PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

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CARDIAC CONTRACTILITY MODULATION: UN'OPZIONE TERAPEUTICA PER IL TRATTAMENTO DELLO SCOMPENSO CARDIACO

ESPERIENZA CLINICA IN PAZIENTI CON INDICAZIONE PRIMARIA ALLA TERAPIA CCM

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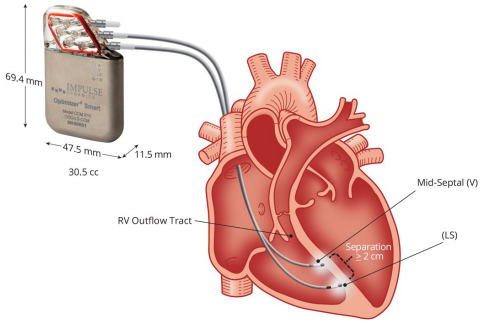
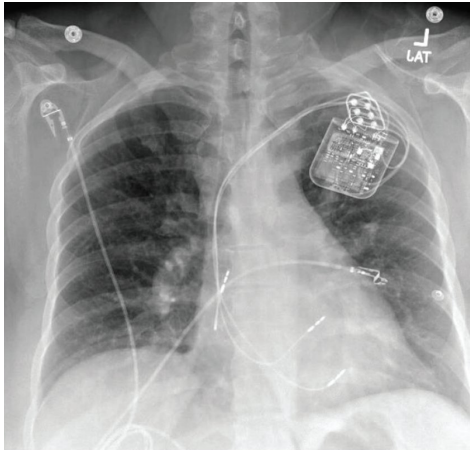
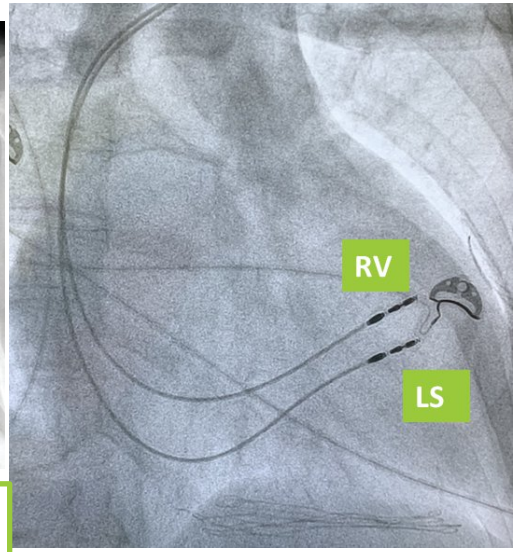
Napoli

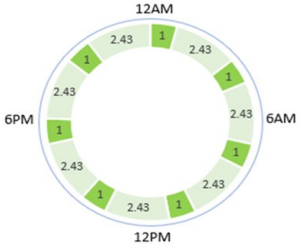
Descrizione del sistema Optimizer Smart







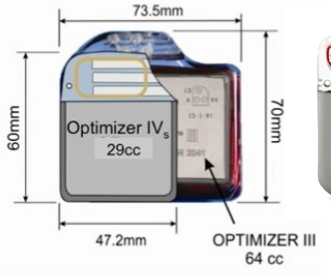
La terapia CCM eroga due impulsi non eccitatori bifasici (20 ms) con un'ampiezza di 7,5 V durante il periodo refrattario ventricolare assoluto.
La terapia CCM viene erogata tra le 5 e le 7 ore al giorno.



