# Actualització en Inotrops

## Ús de Levosimendan en Insuficiència Cardíaca Crònica

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Programa Integrat d' Atenció al Pacient amb IC Litoral Mar de Barcelona

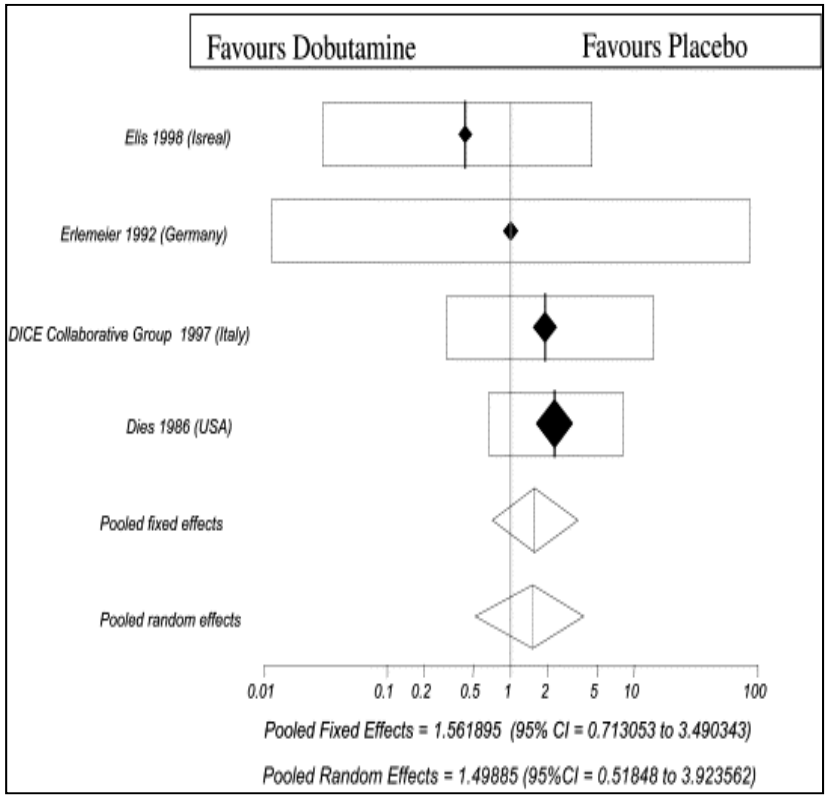
*Dilluns, 1 d' Octubre de 2012*

# Inotròpics Intermitents

Controvèrsies

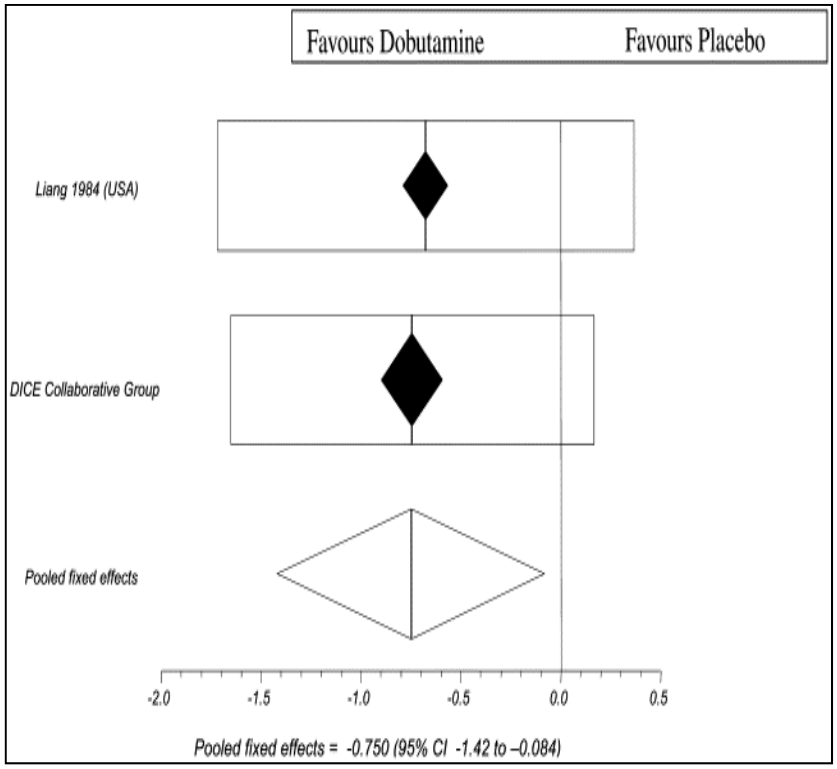
# “Morir de pie o vivir de rodillas!”

