



SUDDEN CARDIAC DEATH IN PATIENTS WITH HEART FAILURE: THE ROLE OF SACUBITRIL- VALSARTAN

**“ A Pesimist person can find difficulty
in each opportunity.
A positive person can find an opportunity
In each difficulty ”**

Heart Failure Unit accredited
by The Spanish Society of Cardiology



Types of Sudden cardiac death

ICD and Sudden Cardiac Death

Heart Failure Medication and Sudden Cardiac Death

The false “stability” of NYHA II

Sacubitril-Valsartan,
Ventricular Arrhythmias
and cardiac remodeling

ESC 2016 and 2019 recommendations
for Sacubitril-valsartan

SUDDEN CARDIAC DEATH
IN PATIENTS WITH HEART
FAILURE:

THE ROLE OF SACUBITRIL-
VALSARTAN

Dr. Carlos de Diego

Heart Failure –Arrhythmia Unit

Hospital Universitario de Torrevieja/Hospital Universitario de Elche/Vinalopó



Types of Sudden cardiac death

SUDDEN CARDIAC DEATH IN PATIENTS WITH HEART FAILURE:

THE ROLE OF SACUBITRIL- VALSARTAN

Dr. Carlos de Diego

Heart Failure –Arrhythmia Unit

Hospital Universitario de Torrevieja/Hospital Universitario de Elche/Vinalopó



How can a heart die?

Pulseless

**No contraction or no effective
contraction**

#1

How can a heart die? pulseless

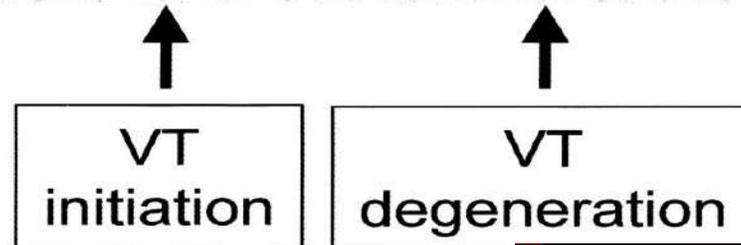
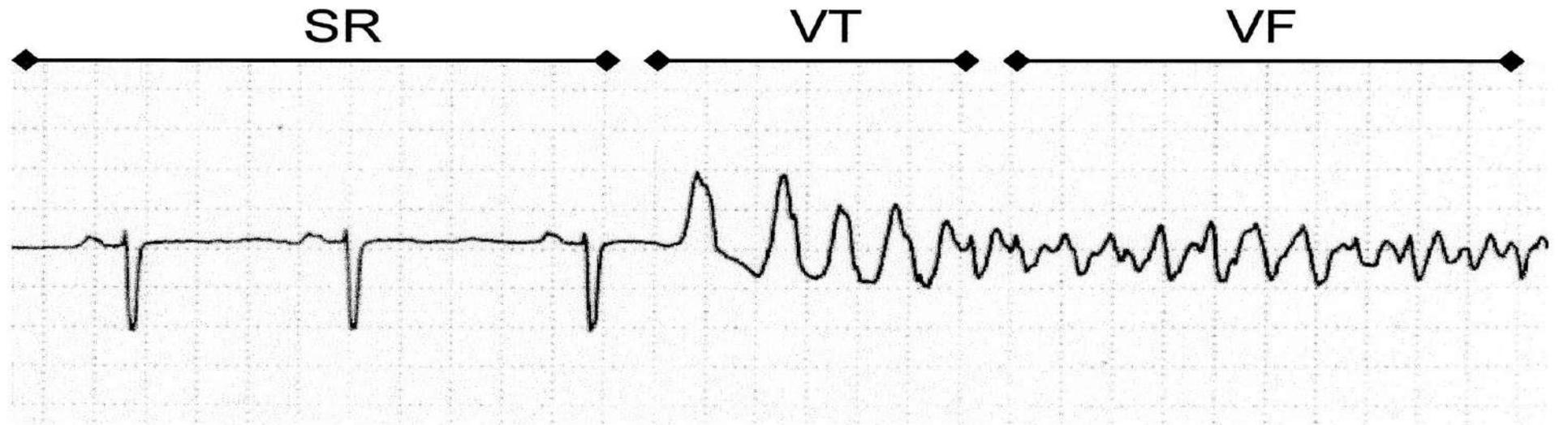
Asystole



#2

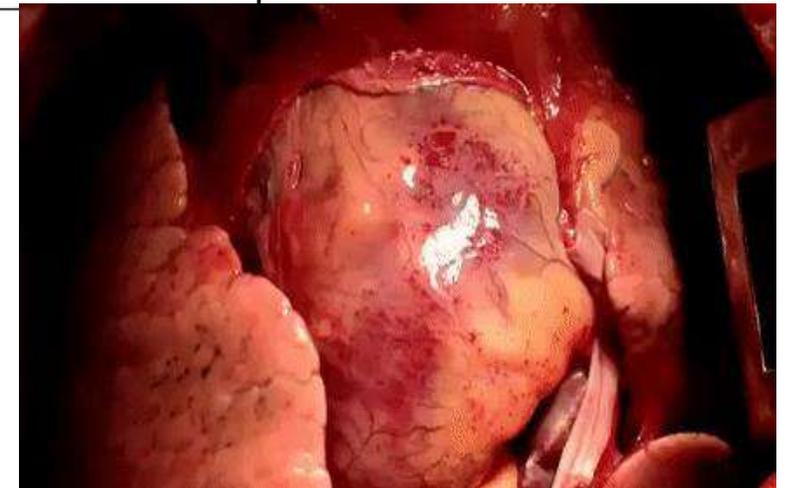
How can a heart die? pulseless

Ventricular fibrillation



“bag of worms”

No effective contraction



#3

How can a heart die? pulseless

Electro- mechanical dissociation

There is electrical activity



Electrical activity and contractility are not coupled (very advanced or severe heart disease)

No contraction



How can a heart die? SOLUTIONS

Asystole

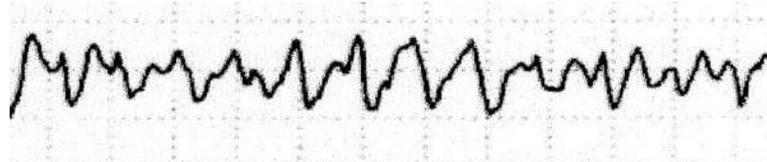


No electrical activity

PACEMAKER

Detection of electrical activity
Electrical stimulation
(low energy)

Ventricular fibrillation



ICD

Detection of electrical activity
Delivers a electrical shock
(high energy)

Electromechanical dissociation



No contraction

TOO LATE

ICD and sudden Cardiac death

SUDDEN CARDIAC DEATH IN PATIENTS WITH HEART FAILURE:

THE ROLE OF SACUBITRIL- VALSARTAN

Dr. Carlos de Diego

Heart Failure –Arrhythmia Unit

Hospital Universitario de Torrevieja/Hospital Universitario de
Elche/Vinalopó



PROCESO INSUFICIENCIA CARDIACA
SEC-EXCELENTE



WHEN IS AN ICD IMPLANTABLE CARDIAC DEFIBRILLATOR IMPLANTED?

SECONDARY PREVENTION

SURVIVOR FROM CARDIAC ARREST DUE TO FAST VENTRICULAR ARRHYTHMIA (VF, FAST VT)

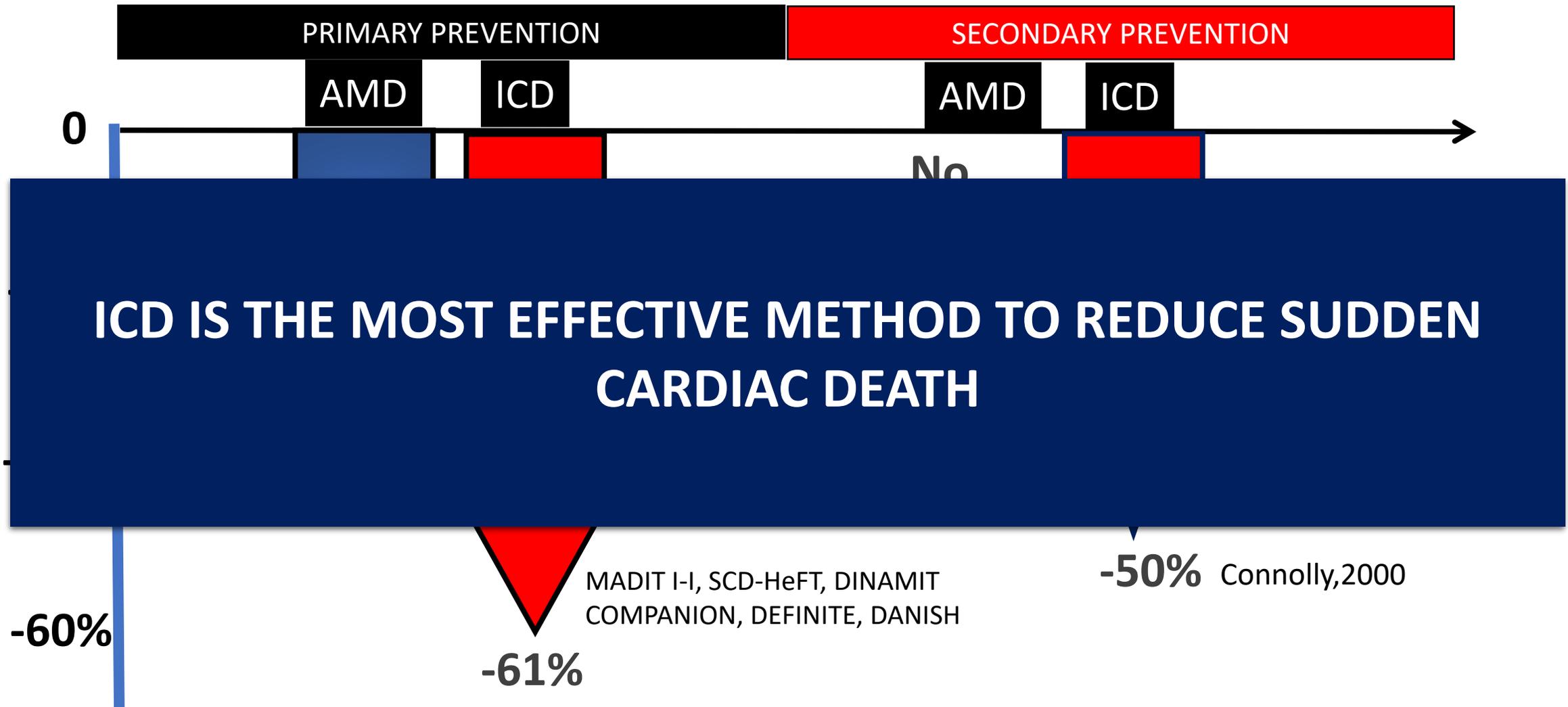
PRIMARY PREVENTION

LVEF \leq 35% AFTER \geq 3 MONTHS OF OPTIMAL MEDICAL THERAPY

- **1) ACEI OR ARB OR ARNI**
- **2) BETABLOCKERS**
- **3) MINERALOID CORTICOIDE ANTAGONIST**



SUDDEN CARDIAC REDUCTION BY ICD



As
Compared to

Placebo
/no intervention

Placebo+ACEI
BBK±MRA

Placebo
/no intervention

Placebo+ACEI
BBK

CAUSES OF SUDDEN CARDIAC DEATH (≤ 24 h)

ICD PREVENTS

ICD DOES NOT PREVENT...