CCM: devices evolution

2000 2017 2022

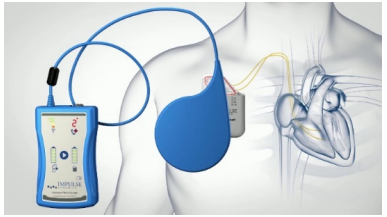
72x68x14mm
115g



30,5cc, 48g

23cc, 31g

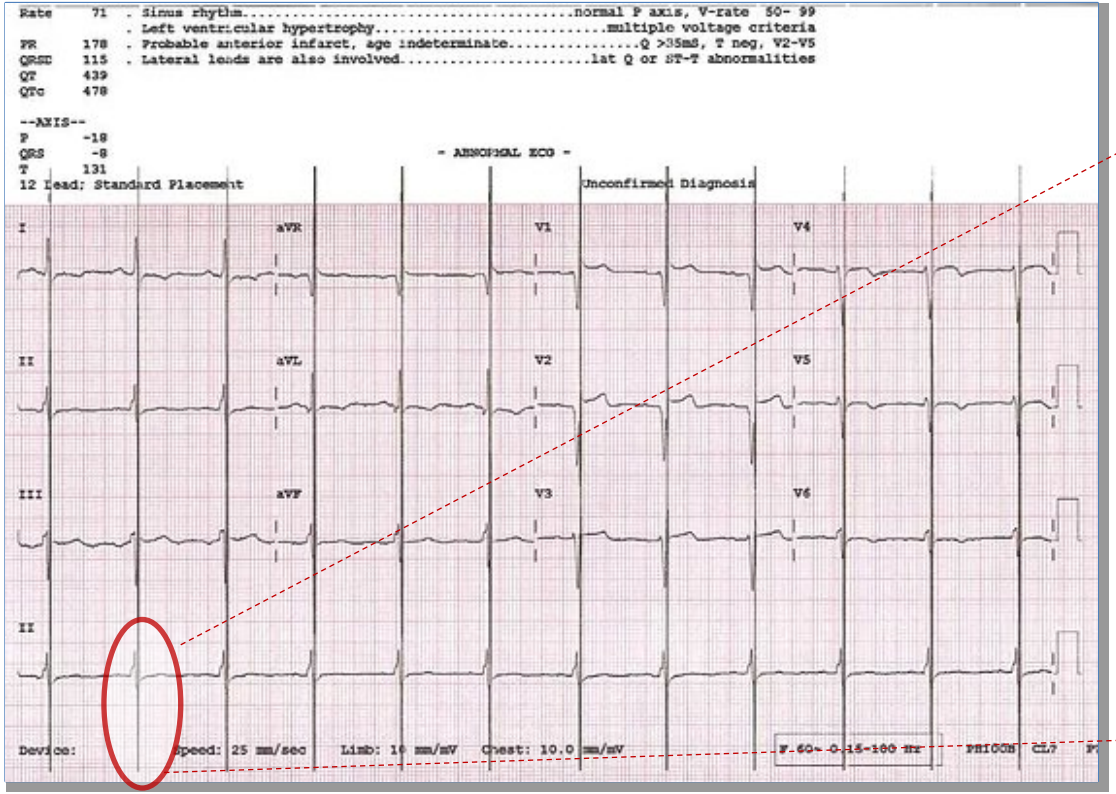
3 elettrocateteri obbligatori
Solo ritmo sinusale
Opt III primo ricaricabile

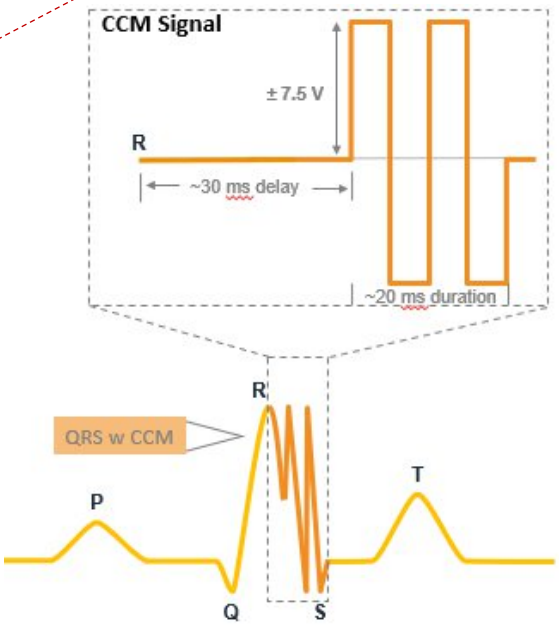


2 elettrocateteri
Ritmo sinusale e FA
MiniCharger
+15 anni di longevità

Telemetria RF
Caricatore Vesta
Funzioni avanzate
+20 anni di longevità

ECG e terapia CCM





Follow up del dispositivo Optimizer Smart

Controlli ambulatoriali

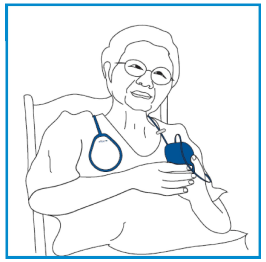
Eseguiti con il programmatore dedicato, con cadenza di 6/12 mesi come da pratica clinica.