ARGUMENTS EN CONTRA




MORTALITAT

ARGUMENTS A FAVOR




QOL

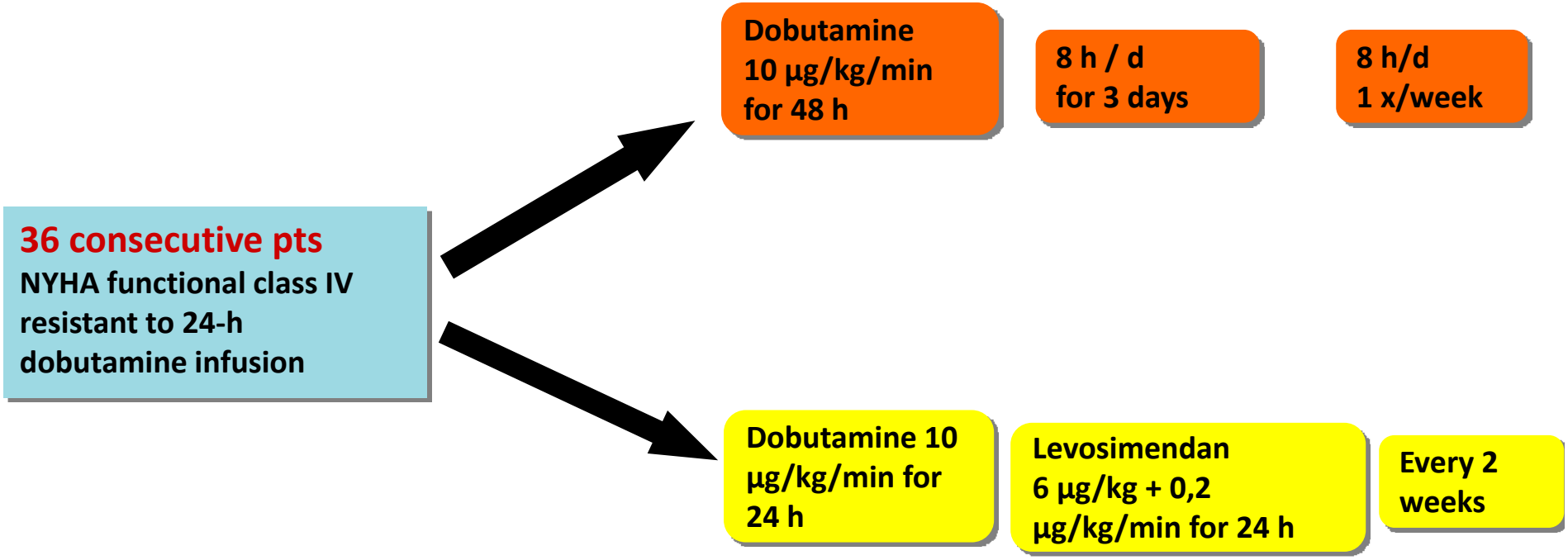
Thackray S et al. Eur Journal Heart Failure 2002;4(4):515

# Levosimendan Intermitent

Experiències Publicades

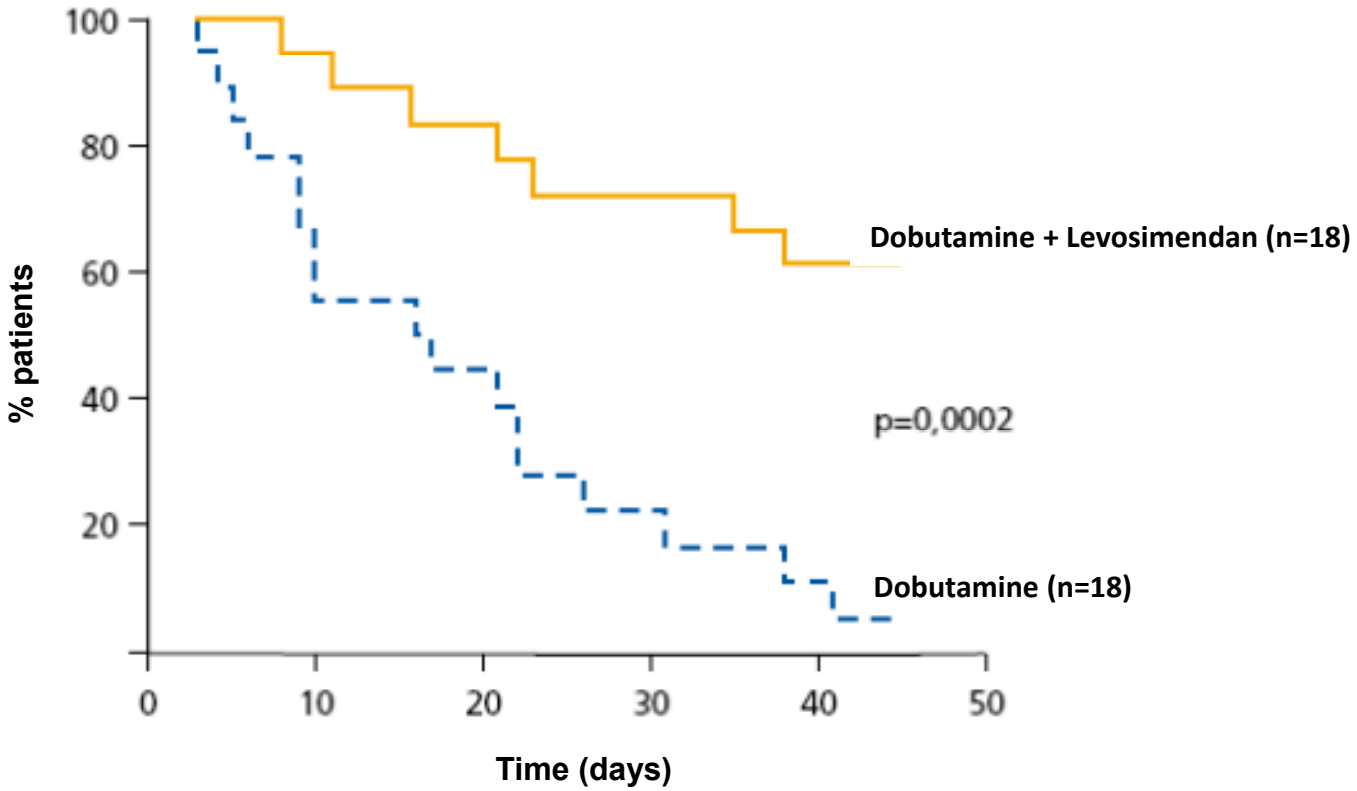
# Efficacy and Safety of Intermittent, Long-Term, Concomitant *Dobutamine* and *Levosimendan* Infusions in Severe Heart Failure Refractory to *Dobutamine* Alone

John N. Nanas, MD, PhD, Panagiotis Papazoglou, MD, Eleftheria P. Tsagalou, MD, Argirios Ntalianis, MD, Elias Tsolakis, MD, John V. Terrovitis, MD, John Kanakakis, MD, Seraphim N. Nanas, MD, George P. Alexopoulos, MD, and Maria I. Anastasiou-Nana, MD




*Nanas NJ et al. Am J Cardiol 2005;95:768-71*

# Supervivència




**Milloria d' Índex cardiac, PCP, FEVE als 3 mesos de seguiment**

*Nanas NJ et al. Am J Cardiol 2005;95:768-71*

# A 6-Month Follow-up of Intermittent Levosimendan Administration Effect on Systolic Function, Specific Activity Questionnaire, and Arrhythmia in Advanced Heart Failure

SOPHIE MAVROGENI, MD, FESC, GREGORY GIAMOUZIS, MD, EVANGELIA PAPADOPOULOU, MD, SOPHIA THOMOPOULOU, MD, ATHANASIOS DRITSAS, MD, GEORGE ATHANASOPOULOS, MD, ELIAS ADREANIDES, MD, IOANNIS VASSILIADIS, MD, KONSTANTINOS SPARGIAS, MD, DIMOSTHENIS PANAGIOTAKOS, MD, AND DENNIS V. COKKINOS, PROF.