**ICD DOES NOT PREVENT 100% OF SUDDEN CARDIAC DEATH
WHEN IS IMPLANTED**

FATAL STROKE

Heart Failure Medication and sudden cardiac death

SUDDEN CARDIAC DEATH IN PATIENTS WITH HEART FAILURE:

THE ROLE OF SACUBITRIL- VALSARTAN

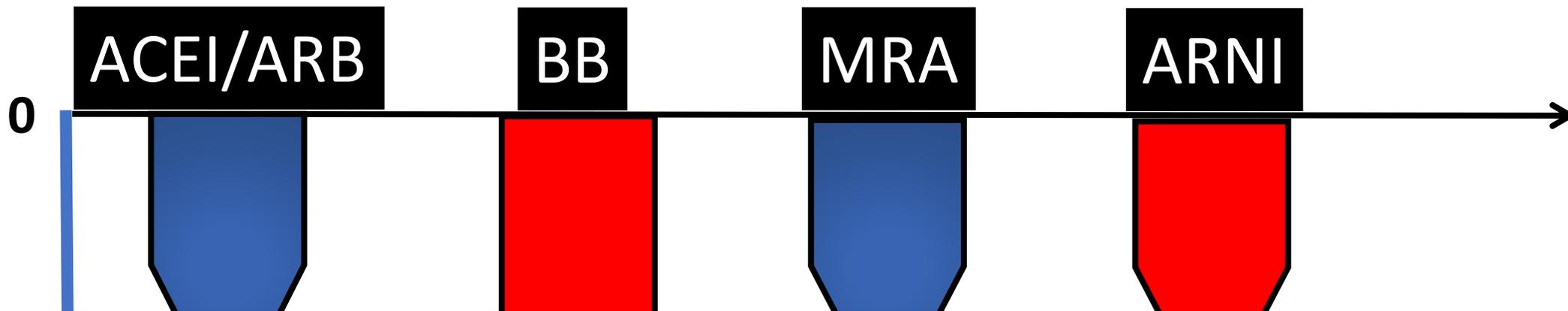
Dr. Carlos de Diego

Heart Failure –Arrhythmia Unit

Hospital Universitario de Torrevieja/Hospital Universitario de
Elche/Vinalopó



ADDITIONAL REDUCTION OF SCD



**OPTIMIZATION OF MEDICAL THERAPY REDUCES SUDDEN CARDIAC DEATH IN HEART FAILURE
BETABLOCKERS AND ARNI HAVE STRONGEST EVIDENCE WITH
RANDOMIZED CONTROLLED TRIALS**

-42%

As compared to

Placebo

Placebo+ACEI

Placebo+ACEI
+BBK

ACEI
+BBK+MRA (both arms)

Clinical
Evidence

Meta-analysis
in post-MI

RCT

Meta-analysis

RCT

SUDDEN CARDIAC DEATH
IN PATIENTS WITH HEART
FAILURE:

THE ROLE OF SACUBITRIL-
VALSARTAN

**The false “stability” of
NYHA II**

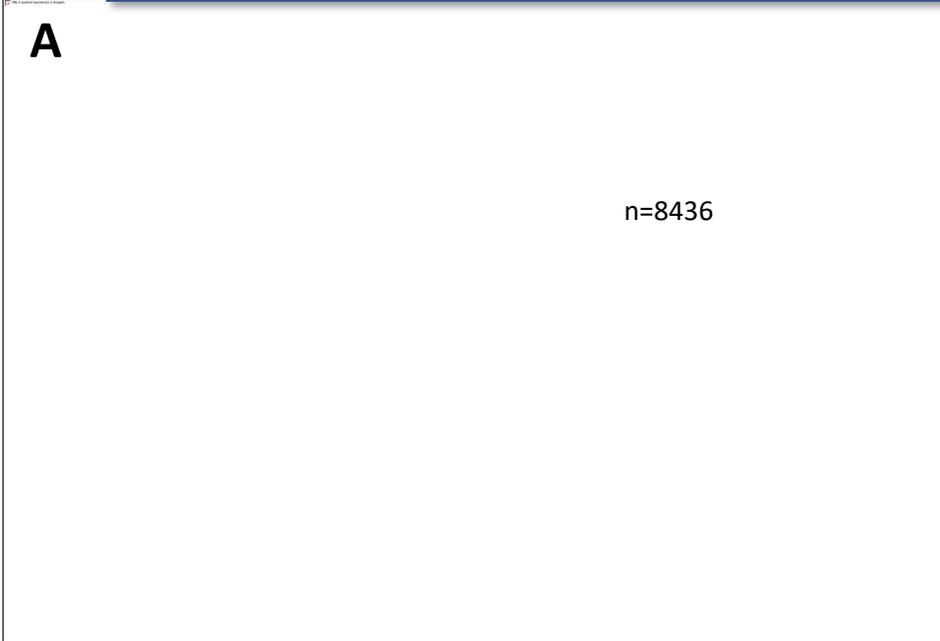
Dr. Carlos de Diego

Heart Failure –Arrhythmia Unit

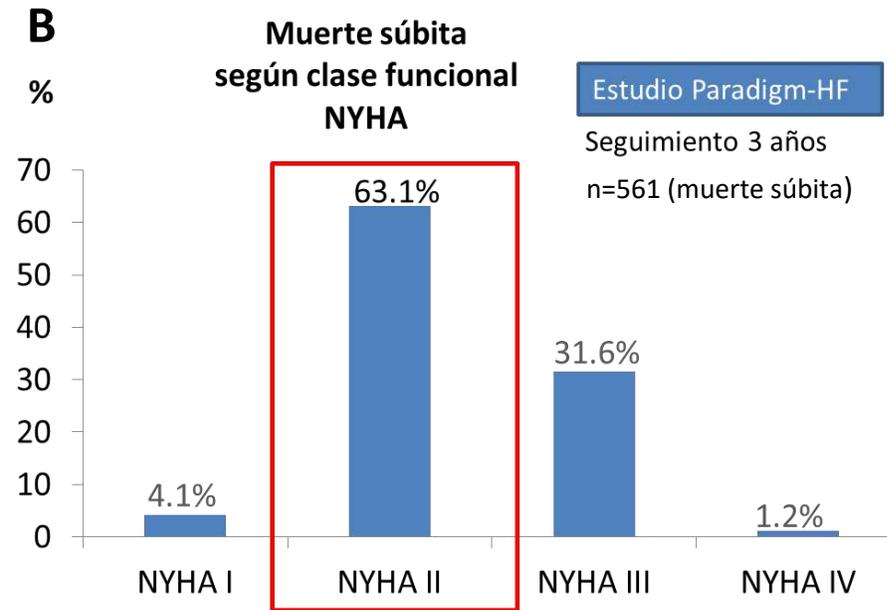
Hospital Universitario de Torrevieja/Hospital Universitario de
Elche/Vinalopó



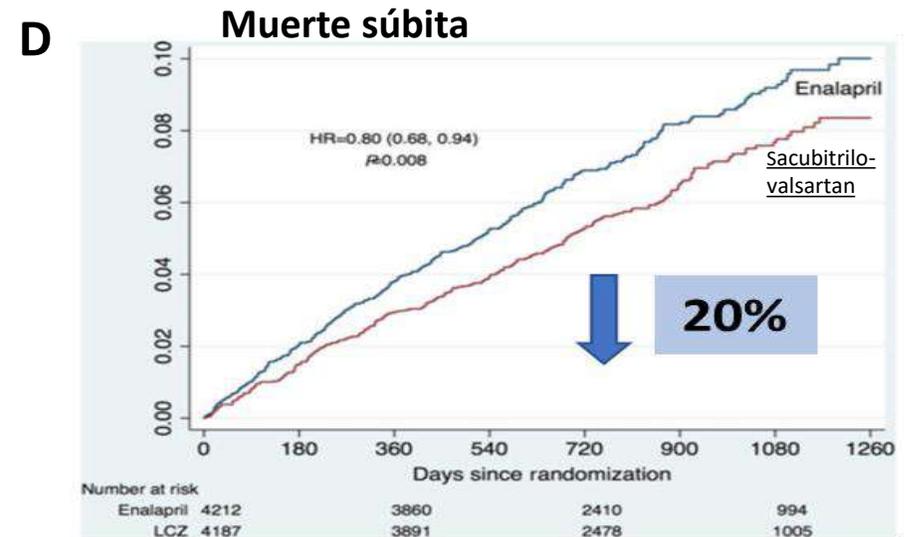
La estabilidad de los síntomas no es sinónimo de estabilidad en la progresión y en el pronóstico de la enfermedad



McMurray et al. Eur J Heart Fail. 2013;15:1062–73;



Desai AS, et al. Eur Heart J. 2015;36(30): 190-7.



