Nouveautés en insuffisance cardiaque systolique

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INSTITUT UNIVERSITAIRE
DE CARDIOLOGIE
ET DE PNEUMOLOGIE
DE QUÉBEC

Affilié à UNIVERSITÉ LAVAL

McGill Faculty of Medicine Faculté de Médecine

Conflits d'intérêt potentiels

V-Wave

- Institutional grant/research support: V-Wave Medical
- V-Wave Core Lab

Sacubitril-Valsartan (Entresto®)

- Investigateur principal
  - PARADYGM-HF
  - PARTHENON
  - PARAGON
  - PARADISE
- Comité de surveillance
  - PARASAIL
- Conférencier

Objectifs

- Mieux connaître les nouvelles molécules dans le traitement de l'insuffisance cardiaque

- Découvrir un nouveau dispositif permettant de traiter l'insuffisance cardiaque.

Patient stable = Fausse perception

Classe II NYHA

- Malade perçu comme stable
- Risque perçu comme étant faible
- Inertie des patients et des soignants pour l'optimisation du traitement
- Changement du traitement seulement lorsque la maladie s'aggrave

Classe III-IV NYHA

- Malade perçu comme instable
- Maladie perçue comme étant au stade avancé ou terminal
- Accent mis sur les traitements avancés ou les soins palliatifs

Stabilité de classe II de la NYHA

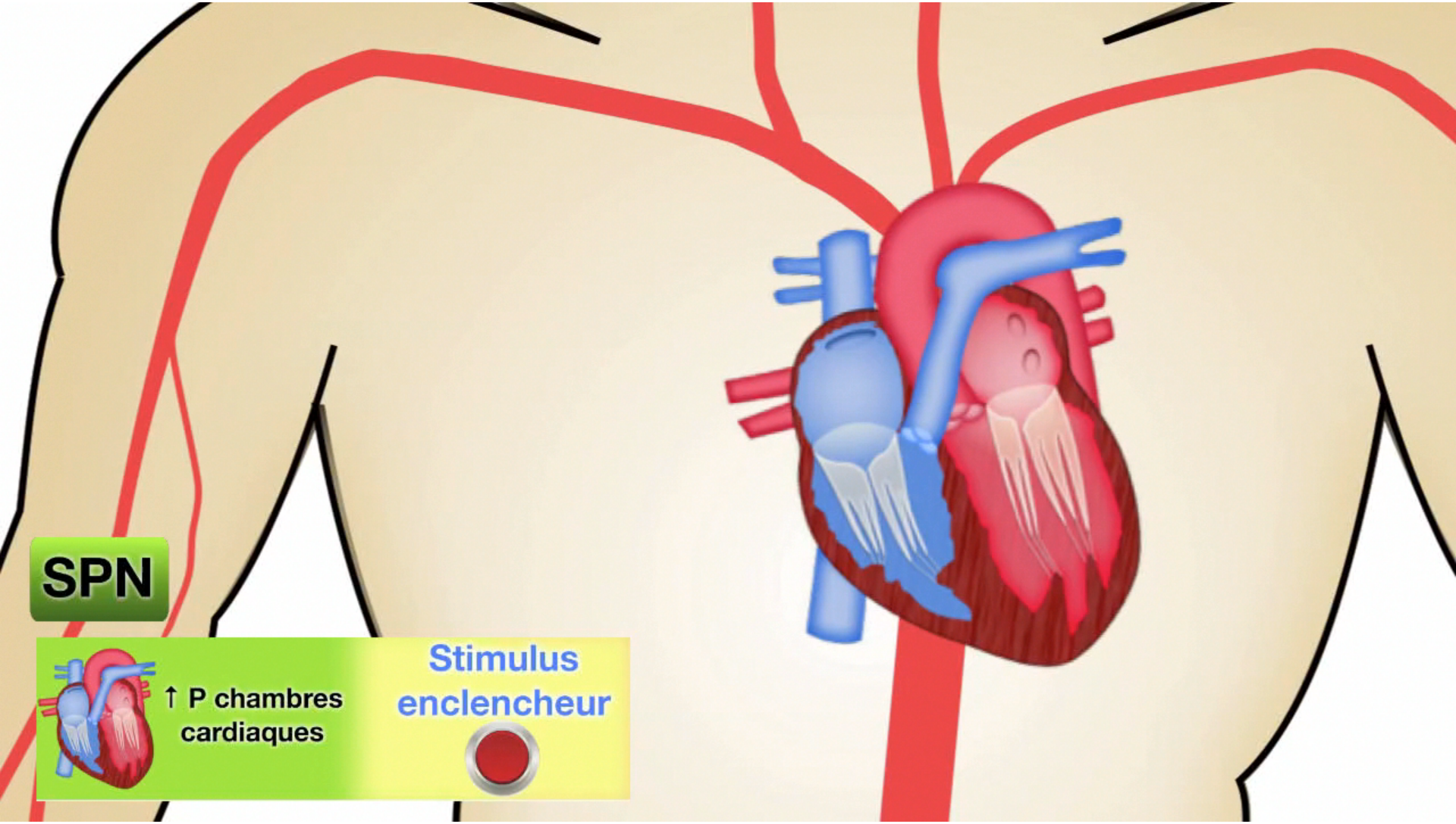
- Taux annuel de mortalité de 6 à 20 %
- Plus d'un million d'hospitalisations USA/UE/Canada
- Risque de mortalité de 25 à 30 % dans l'année suivant le congé de l'hôpital
- 40 % des patients décèdent de mort subite, il n'y a pas de signe avant-coureur ni d'aggravation des symptômes

Butler J, *et al. Eur J Heart Failure.* 2016: 18;350-2.