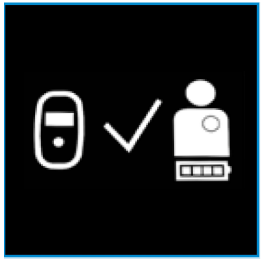
Parametri da valutare:

- % terapia erogata
- Sensing e impedenza
- Programmazione algoritmo CCM

Ricarica settimanale del paziente

Durata circa 40-45 minuti
Check automatico del dispositivo
Indicazione di possibili allerte cliniche





FDA approves new device for treating moderate to severe chronic heart failure in patient

La CCM è stata approvata dalla FDA nel marzo 2019 per il trattamento dei pazienti affetti da SC cronico con **FE 25-45 %, QRS < 130 msec** clinicamente sintomatici **(NYHA > 2)** nonostante terapia medica ottimizzata (OMT)

L'indicazione è maturata dai risultati di FIX-HF-4, FIX-HF-5 e FIX-HF-5C che hanno dimostrato:

- Miglioramento della classe NYHA;
- Miglioramento della qualità di vita valutata con il Minnesota Living with Heart Failure Questionnaire (MLHFQ);
- Incremento della capacità funzionale al 6-minute walking test (6MWT);
- Incremento del consumo di ossigeno di picco (VO2 picco);
- Riduzione end point composito di morte cardiovascolare e ospedalizzazione per SC

FIX-HF-5C Study

JACC: HEART FAILURE
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A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation

OBJECTIVES *The authors sought* ***to confirm*** *a subgroup analysis of the prior FIX-HF-5 (Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects With Moderate-to-Severe Heart Failure) study showing that cardiac contractility modulation (CCM) improved exercise tolerance (ET) and quality of life in patients with ejection fractions between 25% and 45%.*

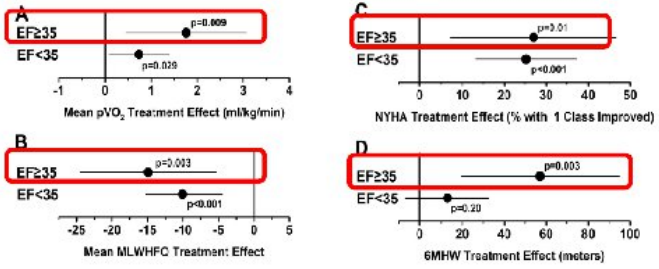
In patients with EF 25%-45%, QRS<130ms,
on Guideline Directed Medical Therapy with persistent
NYHA III/IVa symptoms, CCM is safe and effective
in improving exercise tolerance and QoL
and reduces HF hospitalizations

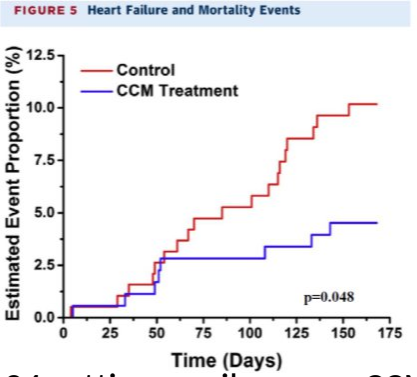
A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation

JACC
(J Am Coll Cardiol HF 2018;6:874-83)

William T. Abraham, MD,[a] Karl-Heinz Kuck, MD,[b] Rochelle L. Goldsmith, PhD,[c] JoAnn Lindenfeld, MD,[d] Vivek Y. Reddy, MD,[e] Peter E. Carson, MD,[f] Douglas L. Mann, MD,[g] Benjamin Saville, PhD,[h] Helen Parise, ScD,[i] Rodrigo Chan, MD,[j] Phi Wiegn, MD,[k] Jeffrey L. Hastings, MD,[k] Andrew J. Kaplan, MD,[l] Frank Edelmann, MD,[m] Lars Luthje, MD,[m] Rami Kahwash, MD,[n] Gery F. Tomassoni, MD,[o] David D. Gutterman, MD,[p] Angela Stagg, BS,[q] Daniel Burkhoff, MD, PhD,[r] Gerd Hasenfuß, MD[s]

