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ERN

GUARD-Heart

Gateway to Uncommon And Rare Diseases of the Heart

Behandeling van lang QT syndroom

A.S. Amin

Cardioloog

European Reference Network
for rare or low prevalence complex diseases

Network Heart Diseases
(ERN GUARD-HEART)

Amsterdam UMC

European Commission

Richtlijnen voor behandeling

HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes

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Document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013

TABLE OF CONTENTS

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Developed in partnership with the Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology, and the Asia Pacific Heart Rhythm Society (APHRS); and in collaboration with the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the Pediatric and Congenital Electrophysiology Society (PACES) and the Association for European Pediatric and Congenital Cardiology (AEPC). **Address correspondence:** Sheila Tynes. E-mail address: STynes@hrsonline.org.

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t Consensus Recommendations on LQTS Diagnosis

≥3.5 in the absence of a secondary cause for QT prolongation *and/or*
pathogenic mutation in one of the LQTS genes *or*
ted for heart rate using Bazett's formula (QTc) ≥500 ms in repeated 12-lead electrocardiogram
ry cause for QT prolongation.
of a QTc between 480–499 ms in repeated 12-lead ECGs in a patient with
secondary cause for QT prolongation and in the absence of a pathogenic

on LQTS Therapeutic Interventions

s are recommended in all patients with a diagnosis of LQTS:
ing drugs (www.qtdrugs.org)
tion of electrolyte abnormalities that may occur during diarrhea, vomiting, metabolic
diets for weight loss.
ded for patients with a diagnosis of LQTS who are:
≥470 ms *and/or*
or documented ventricular tachycardia/ventricular fibrillation (VT/VF).
vation (LCSD) **is recommended** for high-risk patients with a diagnosis of LQTS in whom:
defibrillator (ICD) therapy is contraindicated or refused *and/or*
not effective in preventing syncope/arrhythmias, not tolerated, not accepted or
nded for patients with a diagnosis of LQTS who are survivors of a cardiac arrest.
engage in competitive sports **should be** referred to a clinical expert for evaluation of risk.
in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤470 ms.
ul in patients with a diagnosis of LQTS who experience recurrent syncopal events while
s with a diagnosis of LQTS who experience breakthrough events while on therapy with
be useful, as add-on therapy, for LQT3 patients with a QTc >500 ms who shorten their
acute oral drug test with one of these compounds.
tances, ICD implantation **is not indicated** in asymptomatic LQTS patients who have not
herapy.

rome (LQTS) have
n all ethnic groups.
a paucity of cases
among African-
evalence of LQTS
CG study, comple-
ned on over 44,000
e-causing mutations
infants with a QTc
(ms), respectively.
ce of about 1:2000
1:1583 to 1:4350).
an abnormally long
gnificant number of

Genetic variants

Since 1995, when the first three genes responsible for LQTS were identified,[6–8] molecular genetic studies have revealed a total of 13 genetic forms of congenital LQTS caused by mutations in genes encoding potassium-channel proteins, sodium-channel proteins, calcium channel-related factors, and membrane adaptor proteins. Patients with *LQT1*, *LQT2*, and *LQT3* genotypes with mutations involving *KCNQ1*, *KCNH2*, and *SCN5A* make up over 92% of patients with genetically confirmed LQTS. Up to 15%–20% of patients with LQTS remain genetically elusive.[1] Mutations in auxiliary β-subunits to *KCNQ1* (*KCNE1*, *LQT5*) and *KCNH2* (*KCNE2*, *LQT6*) are infrequent, but they result in clinical phenotypes similar to patients with mutations in their associated α-subunits of *KCNQ1* and *KCNH2*. A recessive form of LQTS, the Jervell and Lange-Nielsen syndrome, involves the same (homozygous) or different (compound heterozygous) *KCNQ1*

lent and is associated
2.1, *LQT7*) result in
en-Tawil syndrome
remaining LQTS
ach been identified
uals.
s (single nucleotide
ses unrelated genes,
penetrance of LQTS
ng the same gene

ail under two main
the electrocardio-

ains of torsades de
duration, produces
eteriorates into VF
atients, the natural
ce of a number of
to sudden death.
epresents the main
atic patients. Atrial
n, are more frequent
10,11

mic events are, to a
arrhythmic events
ress in *LQT1*, at rest
QT2 patients, and at

numerous. While the
ark of LQTS, it is not
T3) and 37% (*LQT1*)
terval within normal
s not only prolonged
alterations, some of
opic T-wave alter-
G pattern of LQTS,
stability. Notches on
and their presence is
events.[36] Long sinus
tients.

on measurement of
QTc) using Bazett's
to diagnose LQTS,
TC prolongation that
conditions, electro-
scoring system has
ount the age of the
ptoms, and QTc and
f LQTS.[17,18]

Approximately 20%–25% of patients with LQTS confirmed by the presence of an LQTS gene mutation may have a normal range QTc.[13,19] The use of provocative tests for QT measurement during change from a supine to standing position,[20] in the recovery phase of exercise testing,[21,22] or during infusion of epinephrine[23,24] has been proposed - to unmask LQTS patients with normal QTc at resting ECG. These tests may be considered in uncertain cases. However, the clinical use of this test requires more extensive validation.

Risk stratification

Individuals at the extremes of the curve, those at very high or at very low risk, are easy to identify. For the larger group, in the gray area, risk stratification is difficult and can be fraught with errors in either direction. There are genetic and clinical clues that facilitate risk assessment.

Specific genetic variants, such as the Jervell and Lange-Nielsen syndrome[25] and the extremely rare Timothy syndrome (*LQT8*)[26] are highly malignant, manifest with major arrhythmic events very early, and respond poorly to therapies. Within the most common genetic groups, specific locations, types of mutations, and degree of mutation dysfunction are associated with different risks. Mutations in the cytoplasmic loops of *LQT1*,[27,28] *LQT1* mutations with dominant-negative ion current effects,[29] and mutations in the pore region of *LQT2*[29,30] are associated with higher risk, and the same is true even for some specific mutations with an apparently mild electrophysiological effect.[31] By contrast, mutations in the C-terminal region tend to be associated with a mild phenotype.[32]

Clinically, there are several patterns and groups associated with differential risk. High risk is present whenever QTc >500 ms[13,33] and becomes extremely high whenever QTc >600 ms. Patients with a diagnosis of LQTS who are identified by genetic testing as having two unequivocally pathogenic variants and a QTc >500 ms (including homozygous mutations as seen in patients with Jervell and Lange-Nielsen syndrome) are also at high risk, in particular when they are symptomatic. The presence of overt T-wave alternans, especially when evident despite proper therapy, is a direct sign of electrical instability and calls for preventive measures. Patients with syncope or cardiac arrest before age 7 have a higher probability of recurrence of arrhythmic events while on beta-blockers.[34] Patients who have syncope or cardiac arrest in the first year of life are at high risk for lethal events and may not be fully protected by the traditional therapies.[35,36] Patients who suffer arrhythmic events despite being on full medical therapy are at higher risk.