SUDDEN CARDIAC DEATH
IN PATIENTS WITH HEART
FAILURE:

THE ROLE OF SACUBITRIL-
VALSARTAN

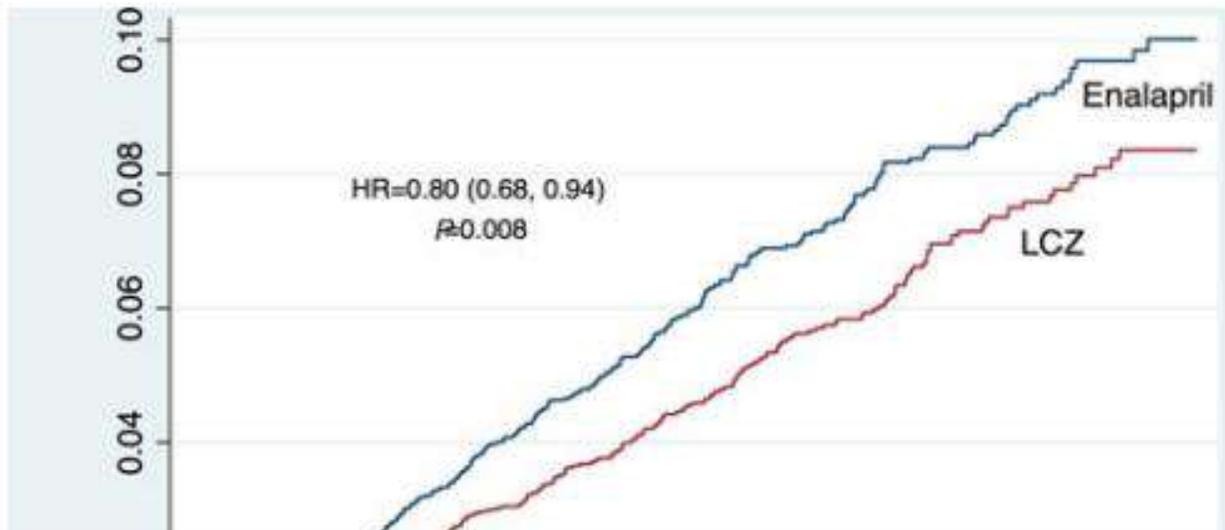
**Sacubitril-valsartan,
ventricular
Arrhythmias and
cardiac remodeling**

Dr. Carlos de Diego

Heart Failure –Arrhythmia Unit

Hospital Universitario de Torrevieja/Hospital Universitario de
Elche/Vinalopó





20% REDUCTION OF
SUDDEN CARDIAC DEATH
(WITHIN 24 HOURS)

PARADIGM-HF STUDY

ⓘ ventricular arrhythmias, asystole or
Cardiogenic shock or others?

Figure 1 Kaplan–Meier survival curve for sudden death, by treatment. HR, hazard ratio.

Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. [Desai et al](#) *European Heart Journal*, Vol 36, Issue 30, 7 August 2015, Pages 1990–1997

Accepted Manuscript

Effects of angiotensin-neprilysin inhibition as compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices

Carlos de Diego, MD, PhD, Luis González-Torres, MD, José María Núñez, MD, Raúl Centurión Inda, MD, David A. Martin-Langerwerf, MD, Antonio D. Sangio, MD, Piotr Chochowski, MD, Pilar Casasnovas, MD, Julio C. Blazquez, MD, Jesús Almendral, MD, PhD

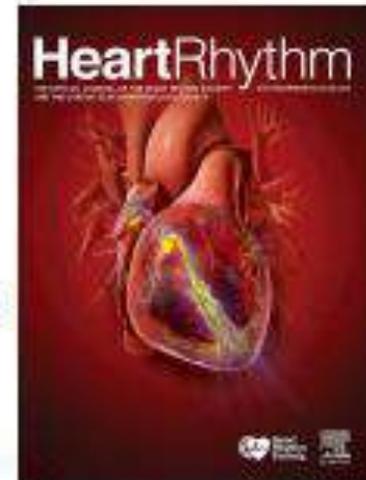
PII: S1547-5271(17)31331-0

DOI: [10.1016/j.hrthm.2017.11.012](https://doi.org/10.1016/j.hrthm.2017.11.012)

Reference: HRTM 7387

To appear in: *Heart Rhythm*

Received Date: 25 September 2017



SACUBITRIL-VALSARTAN
REDUCES
VENTRICULAR ARRHYTHMIAS

Effects of angiotensin-neprilysin inhibition as compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices;

C. De Diego and L. González-Torres et al
Heart Rhythm online 14 November 2017

CRITERIA

N=120 patients

LVEF \leq 40%

+

NYHA \geq II

+

ICD +/-ctr

+

REMOTE
MONITOR

Effects of angiotensin-neprilysin inhibition as compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices;

C. De Diego and L. González-Torres et al
Heart Rhythm online 14 November 2017

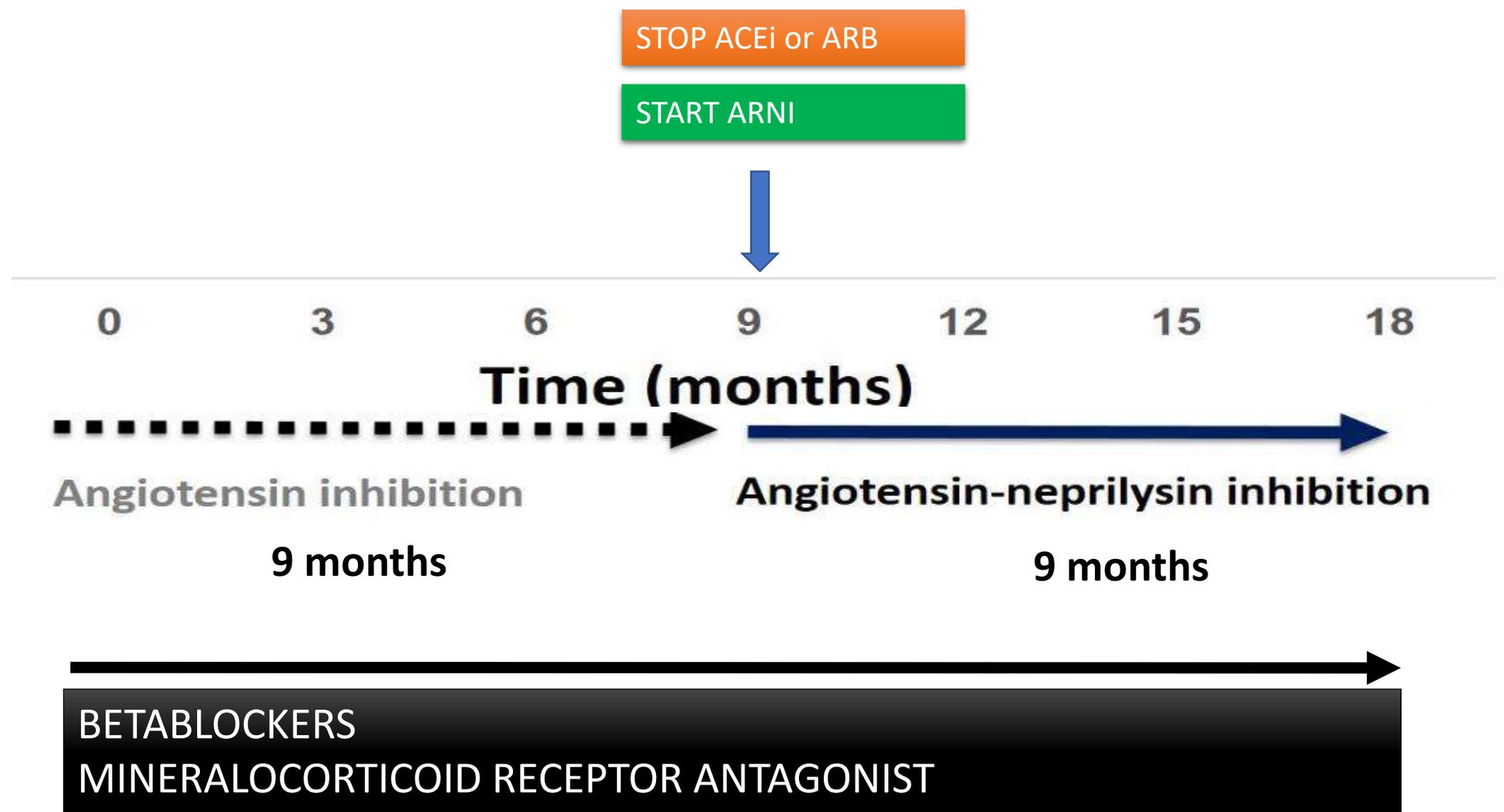


Table 1 Before and after sacubitril-valsartan patient characteristics in outpatient clinic

	Angiotensin inhibition alone (n = 120)	Angiotensin receptor neprilysin inhibition (n = 120)	P value
Clinical characteristics			
Age (yrs)	69 ± 8	70 ± 8	NS
Male	91 (76)	91 (76)	NS
Ischemic cardiopathy	98 (82)	98 (82)	NS
Hypertension	75 (62)	75 (62)	NS
Diabetes	36 (30)	36 (30)	NS
Hypercholesterolemia	62 (52)	63 (52)	NS
Renal insufficiency (filtration rate <60 mL/min)	48 (40)	48 (40)	NS
Medical treatment			
	100% ACEi or ARB	100% sacubitril-valsartan	
Beta-blocker	98	98	NS
Mineraloid antagonist	97	97	NS
Antiarrhythmic drug	30	29	NS
Oral diuretic	75	52	<.03
Rhythm			
Sinus rhythm	85 (71)	84 (70)	NS
Paroxysmal AF	17 (14)	12 (10)	.07
Permanent AF	35 (29)	36 (30)	NS
Echocardiographic data			
LVEF (%)	30.4 ± 4	35.1 ± 8	<.01
LVEDD (mm)	61 ± 5	58 ± 6	<.01
Clinical data			
NYHA functional class (1-4)	2.4 ± 0.4	1.5 ± 0.7	<.0002
Examination data			
Systolic blood pressure (mmHg)	121 ± 38	107 ± 39	<.02
Diastolic blood pressure (mmHg)	73 ± 23	64 ± 26	<.006
Heart rate average (bpm)	67 ± 7	64 ± 5	<.006
Blood tests			
Potassium level (mEq/L)	4.4 ± 0.5	4.7 ± 0.5	<.03
Pro-BNP (pg/mL)	1971 ± 1530	1172 ± 955	<.01
Glomerular filtration rate (mL/min)	55 ± 19	57 ± 19	NS
Device			
ICD only	56	56	NS
ICD + CRT	44	44	NS
Primary prevention	65	65	NS
Secondary prevention	35	35	NS

Effects of angiotensin-neprilysin inhibition as compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices

C. De Diego and L. González-Torres et al
Heart Rhythm

online 14 November 2017

**INCREASE OF
LEFT VENTRICULAR
EJECTION FRACTION**

Table 1 Before and after sacubitril-valsartan patient characteristics in outpatient clinic

	Angiotensin inhibition alone (n = 120)	Angiotensin receptor neprilysin inhibition (n = 120)	P value
Clinical characteristics			
Age (yrs)	69 ± 8	70 ± 8	NS
Male	91 (76)	91 (76)	NS
Ischemic cardiopathy	98 (82)	98 (82)	NS
Hypertension	75 (62)	75 (62)	NS
Diabetes	36 (30)	36 (30)	NS
Hypercholesterolemia	62 (52)	63 (52)	NS
Renal insufficiency (filtration rate <60 mL/min)	48 (40)	48 (40)	NS
Medical treatment			
	100% ACEi or ARB	100% sacubitril-valsartan	
Beta-blocker	98	98	NS
Mineraloid antagonist	97	97	NS
Antiarrhythmic drug	30	29	NS
Oral diuretic	75	52	<.03
Rhythm			
Sinus rhythm	85 (71)	84 (70)	NS
Paroxysmal AF	17 (14)	12 (10)	.07
Permanent AF	35 (29)	36 (30)	NS
Echocardiographic data			
LVEF (%)	30.4 ± 4	35.1 ± 8	<.01
LVEDD (mm)	61 ± 5	58 ± 6	<.01
Clinical data			
NYHA functional class (1-4)	2.4 ± 0.4	1.5 ± 0.7	<.0002
Examination data			
Systolic blood pressure (mmHg)	121 ± 38	107 ± 39	<.02
Diastolic blood pressure (mmHg)	73 ± 23	64 ± 26	<.006
Heart rate average (bpm)	67 ± 7	64 ± 5	<.006
Blood tests			
Potassium level (mEq/L)	4.4 ± 0.5	4.7 ± 0.5	<.03
Pro-BNP (pg/mL)	1971 ± 1530	1172 ± 955	<.01
Glomerular filtration rate (mL/min)	55 ± 19	57 ± 19	NS
Device			
ICD only	56	56	NS
ICD + CRT	44	44	NS
Primary prevention	65	65	NS
Secondary prevention	35	35	NS