Analisi combinata (FIX-HF-5+FIX-HF-5C) su 371 pazienti: 275 con FE < 35%, 96 con FE≥35%





Benefici della terapia CCM in **<u>tutte le classi di FE</u>**
81% dei pazienti con miglioramento almeno di una classe NYHA
Responder migliori in FE>35%: +1,76 mL/Kg/min VO2 picco

A 24 settimane, il gruppo CCM aveva maggiore sopravvivenza libera da morte cardiaca e ospedalizzazioni per SC: 97,1% nel gruppo studio vs 89,2% nel gruppo controllo

A comprehensive individual patient data meta-analysis of the effects of cardiac contractility modulation on functional capacity and heart failure-related quality of life

Francesco Giallauria[1]*, Gianluigi Cuomo[1], Alessandro Parlato[1], Nirav Y. Raval[2], Jürgen Kuschyk[3] and Andrew JS Stewart Coats[4]

ESC HEART FAILURE
ESC Heart Failure (2020)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12902

ORIGINAL RESEARCH ARTICLE

861 pts in totale per valutazione del pVO_2, della QoL e 6MWT.

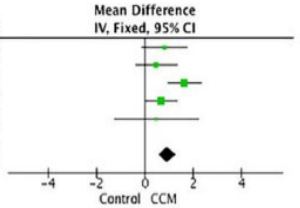
Effetti statisticamente significativi e clinicamente utili della terapia CCM sono emersi rispetto a:

- Capacità Funzionale (CPET);
- Capacità di Esercizio (6MWT);
- Qualità della Vita (MLWHFQ)

Panel A. Peak VO_2 (ml/kg/min)

Study or Subgroup	CCM Mean	CCM SD	CCM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
FIX-CHF-4 (24 weeks)	0.39	3.47	84	-0.44	2.59	80	15.5%	0.83 [-0.10, 1.76]
FIX-CHF-5C	-0.026	2.74	66	-0.504	2.36	71	18.3%	0.48 [-0.38, 1.34]
FIX-CHF-5C2	1.12	1.49	52	-0.504	2.36	71	29.0%	1.62 [0.94, 2.31]
FIX-HF-5	0.28	3.16	176	-0.4	2.91	167	32.7%	0.68 [0.04, 1.32]
FIX-HF-5 Pilot (24 weeks)	-0.96	2.6	23	-1.43	3.01	19	4.6%	0.47 [-1.25, 2.19]
Total (95% CI)			**401**			**408**	**100.0%**	**0.93 [0.56, 1.30]**

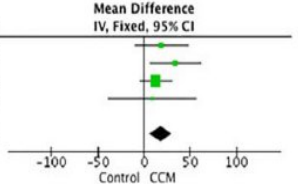
Heterogeneity: $Chi^2 = 5.94$, $df = 4$ ($P = 0.20$); $I^2 = 33\%$
Test for overall effect: $Z = 4.96$ ($P < 0.00001$)



Panel B. 6MWT distance (m)

Study or Subgroup	CCM Mean	CCM SD	CCM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
FIX-CHF-4 (24 weeks)	23.09	81.69	82	4.1	99	76	19.3%	18.99 [-9.44, 47.42]
FIX-CHF-5C	43	80.7	69	9.3	87.4	73	20.4%	33.70 [6.05, 61.35]
FIX-HF-5	21.1	77.9	185	8.3	85.7	170	53.4%	12.80 [-4.29, 29.89]
FIX-HF-5 Pilot (24 weeks)	49.1	97.1	24	40.5	64.5	21	6.9%	8.60 [-39.05, 56.25]
Total (95% CI)			**360**			**340**	**100.0%**	**17.97 [5.48, 30.46]**

Heterogeneity: $Chi^2 = 1.75$, $df = 3$ ($P = 0.63$); $I^2 = 0\%$
Test for overall effect: $Z = 2.82$ ($P = 0.005$)



How many patients with heart failure are eligible for cardiac contractility modulation therapy?