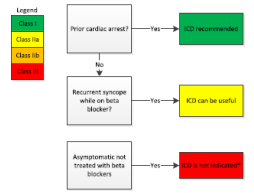
By contrast, it also is possible to identify patients at lower risk. Concealed mutation-positive patients are at low, but not zero, risk for spontaneous arrhythmic events. The risk for an arrhythmic event in this group has been estimated around 10% between birth and age 40 in the absence of therapy.[13] A major risk factor for patients with asymptomatic genetically diagnosed LQTS comes from drugs that block the I_{Kr} current and by conditions that lower their plasma potassium level.

s, who are asympto-
risk of becoming
ales, and especially
age 40.

h LQTS is related in
rhythmic events, as
CC/ESC Guidelines
are still relevant in
oidance of strenuous
upervision in *LQT1*
loud noises (alarm
ts, and avoidance of
S patients, should be
competitive sports is
. Recently available
sion in competitive
be safe.[38] Based on
n, low-risk patients,
with borderline QTc
toms, and no family
ths (SCD), may be
orts in special cases
f appropriate LQTS
is performed where
liable and personnel
pplies especially to
patients with a high
tients with exercise-
should be avoided.
ts with LQTS and
ow.

n LQTS, including
al QTc, unless there
hma.[34,35] Presently,
r cardioselective or
ver, the former is
from asthma. Long-
r sustained-release
medications can be
ce of wide fluctua-
suggest that, partic-
drugs may perform
While studies are not
sage, full dosing for
mmended. Abrupt
be avoided as this

D) (Figure 1)
ts who are resusci-
tated from cardiac arrest.[40] ICD is often favored in patients with LQTS-related syncope who also receive beta-



*Except under special circumstances, ICD implantation is not indicated in asymptomatic patients who have not been tried on beta-blocker therapy

Figure 1 Consensus recommendations for ICDs in patients diagnosed with long QT syndrome.

blockers.[41] Prophylactic ICD therapy should be considered in very-high-risk patients such as symptomatic patients with two or more gene mutations, including those with the Jervell and Lange-Nielsen variant with congenital deafness.[25] ICD therapy has life-time implications. Complications are not infrequent, especially in the younger age group, and risk/benefit considerations should be carefully considered before initiating this invasive therapy.[42,43] Accordingly, *LQT1* patients who experience a cardiac arrest while not receiving beta-blockers may only be treated with beta-blockers or with LCSD (see below) in settings when the implant of an ICD is likely to be associated with high risk, such as in infants and pediatric patients.[44,45] LQTS-related sudden death in one family member is not an indication for ICD in surviving affected family members unless they have an individual profile of high risk for arrhythmic events.[46]

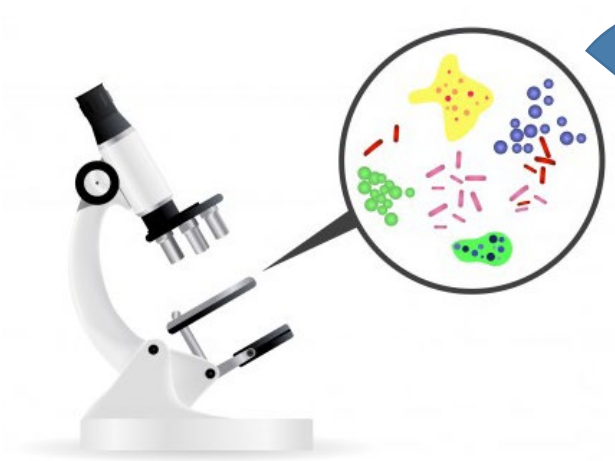
Considering the potential complications associated with the implantation of an ICD in young individuals, we recommend caution when using a device in asymptomatic patients. We suggest that ICD therapy not be used as first-line therapy in an asymptomatic LQTS patient; beta-blockers remain the first-line therapy in LQTS patients. However, an ICD may be considered in those patients who are deemed to be at very high risk, especially those with a contraindication to beta-blocker therapy. A decision to have an ICD implanted should be made only after a careful consideration of (1) risk of sudden death; (2) the short- and long-term risks of ICD implantation; and (3) values and preferences of the patient. The physician must discuss the risks and benefits of ICD therapy with the patient, and patient's values and preferences are important in this decision.

Whenever ICD therapy is chosen, thoughtful programming (in particular to prevent inappropriate shocks) is pertinent and usually requires a VF-only zone, with a cutoff rate greater than 220–240 bpm.

SD)
ng the probability for
luding those who are
kers alone.[47] The
a left supraclavicular
procedure in experi-
ly used in very-high-
D therapy may be
al size of the patient,
-blocker therapy, and
ant of beta-blockers.

Other therapies: Gene-specific LQTS therapies including oral mexiletine,[48] flecainide,[33] and ranolazine[34] have been utilized to a limited extent in high-risk LQTS patients refractory to beta-blockers or in patients with recurrent events despite ICD and LCSD therapies. The use of these sodium channel blockers has generally been limited to LQT3 patients. In brief, the use of these agents is usually carried out on an observational trial basis, with, occasionally, some dramatic results for individual subjects. Follow-up experience with these therapies is limited. No general recommendations can be made at this time in the use of gene-specific therapies.