Effects of angiotensin-neprilysin inhibition as compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices

C. De Diego and L. González-Torres et al
Heart Rhythm

online 14 November 2017

IMPROVEMENT OF
NYHA FUNCIONAL
CLASS

Table 1 Before and after sacubitril-valsartan patient characteristics in outpatient clinic

	Angiotensin inhibition alone (n = 120)	Angiotensin receptor neprilysin inhibition (n = 120)	P value
Clinical characteristics			
Age (yrs)	69 ± 8	70 ± 8	NS
Male	91 (76)	91 (76)	NS
Ischemic cardiopathy	98 (82)	98 (82)	NS
Hypertension	75 (62)	75 (62)	NS
Diabetes	36 (30)	36 (30)	NS
Hypercholesterolemia	62 (52)	63 (52)	NS
Renal insufficiency (filtration rate <60 mL/min)	48 (40)	48 (40)	NS
Medical treatment			
	100% ACEi or ARB	100% sacubitril-valsartan	
Beta-blocker	98	98	NS
Mineraloid antagonist	97	97	NS
Antiarrhythmic drug	30	29	NS
Oral diuretic	75	52	<.03
Rhythm			
Sinus rhythm	85 (71)	84 (70)	NS
Paroxysmal AF	17 (14)	12 (10)	.07
Permanent AF	35 (29)	36 (30)	NS
Echocardiographic data			
LVEF (%)	30.4 ± 4	35.1 ± 8	<.01
LVEDD (mm)	61 ± 5	58 ± 6	<.01
Clinical data			
NYHA functional class (1-4)	2.4 ± 0.4	1.5 ± 0.7	<.0002
Examination data			
Systolic blood pressure (mmHg)	121 ± 38	107 ± 39	<.02
Diastolic blood pressure (mmHg)	73 ± 23	64 ± 26	<.006
Heart rate average (bpm)	67 ± 7	64 ± 5	<.006
Blood tests			
Potassium level (mEq/L)	4.4 ± 0.5	4.7 ± 0.5	<.03
Pro-BNP (pg/mL)	1971 ± 1530	1172 ± 955	<.01
Glomerular filtration rate (mL/min)	55 ± 19	57 ± 19	NS
Device			
ICD only	56	56	NS
ICD + CRT	44	44	NS
Primary prevention	65	65	NS
Secondary prevention	35	35	NS

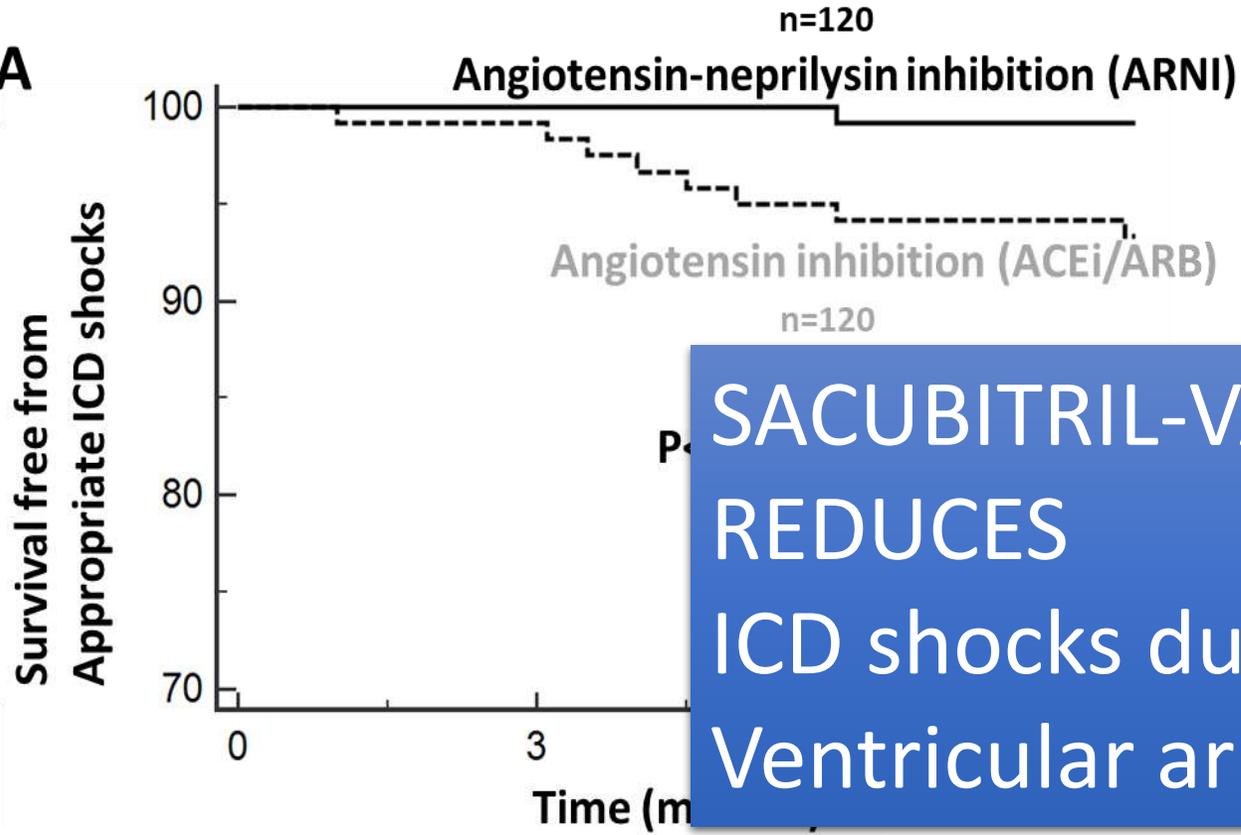
Effects of angiotensin-neprilysin inhibition as compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices

C. De Diego and L. González-Torres et al
Heart Rhythm

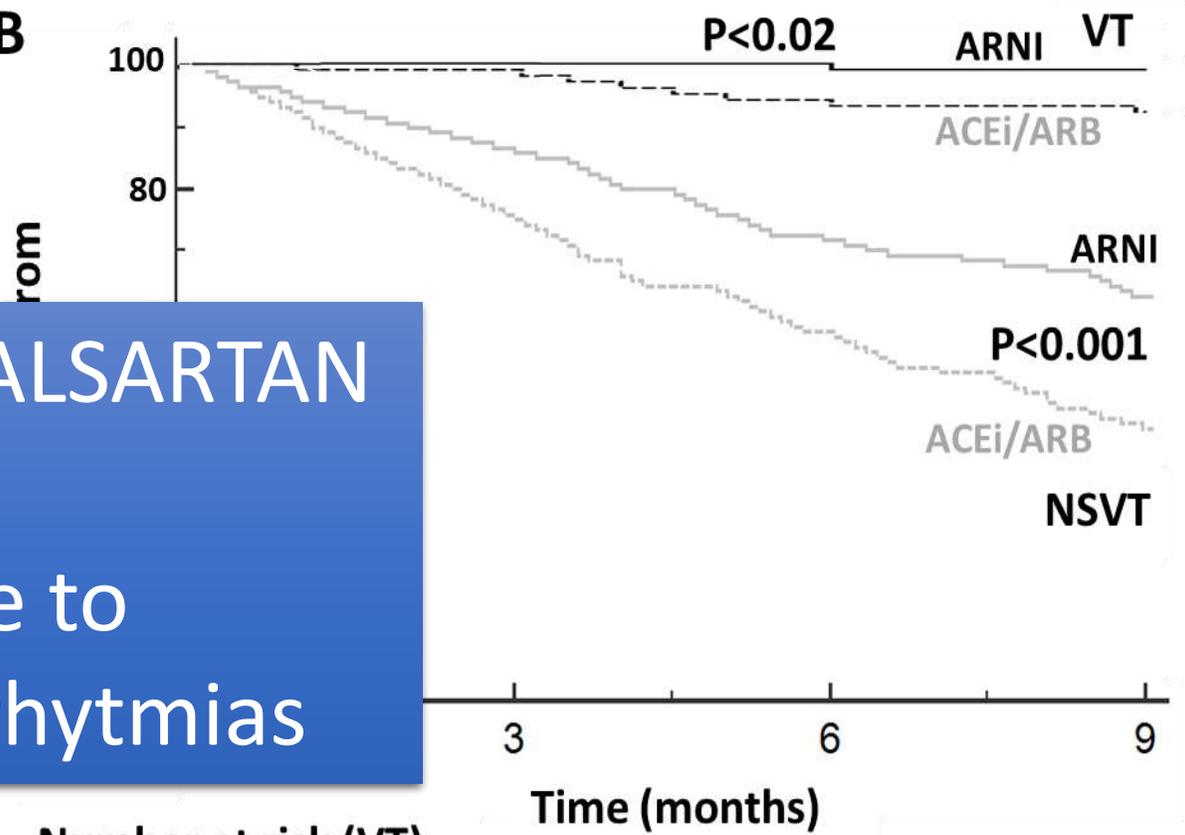
online 14 November 2017

MILD INCREASE OF POTASSIUM

DECREASE OF PROBNP

A

**SACUBITRIL-VALSARTAN
REDUCES
ICD shocks due to
Ventricular arrhythmias**

B**Number at risk**

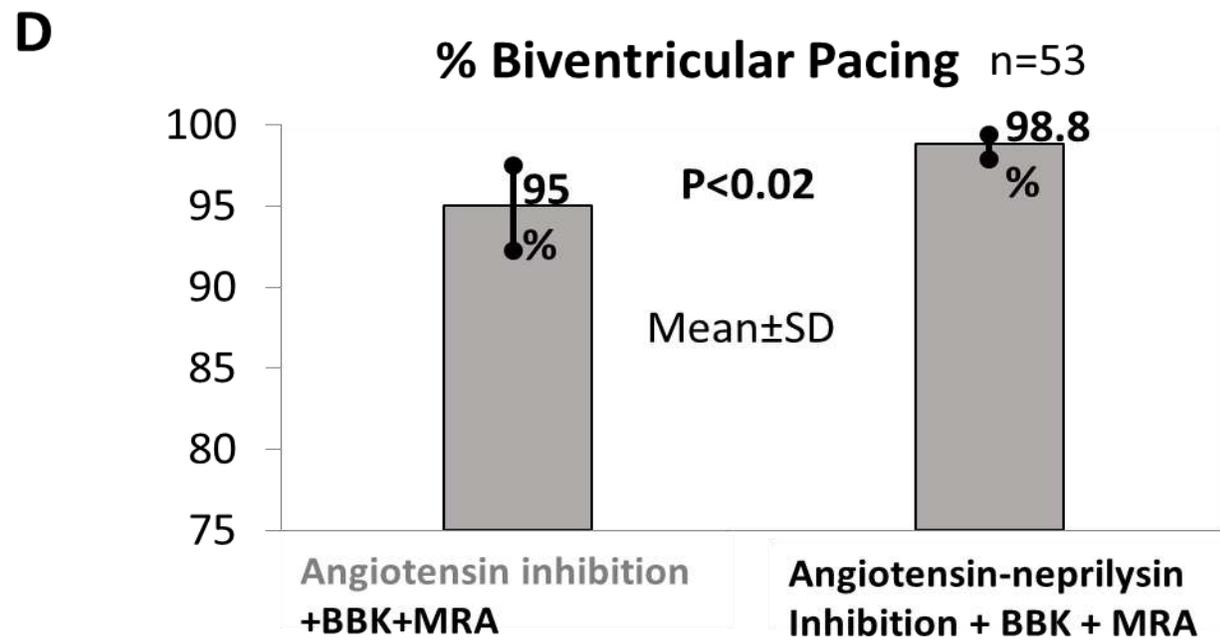
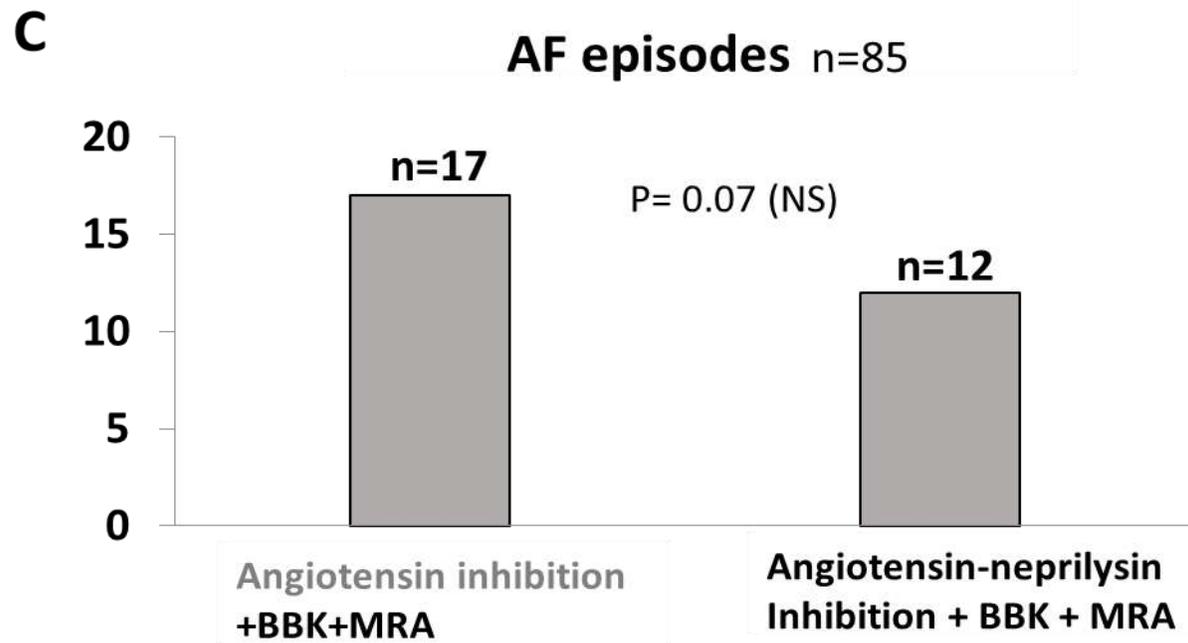
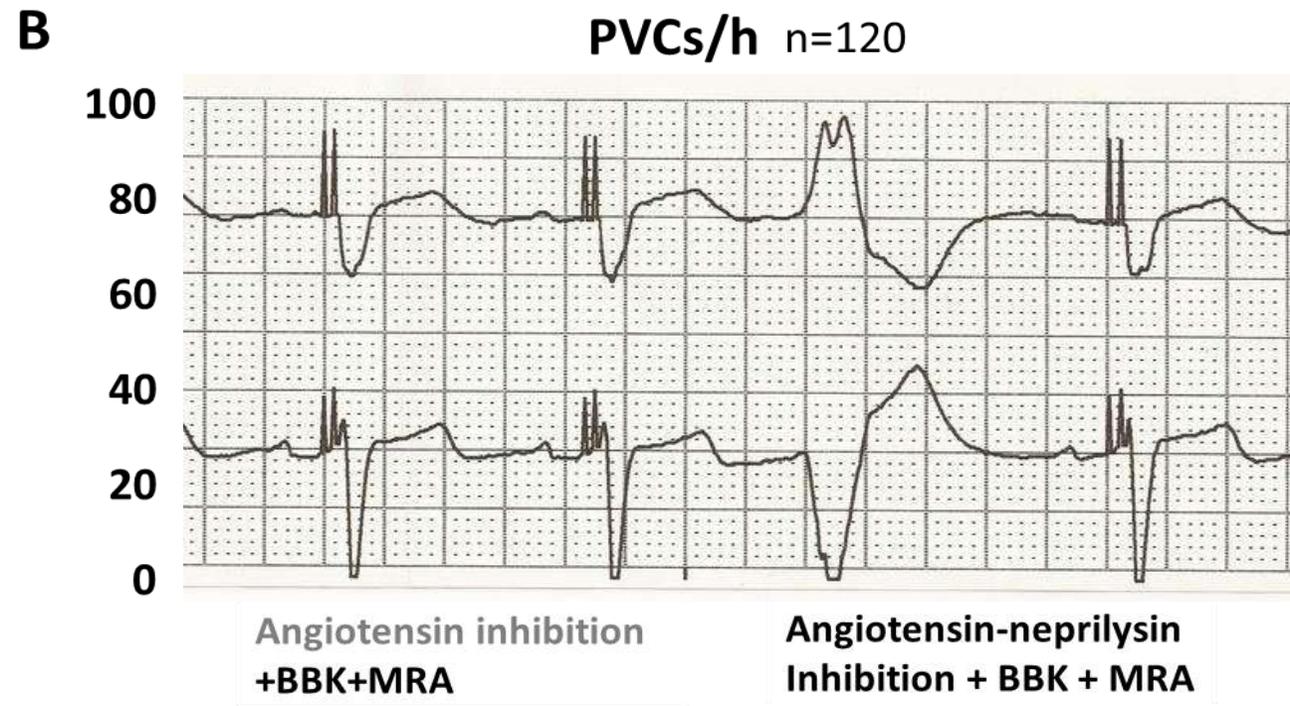
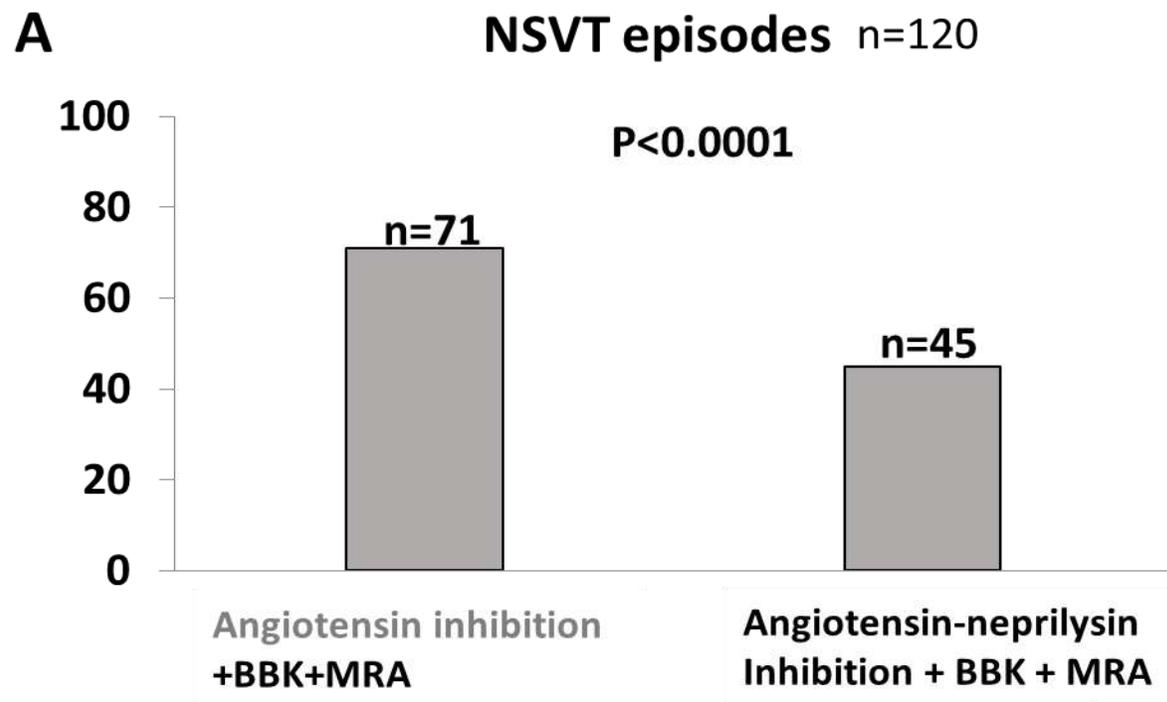
ARNI	120	120	120	120	119	119
ACEi /ARB	120	119	119	115	113	113