Rajdip Dulai | Ahmed Chilmeran | Mazin Hassan | Rick A. Veasey | Stephen Furniss | Nikhil R. Patel | Neil Sulke

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DOI: 10.1111/ijcp.13646

ORIGINAL PAPER
CARDIOVASCULAR MEDICINE

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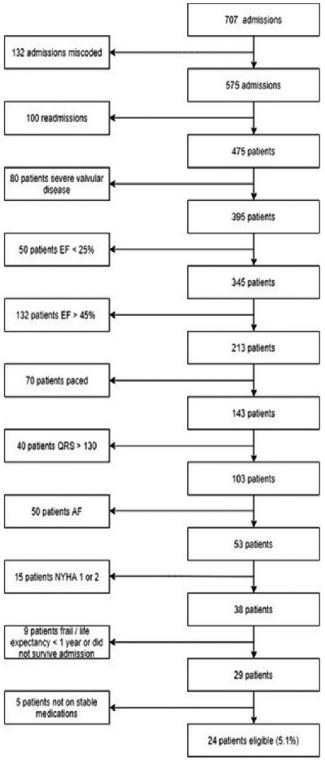


Results: A total of 475 patients were admitted with heart failure during the study period. From this group, 24 (5.1%) patients fulfilled the criteria for CCM therapy. The mean age and ejection fraction were 70.8 ± 10.2 and 32.5% ± 7.4%. The majority of patients were men (71%) and had an ischaemic cardiomyopathy (75%). If patients with atrial fibrillation were included, an additional 18 (3.8%) patients potentially may be eligible for CCM.

Conclusion: Only 5.1% of all patients presenting with heart failure might benefit from cardiac CCM. This is a small proportion of the overall heart failure population. However, this population has no other current option for device therapy of their condition.

TABLE 3 Comparison of baseline characteristics of patients eligible for CCM therapy (Sinus rhythm patients vs atrial fibrillation patients)

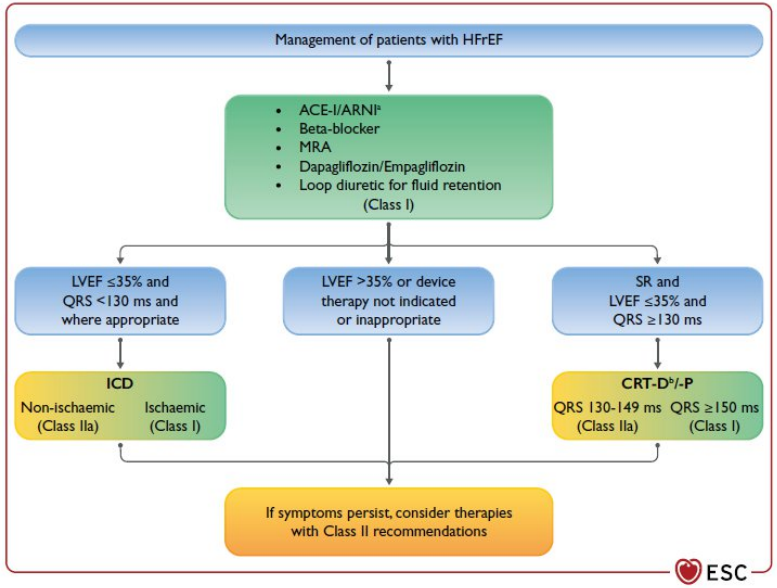
	Sinus Rhythm patients (N = 24)	Atrial fibrillation patients (N = 18)	P value
Age	70.9 ± 10.2	77.2 ± 7.7	.03
Male Gender (%)	17 (70.8)	11 (61.1)	.53
Ejection fraction (%)	32.5 ± 7.4	35.7 ± 8.4	.20
QRS duration (msec)	106.0 ± 13.0	102.3 ± 12.4	.36
Ischaemic aetiology (%)	21 (87.5)	12 (66.7)	.14
Hypertension (%)	11 (45.8)	13 (72.2)	.12
Diabetes (%)	9 (37.5)	4 (22.2)	.33
COPD (%)	3 (12.5)	2 (11.1)	1.00
CKD (%)	18 (75.0)	10 (55.6)	.20
MRA (%)	15 (62.5)	7 (38.9)	.21
NYHA class			
3	14 (58.3)	7 (38.9)	.35
4	10 (41.7)	11 (61.1)	.35

Abbreviations: CCM, contractility modulation; CKD chronic kidney disease; COPD Chronic obstructive pulmonary disease; EF, ejection fraction; MRA mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

2021 ESC HF Guidelines Update

What do the Guidelines recommend for patients with reduced ejection fraction HFrEF?