Richtlijnen zijn vaak evidence-based



Basaal onderzoek

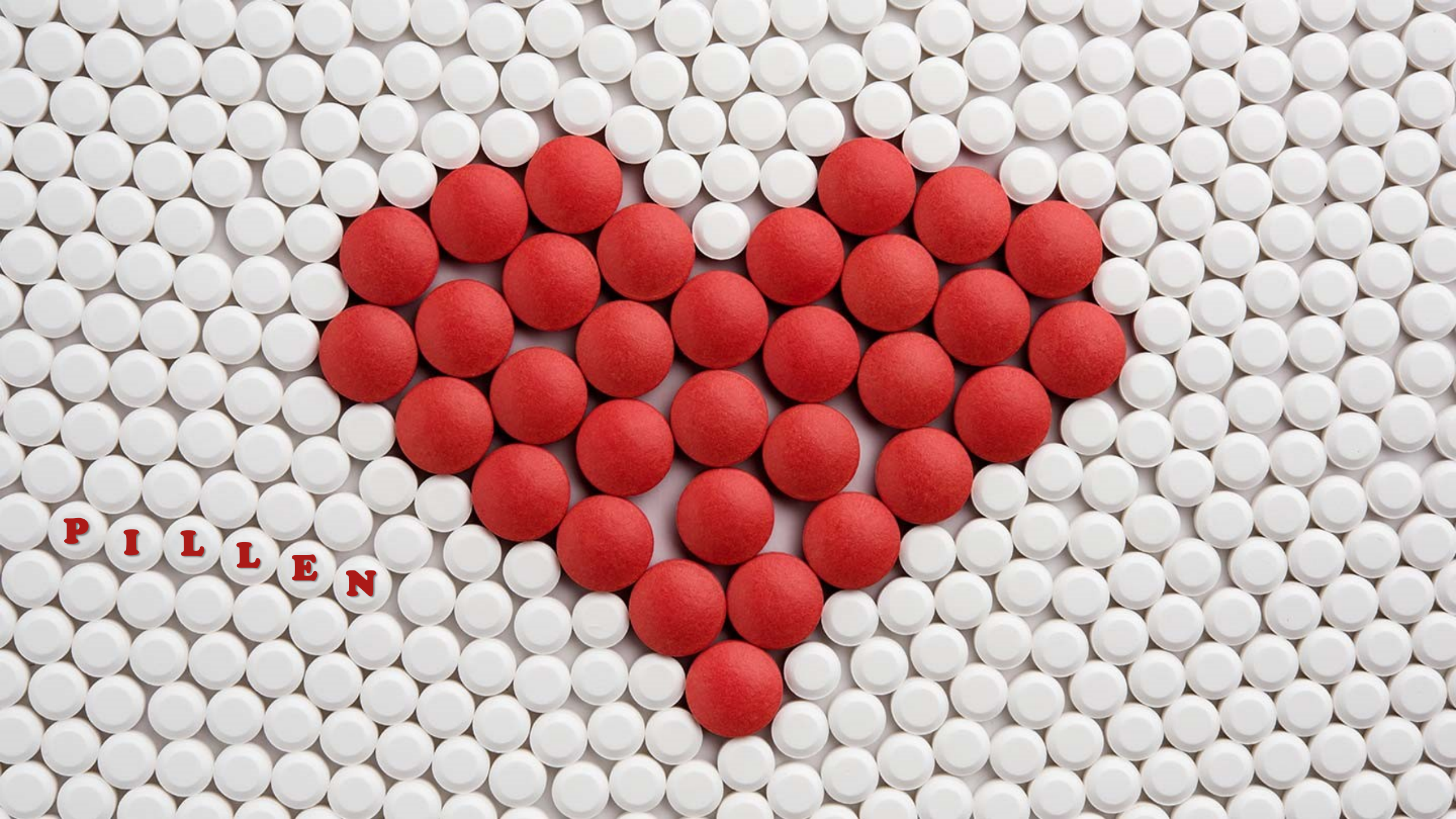
Dierexperimenteel onderzoek

Cohort studies

Richtlijnen zijn soms aanbevelingen van experts

Leefstijladviezen

(voor alle patiënten met lang QT syndroom)


PILLEN

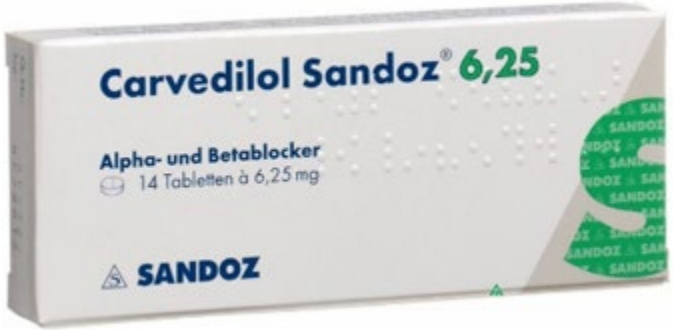
β-blokkers


Metoprolol
Farmacias del Ahorro
Metoprolol
Tabletas
100 mg
Vía de Administración: Oral.
Caja con 20 tabletas


Nabila® 2,5
Nebivolol 2,5 mg
2,5
Industria Argentina
Venta bajo receta
28 comprimidos
RAFFO


Crescent Pharma
ATENOLOL
Tablets 25mg
Calendar Pack
Each film-coated tablet contains Atenolol 25mg.
Also contains E110 (see leaflet for further information).
28 Tablets


Bei Bluthochdruck und koronarer Herzkrankheit
Bisoprolol AbZ
5 mg Tabletten
Wirkstoff: Bisoprololfumarat
30 Tabletten N1
AbZ pharma

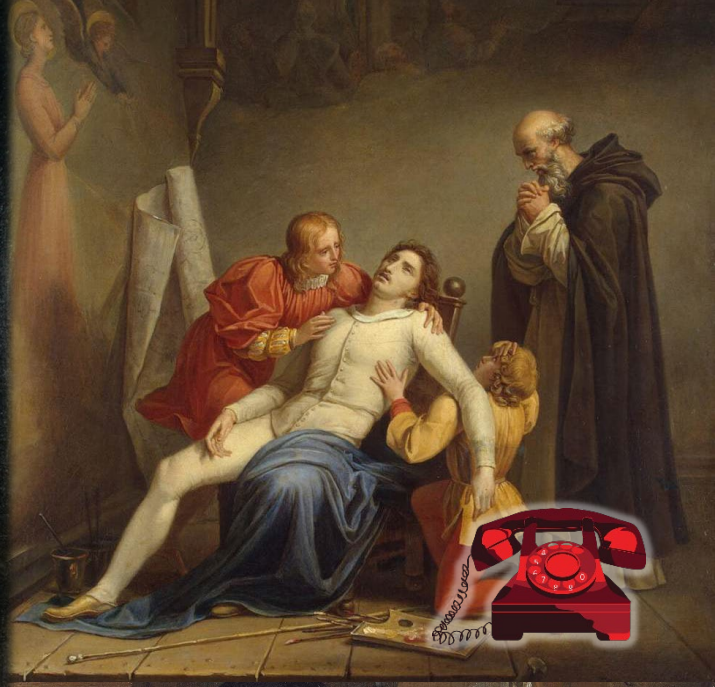

Carvedilol Sandoz® 6,25
Alpha- und Betablocker
14 Tabletten à 6,25 mg
SANDOZ


Propranolol Tablets
28 tablets
10 mg
actavis
Propranolol Tablets
10 mg
28 tablets
For Oral