Le rôle du Système Rénine-Angiotensine-Aldostérone *(en 50 secondes)*

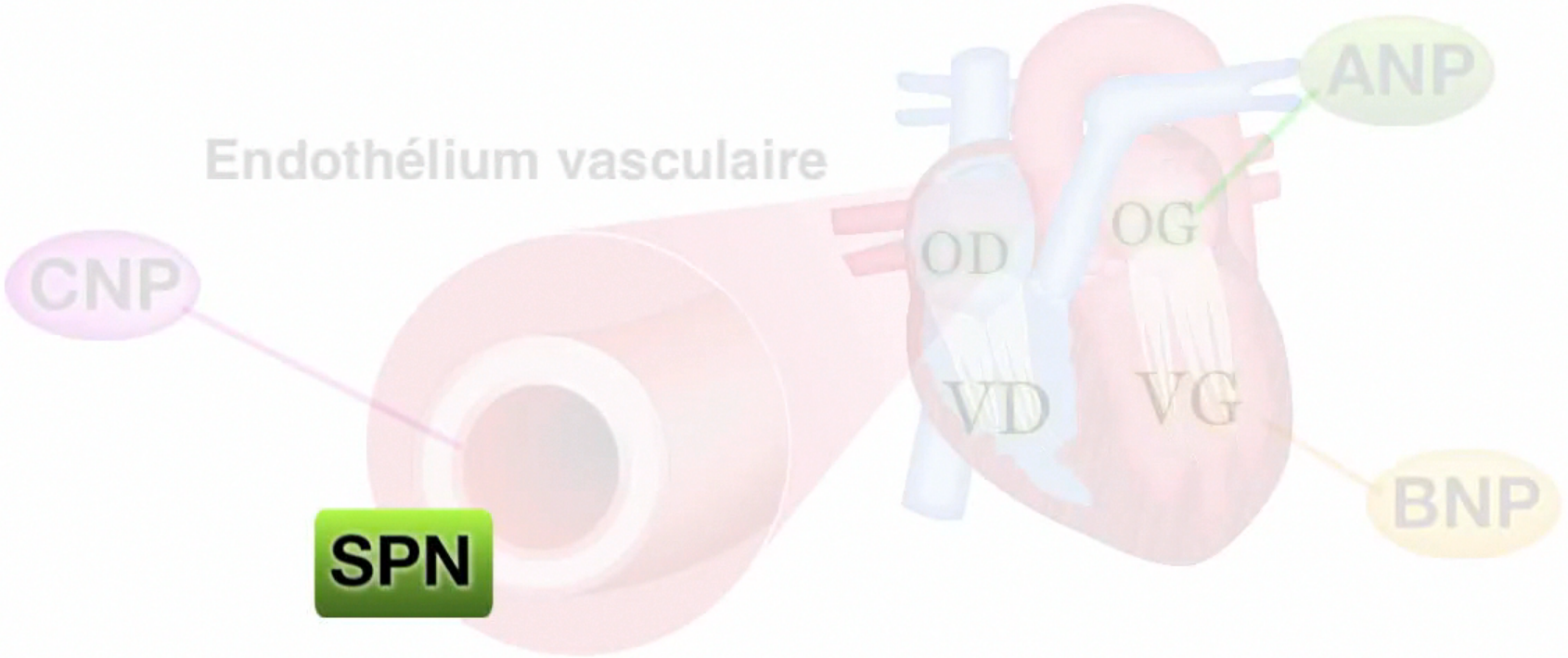
Application Apple Cardio Virtuel

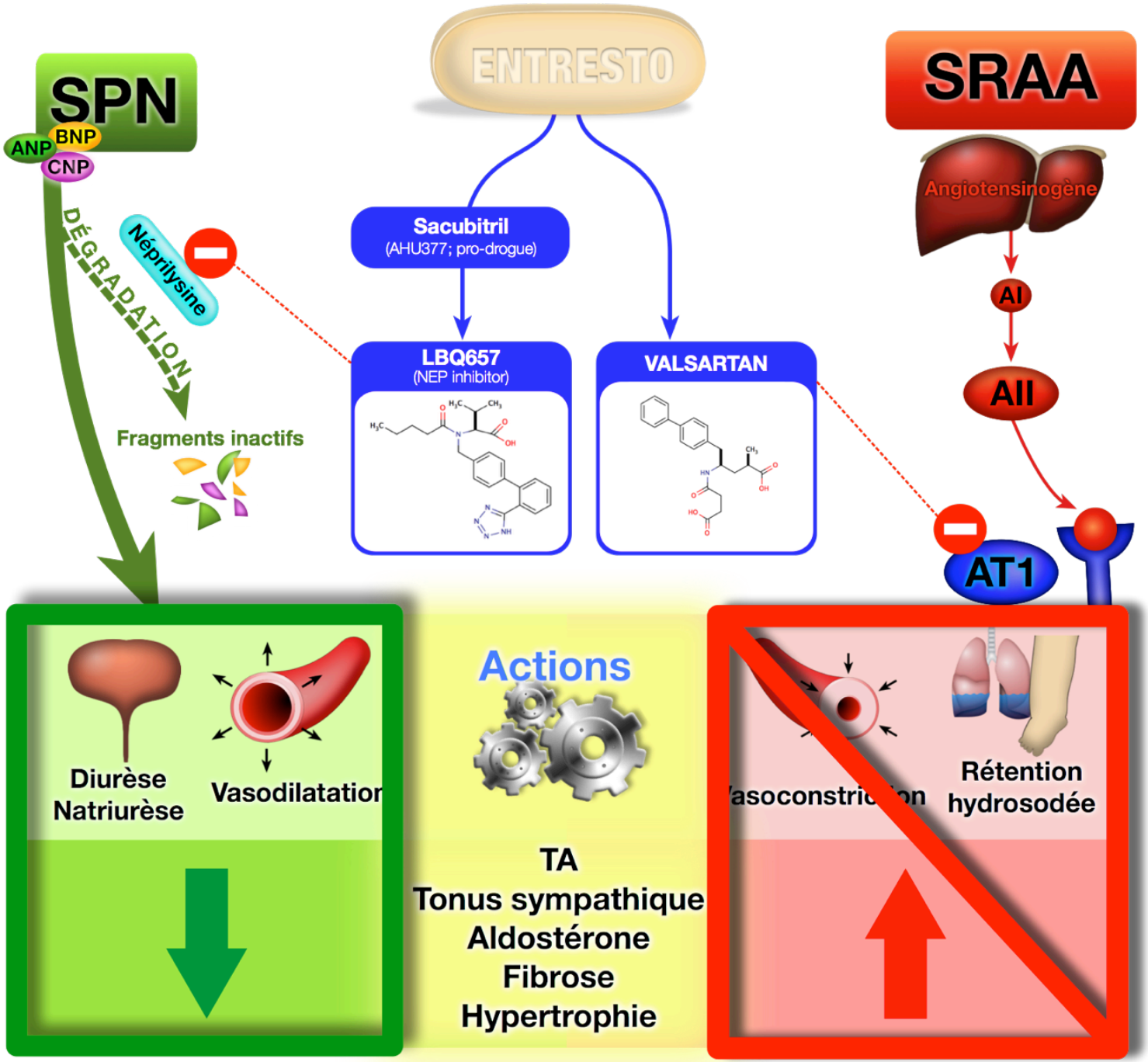
Le système des peptides natriurétiques



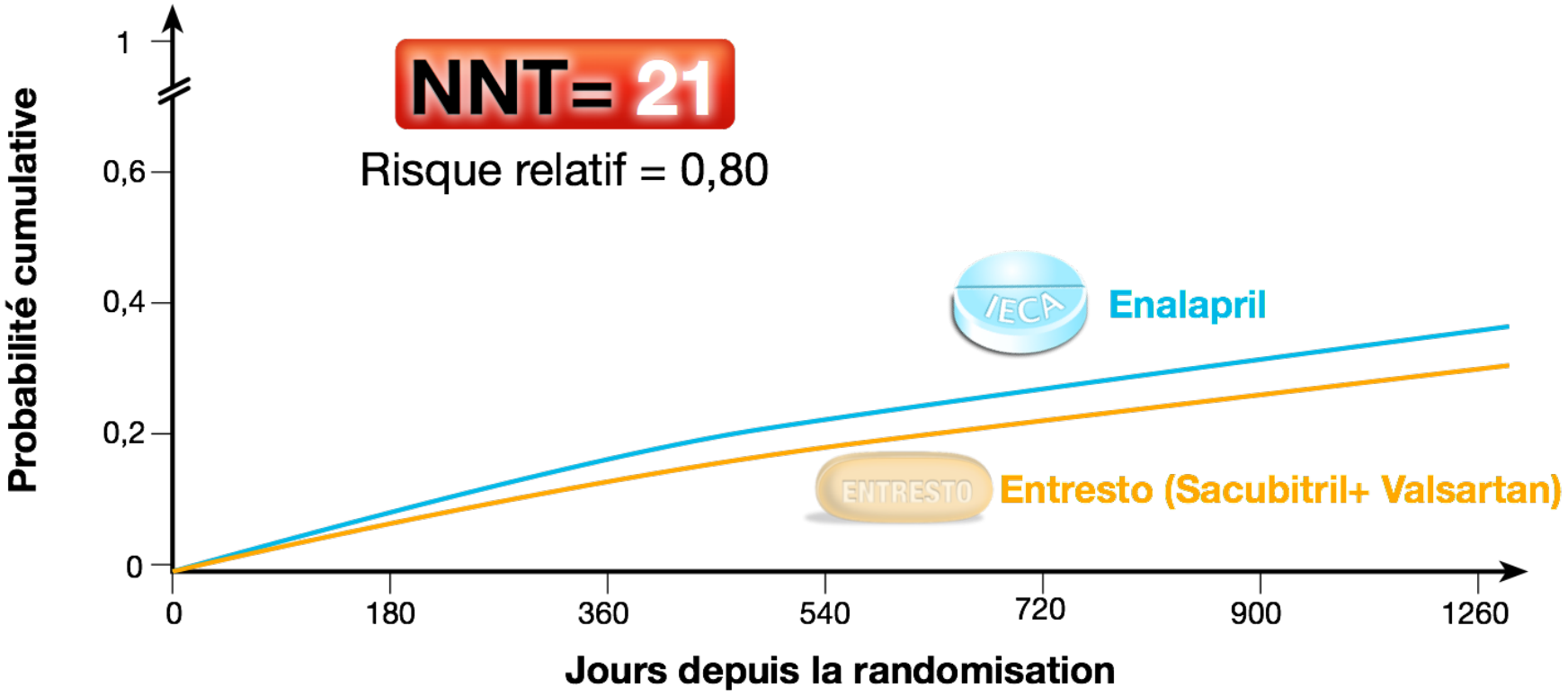
Application Apple Cardio Virtuel

Système des Peptides Natriurétiques (SPN)



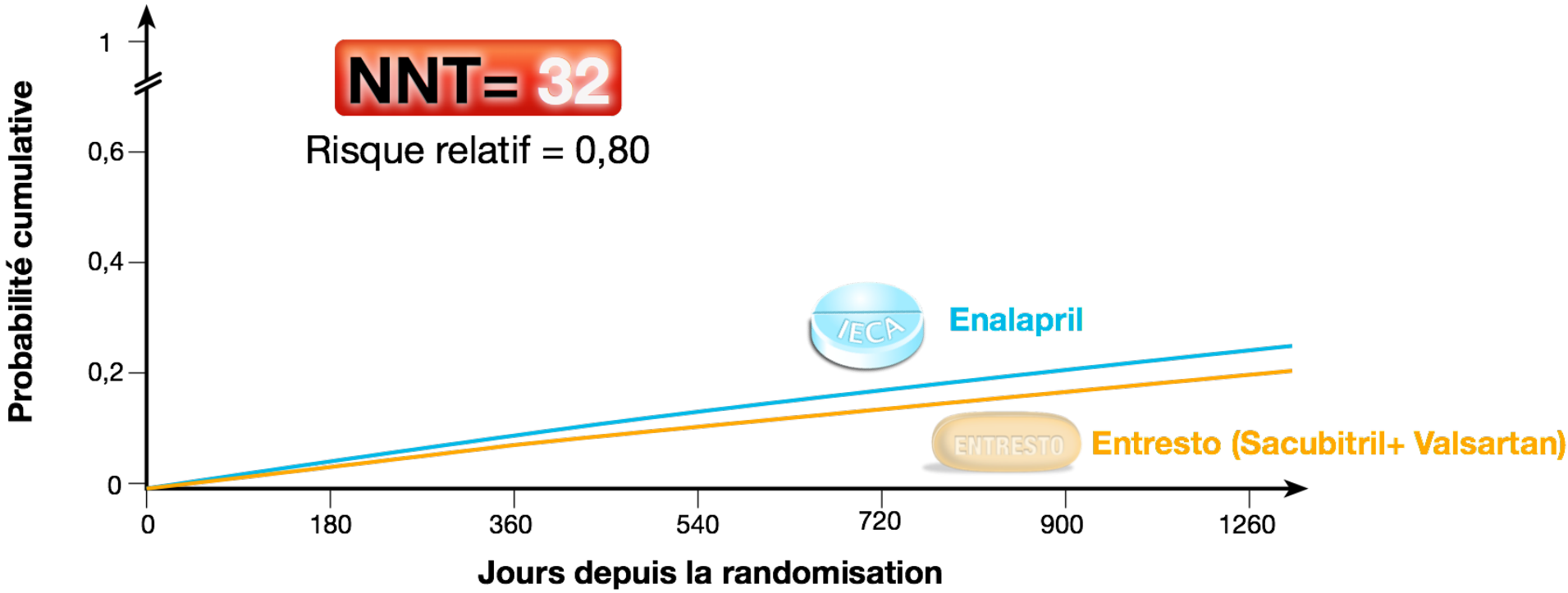

SPN
ANP
BNP
CNP
DÉGRADATION
Néprilysine
Fragments inactifs
ENTRESTO
Sacubitril
(AHU377; pro-drogue)
LBQ657
(NEP inhibitor)
VALSARTAN
SRAA
Angiotensinogène
AI
AII
AT1
Diurèse
Natriurèse
Vasodilatation
Actions
TA
Tonus sympathique
Aldostérone
Fibrose
Hypertrophie
Rétention
hydrosodée

Mortalité cardiovasculaire ou première hospitalisation pour IC



McMurray et al. N Engl J Med 2014; 371:993-1004

Mortalité cardiovasculaire



McMurray et al. N Engl J Med 2014; 371:993-1004

I	**ARNI: B-R**	**In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (138).**	**NEW**: New clinical trial data necessitated this recommendation.
See Online Data Supplements 1 and 18.		Benefits of ACE inhibitors with regard to decreasing HF progression, hospitalizations, and mortality rate have been shown consistently for patients across the clinical spectrum, from asymptomatic to severely symptomatic HF. Similar benefits have been shown for ARBs in populations with mild-to-moderate HF who are unable to tolerate ACE inhibitors. In patients with mild-to-moderate HF (characterized by either 1) mildly elevated natriuretic peptide levels, BNP [B-type natriuretic peptide] >150 pg/mL or NT-proBNP [N-terminal pro-B-type natriuretic peptide] ≥600 pg/mL; or 2) BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL with a prior hospitalization in the preceding 12 months) who were able to tolerate both a target dose of enalapril (10 mg twice daily) and then subsequently an ARNI (valsartan/sacubitril; 200 mg twice daily, with the ARB component equivalent to valsartan 160 mg), hospitalizations and mortality were significantly decreased with the valsartan/sacubitril compound compared with enalapril. The target dose of the ACE inhibitor was consistent with that known to improve outcomes in previous landmark clinical trials (129). This ARNI has been approved for patients with symptomatic HF*r*EF and is intended to be substituted for ACE inhibitors or ARBs. HF effects and potential off-target effects may be complex with inhibition of the neprilysin enzyme, which has multiple biological targets. Use of an ARNI is associated with hypotension and a low-frequency incidence of angioedema. To facilitate initiation and titration, the approved ARNI is available in 3 doses that include a dose that was not tested in the HF trial; the target dose used in the trial was 97/103 mg twice daily (147). Clinical experience will provide further information about the optimal titration and tolerability of ARNI, particularly with regard to blood pressure, adjustment of concomitant HF medications, and the rare complication of angioedema (14).	
III: Harm	**B-R**	**ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (148, 149).**	**NEW**: Available evidence demonstrates a potential signal of harm for a concomitant use of ACE inhibitors and ARNI.

Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
Diuretics			
Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.	I	B	178, 179
Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion.	IIa	B	178, 179
Angiotensin receptor neprilysin inhibitor			
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	162
If-channel inhibitor			
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).	IIa	B	180
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).	IIa	C	181
ARB			
An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE-I (patients should also receive a beta-blocker and an MRA).	I	B	182
An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate an MRA.	IIb	C	-
Hydralazine and isosorbide dinitrate			
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.	IIa	B	183
Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death.	IIb	B	184
Other treatments with less-certain benefits			
Digoxin			
Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).	IIb	B	185
N-3 PUFA			
An n-3 PUFA[e] preparation may be considered in symptomatic HF patients to reduce the risk of cardiovascular hospitalization and cardiovascular death.	IIb	B	186

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; bpm = beats per minute; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; PUFA = polyunsaturated fatty acid. OMT = optimal medical therapy (for HFrEF this mostly comprises an ACEI or sacubitril/valsartan, a beta-blocker and an MRA).

[a]Class of recommendation.

[b]Level of evidence.

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

ENTRESTO[MC] – Insuffisance cardiaque

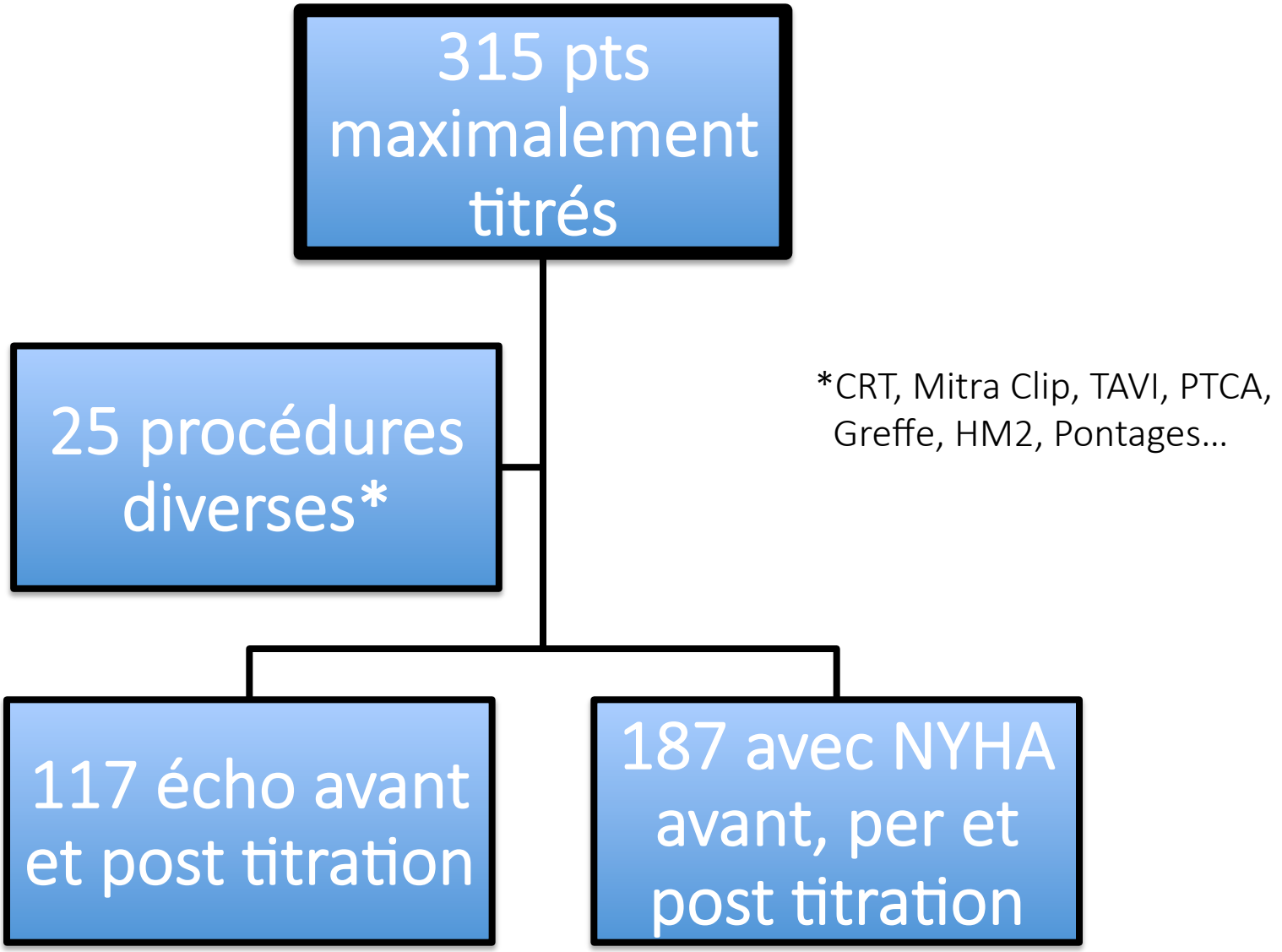
JUIN 2016

Marque de commerce : Entresto
Dénomination commune : Sacubitril/valsartan
Fabricant : Novartis
Forme : Comprimé
Teneurs : 24,3 mg – 25,7 mg, 48,6 mg – 51,4 mg et 97,2 mg – 102,8 mg

Indication reconnue pour le paiement

- pour le traitement des personnes atteintes d'insuffisance cardiaque de classe II ou III de la New York Heart Association (NYHA) présentant une dysfonction systolique ventriculaire gauche (avec une fraction d'éjection ≤ 40 %);
  - en association avec un bêta-bloquant à moins de contre-indication ou d'intolérance et
  - en remplacement d'un traitement en cours depuis au moins 4 semaines avec un inhibiteur de l'enzyme de conversion de l'angiotensine (IECA) ou un antagoniste des récepteurs de l'angiotensine II (ARA).

Analyse de paramètres échocardiographiques et NYHA (IUCPQ)



Modification NYHA et FEVG sous Sacubitril/Valsartan chez 187 pts

NYHA	Fréquence	Pourcentage
Après < Avant	n=36	19.25 %
FEVG Après vs Avant	**Fréquence**	**Pourcentage**
Améliorée	n=36	31%
Détériorée	n=7	6%
Stable	n=74	63%

Diminution furosémide chez 20% des patient
De ce nombre, diminution de plus 50% chez la moitié d'entre eux.

The PARASAIL study – Patient reported outcomes from the Canadian real-world experience use of sacubitril/valsartan in heart failure with reduced ejection fraction

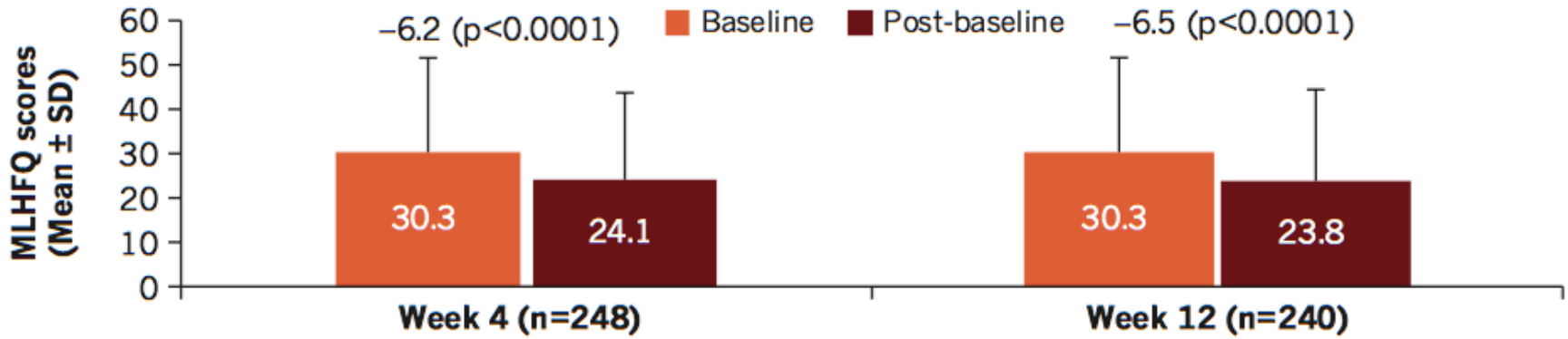
Haissam Haddad[1], Sébastien Bergeron[2], Andrew Ignaszewski[3], Greg Searles[4], Natacha Bastien[5]

[1]University of Saskatchewan, Saskatoon, Canada; [2]Centre de Recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Quebec, Quebec, Canada; [3]University of British Columbia, Vancouver, Canada; [4]Saint John Regional Hospital, Saint John, Canada; [5]Novartis Pharmaceuticals Canada Inc, Dorval, Canada

Minnesota Living with Heart Failure Questionnaire

- Using the MLHFQ, a statistically significant improvement in the QoL was observed at both weeks 4 and 12 as reflected by 20% and 21% decrease in the score compared with baseline, respectively ($p<0.0001$ for both weeks 4 and weeks 12) (**Figure 5**)

Figure 5. Changes in the MLHFQ scores, by visit versus baseline

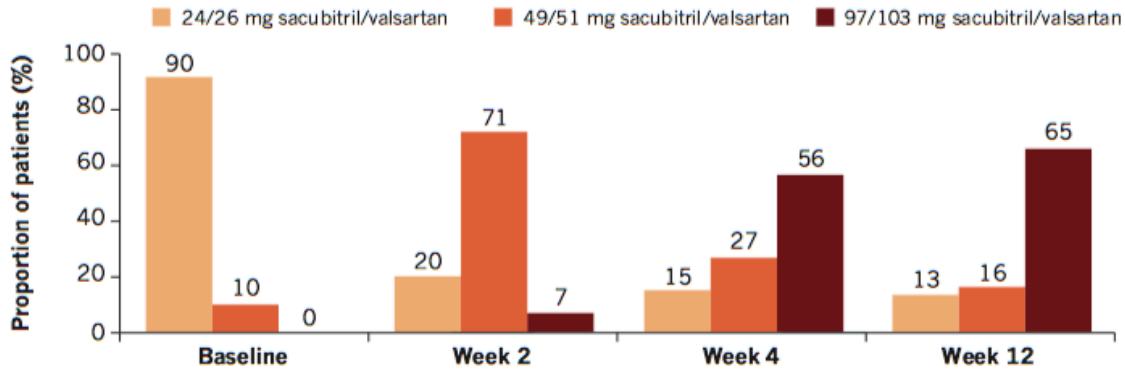


Note: Higher MLHFQ scores indicate poor quality of life
MLHFQ, Minnesota Living with Heart Failure Questionnaire; SD, standard deviation

Tolerability

- Sacubitril/valsartan was initiated at the 24/26 mg bid dose for most patients (90%), and up-titration to the target dose of 97/103 mg bid was achieved for 65% patients at 12 weeks **(Figure 3)**