- **Open**, randomised, prospective design
- **50 patients** with left ventricular dysfunction and NYHA class III-IV randomised to two groups
- Dosing:
  - **Levosimendan group: 10-min bolus of 6 mcg/kg followed by 24-h infusion of 0.1 mcg/kg/min with uptitration to 0.2 mcg/kg/min) given monthly for 6 months** (n=25)
  - Control group: Standard treatment (n=25)

*Mavrogeni et al. J Cardiac Fail 2007;13:556-9*

# Eficàcia i Seguretat

**Table 3.** Comparison of ECHO, Holter, and SAQ Parameters in Patients Treated With Levosimendan and Controls at Inclusion and After 6 Months Treatment

| | Levosimendan | | Controls | | RANOVA |
|---|---|---|---|---|---|
| Parameter | Inclusion | 6 Months | Inclusion | 6 Months | *P* Value* |
| FS (%) | 12 ± 3 | 15 ± 3 | 12 ± 3 | 11 ± 3 | .006 |
| LVEF (%) | 22 ± 6 | 28 ± 7 | 22 ± 5 | 21 ± 4 | .003 |
| EDV (mL/m$^2$) | 138 ± 20 | 120 ± 20 | 145 ± 30 | 157 ± 25 | .0001 |
| ESV (mL/m$^2$) | 98 ± 25 | 82 ± 20 | 99 ± 28 | 107 ± 21 | .044 |
| MR grade | 2.4 ± 1.0 | 1.5 ± 0.8 | 2.5 ± 0.6 | 2.7 ± 0.6 | .0001 |
| RVSP (mm Hg) | 61 ± 16 | 50 ± 13 | 61 ± 14 | 63 ± 14 | .052 |
| Max HR | 95 ± 21 | 108 ± 16 | 93 ± 15 | 98 ± 20 | .134 |
| Min HR | 61 ± 10 | 58 ± 19 | 58 ± 8 | 61 ± 8 | .917 |
| Mean HR | 78 ± 13 | 79 ± 6 | 80 ± 13 | 82 ± 10 | .348 |
| SVB | 393 ± 115 | 358 ± 63 | 402 ± 120 | 415 ± 180 | .319 |
| PVB | 1535 ± 1256 | 2010 ± 1188 | 1610 ± 1150 | 1710 ± 1190 | .689 |
| Couplets | 89 ± 57 | 104 ± 88 | 95 ± 40 | 100 ± 45 | .899 |
| NSVT | 8 ± 5 | 12 ± 6 | 10 ± 7 | 13 ± 6 | .190 |
| SAQ (METS) | 1.7 ± 1.6 | 2.7 ± 1.2 | 2.2 ± 1.1 | 1.7 ± 1.6 | .423 |

ECHO, echocardiogram; SAQ, specific activity questionnaire; FS, shortening fraction of left ventricle; LVEF, left ventricular ejection fraction; EDV, end-diastolic volume of left ventricle; ESV, end-systolic volume of left ventricle; MR, mitral regurgitation; RVSP, right ventricular systolic pressure; HR, heart rate; SVB, supraventricular beats; PVB, premature ventricular beats; NSVT, nonsustained ventricular tachycardia (*$P$ value for repeated measures analysis of variance [RANCOVA] [inclusion vs. 6 months] between levosimendan and controls).

- **Symptomatic improvement**: LEVO 65% vs. CONTROL 20%, p<0.01
- **6-month mortality**: LEVO 2 pts vs. CONTROL 8 patients (8% vs. 32%, p<0.05).

*Mavrogeni et al. J Cardiac Fail 2007;13:556-9*

CARDIOVASCULAR MEDICINE

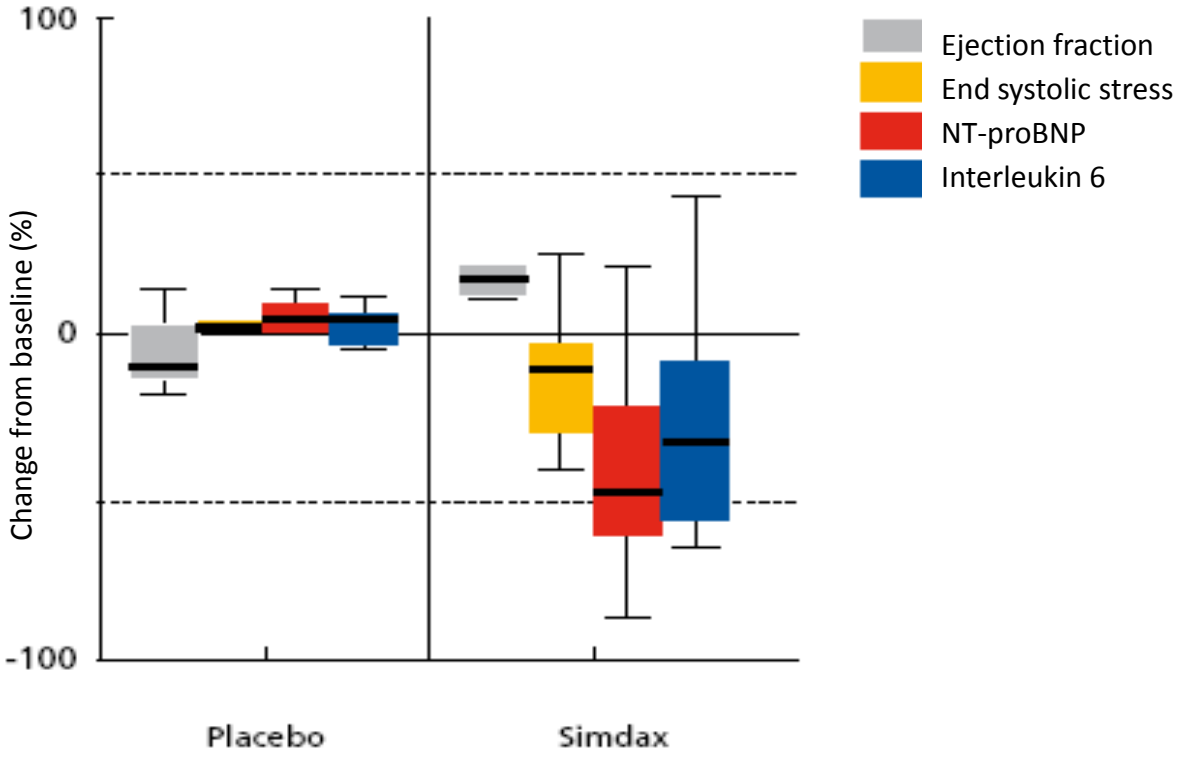
# Effects of serial levosimendan infusions on left ventricular performance and plasma biomarkers of myocardial injury and neurohormonal and immune activation in patients with advanced heart failure

