may be considered for patients who have LVEF of 35% or less , sinus rhythm, a non-LBBB pattern with a QRS duration of 150 ms or greater, and NYHA class II symptoms on GDMT.

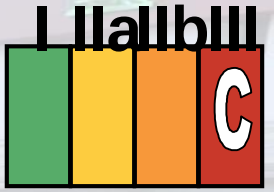
CRT may be considered for patients who have LVEF of 30% or less, ischemic etiology of HF, sinus rhythm, LBBB with a QRS duration of 150 ms or greater, and NYHA class I symptoms on GDMT.

Device Therapy for Stage C HF*r*EF (cont.)



No Benefit

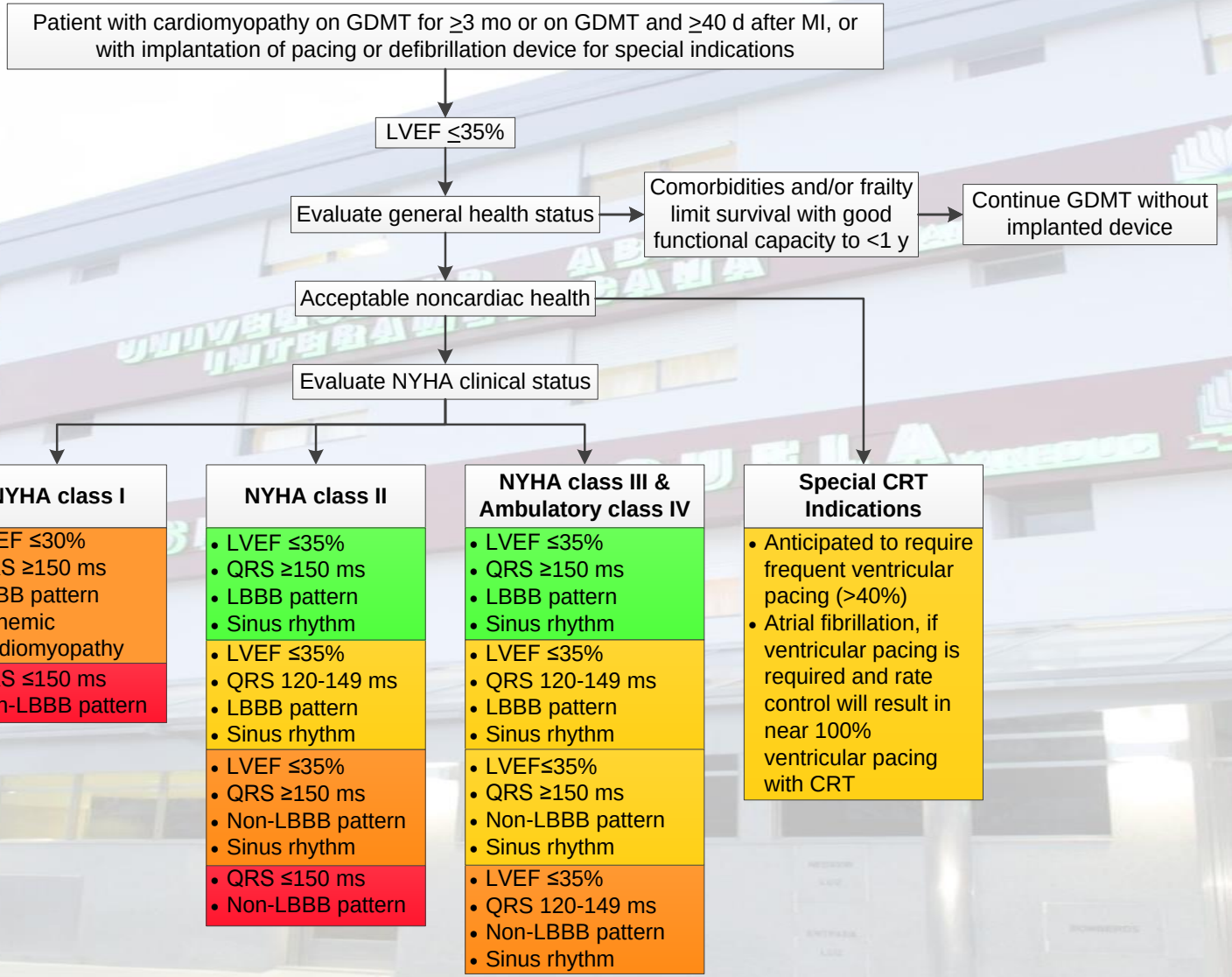
CRT is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with a QRS duration of less than 150 ms.