Figure 3. Summary of sacubitril/valsartan treatment by dose



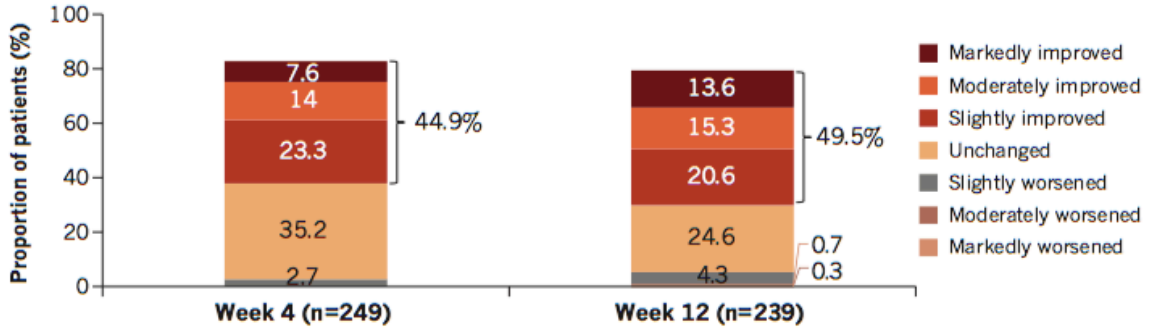
AE, adverse event; IC, informed consent

Quality of Life

Physician Global Assessment

- Using the PGA, 45% patients (135 of 249) experienced improvement in quality of life (slight, moderate and marked) at Week 4 and 49.5% (149 of 239) experienced improvement at Week 12 (**Figure 4**)

Figure 4. Changes in PGA at weeks 4 and 12 relative to baseline*



*A patient must have both week 4 and week 12 values to be included in the summary

Sacubitril /Valsartan (Entresto) Expérience clinique concluante

- Applicabilité clinique facile
- « Moins de variation rénale qu'à l'introduction d'un IECA-ARA »
- « C'est comme un pacemaker biventriculaire pos… »
- Remarquable réponse clinique
  - Commentaires patients
  - Diminution Furosémide
  - Amélioration NYHA
  - Signaux positifs paramètres échocardiographiques

Ivabradine (Lancora®)

- Approuvé par santé Canada janvier 2017
- Agit en réduisant uniquement la FC, par inhibition sélective et spécifique du canal If qui contrôle la dépolarisation diastolique spontanée au niveau du NS.
- Les effets cardiaques sont spécifiques au nœud sinusal sans effet
  - Les temps de conduction
    - Intra-auriculaires
    - Auriculoventriculaires
    - Intraventriculaires
  - Sur la contractilité myocardique ou sur la repolarisation ventriculaire.

SHIFT

(Ivabradine vs Placebo)

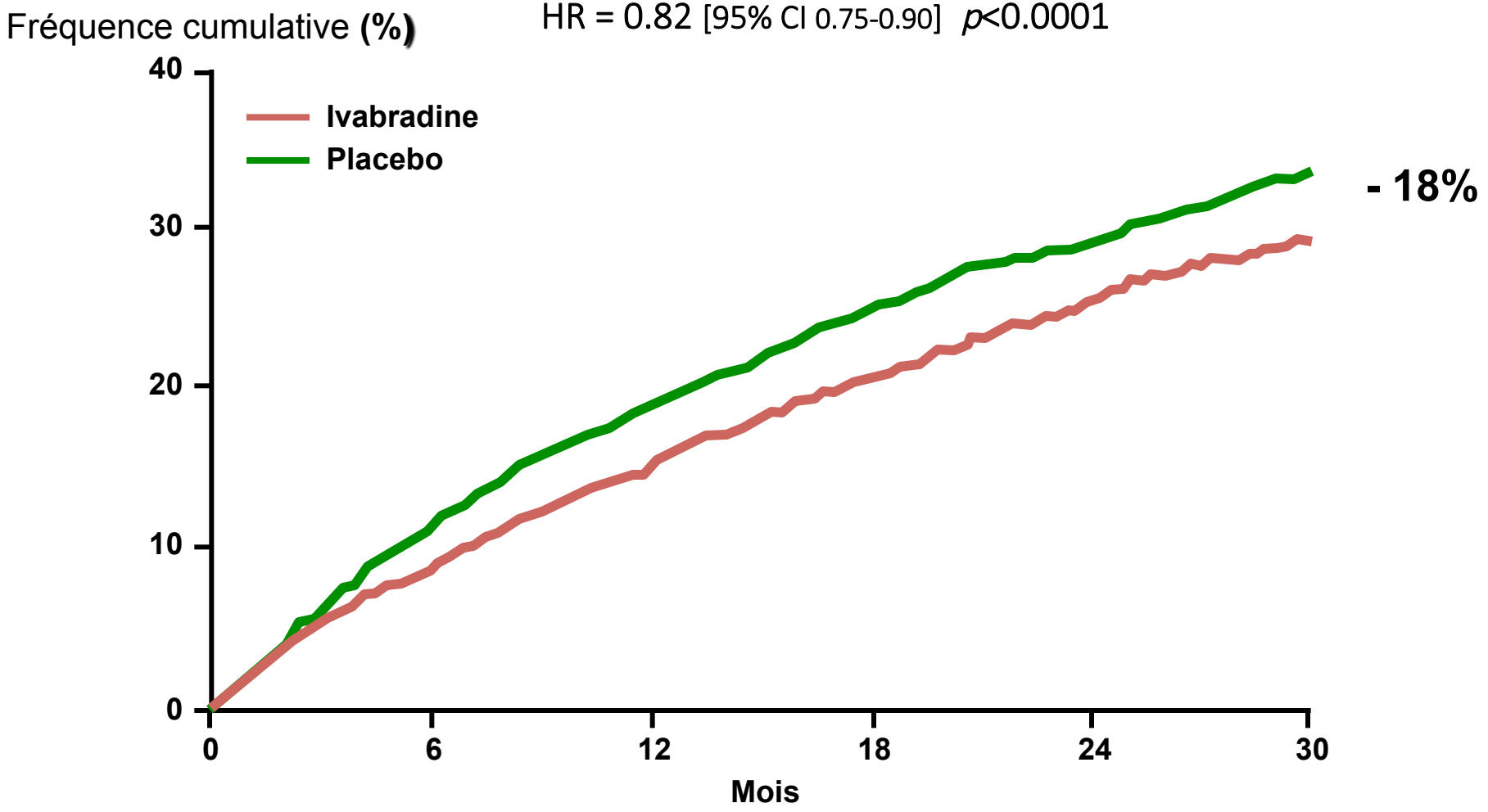
Critères d'inclusion

- Publiée en 2010
- 6558 patients
- NYHA classe 2-3, ischémique ou non
- FEVG ≤ 35%
- Heart rate ≥70 bpm
- Rythme sinusal
- Hospitalisation pour IC ≤ 12 mois

Point d'aboutissement primaire composé (décès CV + hospitalisation IC)

Ivabradine n=793 (14.5%PY) Placebo n=937 (17.7%PY)

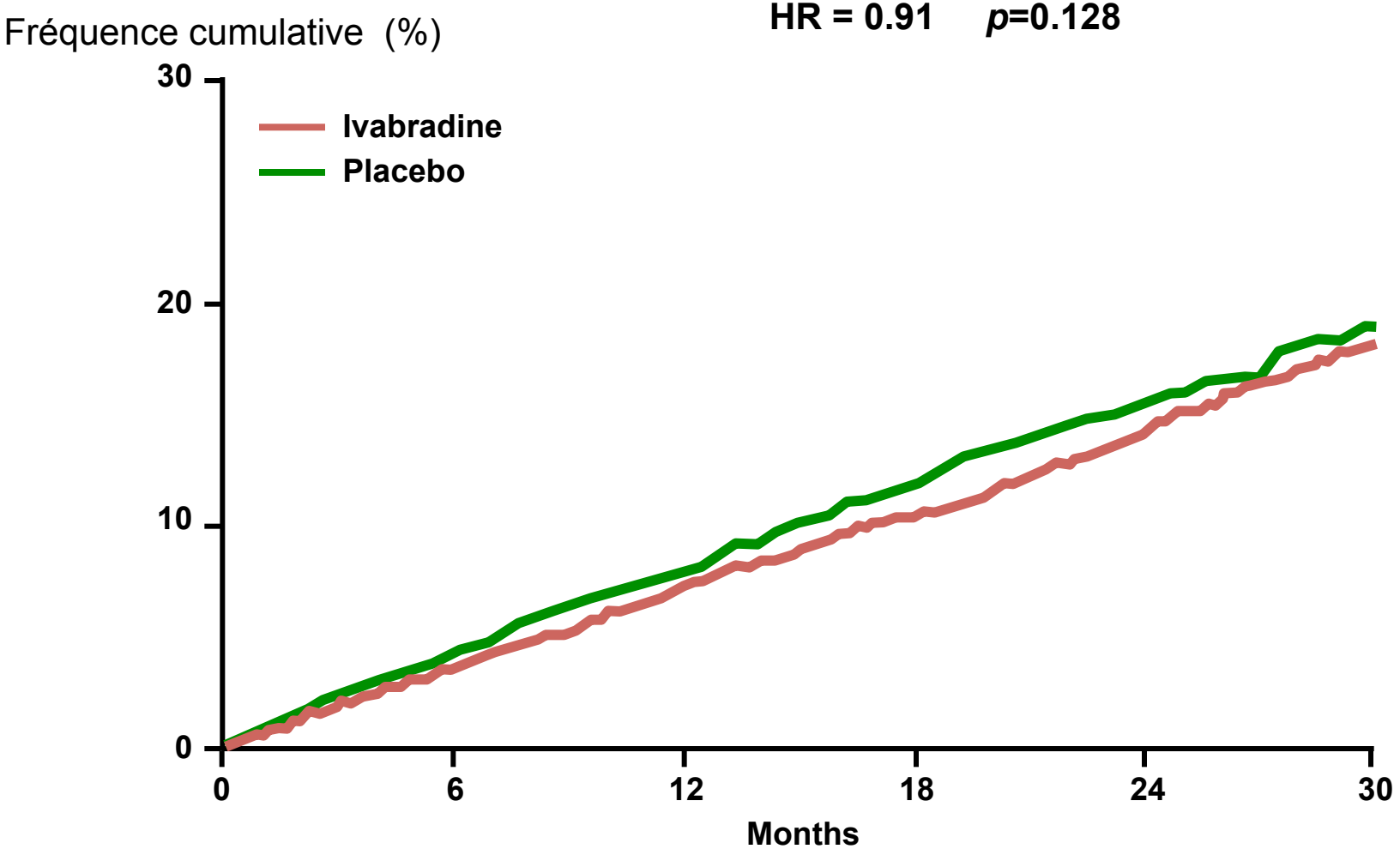
HR = 0.82 [95% CI 0.75-0.90] $p<0.0001$



Mortalité Cardiovasculaire

Ivabradine n=449 (7.5%PY) **Placebo n=491 (8.3%PY)**

HR = 0.91 ***p*=0.128**



7.3.2.11. Ivabradine: Recommendation

Recommendation for Ivabradine			
COR	**LOE**	**Recommendation**	**Comment/Rationale**
IIa	**B-R**	**Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF*r*EF (LVEF ≤35%) who are receiving GDEM*, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (154-157).**	**NEW**: New clinical trial data.
See Online Data Supplement 4.		Ivabradine is a new therapeutic agent that selectively inhibits the I_f current in the sinoatrial node, providing heart rate reduction. One RCT demonstrated the efficacy of ivabradine in reducing the composite endpoint of cardiovascular death or HF hospitalization (155). The benefit of ivabradine was driven by a reduction in HF hospitalization. The study included patients with HF*r*EF (NYHA class II-IV, albeit with only a modest representation of NYHA class IV HF) and left ventricular ejection fraction (LVEF) ≤35%, in sinus rhythm with a resting heart rate of ≥70 beats per minute. Patients enrolled included a small number with paroxysmal atrial fibrillation (<40% of the time) but otherwise in	

Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
Diuretics			
Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.	I	B	178, 179
Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion.	IIa	B	178, 179
Angiotensin receptor neprilysin inhibitor			
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	162
If-channel inhibitor			
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).	IIa	B	180
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).	IIa	C	181
ARB			
An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE-I (patients should also receive a beta-blocker and an MRA).	I	B	182
An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate an MRA.	IIb	C	-
Hydralazine and isosorbide dinitrate			
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.	IIa	B	183
Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death.	IIb	B	184
Other treatments with less-certain benefits			
Digoxin			
Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).	IIb	B	185
N-3 PUFA			
An n-3 PUFA[e] preparation may be considered in symptomatic HF patients to reduce the risk of cardiovascular hospitalization and cardiovascular death.	IIb	B	186

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; bpm = beats per minute; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; PUFA = polyunsaturated fatty acid. OMT = optimal medical therapy (for HFrEF this mostly comprises an ACEI or sacubitril/valsartan, a beta-blocker and an MRA).