22 ESC Guideline



Blank space for patients with HFrEF

No therapeutic recommendation for CCM-indicated population.

2021 ESC HF Guidelines Update

What do the Guidelines say about CCM?

morphology often have wider QRS durations, and there is a current debate about whether QRS durations or QRS morphology is the main predictor of a beneficial response to CRT. Evidence from two IPD meta-analyses indicates that after accounting for QRS duration, there is little evidence to suggest that QRS morphology or aetiology of disease influence the effect of CRT on morbidity or mortality.[212,230] In addition, none of the landmark trials selected patients for inclusion according to QRS morphology, sex, or ischaemic aetiology, nor were they powered for subgroup analyses.

The Echo-CRT trial[222,223] and an IPD meta-analysis[213] suggest possible harm from CRT when QRS duration is <130 ms, thus implantation of CRT is not recommended if QRS duration is <130 ms.

If a patient is scheduled to receive an ICD and is in SR, with a LBBB, CRT-D should be considered if the QRS is between 130 and 149 ms and is recommended if QRS is ≥150 ms. However, clinical practice varies widely among countries and if the primary reason for implanting CRT is for the relief of symptoms, then the clinician should choose CRT-P or CRT-D, whichever they consider appropriate. The only randomized trial to compare CRT-P and CRT-D[210] did not demonstrate a difference in morbidity or mortality between these technologies (although the trial was not powered to show such a difference). Furthermore, in the DANISH study in patients with NICM where 58% of patients received CRT there was no suggestion from subgroup analysis that CRT-P was inferior to CRT-D.[166,167]

When LVEF is reduced, RV pacing may exacerbate cardiac dyssynchrony. This can be prevented by CRT, which might improve patient outcomes.[236–238,231] However, a difference in outcome was not observed between CRT and RV pacing in a subgroup analysis of RAFT.[238] On balance, CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing in order to reduce morbidity, although no clear effect on mortality was observed. Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF with a high proportion of RV pacing, despite CMT, should be considered for 'upgrading' to CRT.

Only two small trials have compared pharmacological therapy alone vs. CRT in patients with AF, with conflicting results. Several studies have indicated that CRT is superior to RV pacing in patients undergoing atrio-ventricular (AV) node ablation.[217,218,231] However, AF is not an indication to carry out AV node ablation in patients with CRT except in a few cases when ventricular rate remains persistently high despite attempts at pharmacological rate control. A subgroup analysis of patients with AF from the RAFT study found no benefit from CRT-D compared with ICD, although less than half of patients had >90% biventricular capture.[239] In view of the paucity of evidence for the efficacy of CRT in patients with AF, it may be an option in selected patients—particularly those with a QRS ≥150 ms—ensuring a proportion of biventricular pacing as high as possible.

Observational studies report that when biventricular capture is <98%, the prognosis of patients with CRT declines.[218,232] Whether this association reflects a loss of resynchronization (which might be remedied by device programming), poor placement of the LV lead, or greater difficulty in pacing severely diseased myocardium is uncertain. This observation has not been confirmed in any randomized trial.

Early studies suggested that imaging tests for dyssynchrony were not of value in selecting patients for CRT.[233] However, a recent study has suggested that two novel markers of dyssynchrony (apical rocking and septal flash) are associated with a response to CRT, but these have not been tested as selection criteria or as prespecified subgroups in a randomized trial.[234] Patients with extensive myocardial scar will have less improvement in LV function with CRT, but this is true of any treatment for HFrEF and does not reliably predict less clinical benefit. Pacing thresholds are higher in scarred myocardium and, if possible, lead placement should avoid such regions.[235,236] Although patients with extensive scarring have an intrinsically worse prognosis, there is little evidence that they obtain less prognostic benefit from CRT.[211]

The value of trying to optimize AV intervals or interventricular delay intervals (VV intervals) after implantation using echo- or electrocardiographic criteria or BP response is uncertain but may be considered for patients who have had a disappointing response to CRT.[237,238] Other options to consider to optimize response to CRT are covered in a recently published practical article.[239]

Following CRT implantation, a review of diuretic therapy is advised as a reduction in dose or its discontinuation may be required. In addition, CRT implantation may afford an opportunity to further optimize MT for HFrEF.[240]

The reader is directed to guidelines on pacing and CRT for recommendations on device implantation procedures.[240a]