No Benefit

CRT is not indicated for patients whose comorbidities and/or frailty limit survival with good functional capacity to less than 1 year.

Indications for CRT Therapy



Colors correspond to the class of recommendations in the ACCF/AHA Table 1.

Benefit for NYHA class I and II patients has only been shown in CRT-D trials, and while patients may not experience immediate symptomatic benefit, late remodeling may be avoided along with long-term HF consequences. There are no trials that support CRT-pacing (without ICD) in NYHA class I and II patients. Thus, it is anticipated these patients would receive CRT-D unless clinical reasons or personal wishes make CRT-pacing more appropriate. In patients who are NYHA class III and ambulatory class IV, CRT-D may be chosen but clinical reasons and personal wishes may make CRT-pacing appropriate to improve symptoms and quality of life when an ICD is not expected to produce meaningful benefit in survival.

Device Therapy for Stage C HF*r*EF (cont.)

Recommendations	COR	LOE
ICD therapy is recommended for primary prevention of SCD in selected patients with HFrEF at least 40 days post-MI with LVEF ≤35%, and NYHA class II or III symptoms on chronic GDMT, who are expected to live ≥1 year*	I	A
CRT is indicated for patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS ≥150 ms	I	A (NYHA class III/IV) B (NYHA class II)
ICD therapy is recommended for primary prevention of SCD in selected patients with HFrEF at least 40 days post-MI with LVEF ≤30%, and NYHA class I symptoms while receiving GDMT, who are expected to live ≥1 year*	I	B
CRT can be useful for patients who have LVEF ≤35%, sinus rhythm, a non-LBBB pattern with a QRS ≥150 ms, and NYHA class III/ambulatory class IV symptoms on GDMT.	IIa	A
CRT can be useful for patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS 120 to 149 ms, and NYHA class II, III or ambulatory IV symptoms on GDMT	IIa	B
CRT can be useful in patients with AF and LVEF ≤35% on GDMT if a) the patient requires ventricular pacing or otherwise meets CRT criteria and b) AV nodal ablation or rate control allows near 100% ventricular pacing with CRT	IIa	B

A tener en cuenta…

- ✓ El implante de un CDI es un procedimiento invasivo y no conlleva beneficios en la fisiopatología de la enfermedad ni mejora la calidad de vida. ¡Simplemente reduce la mortalidad!
- ✓ No actúa sobre el sustrato, sino sobre la consecuencia.
- ✓ Aquellos que tuvieron descarga efectiva del CDI en general son pacientes más graves y tendrán peor pronóstico.
- ✓ La efectividad del CDI es baja
- ✓ La Fey es el parámetro que mas contribuye a la indicación pero varía con el tiempo y con distintos métodos en un mismo centro
- ✓ Las guías actuales de MS son difícilmente generalizables. Es necesario individualizar con cada paciente.