[a]Class of recommendation.

[b]Level of evidence.

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

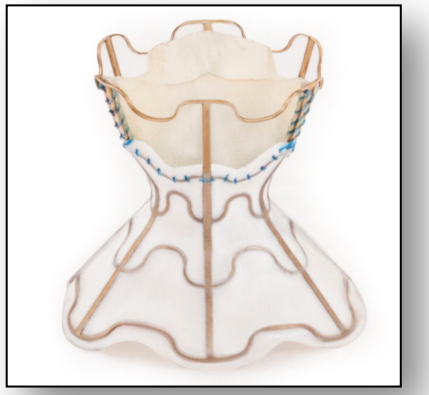
The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Proposition d'utilisation de l'Ivabradine (Lancora®) pour CLIC IUCPQ

- Patient classe NYHA 2-3
  - maximalement traité (incluant Sacubitril-Valsartan sauf exception)
  - FC > 70 - 77 BPM au repos
  - Absence de FAP
  - Sans amiodarone
  - Sans dépendance au pacemaker
  - Hypotension, IRC, CI Bêtabloqueurs…

- Rationnelle
  - FA plus fréquente chez les pts traités avec Ivabradine et Amiodarone. On doit éviter l'emploi concomitant de LANCORA et d'Amiodarone. (monographie canadienne)
  - Ivabradine a démontré un diminution de la mortalité en 2010 dans l'étude SHIFT chez les patients avec une FC ≥77 BPM.
  - Niveau d'indication dans lignes de conduite américaine et européenne

Dispositif V-Wave
Décompression de OG



Étude préliminaire avec un modèle de mouton ischémique

(Del Rio CL, AHA 2013)

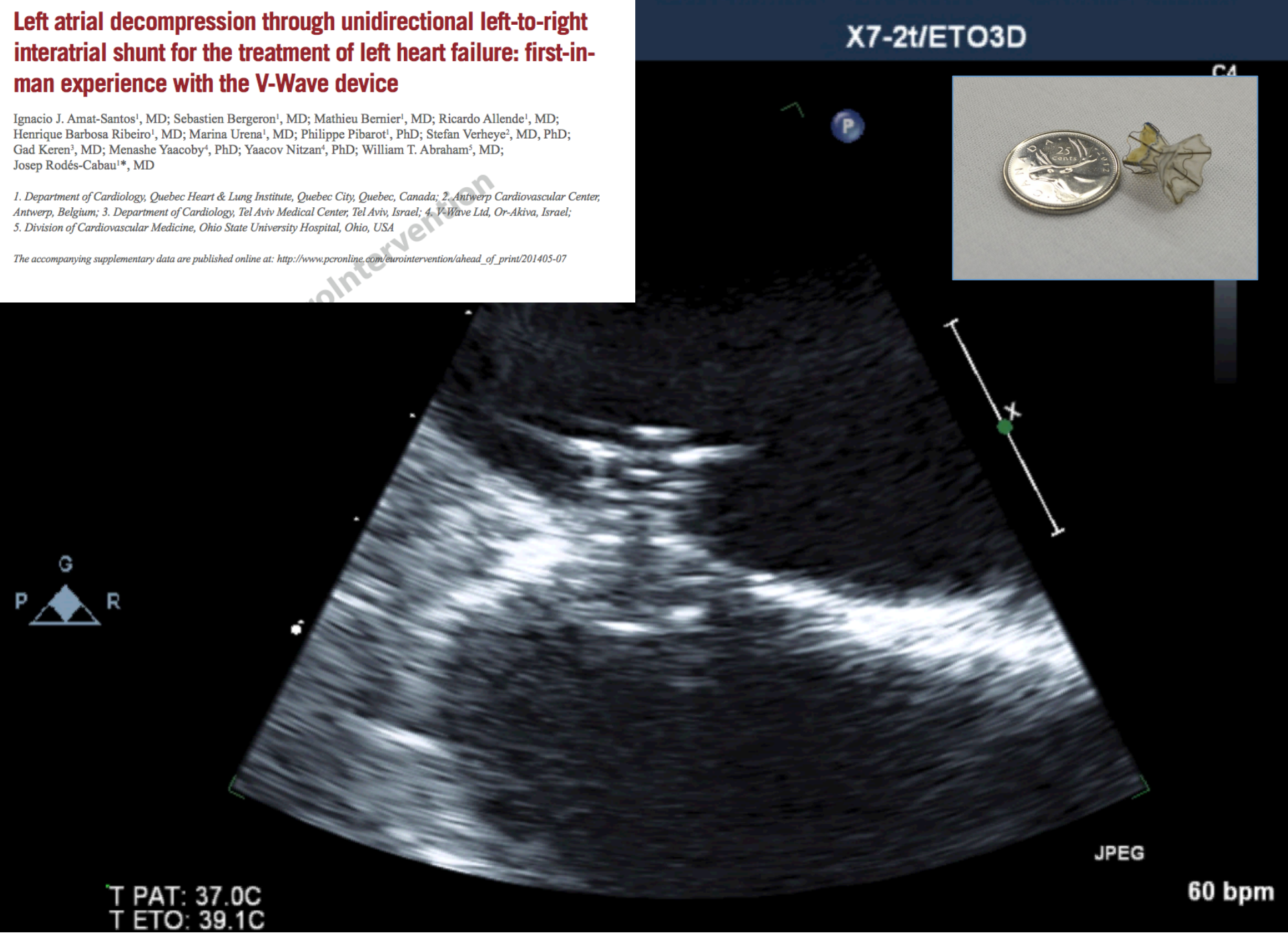
- ü ? pression OG
- ü Aucune Δ pression OD ou pulmonaire.
- ü Perméabilité durant la durée de l'étude (12 sem.)
- ü Amélioration hémodynamique et FEVG
- ü Diminution de remodelage cardiaque

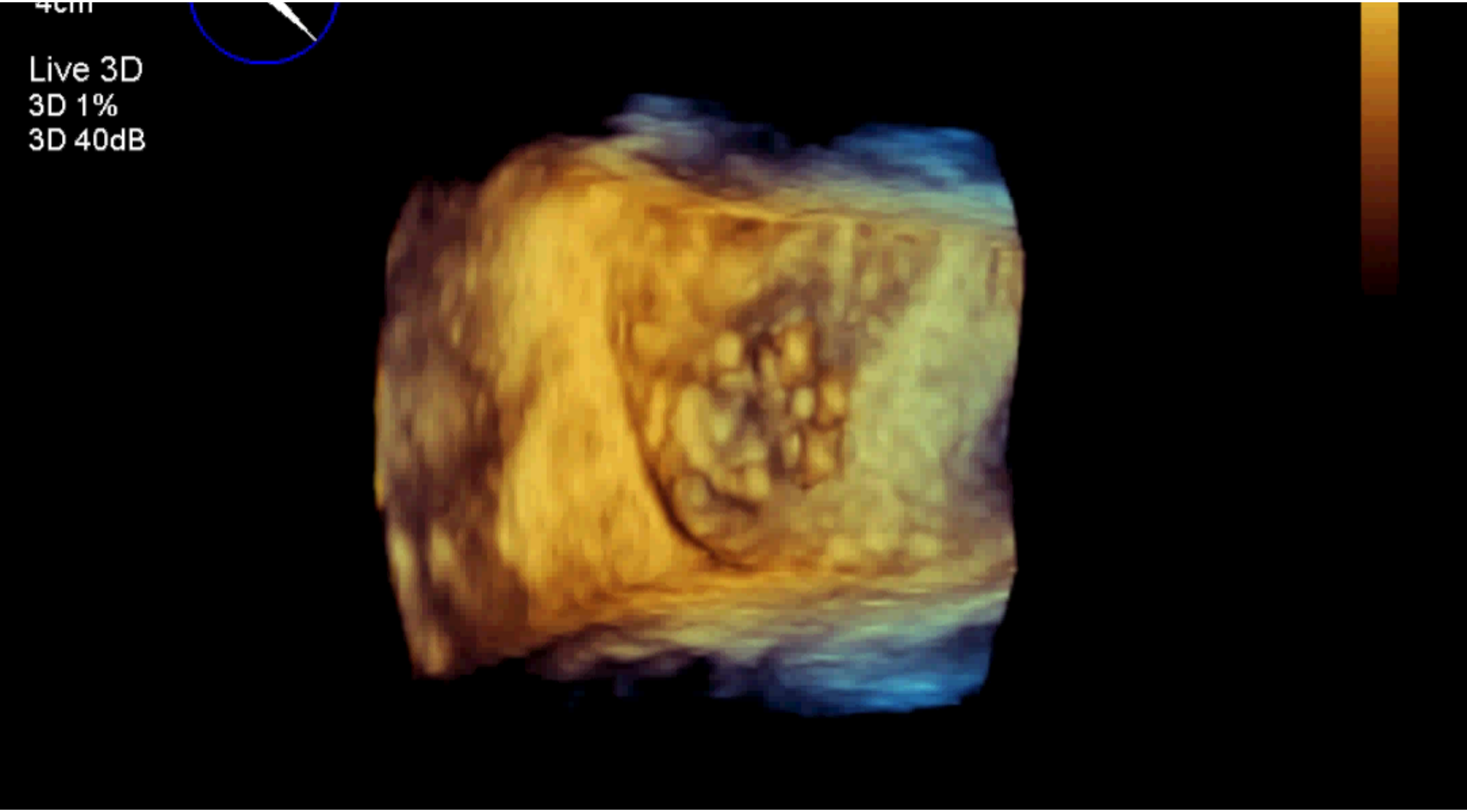
Left atrial decompression through unidirectional left-to-right interatrial shunt for the treatment of left heart failure: first-in-man experience with the V-Wave device