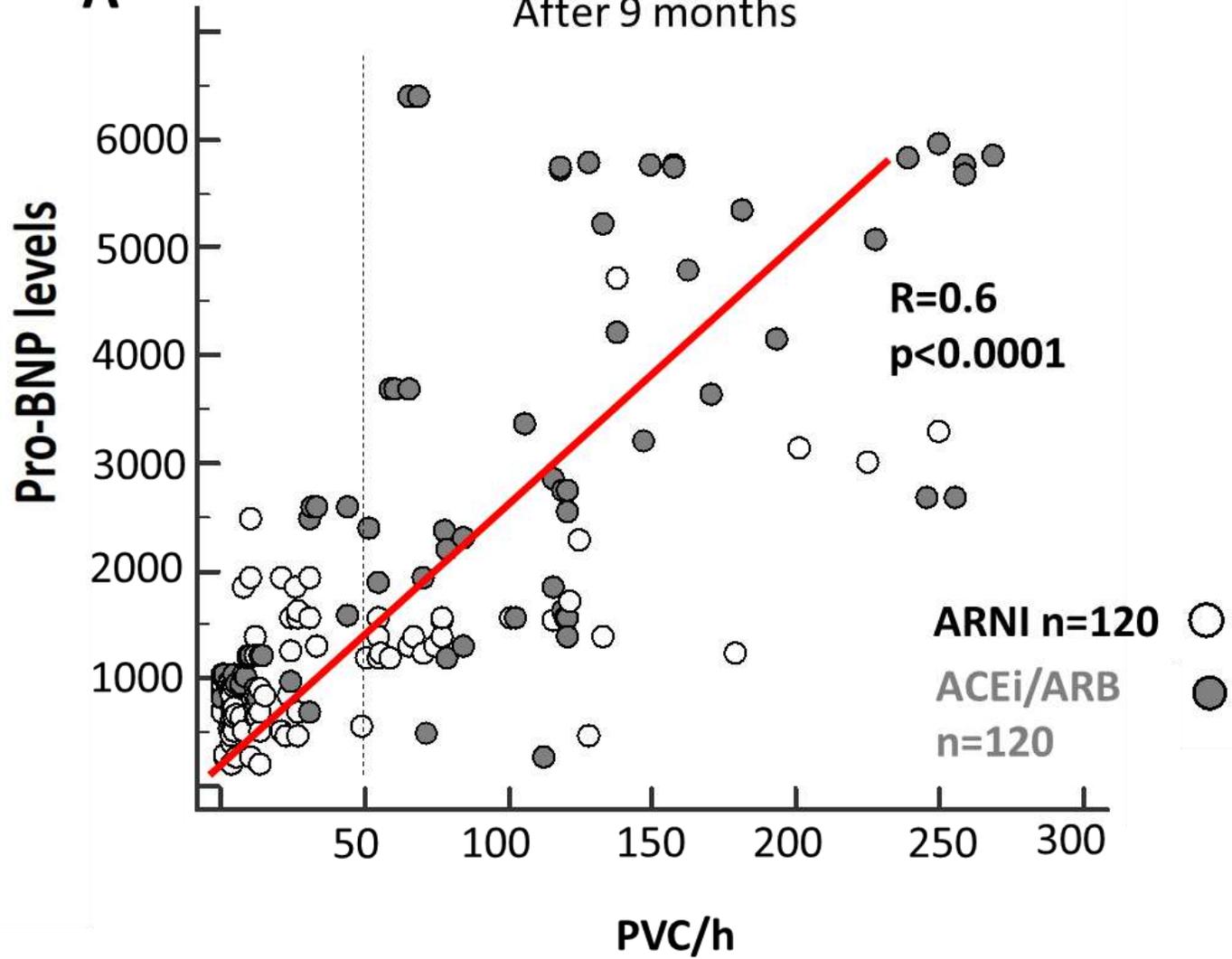
Number at risk (VT)

ARNI	120	120	120	120	119	119
ACEi /ARB	120	119	119	115	113	113

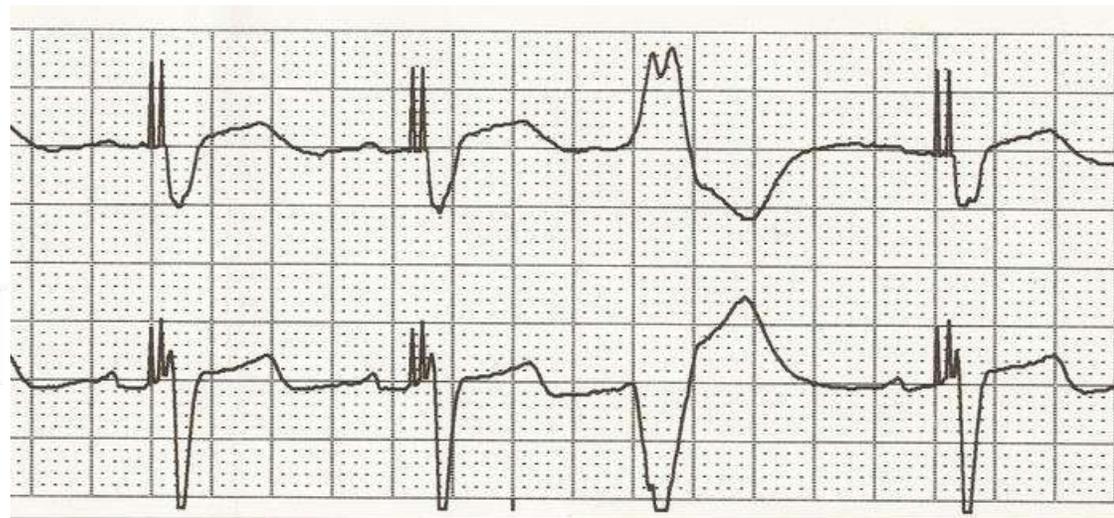
Number at risk (NSVT)

ARNI	120	111	103	95	86	82
ACEi /ARB	120	104	90	77	67	59





LINEAR CORRELATION
PROBNP - PVC BURDEN



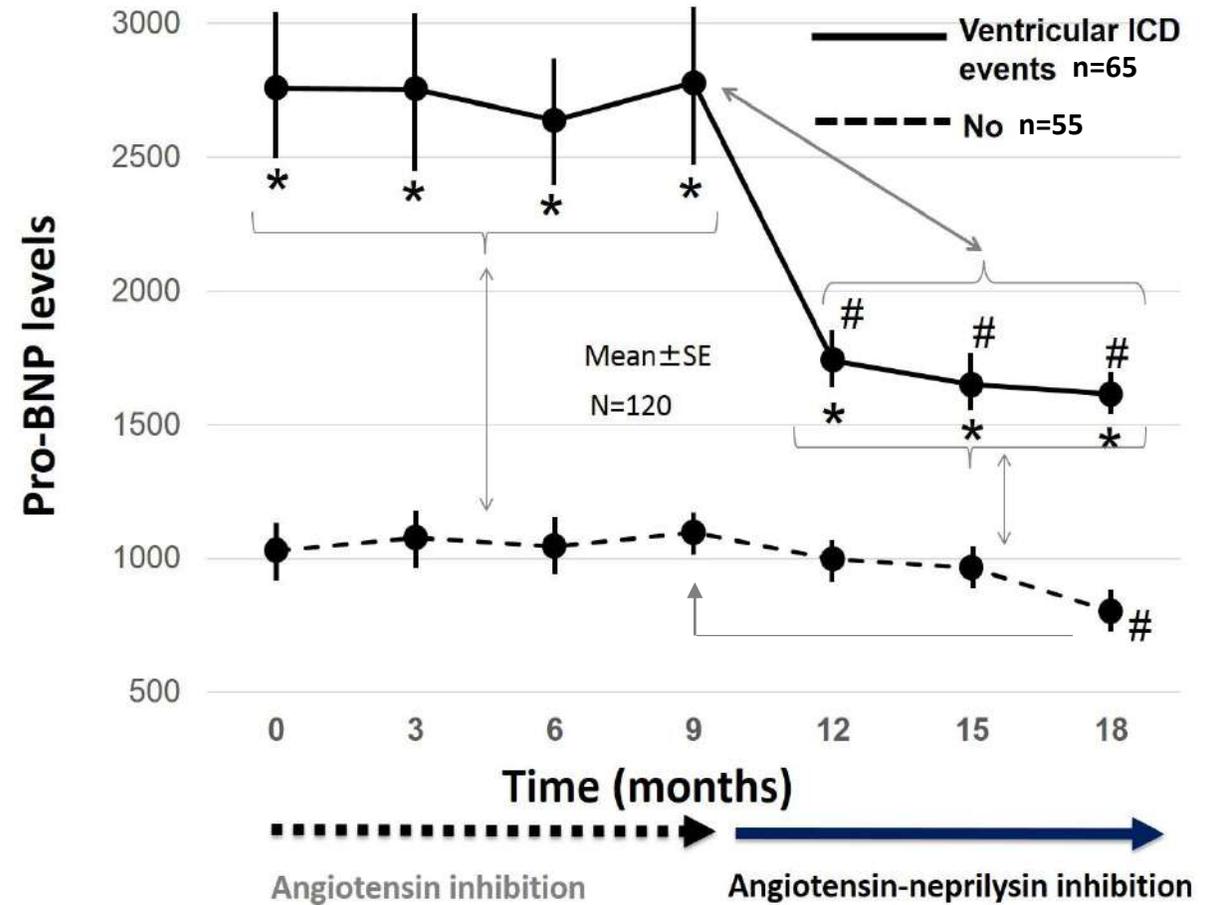
THE MORE PROBNP,
THE MORE PVCs

TIMELINE COURSE OF PROBNP WITH/WITHOUT VENTRICULAR ARRHYTHMIAS

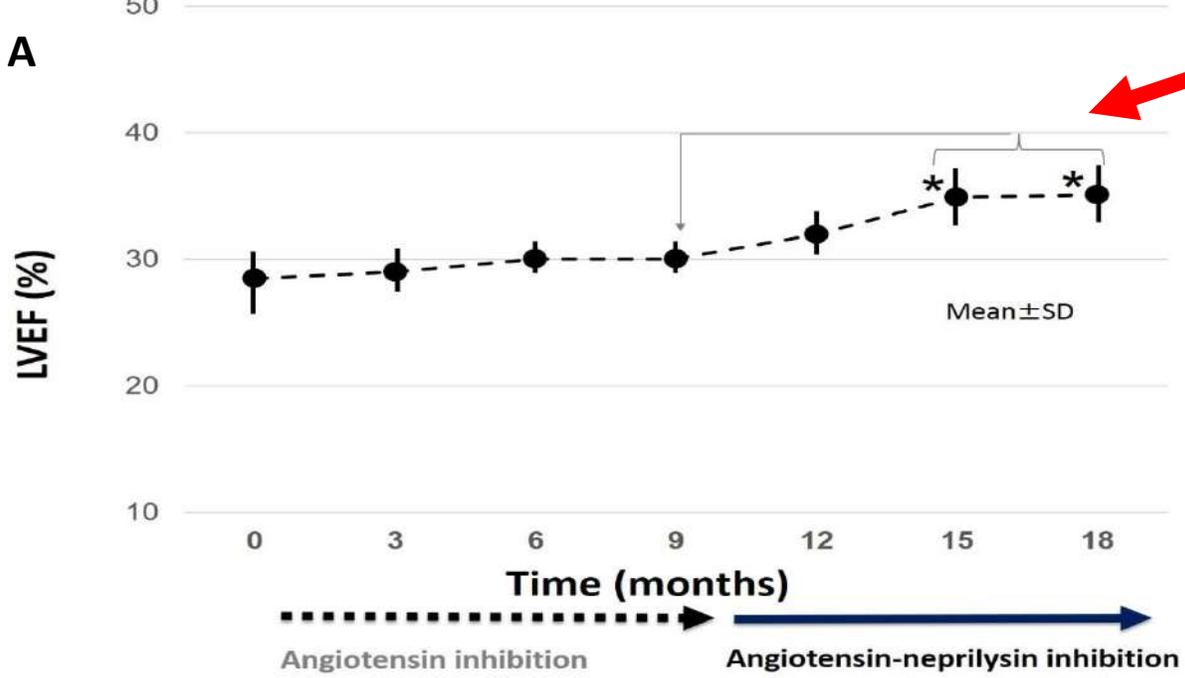
THE MORE PROBNP,
THE MORE VENTRICULAR ARRHYTHMIAS