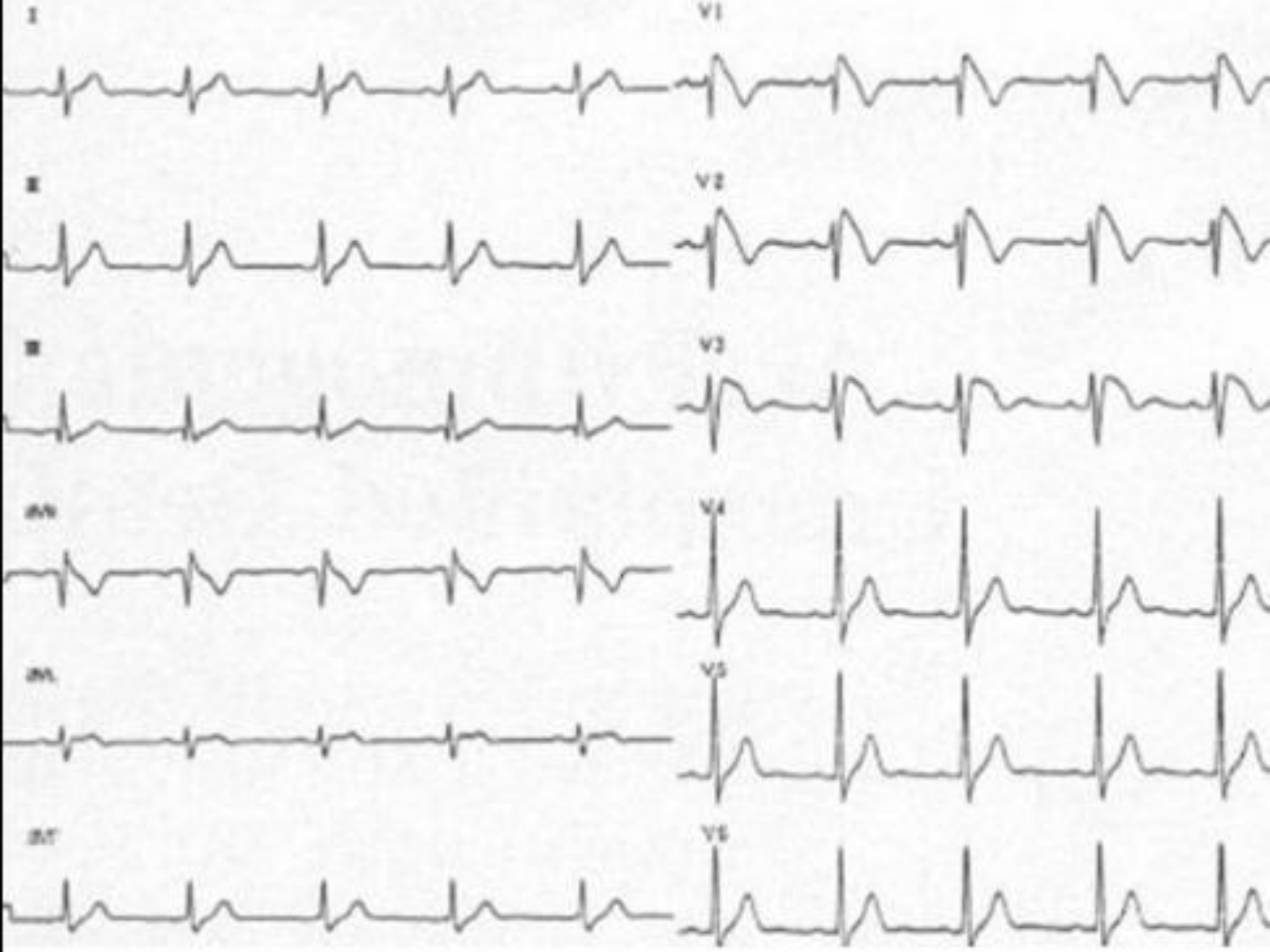
A tener en cuenta….