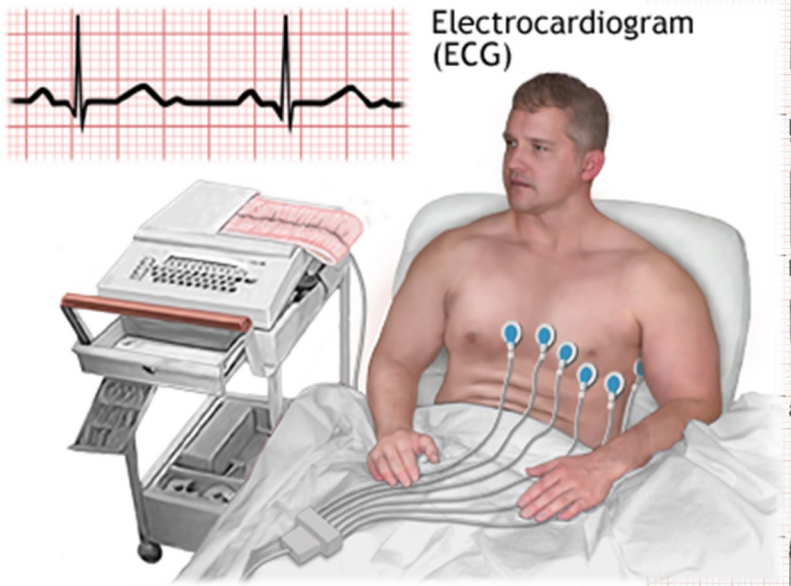

Céliprolol
RANBAXY
200 mg
Adulte
84 Comprimés pelliculés

Wegraking

(en hartstilstand!)




QT tijd > 470 ms



QT tijd > 470 ms

BTL-08 LT 25.07.2011 12:39:52 6.01.0000R100 d3245 page 1

patient

first name:	Ram
surname:	Kishor
ID:	1335
sex:	male
Age:	23
Doctor`s Name:	xxyz

measurement

RR:	752 ms
QRS:	92 ms
QT / QTc:	328 / 378 ms
P / PQ(PR):	88 / 146 ms
P / QRS / T:	66° / 79° / 21°

BTL-08 LT 25.07.2011 12:39:52 6.01.0000R100 d3245 page 2

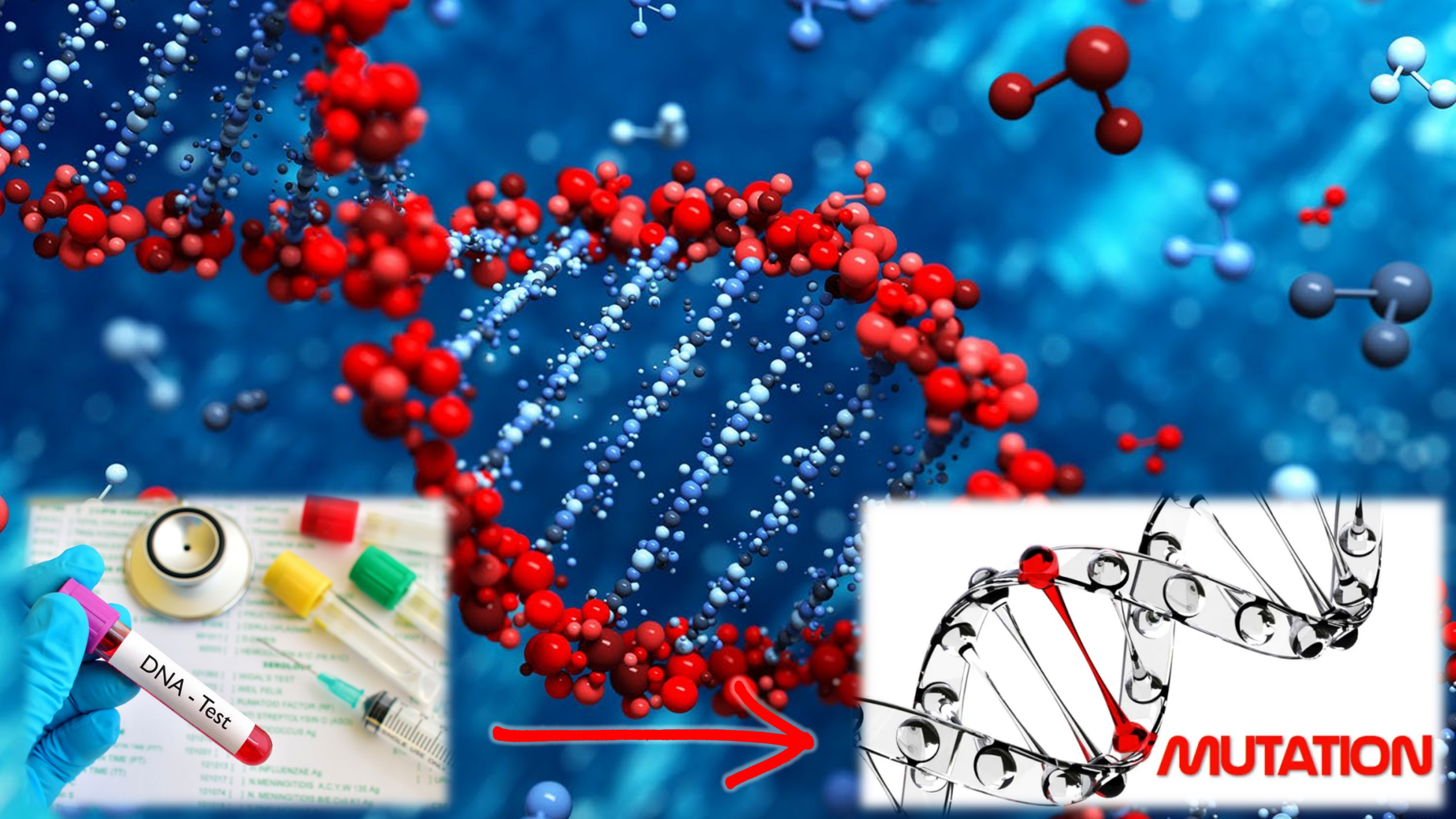
interpretation (unconfirmed report)

SINUS RYTHM
ECG WITHIN NORMAL LIMITS

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

0s 1s 2s 3s 4s 5s 6s 7s 8s 9s 10s

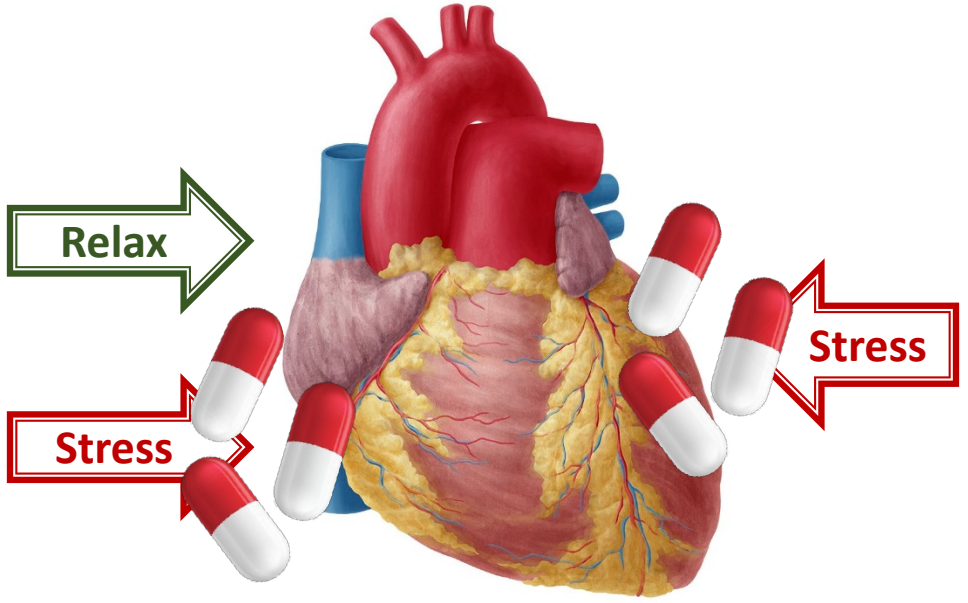
*Sarvodya Hospital 25 mm/s 10/10 mm/mV in time HR = 80 B T L