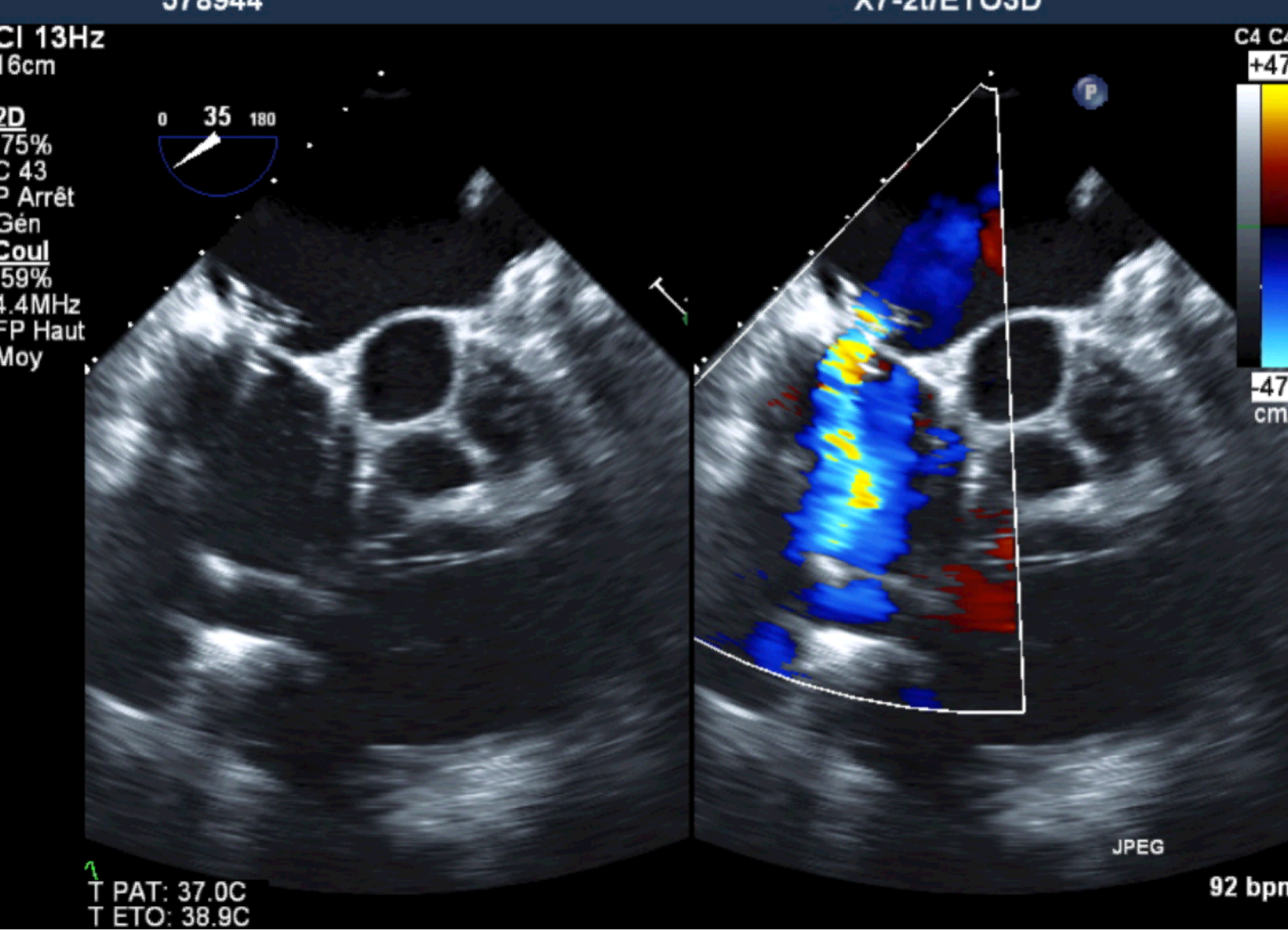
Ignacio J. Amat-Santos[1], MD; Sebastien Bergeron[1], MD; Mathieu Bernier[1], MD; Ricardo Allende[1], MD; Henrique Barbosa Ribeiro[1], MD; Marina Urena[1], MD; Philippe Pibarot[1], PhD; Stefan Verheye[2], MD, PhD; Gad Keren[3], MD; Menashe Yaacoby[4], PhD; Yaacov Nitzan[4], PhD; William T. Abraham[5], MD; Josep Rodés-Cabau[1]*, MD

1. Department of Cardiology, Quebec Heart & Lung Institute, Quebec City, Quebec, Canada; 2. Antwerp Cardiovascular Center, Antwerp, Belgium; 3. Department of Cardiology, Tel Aviv Medical Center, Tel Aviv, Israel; 4. V-Wave Ltd, Or-Akiva, Israel; 5. Division of Cardiovascular Medicine, Ohio State University Hospital, Ohio, USA

The accompanying supplementary data are published online at: http://www.pcronline.com/eurointervention/ahead_of_print/201405-07




Live 3D
3D 1%
3D 40dB


CI 13Hz
16cm
2D
75%
C 43
P Arrêt
Gén
Coul
59%
4.4MHz
FP Haut
Moy
0 35 180
C4 C
+47
-47
cm
JPEG
T PAT: 37.0C
T ETO: 38.9C
92 bpm

Unidirectional left-to-right interatrial shunting for treatment of patients with heart failure with reduced ejection fraction: a safety and proof-of-principle cohort study

Maria Del Trigo, Sebastien Bergeron, Mathieu Bernier, Ignacio J Amat-Santos, Rishi Puri, Francisco Campelo-Parada, Omar Abdul-Jawad Altisent, Ander Regueiro, Neal Eigler, Erez Rozenfeld, Philippe Pibarot, William T Abraham, Josep Rodés-Cabau

Lancet 2016; 387: 1290–97

See Editorial page 1252

See Comment page 1253

Quebec Heart and Lung Institute, Laval University, Quebec City, QC, Canada (M Del Trigo MD, S Bergeron MD, M Bernier MD, I J Amat-Santos MD, R Puri PhD, F Campelo-Parada MD, O Abdul-Jawad Altisent MD, A Regueiro MD, Prof P Pibarot PhD, J Rodés-Cabau MD); **V-Wave, Caesarea, Israel** (N Eigler MD, E Rozenfeld); **and Ohio State University, Columbus, OH, USA** (Prof W T Abraham MD)

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Summary

Background In patients with heart failure, interventions to reduce elevated left atrial pressure improve symptoms and reduce the risk of hospital admission. We aimed to assess the safety and potential efficacy of therapeutic left-to-right interatrial shunting in patients with heart failure with reduced ejection fraction.

Methods We did this proof-of-principle cohort study at one centre in Canada. Patients (aged ≥18 years) with New York Heart Association (NYHA) class III chronic heart failure with reduced ejection fraction were enrolled under the Canadian special access programme. Shunt implants were done after transseptal catheterisation with transoesophageal echocardiographic guidance under general anaesthesia. Patients had clinical and echocardiography evaluations at baseline and months 1 and 3 after shunt implantation.

Findings Between Oct 10, 2013, and March 27, 2015, we enrolled ten patients. The device was successfully implanted in all patients; no device-related or procedural adverse events occurred during follow-up. Transoesophageal echocardiography at 1 month showed that all shunts were patent, with no thrombosis or migration. From baseline to 3 month follow-up, we recorded improvements in NYHA classification (from class III to class II in seven [78%] of nine patients, from class III to class I in one [11%] patient, and no change in one [11%] patient; p=0·0004); quality of life, as assessed by the Duke Activity Status Index (from a mean score of 13 [SD 6·2] to 24·8 [12·9]; p=0·016) and the Kansas City Cardiomyopathy Questionnaire (from a mean score of 44·3 [SD 9·8] to 79·1 [13·0]; p=0·0001); and 6 min walk test distance (from a mean of 244 m [SD 112] to 318 m [134]; p=0·016). Pulmonary capillary wedge pressure was reduced from a mean of 23 mm Hg (SD 5) at baseline to 17 mm Hg (8) at 3 months (p=0·035), with no changes in right atrial pressure, pulmonary arterial pressure, or pulmonary resistance. No patient was admitted to hospital for worsening heart failure. One (10%) patient was admitted to hospital with gastrointestinal bleeding at month 1; one (10%) patient died after incessant ventricular tachycardia storm, which led to terminal heart failure 2 months post-procedure.

Interpretation This first-in-man experience with an implanted left-to-right interatrial shunt demonstrates initial safety and early beneficial clinical and haemodynamic outcomes in patients with heart failure with reduced ejection fraction. Further large-scale randomised studies are warranted.

Del Trigo M, et al. Lancet 2016; 387: 1290-1297.

	Baseline (N=9)	3 months (N=9)	p value
Functional status and quality of life			
NYHA class*			0·0004
III–IV	9 (100%)	1 (11%)	..
I–II	0	8 (89%)	..
Duke Activity Status Index	13 (6·2)	24·8 (12·9)	0·016
Kansas City Cardiomyopathy Questionnaire	44·3 (9·8)	79·1 (13·0)	0·0001
6 min walk test (m)	244 (112)	319 (134)	0·016
Laboratory tests			
NT-pro BNP (pg/mL)	2485 (3318)	2473 (2984)	0·96
eGFR (mL/min)	55 (20)	49 (20)	0·27
Echocardiographic variables			
Left ventricular ejection fraction (%)	24·5 (8·3)	25·3 (8·8)	0·91
Stroke volume (mL)	56 (16)	51 (17)	0·082
Left ventricular end-diastolic volume (mL)	223 (65)	203 (49)	0·031
Left ventricular end-systolic volume (mL)	168 (58)	153 (51)	0·010
Tricuspid annular plane systolic excursion (mm)	16·1 (4·7)	18·7 (5·2)	0·10
Haemodynamics			
Heart rate (beats per min)	70 (7)	73 (7)	0·069
Mean arterial pressure (mm Hg)	81 (7)	90 (10)	0·027
Pulmonary capillary wedge pressure (mm Hg)	23 (5)	17 (8)	0·035
Right atrial pressure (mm Hg)	9 (4)	8 (5)	0·18
Mean pulmonary artery pressure (mm Hg)	29 (7)	26 (11)	0·37
Cardiac output (L/min)†	4·4 (1·0)	5·5 (0·9)‡	0·011
Cardiac index (L/min per m^2)§	2·1 (0·3)	2·6 (0·4)¶	0·020
Pulmonary vascular resistance (mm Hg × L^{-1} × min)	2·5 (1·1)	1·9 (0·7)	0·11
Pulmonary vascular resistance index (mm Hg × L^{-1} × min × m^2)	5·1 (1·8)	4·0 (1·2)	0·16
Ratio of pulmonary to systemic blood flow (Qp:Qs)	0·98 (0·05)‖	1·08 (0·10)	0·033

Del Trigo M, et al.
Lancet 2016; 387: 1290-1297.