J T Parissis, S Adamopoulos, D Farmakis, G Filippatos, I Paraskevaidis, F Panou, E Iliodromitis, D Th Kremastinos

- **Open**, randomised, **placebo-controlled trial**
- 25 patients with decompensated chronic heart failure
- Dosing:
  - **Levosimendan group: 5 infusions of 24-h (10-min bolus 6mcg/kg followed by 0.1 mcg/kg/min) every 3 weeks (n=17)**
  - Placebo group (n=8)

*Parissis et al. Heart 2006;92:1768-72*

# Eficàcia




*Parissis et al. Heart 2006;92:1768-72*

# Effects of *Levosimendan* on Right Ventricular Function in Patients With Advanced Heart Failure

John T. Parissis, MD*, Ioannis Paraskevaidis, MD, Vasiliki Bistola, MD, Dimitrios Farmakis, MD, Fotios Panou, MD, Kallirrhoe Kourea, MD, Maria Nikolaou, MD, Gerasimos Filippatos, MD, and Dimitrios Kremastinos, MD

New York Heart Association functional class, echocardiographic indexes, and B-type natriuretic peptide and interleukin levels in the levosimendan and placebo groups before and after therapeutic intervention

| Variable | Levosimendan (n = 36) | | Placebo (n = 18) | |
|---|---|---|---|---|
| | Before | After | Before | After |
| New York Heart Association class | 3.5 ± 0.6 | 2.4 ± 0.7* | 3.5 ± 0.5 | 3.6 ± 0.6 |
| LV ejection fraction (%) | 21 ± 6 | 28 ± 6* | 23 ± 6 | 24 ± 7 |
| Tricuspid annular displacement (mm) | 13.7 ± 4.3 | 15.0 ± 4.0 | 12.2 ± 3.5 | 12.2 ± 3.5 |
| Systolic pulmonary arterial pressure (mm Hg) | 54 ± 11 | 43 ± 11* | 50 ± 16 | 51 ± 14 |
| RV TDI | | | | |
| S (cm/s) | 8.2 ± 3.2 | 9.0 ± 3.0* | 7.5 ± 1.5 | 8.0 ± 1.7 |
| QS (ms) | 156 ± 32 | 156 ± 30 | 165 ± 32 | 159 ± 26 |
| E (cm/s) | 8.5 ± 3.6 | 10.8 ± 4.1* | 7.5 ± 1.6 | 7.6 ± 2.6 |
| A (cm/s) | 10.5 ± 6.0 | 7.9 ± 4.8* | 8.0 ± 3.9 | 9.1 ± 4.5 |
| E/A | 1.5 ± 1.4 | 1.9 ± 1.5* | 1.2 ± 0.7 | 1.2 ± 1.1 |
| BNP (pg/ml) | 1,062 ± 804 | 636 ± 540* | 1,101 ± 541 | 1,140 ± 536 |
| Interleukin-6 (pg/ml) | 16.2 ± 5.6 | 12.3 ± 4.1* | 15.1 ± 4.9 | 15.8 ± 5.1 |
| Interleukin-10 (pg/ml) | 8.6 ± 2.1 | 10.3 ± 2.5* | 8.5 ± 2.3 | 8.4 ± 2.6 |
| Interleukin-6/interleukin-10 | 2.2 ± 1.5 | 1.3 ± 0.7* | 2.1 ± 1.2 | 2.2 ± 1.4* |

* Significantly different versus the corresponding value before therapy in the same group (paired *t* test or Wilcoxon's paired test).