DNA - Test
MUTATION

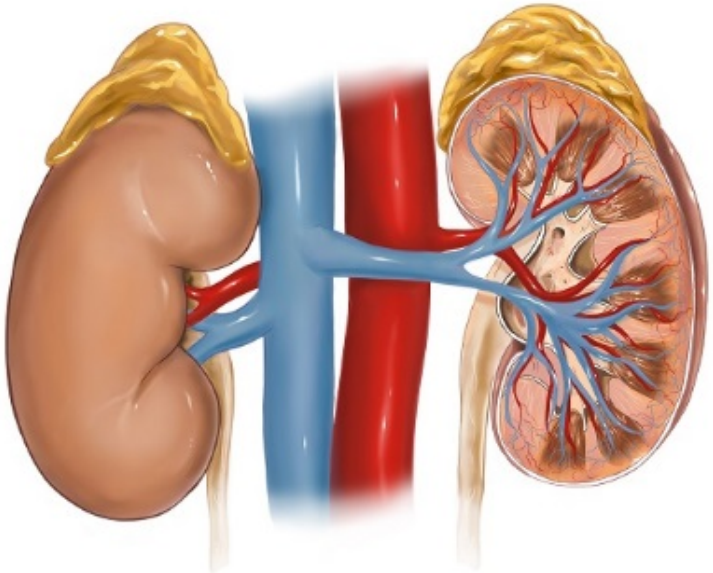
Hoe werken β-blokkers?

Hersenen

Hart



Bijnieren



ADRENALINE

METOPROLOL

Vermoeidheid, hypotensie, duizeligheid, hoofdpijn, trage hartslag.