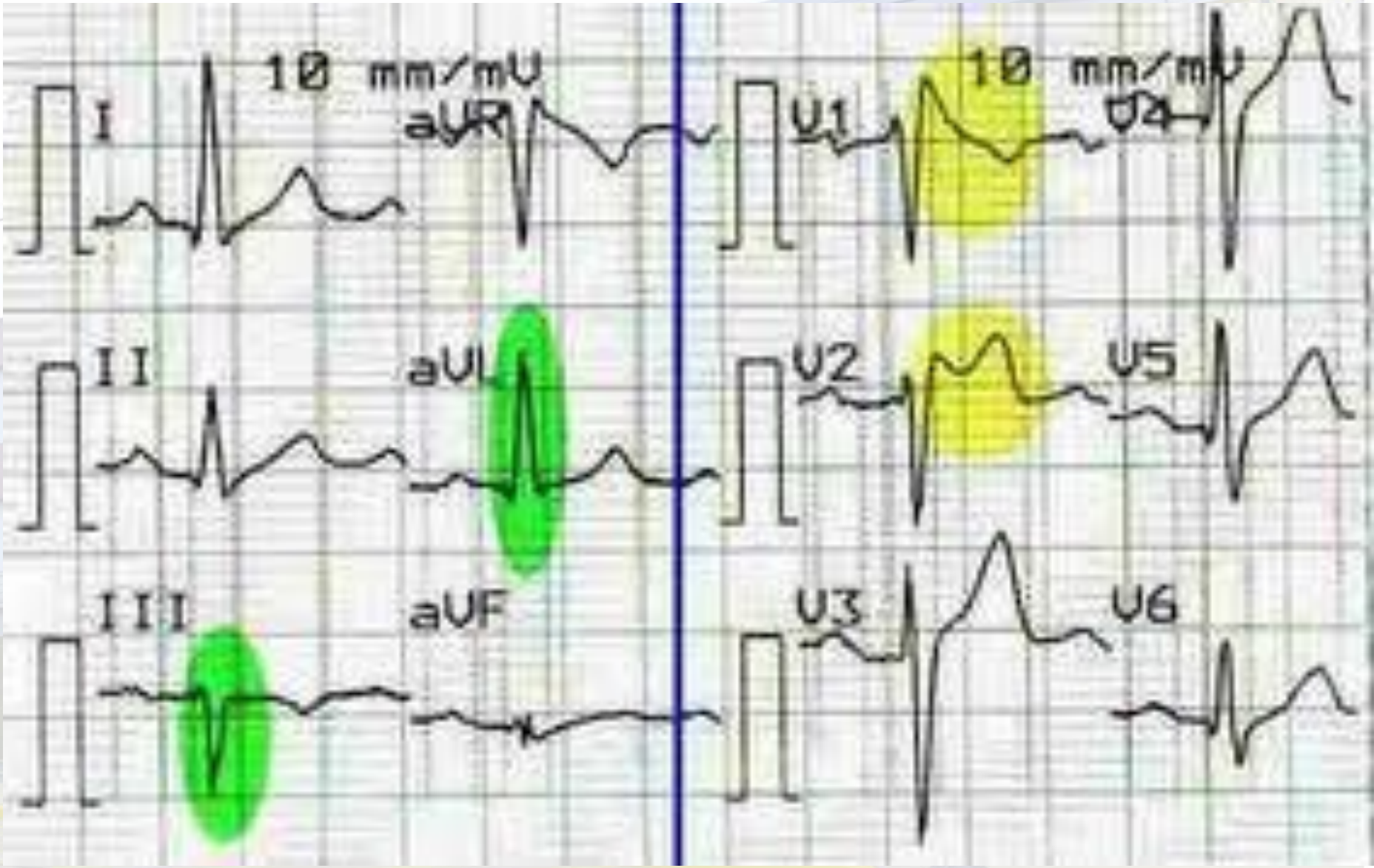
- Dado el fracaso de las drogas antiarrítmicas, el CDI representa un aporte muy valioso para prevenir la muerte súbita en el paciente con disfunción ventricular severa.