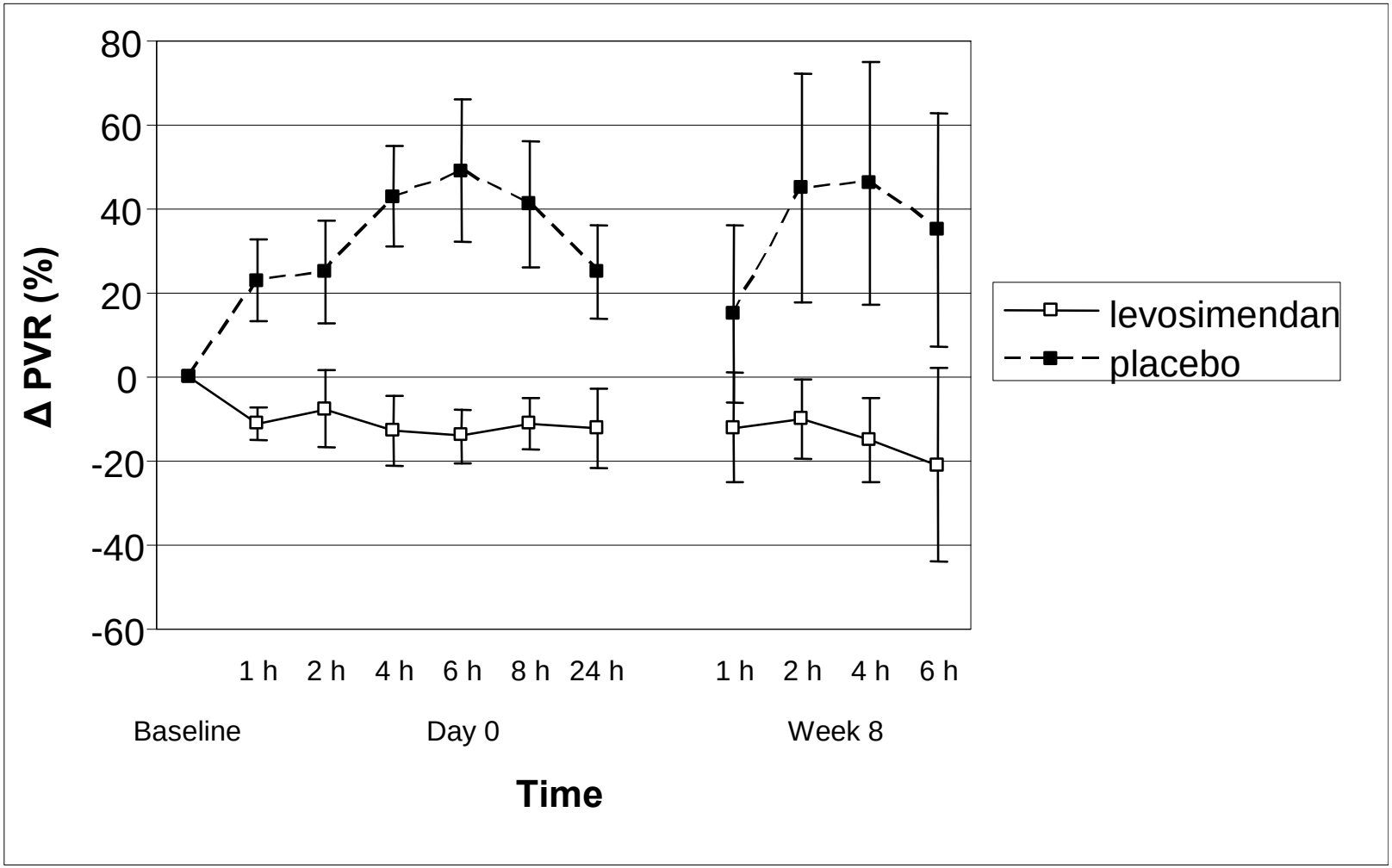
# Repetitive Dosing of Intravenous Levosimendan Improves Pulmonary Hemodynamics in Patients With Pulmonary Hypertension: Results of a Pilot Study

*Franz X. Kleber, MD, FESC, Tom Bollmann, MD, Mathias M. Borst, MD, Angelika Costard-Jäckle, MD, Ralf Ewert, MD, Matti Kivikko, MD, Tiina Petterson, PhD, Pasi Pohjanjousi, MSc, Steffen Sonntag, MD, and Gerhard Wikström, MD, FESC*

- **Randomised, double-blind placebo-controlled parallel-group** trial in patients with pulmonary hypertension
- 28 patients with **pulmonary hypertension** in four centres in Germany, one in Sweden
- Dosing:
  - initial: 12 mcg/kg/10 min bolus + 0.1 mcg/kg/min for 50 min + 0.2 mcg/kg/min up to 24 h
  - **repeated doses: 0.2 mcg/kg/min for 6 h, in total 4 times with 2-week interval**
- PEP: **Change in pulmonary vascular resistance (PVR)**

*Kleber et al. J Clin Pharmacol 2009;49:109-115*

# Change in PVR (mean ± SEM)




*Kleber et al. J Clin Pharmacol 2009;49:109-115*

# Levin et al. Circulation 2009;120:S865

- **80 advanced heart failure pts**, with a recent hospitalization for HF requiring iv. inotropes randomly assigned to
  - **24-h levo (0.1 mcg/kg/min) or placebo every 2-3 months,** in addition to optimal medical treatment
- Baseline characteristics were similar
- **Mortality**
  - 6 months: 4 (10%) versus 13 (32.5%) in favor of levosimendan
  - 12 months: 6 (15%) versus 19 (47.5%)
- **Re-admission**
  - 6 months: 9 (22.5%) versus 31(77.5%)
  - 12 months: 17 (42.5%) versus 39 (97.5%)
    - $p < 0.05$ for all comparisons.

**Intermittent Levosimendan Infusions in Advanced Heart Failure: Favourable Effects on Left Ventricular Function, Neurohormonal Balance and One-year Survival**

- **33 pacients amb ICC** que consulten per IC reaguditzada
- **Randomització 2:1 a infusions mensuals de Levosimendan (n=22) vs. Placebo (11)**
- Milloria significativa al final del seguiment de
  - **FEVE**
  - Funció diastòlica
  - Volums Ventriculars
  - **Grau IM**
  - **Nivells BNP**
- Tendència no significativa a menor mortalitat en el grup Levosimendan

*Malfatto G et al. J Cardiovasc Pharmacol 2012 (Aug 28, Epub ahead of print)*

# Rationale and design of the multicentre randomized trial investigating the efficacy and safety of pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep study)

Johann Altenberger[1]*, John T. Parissis[2], Hanno Ulmer[3] and Gerhard Poelzl[4] on behalf of the LevoRep Investigators

120 advanced chronic heart failure pts will be randomly assigned to 6-h levo (0.2 mcg/kg/min) or placebo every 2 weeks, in total 4 times in addition to optimal medical treatment