ATENOLOL

Koude extremiteiten, vermoeidheid, duizeligheid, hoofdpijn, lage bloeddruk

BIJWERKINGEN

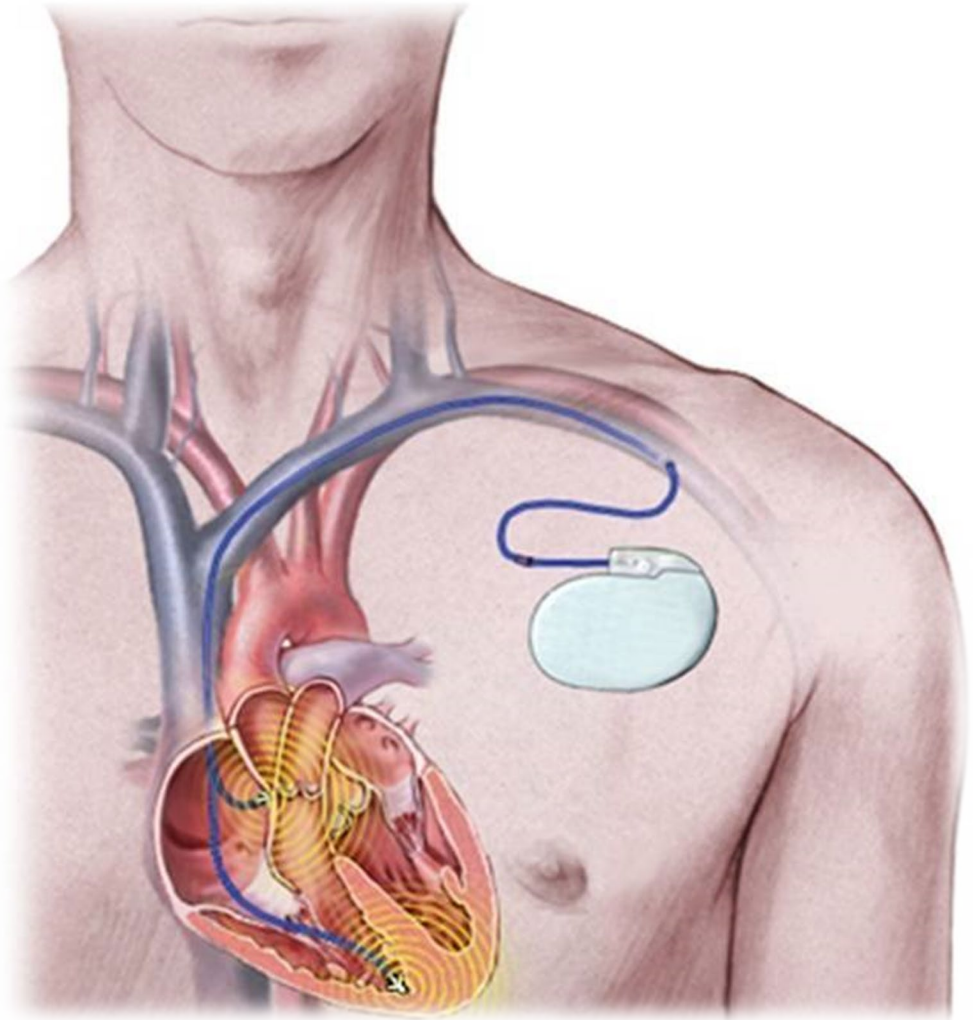
BISOPROLOL

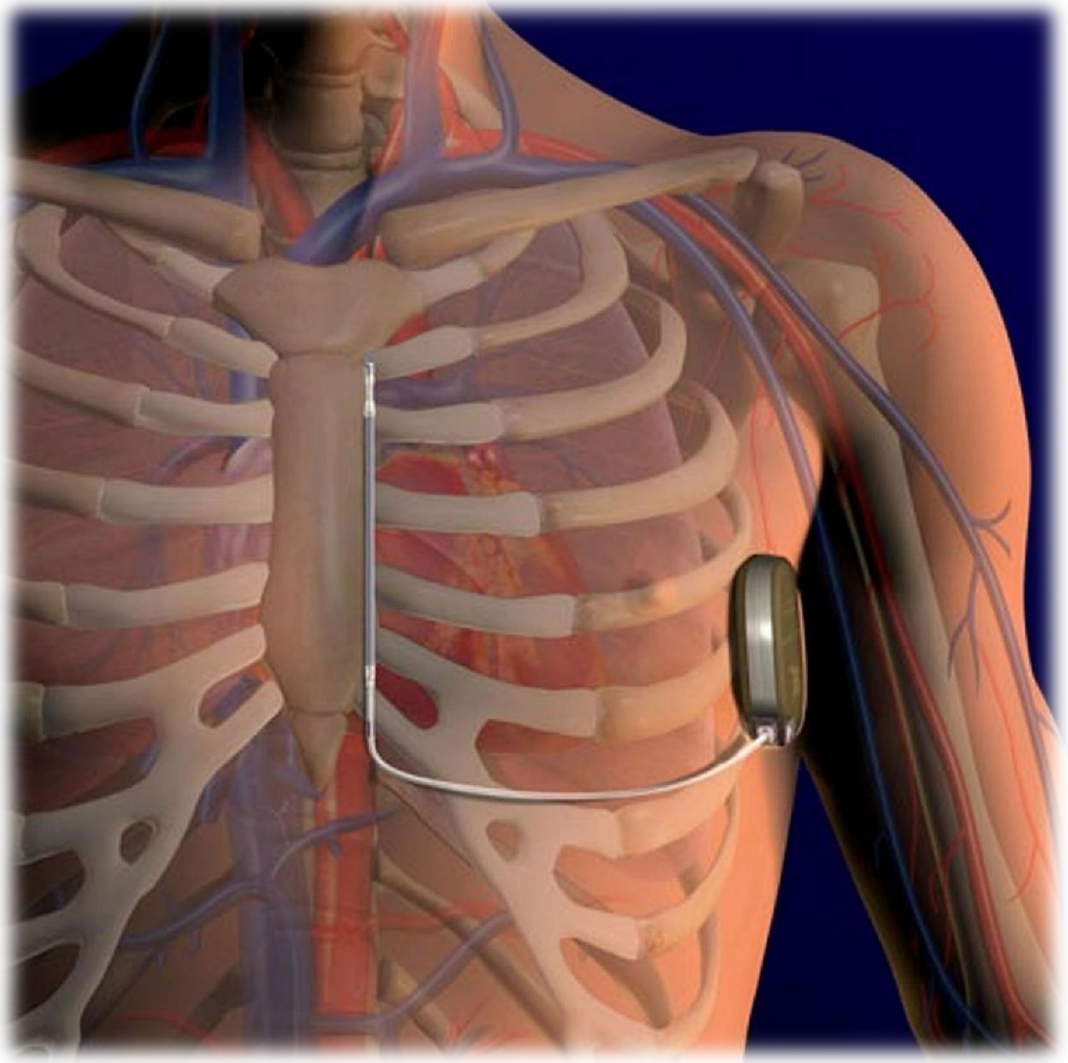
Trage hartslag, vermoeidheid, duizeligheid, hoofdpijn.

PROPRANOLOL

Trage hartslag, nachtmerries, koude handen/voeten, vermoeidheid, traagheid.