V-Wave
(dispositf palliatif expérimental)

- L'implantation du V-Wave en HFPEF-HFREF est réalisable et sécuritaire.
- Le shunt inter auriculaire est associée à des améliorations
  - NYHA
  - Capacité à l'effort
  - Qualité de vie
- Les effets bénéfiques ne se font pas au détriments des paramètres hémodynamiques ou échocardiographiques du VD.
- Une étude multicentrique randomisée est nécessaire et débutera sous peu.

Conclusions

- Le concept de stabilité en IC. doit être abandonné
- L'inertie médicale (NHYA 2) est un fardeau médical payé par le patient
- Valorisation de la cardiologie clinique : on peut faire mieux

Nouveautés en insuffisance cardiaque systolique

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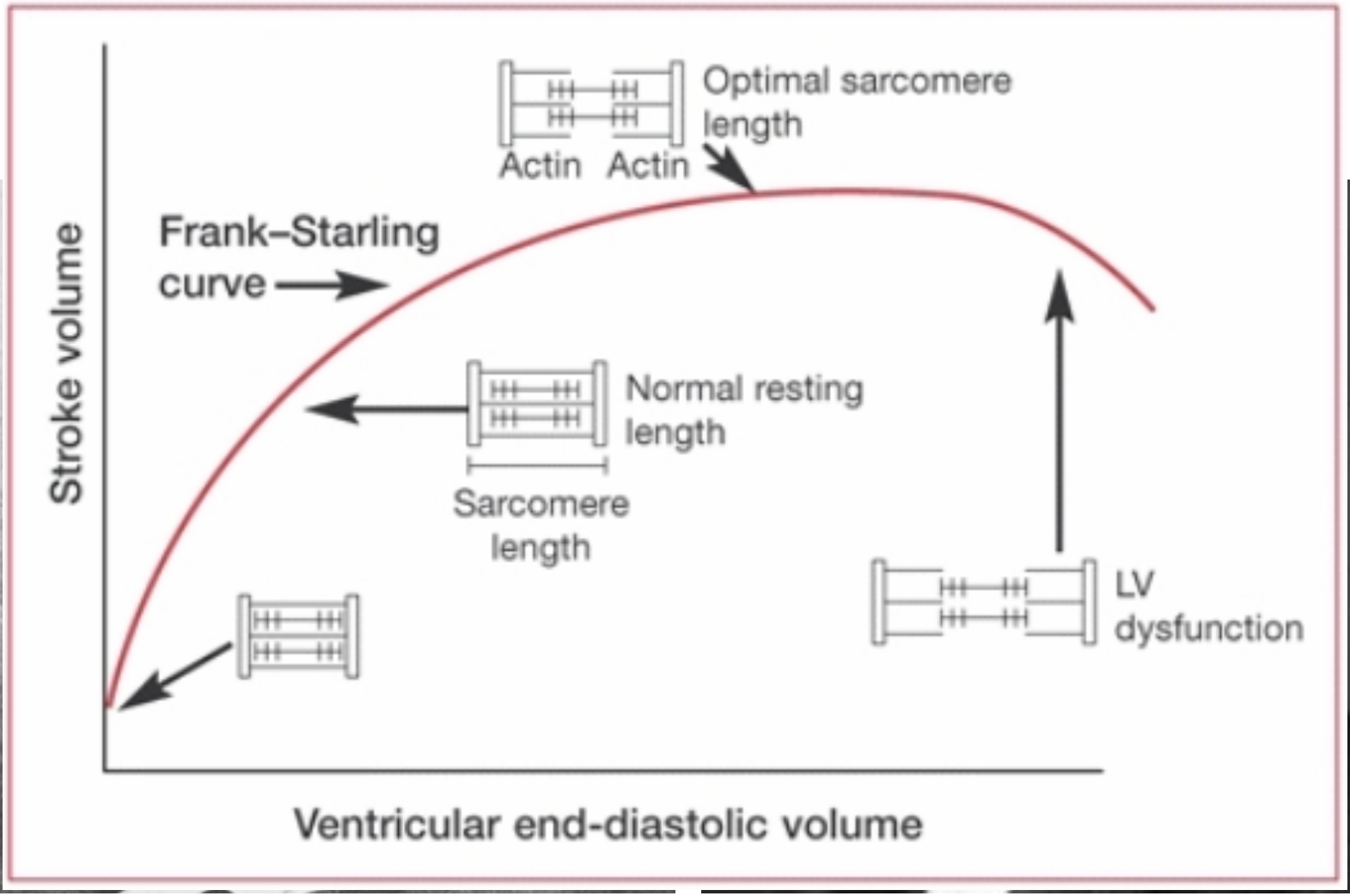
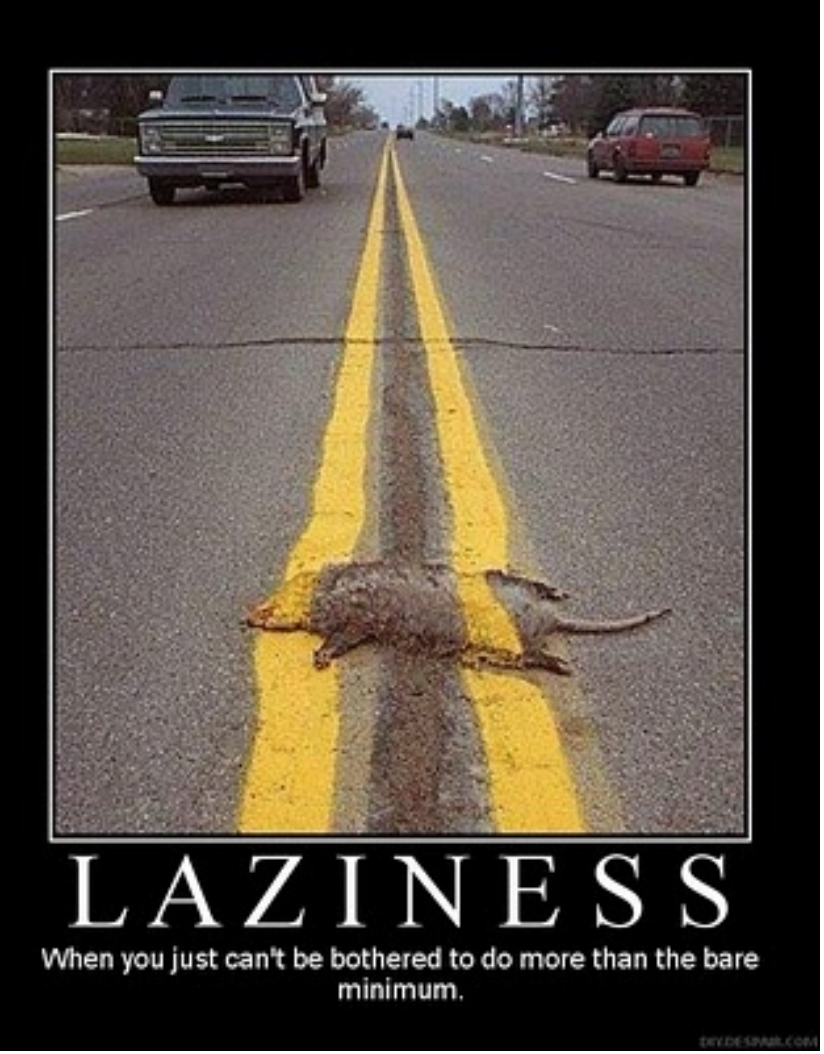
McGill Faculty of Medicine Faculté de Médecine

Relation Entresto-FEVG ???



Otto Frank (1865-1944)

Ernest H. Starling (1866-1927)



Ne rien faire sans savoir pourquoi on le fait…

- Le patient est NYHA 2 depuis 3 ans pourquoi changer Rx ?
- Ce patient est gériatrique pourquoi changer Rx ?
- Il me faudra revoir le patient si je fais un changement Rx ?

Programme Entresto[md] (pour le clinicien au bureau)

chez patients stable sous traitement de base optimal

INSTITUT UNIVERSITAIRE DE CARDIOLOGIE ET DE PNEUMOLOGIE DE QUÉBEC

Affilié à UNIVERSITÉ LAVAL

TOUS ces critères sont présents ?

- FeVG ≤ 40%
- NYHA II-III
- K+ < 5,4 mmol/L sous IECA/ARA ou K+ < 5,2 mmol/L sans IECA/ARA

NON → Exclusion immédiate du programme

OUI

Présence d'UN ou plusieurs de ces critères ?

- ATCD angioedème
- Dialyse rénale
- HTO
- Chute sur hypoTA

OUI → Exclusion immédiate du programme

NON

Sous ARA : cesser **l'ARA** et débuter Entresto[md] 24/26 mg† BID **LE LENDEMAIN**

Sous IECA : cesser **l'IECA** et débuter Entresto[md] 24/26 mg† BID **LE SURLENDEMAIN**

† Envisager **Entresto[md] à 49/51 mg BID** si TAS ≥ 140 mmHg **ET** >50% de la dose cible recommandée d'IECA/ARA*

7 à 14 jours plus tard (selon Cr/K+) :

- IUC de contrôle

21 à 28 jours plus tard :

- Titrer **Entresto[md] à 49/51 mg BID** †† si labos & TA le permettent et Entresto[md] bien toléré

†† Envisager dose intermédiaire d'Entresto[md] (ex : 24/26 mg AM + 49/51 mg PM) selon la clinique et répéter cette étape puis poursuivre

Répéter cette étape jusqu'à atteinte de la dose cible ou de la dose maximale tolérée

ANALYSE DES LABOS

Si K+ >5,5 mmol/L **OU** si ↑ créat ≥30% p/r au niveau de base = **réévaluer dose Entresto[md] et/ou ARM**

Considérer ↓ diurétique ou anti-HTA selon volémie et TA

***Dose quotidienne cible recommandée d'IECA / ARA selon les guides de pratique :**

IECA :	Énalapril 20 mg/j	**ARA** :	Candésartan 32 mg/j
	Fosinopril 20 mg/j		Irbésartan 300 mg/j
	Lisinopril 20 mg/j		Losartan 100 mg/j
	Périndopril 8 mg/j		Telmisartan 80 mg/j
	Quinapril 20 mg/j		Valsartan 320 mg/j
	Ramipril 10 mg/j		
	Trandolapril 4 mg/j		

Hautes doses d'IECA ???

Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure

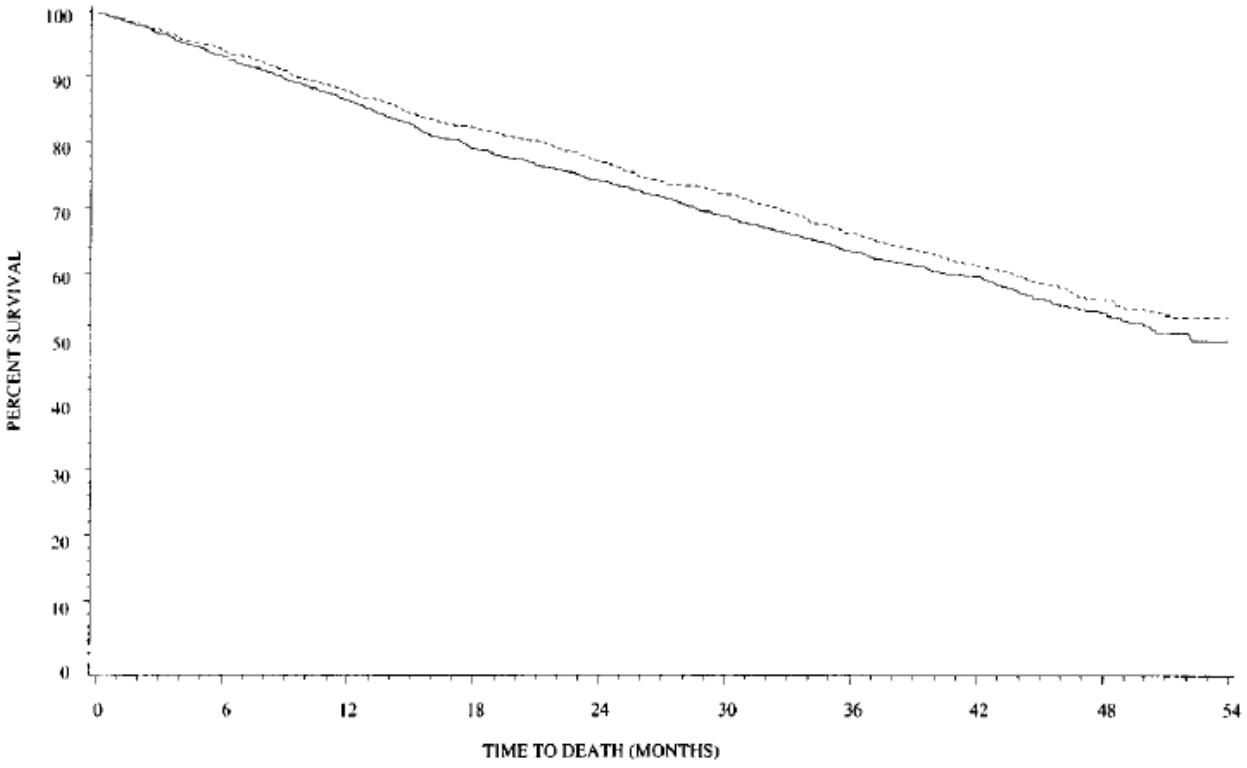


Figure 1. Kaplan-Meier analysis showing time to death in the low-dose and high-dose lisinopril groups. Solid line indicates low-dose group; dotted line, high-dose group. Compared with low-dose group, patients in high-dose group had an 8% lower risk, $P=0.128$.

Packer et al. Circulation. 1999;100:2312-2318.

Introduction

The most recent medical addition to heart failure management, in those with reduced left ventricular ejection fraction, has been the use of Sacubitril/Valsartan.

Methods:

Several clinical parameters were investigated, including some that were not studied in PARADIGM. Our goal was to perform a single center, retrospective, descriptive study, evaluating our patients' clinical outcomes, on Sacubitril/Valsartan.

Results

Demographics

From December 2015-December 2016: Sacubitril/Valsartan was initiated in 140 patients. More than half of the patients (51%) suffered from ischemic cardiomyopathy; 21% were females. The mean age and left ventricular ejection fraction were 62 and 25%, respectively. The majority were NYHA 2 and 28% were NYHA 3.

Diuresis

Following initiation of Sacubitril/Valsartan, 16% were able to have doses of diuretics decreased, 12% had to have diuretics dosage increased, 58% had unchanged doses of diuretics (6% were not on diuretics before initiation of Sacubitril/Valsartan).

Blood pressure

Sacubitril/Valsartan was initiated in 19 patients with systolic blood pressures of less than or equal to 100mmHg. The lowest measured blood pressure at initiation was 84/53. The medication was well tolerated in 79% of these patients and 52% were able to have up-titration of Sacubitril/Valsartan

Left ventricular Ejection Fraction

Of 31 patients who obtained repeat left ventricular ejection fraction (LVEF) measurement, 13 (42%) had improved LVEF.

Cardiac Transplantation

On our transplantation and Ventricular assist device (VAD) list, 17 patients were on Sacubitril/Valsartan. 4 of these patients were deactivated from the transplant list, once on Sacubitril/Valsartan due to improving clinical status. 3 of these patients reached maximal dose Sacubitril/ Valsartan, while 1 patient reached medium dose.

Conclusion:

In this single-center retrospective cohort study, we showed that Sacubitril/Valsartan was well tolerated even in patients with baseline hypotension. We observed decreases of diuretics requirement and improvement in LVEF in several patients. Moreover, there was no further need for cardiac transplantation and/or LVAD in some patients. Overall, our data suggested that Sacubitril/Valsartan had good safety and effectiveness in "real-life" practice.

Giannetti N et all, ESC 2017

VIEWPOINT

Angiotensin Neprilysin Inhibition for Patients With Heart Failure

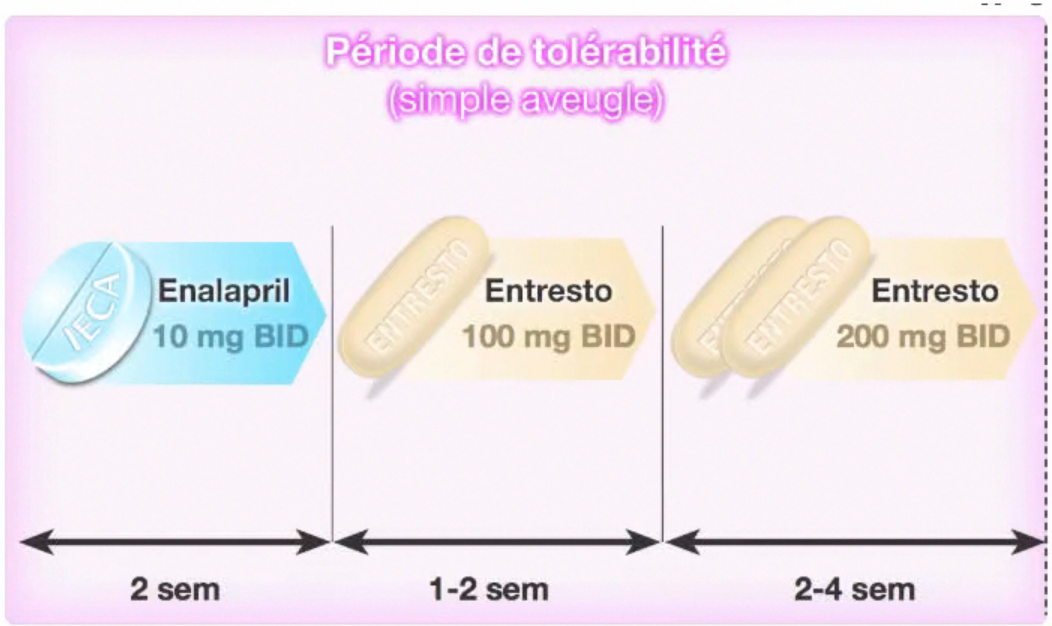
What If Sacubitril/Valsartan Were a Treatment for Cancer?

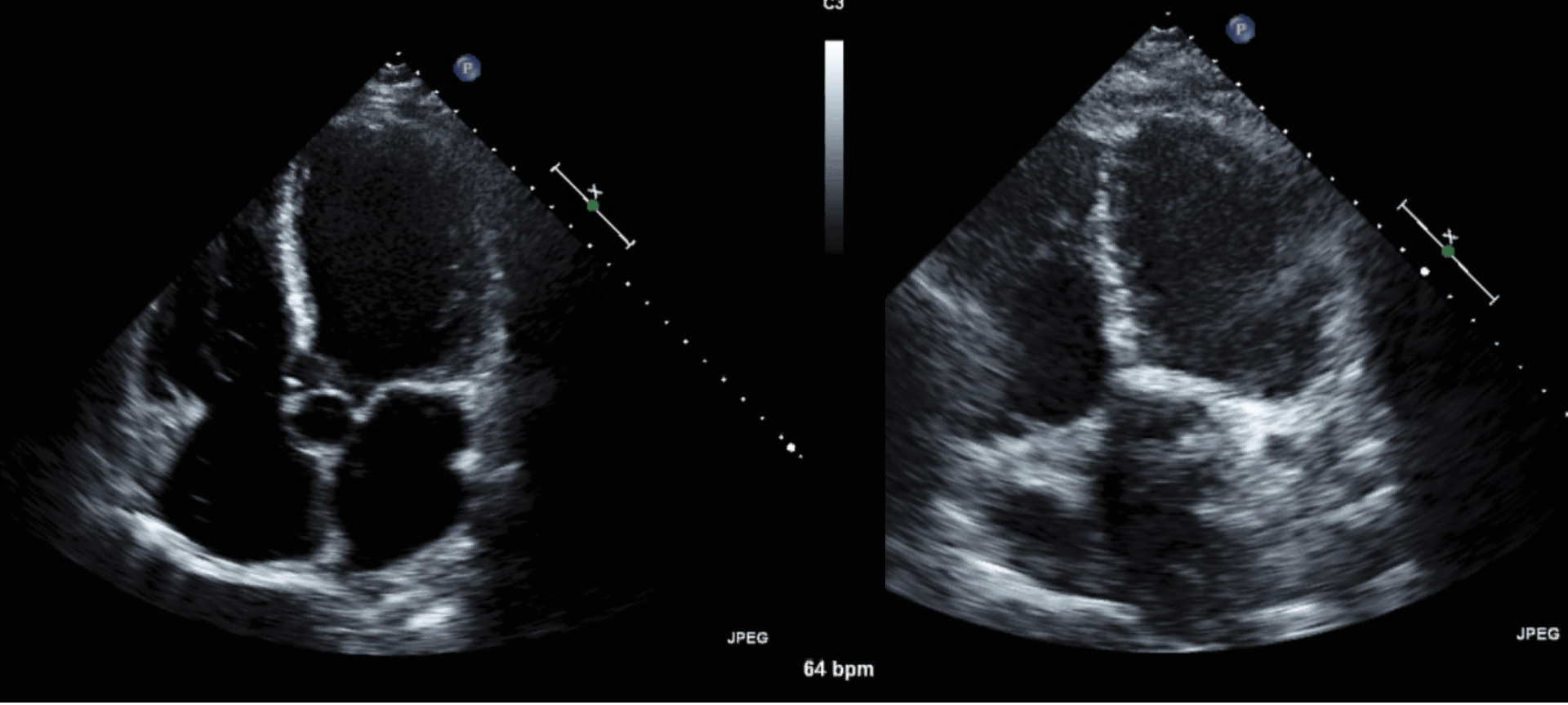
Milton Packer JAMA dec 2016

Conclusions

The fact that sacubitril/valsartan prolongs life more than the highest doses of an ACE inhibitor achieved in a clinical trial should encourage its broad use in patients who can tolerate initial doses of a renin-angiotensin inhibitor. Patients with heart failure and a reduced ejection fraction have a clinical course similar to serious forms of cancer; the risk of progression and death are high even in patients in clinical remission. Accordingly, patients with heart failure should be treated with as much energy as those with cancer. They deserve nothing less.

PARADIGM-HF: Plan de l'étude

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