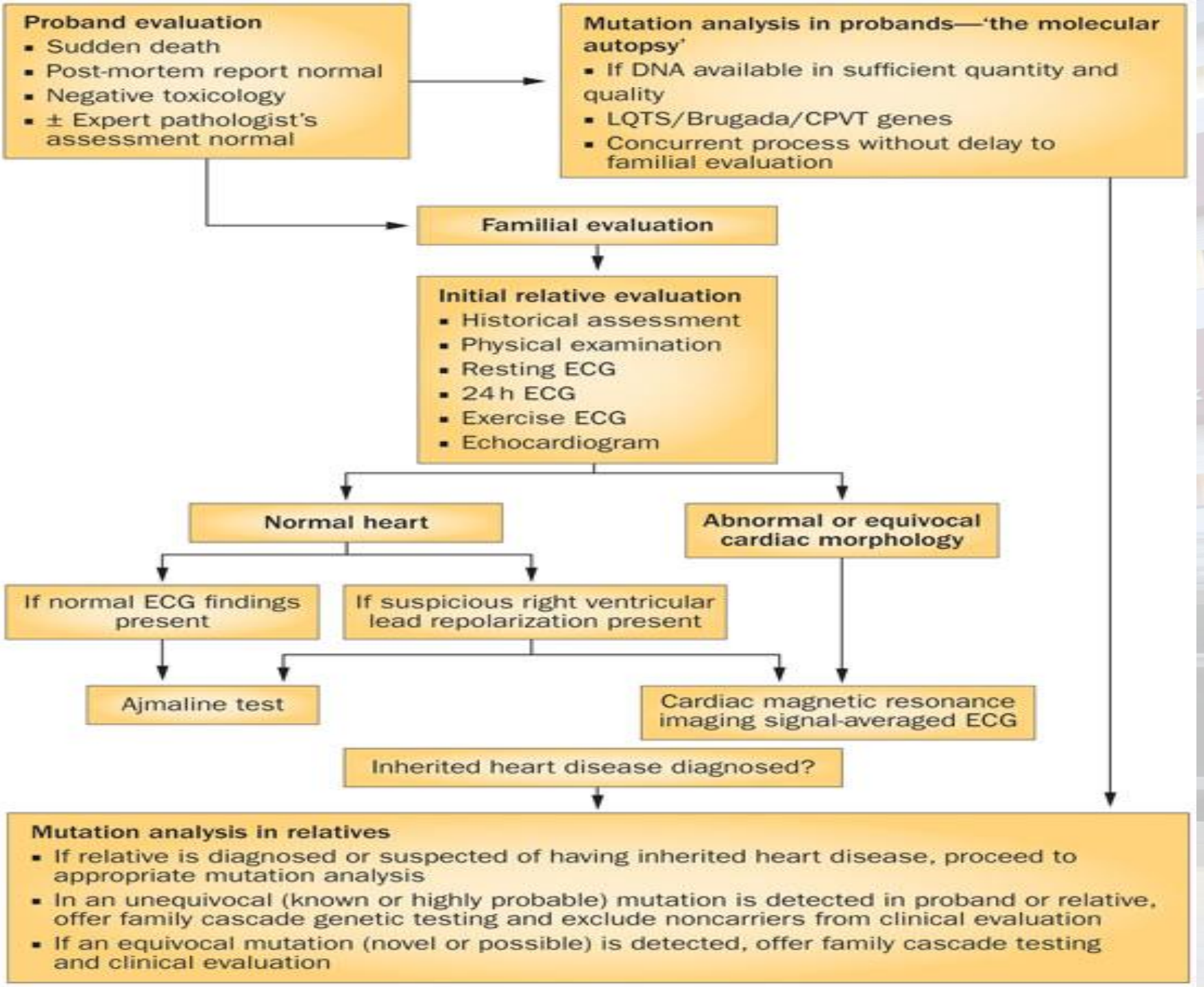
- Hay que optimizar el tratamiento médico y revascularizar zonas isquémicas para corregir el sustrato arritmogénico.

- Se necesitan mejores métodos de estratificación de riesgo para el implante de ICD en prevención primaria.

- Es un dispositivo costoso, de dificil acceso en ámbito público con indicaciones cada vez mas amplias.


I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6


10 mm/mV
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6


Proband evaluation
Sudden death
Post-mortem report normal
Negative toxicology
± Expert pathologist's assessment normal
Mutation analysis in probands—'the molecular autopsy'
If DNA available in sufficient quantity and quality
LQTS/Brugada/CPVT genes
Concurrent process without delay to familial evaluation
Familial evaluation
Initial relative evaluation
Historical assessment
Physical examination
Resting ECG
24 h ECG
Exercise ECG
Echocardiogram
Normal heart
Abnormal or equivocal cardiac morphology
If normal ECG findings present
If suspicious right ventricular lead repolarization present
Ajmaline test
Cardiac magnetic resonance imaging signal-averaged ECG
Inherited heart disease diagnosed?
Mutation analysis in relatives
If relative is diagnosed or suspected of having inherited heart disease, proceed to appropriate mutation analysis
In an unequivocal (known or highly probable) mutation is detected in proband or relative, offer family cascade genetic testing and exclude noncarriers from clinical evaluation
If an equivocal mutation (novel or possible) is detected, offer family cascade testing and clinical evaluation