ICD

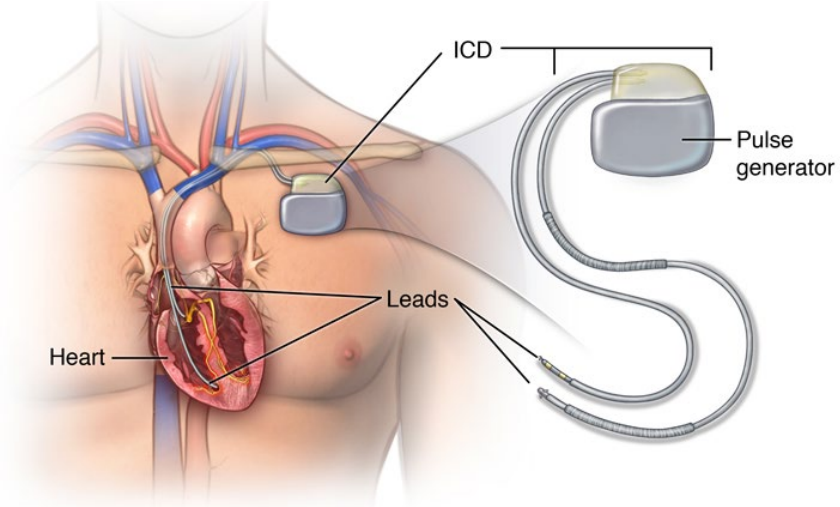




Hartstilstand

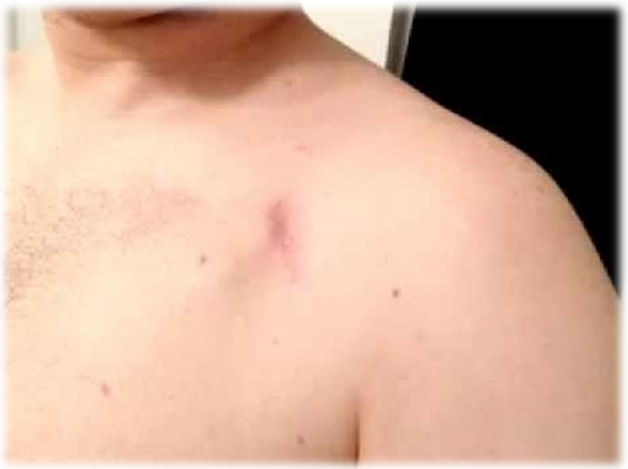
Wegraking

onder β-blokker



BIJWERKINGEN VAN ICD

Onterechte SHOCK



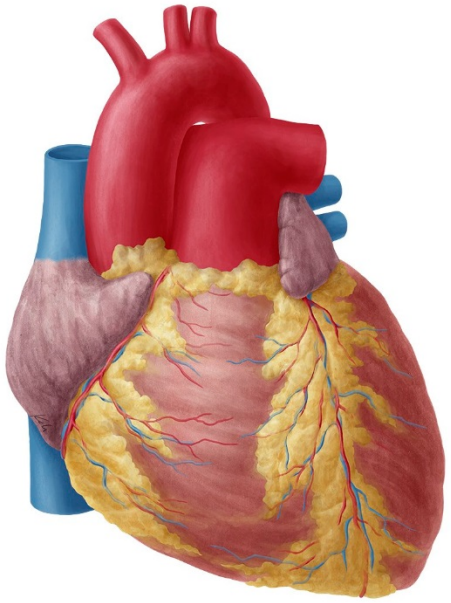
Ganglion stellatum blok

Hersenen

Relax

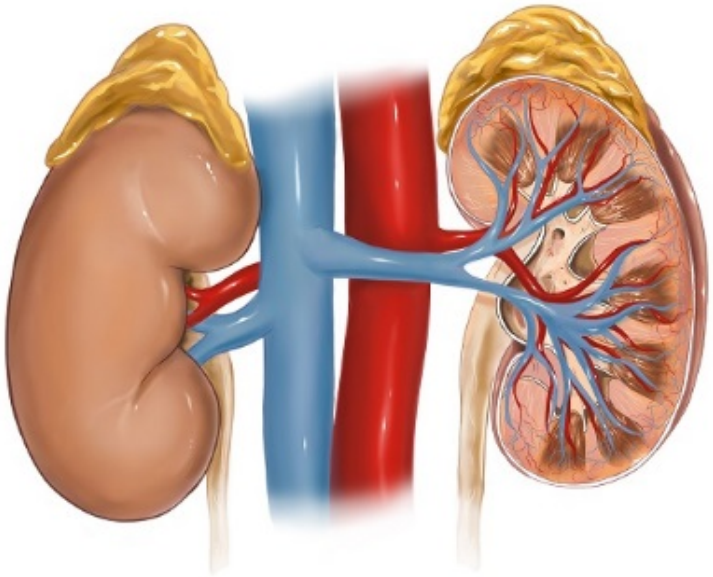
Stress

Hart

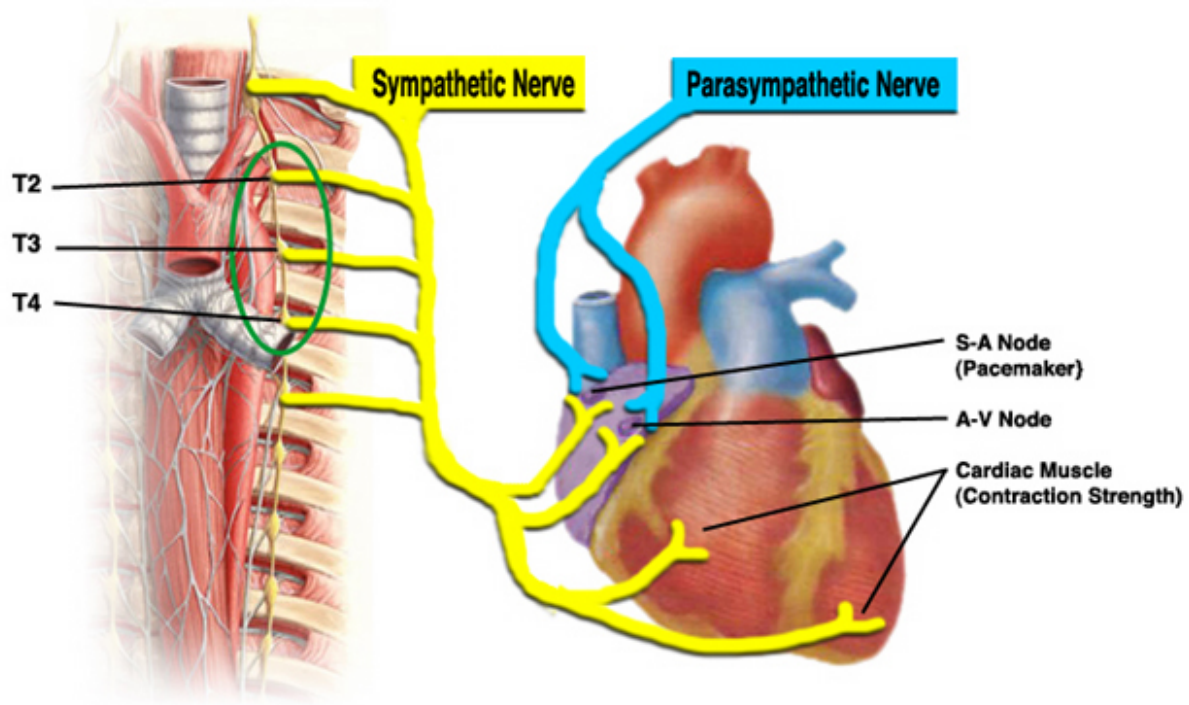


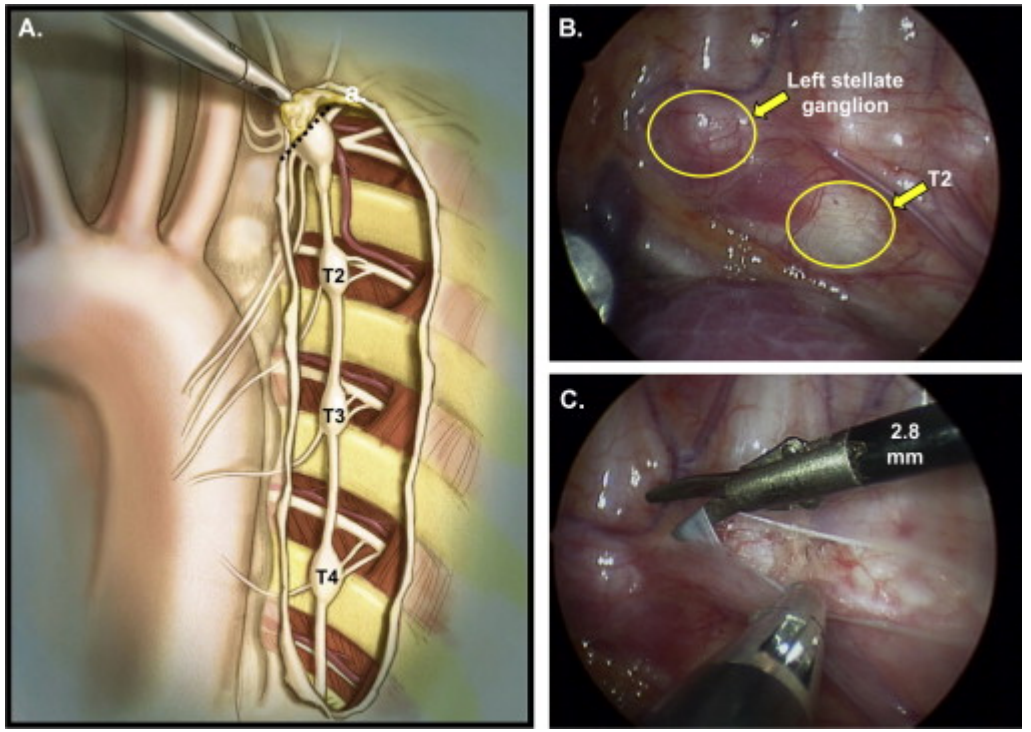
Stress

Bijnieren



Ganglion stellatum blok

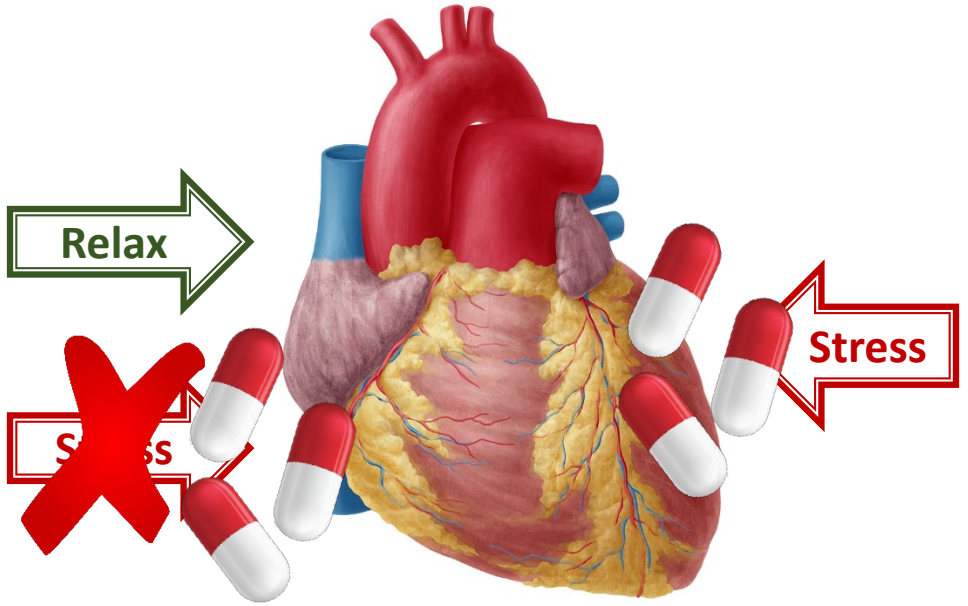




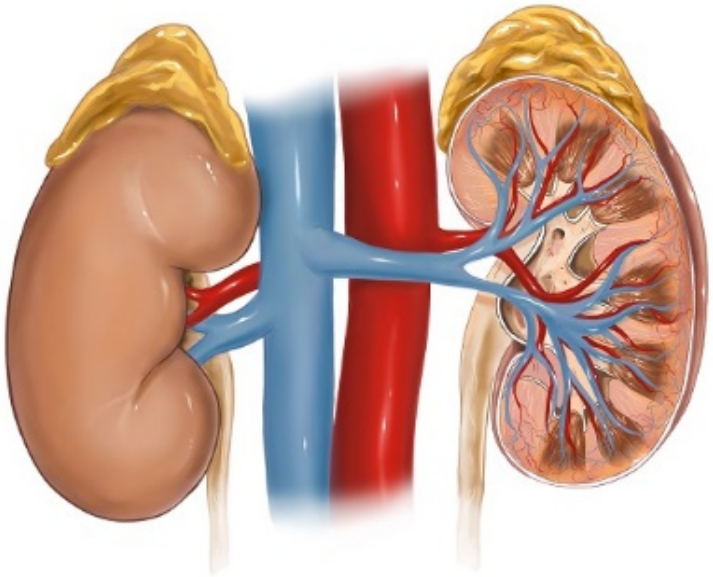
Ganglion stellatum blok

Hersenen

Hart



Bijnieren



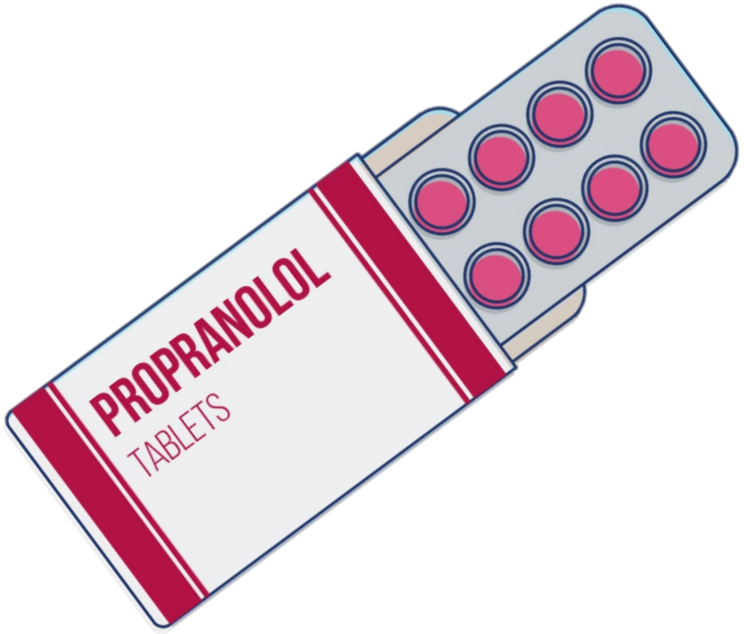
Wanneer een ganglion stellatum blok?

ICD niet mogelijk