ARNI DECREASES PROBNP
IN ALL PATIENTS (WITH OR WITHOUT
VENTRICULAR ARRHYTHMIAS)

B



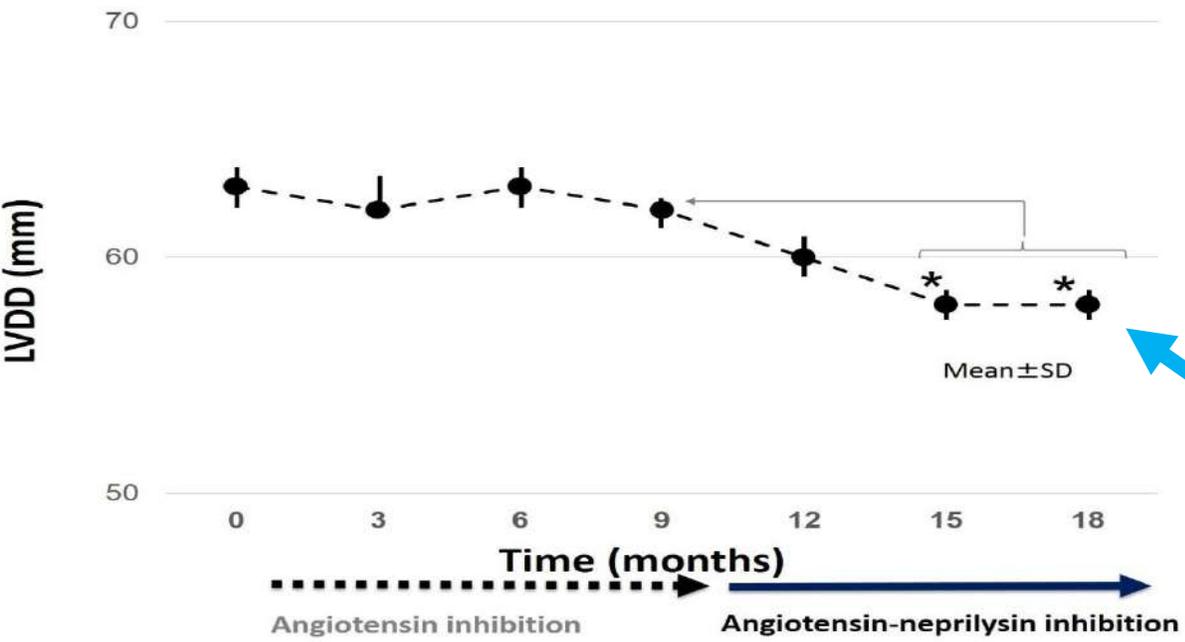
A



TIMELINE COURSE OF LVEF AND LVDD

ARNI INCREASES OF LVEF

C



ARNI DECREASES LVDD

Effects of angiotensin-neprilysin inhibition as compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices;

C. De Diego and L. González-Torres et al
Heart Rhythm online 14 November 2017

CONCLUSIONS

Angiotensin-neprilysin inhibition decreased ventricular arrhythmias and appropriate ICD shocks in rEFHF patients under home monitoring compared to angiotensin inhibition

BENEFICIAL EFFECTS OF ARNI AS COMPARED TO ACEI

IMPROVEMENT OF NYHA FUNCIONAL CLASS

IMPROVEMENT LVEF (about 5%)

**Change in NYHA functional class
from baseline to month 8**

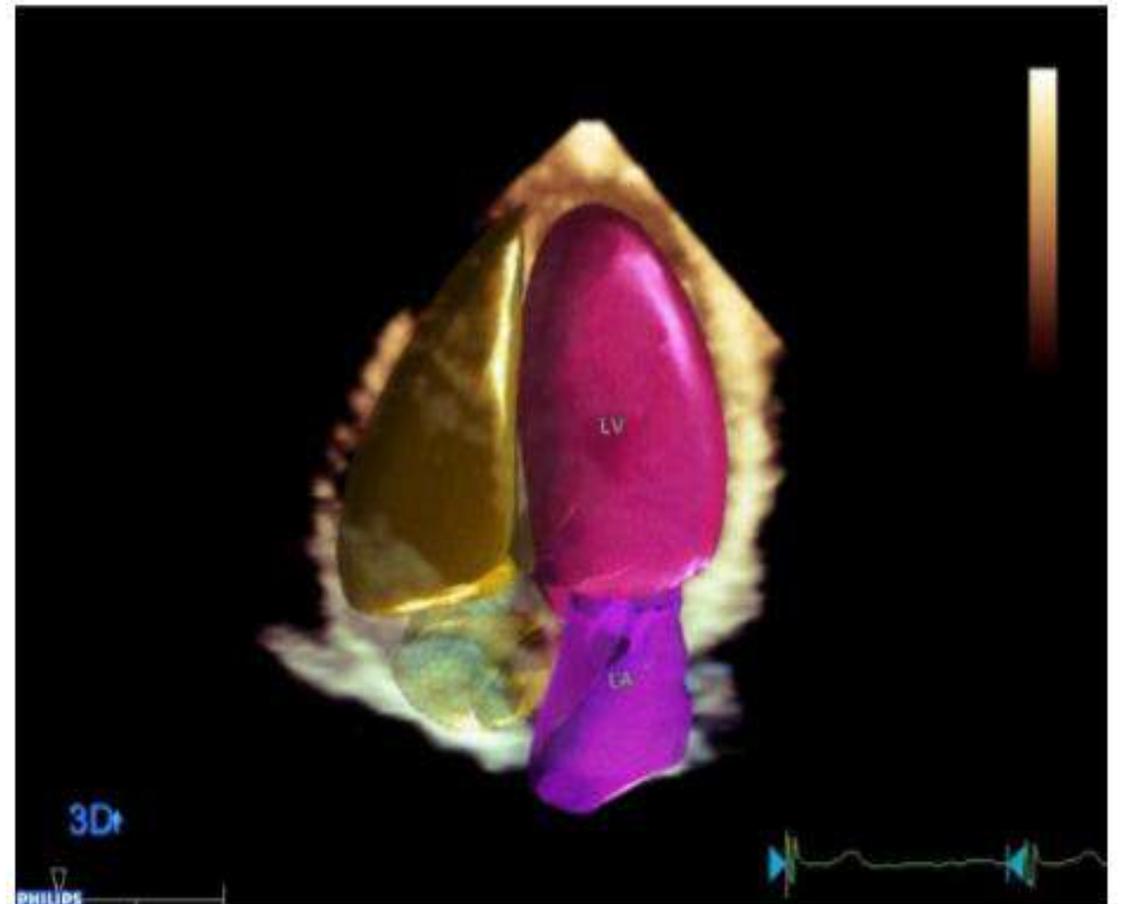
**TO RECOMMEND AN ICD, GUIDELINES AND CARDIOLOGISTS USE
NYHA AND LVEF**

Angiotensin-neprilysin inhibition further reverses cardiac remodeling as compared to angiotensin inhibition in reduced heart failure patients

Gonzalez-Torres L^{1,2}, De Diego C^{1,2}, Centurion R¹, Macias M¹, De Lara G¹, Carrasco R^{1,2}, Almendral J²

ACEI vs sacubitril-valsartan (n=250, F-U 9 MONTHS)