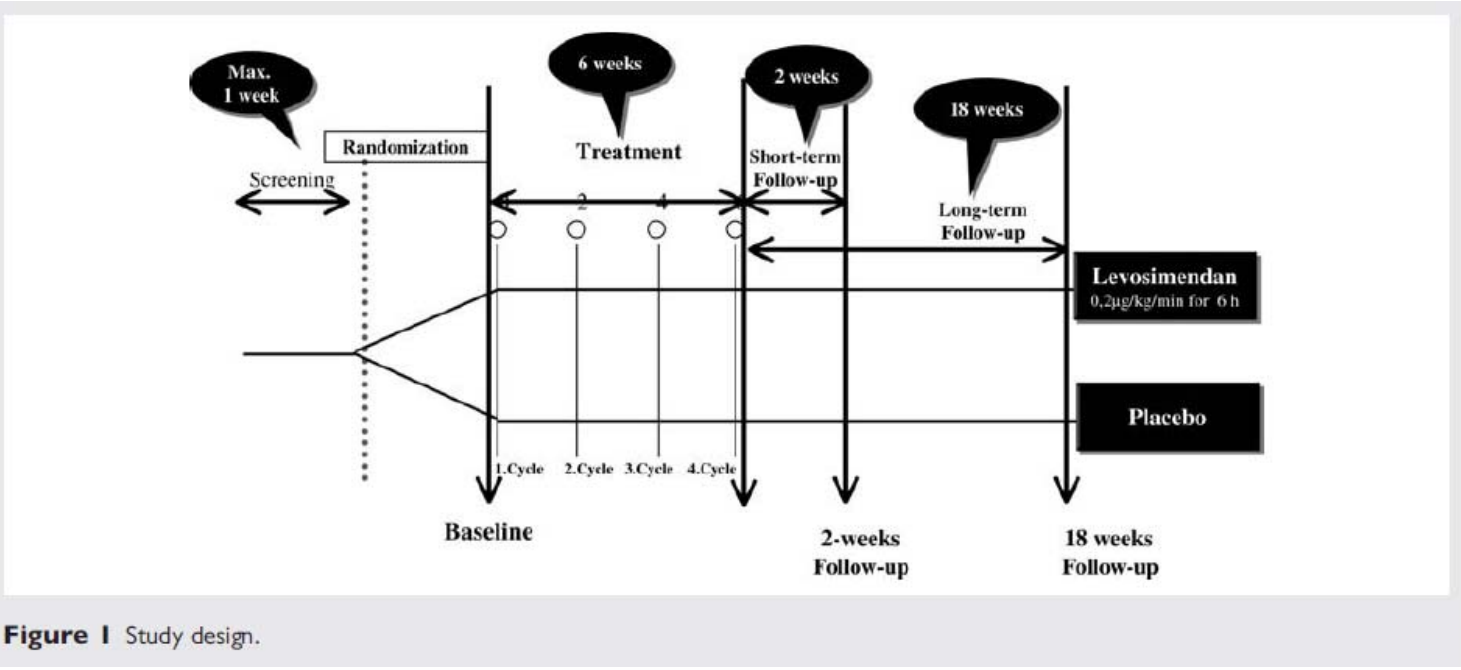



**Figure 1** Study design.

*Altenberger et al. Eur J Heart Fail 2010;12:186-192*

# LION-Heart

**Estudi multicèntric, doble cec, aleatori i controlat amb placebo per a avaluar l' eficàcia i seguretat de l' administració per via endovensosa de dosi intermitents de levosimendan en pacients ambulatoris amb IC crònica avançada**