én hartstilstand
of wegraking
ondanks β-blokker

β-blokker niet mogelijk
én hartstilstand
of wegraking
of lange QT tijd

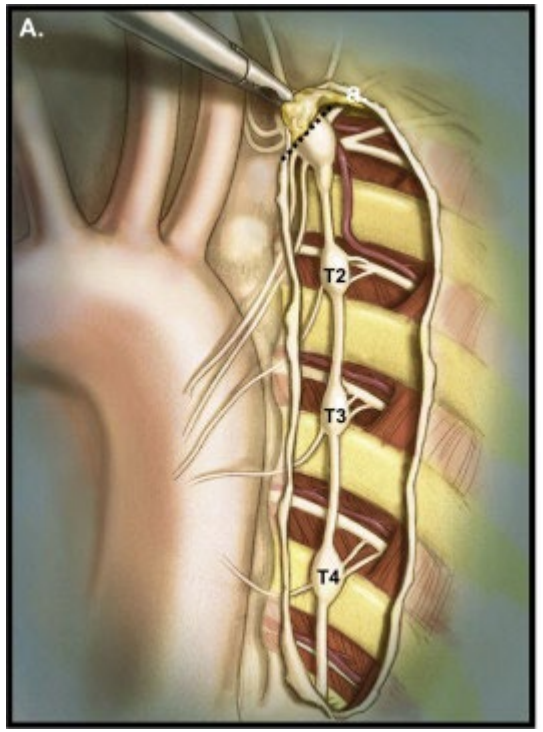
β-blokker en ICD
én ICD shocks

Behandeling van lang QT syndroom



β-blokkers

ICD



Ganglion stellatum blok

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Share. Care. Cure.

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GUARD-Heart

Gateway to Uncommon And Rare Diseases of the Heart

Behandeling van lang QT syndroom

A.S. Amin

Cardioloog

European Reference Network
for rare or low prevalence complex diseases

Network Heart Diseases
(ERN GUARD-HEART)

Amsterdam UMC

European Commission