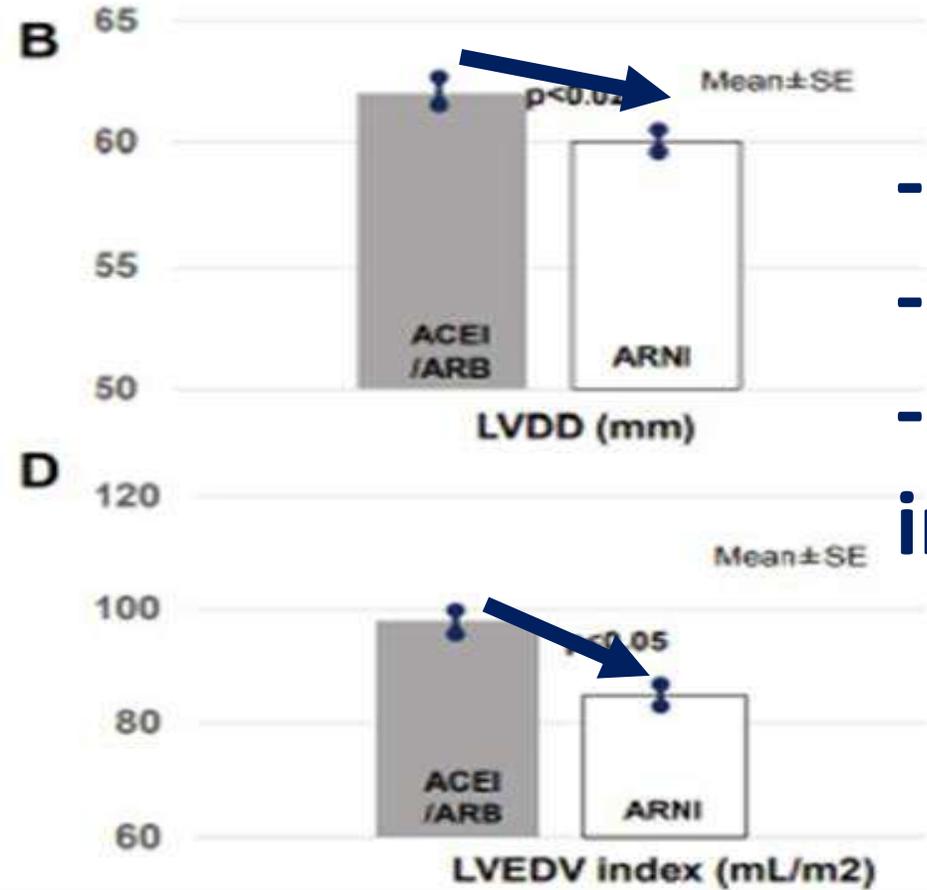
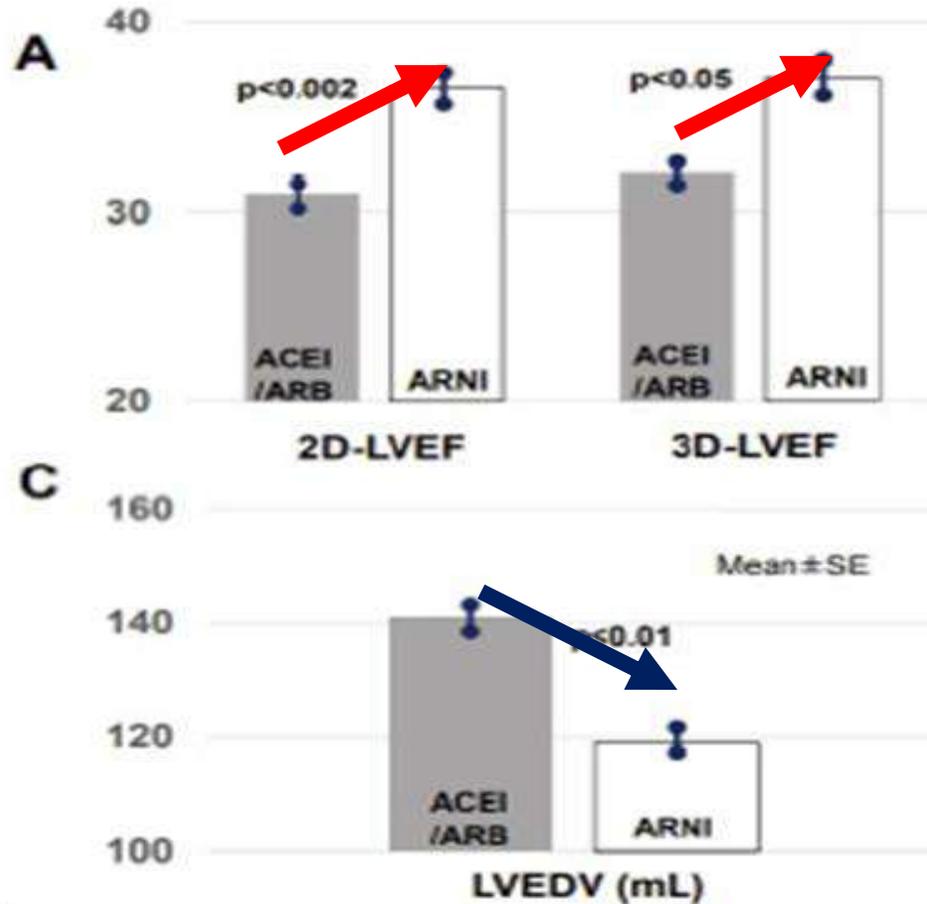
	Angiotensin inhibition alone (n=250) n or Mean \pm SD or %	Angiotensin- neprilysin inhibition (n=250) n or Mean \pm SD or %	P-value
2D-Echocardiogram			
2D LVEF (%)	31 \pm 6	36.5 \pm 8	p<0.002
2D LVDD (mm)	62 \pm 6	60 \pm 6	p<0.02
2D LVEDV (mL)	141 \pm 17	119 \pm 15	p<0.01
3D-Echocardiogram (n=50)			
Automatic 3D LVEF (%)	32 \pm 4	37 \pm 8	p<0.05
Automatic 3D LVEDV Index (mL/m ²)	98 \pm 7	85 \pm 8	p<0.05



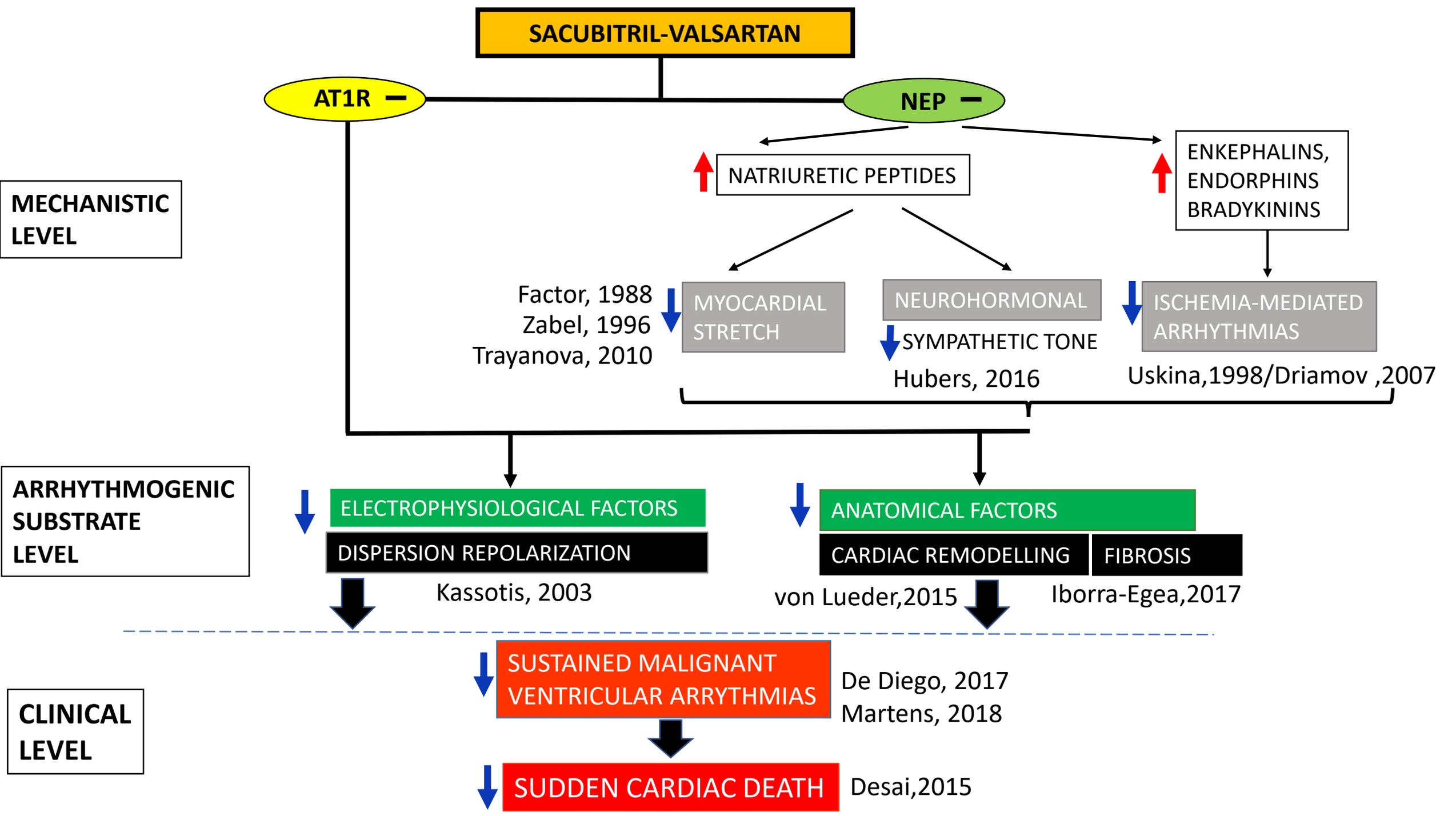
Angiotensin-neprilysin inhibition further reverses cardiac remodeling as compared to angiotensin inhibition in reduced heart failure patients

Gonzalez-Torres L^{1,2}, De Diego C^{1,2}, Centurion R¹, Macias M¹, De Lara G¹, Carrasco R^{1,2}, Almendral J¹

LVEF



-LVDD
-LV DVol
-LV DVol index



ESC 2016 and 2019 recommendations for sacubitril-valsartan

SUDDEN CARDIAC DEATH IN PATIENTS WITH HEART FAILURE:

THE ROLE OF SACUBITRIL- VALSARTAN

Dr. Carlos de Diego

Heart Failure –Arrhythmia Unit

Hospital Universitario de Torrevieja/Hospital Universitario de
Elche/Vinalopó



IN SYMPTOMATIC AMBULATORY HF PATIENTS DESPITE ACEI , BBK AND MRA (ESC 2016)

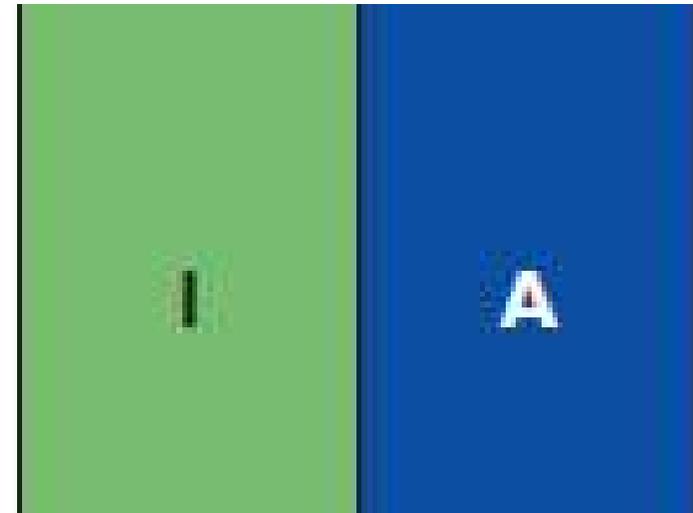
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA^d

I

B

FIRST LINE TO REDUCE SUDDEN CARDIAC DEATH IN PATIENTS WITH VENTRICULAR ARRHYTHMIAS (ESC 2016)

Treatment with beta-blocker, MRA and sacubitril/valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias



FIRST LINE HOSPITALISED OR DECOMPENSATED CHF (ESC CONSENSUS 2019)

- Initiation of sacubitril/valsartan rather than an ACE-I or an ARB **may be considered** for patients hospitalised with new-onset HF or decompensated CHF to reduce the short-term risk of adverse events and to simplify management (by avoiding the need to titrate ACE-I first and then switch to sacubitril/valsartan). Because these patients are already at high risk of

Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the ESC

[Eur J Heart Fail.](#) 2019 May 26

conclusions

Combined angiotensin and neprilysin inhibition produces:

- Decrease of SCD and ventricular arrhythmias
- Reversal of cardiac remodeling and improvement of LVEF
- Optimization of heart failure therapy decreases sudden cardiac death before and after implanting an ICD.



PROCESO INSUFICIENCIA CARDIACA
SEC-EXCELENTE



**This is not MARS, This is TORREVIEJA
THANKS FOR YOUR ATTENTION**