**Estudi LION-HEART**

**Codi de l' assaig: IMIM-LEV-0901**

**EudraCT: 2009-014242-28**

**ClinicalTrials.gov Registration Number:**

**NCT01536132**

# GRUP DE TREBALL

**PROMOTOR**

CONSORCI SANITARI MAR PARC SALUT DE BARCELONA

*Dr. Jordi Bruguera*

**INVESTIGADOR COORDINADOR**

*Dr. Josep Comín*

Hospital del Mar, Barcelona

**STEERING COMMITTEE**

*Nicolás Manito*

*Juan Delgado*

*Javier Segovia*

*Josep Comín*

*Jordi Bruguera*

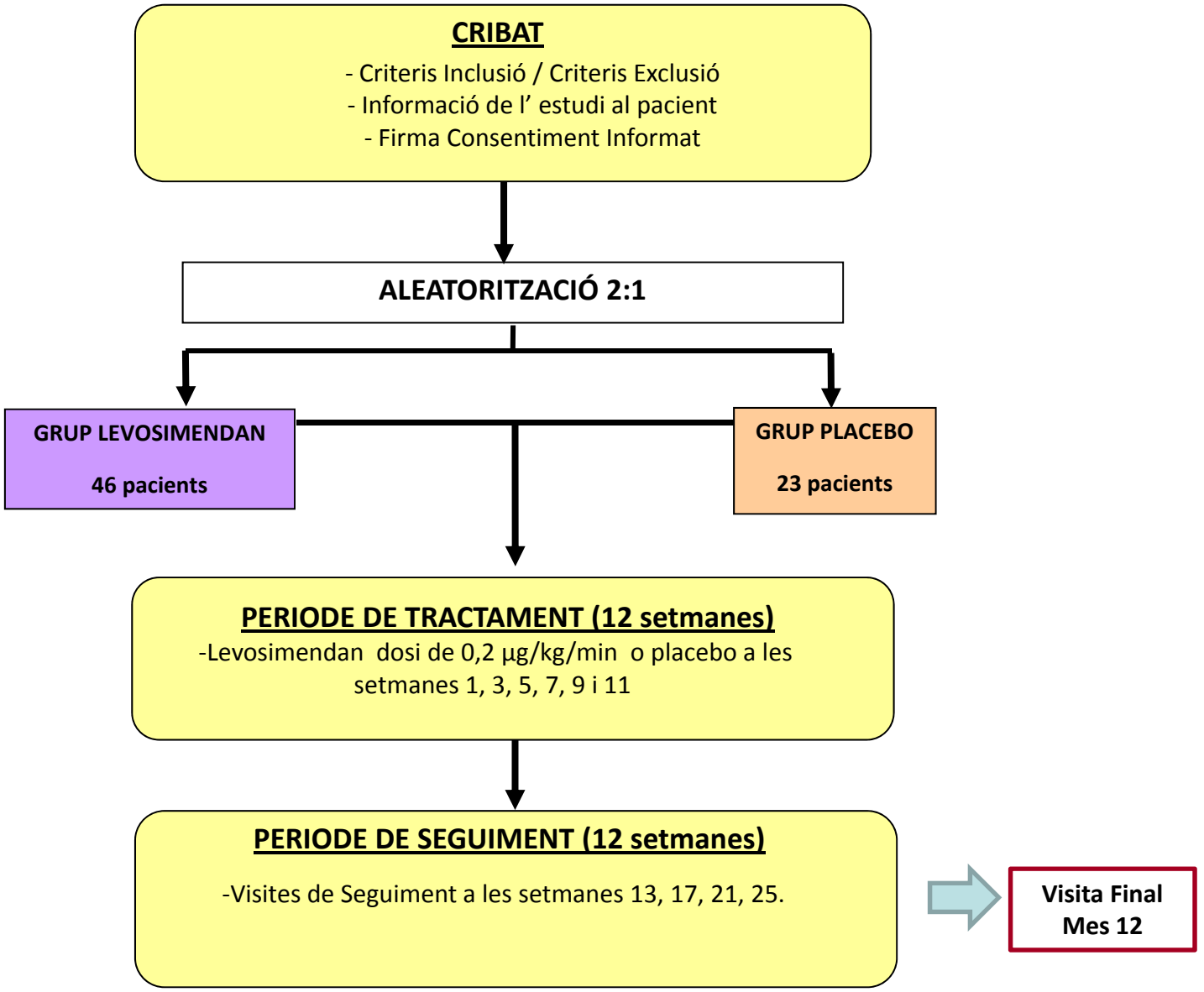
CRO

3D Health
CONSULTORA GLOBAL EN SALUD

**INVESTIGACIÓN**

# 14 CENTRES PARTICIPANTS

| | | | | | |
|---|---|---|---|---|---|
| 1 | Hospital del Mar | Josep Comín | 9 | Hospital de Basurto | Nekane Murga |
| 2 | Hospital Universitari de Bellvitge | Nicolás Manito | 10 | Hospital Miguel Servet | Marisa Sanz |
| 3 | Hospital Puerta de Hierro | Javier Segovia | | | |
| 4 | Hospital Univ 12 Octubre | Juan Delgado | 11 | Hospital Univ Virgen de la Victoria | Eduardo de Teresa |
| 5 | Hospital Univ La Fe | Luis Almenar | 12 | Hospital Univ Marqués de | Francisco Gonzalez Vilchez |
| 6 | Hospital Univ Virgen del Rocío | Ernesto Lage | 13 | Hospital Central de Asturias | J.L Rodriguez Lambert |
| 7 | Hospital Univ Virgen Arrixaca | Domingo Pascual | 14 | Hospital de la Santa Creu i Sant Pau | Alessandro Sionis |
| 8 | Complexo Hospitalario A Coruña | Marisa Crespo | | | |


CRIBAT
- Criteris Inclusió / Criteris Exclusió
- Informació de l' estudi al pacient
- Firma Consentiment Informat
ALEATORITZACIÓ 2:1
GRUP LEVOSIMENDAN
46 pacients
GRUP PLACEBO
23 pacients
PERIODE DE TRACTAMENT (12 setmanes)
-Levosimendan dosi de 0,2 µg/kg/min o placebo a les setmanes 1, 3, 5, 7, 9 i 11
PERIODE DE SEGUIMENT (12 setmanes)
-Visites de Seguiment a les setmanes 13, 17, 21, 25.
Visita Final
Mes 12

# Pautes Pràctiques Ús Ambulatori

Candidats, dosi i ajustos

## Candidats

- IC crònica
- FEVE<35%
- NYHA IV o IIIb
- NYHA IIIa + descompensacions
- TAs>90 o 80-90 si ha tolerat previament levosimendan
- No altres opcions de tx (objectiu pal·liatiu)


Dosi 0.2µg/kg/min

½ VIAL SIMDAX
2,5cc (6,25 mg) en 100 cc SG5%

14-16 mL/h (infusió de 6 hores)

# Ajust de Dosi Inicial

TAs Inicial

**TAs>80 i <90 mmHg**

Dosi 0.05µg/kg/min

3-4 mL/h

30-60 min

Dosi 0.1µg/kg/min

7-8 mL/h

Dosi 0.2µg/kg/min

14-16 mL/h

**TAs≥90 i <100 mmHg**

Dosi 0.1µg/kg/min

7-8 mL/h

Dosi 0.2µg/kg/min

14-16 mL/h

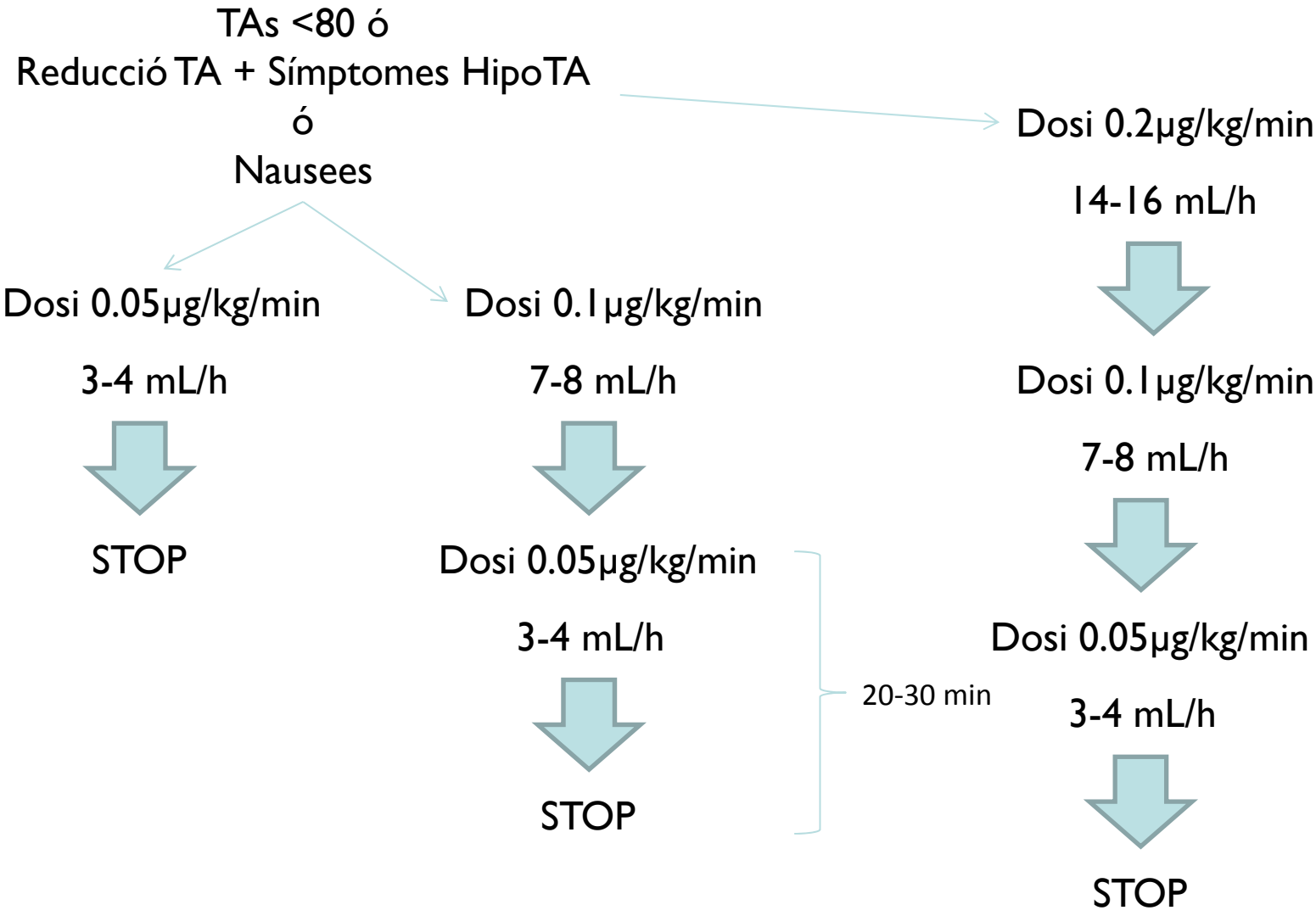
**TAs≥100 mmHg**

Dosi 0.2µg/kg/min

14-16 mL/h

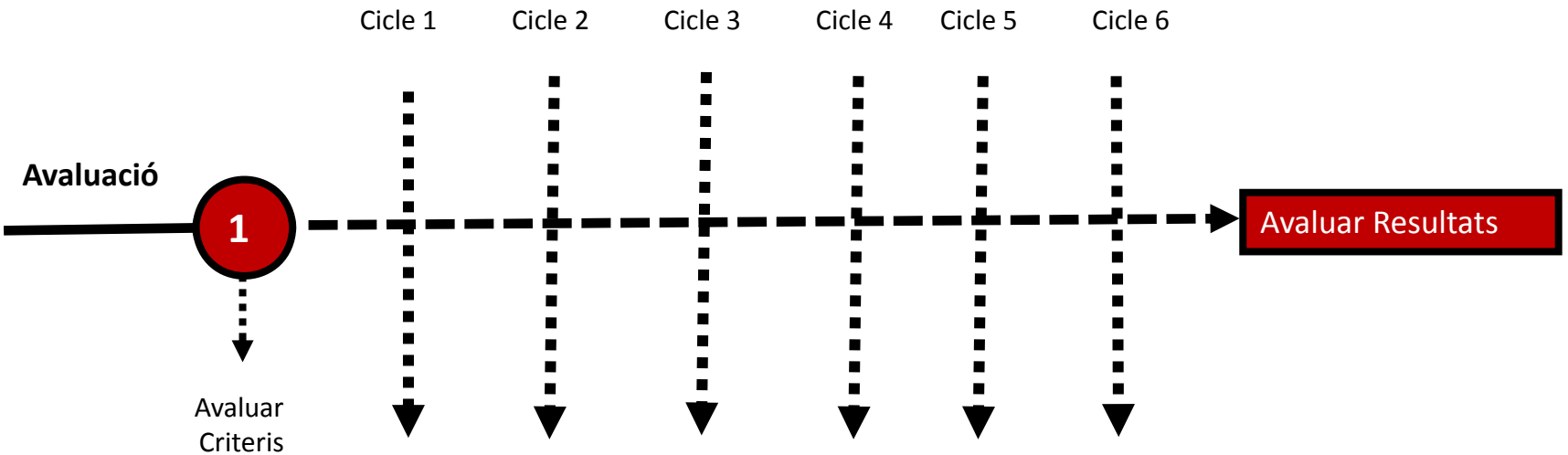

½ VIAL SIMDAX
2,5cc (6,25 mg) en 100 cc SG5%

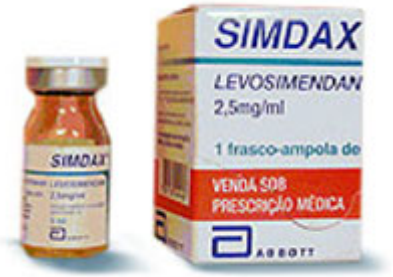
# Ajust de Dosi Durant la Infusió



# Procés de Planificació dels Cicles

*Optimització Tx segons GPC ESC*
*Re-avaluar Resposta*



# Gràcies!