6.3 Devices under evaluation

Cardiac contractility modulation (CCM) has been evaluated in patients with NYHA class III–IV HF, with an LVEF ≥25% to ≤45% and QRS duration <130 ms, and was associated with a small improvement in exercise tolerance and QOL.[241,242]

Technologies that involve modification of the activity of the autonomic nervous system, e.g. baroreflex activation therapy,[243,244] have also been shown to offer a modest improvement in effort capacity and QOL. However, currently, the evidence is considered insufficient to support specific guideline recommendations for a reduction in mortality or hospitalization for these and a variety of other implantable electrical therapeutic technologies (see also Gaps in Evidence in section 16).

7 Heart failure with mildly reduced ejection fraction

7.1 The diagnosis of heart failure with mildly reduced ejection fraction

The diagnosis of HFmrEF requires the presence of symptoms and/or signs of HF, and a mildly reduced EF (41–49%). The presence of elevated NPs (BNP ≥35 pg/mL or NT-proBNP ≥125 pg/mL) and other evidence of structural heart disease (e.g. increased left atrial (LA) size, LVH or echocardiographic measures of LV filling) make the diagnosis more likely but are not mandatory for diagnosis if there is certainty regarding the measurement of LVEF.

An algorithm for the diagnosis of HFmrEF is depicted in *Figure 1*. For the investigation of the underlying aetiology, please refer to *Table 3* (which refers to investigations regardless of LVEF).

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6.3 Devices under evaluation
Cardiac contractility modulation (CCM) has been evaluated in patients with NYHA class III/V HF, with an LVEF >25% to <45% and QRS duration <130 ms and was associated with a small improvement in exercise tolerance andQOL.[241,242]

ClinicalTrials.gov PRS
Protocol Registration and Results System

Contact ClinicalTrials.gov PRS
Org: MonaldiH User: ADOnofrio Logout

Home > Record Summary

ID: CCM-001Mon Observational and Prospective Registry on Cardiac Contractility Modulation (CCM) Therapy NCT04902079

Anamnesi	N=26
Età in anni	70 (52-77 mediana, IR)
Maschi	22 (85%)
BMI in kg/m^2	27,4 (24,5-31 mediana,IR)
Eziologia ischemica	16 (64%)
Ipertensione	17 (68%)
Diabete	11 (44%)
Dislipidemia	13 (52%)
IRC	12 (48%)
Storia di FA	15 (60%)
QRS (ms)	115 (90-152)
Altro device già impiantato	25 (96%)
ICD	16 (64%)
CRT-D	9 (36%)

Terapia Farmacologica	n (%)
Ace inibitori	8 (32%)
Beta bloccanti	23 (92%)
Allopurinolo	10 (40%)
Sacubitril/Valsartan	15 (58%)
Sartani	2 (8 %)
Antagonisti dell'Aldosterone	14 (56%)
Diuretici Ansa	24 (96%)
Glifozine	5 (20%)
Antiaritmici	11 (44%)

Valutazione clinica	n (%)
Classe NYHA	
Classe I	0 (0.0%)
Classe II	6 (23%)
Classe III	20 (77%)
Classe IV	0 (0.0%)

	Valori in mediana (I.R.)
FE (%)	30 (25-33)
NT-ProBNP (pg/ml)	2345 (1254-3486)
MLWHFQ	50 (38-59)

Pazienti con indicazione primaria

- 16 pazienti con QRS basale < 130 ms: 90 ms (88-110)

- FE 25-45 %

13 in NYHA III

Parametro	Valore mediano	Range interquartile
QRS basale [ms]	90	88-110
FE basale [%]	31	25-32,5
Età [anni]	67	49-75
NT-ProBNP [2617,5]	2617,5	742,25 – 3415,5
MLWHFQ	51	37,5-58

Follow Up a 6 mesi

Parametro	Basale	6 Mesi	
NT-ProBNP pg/mL (10 paz)	2005 (598, 75 – 3266,5)	1804,5 (542,75-4021)	p = 0.24
FE % (12 paz)	32,5 (25 – 35,75)	35,5 (29 – 42,25)	p = 0.045*
MLWHFQ (11 paz)	51 (31 – 54,5)	43 (24 – 61)	p = 0.9

ClinicalTrials.gov PRS
Protocol Registration and Results System

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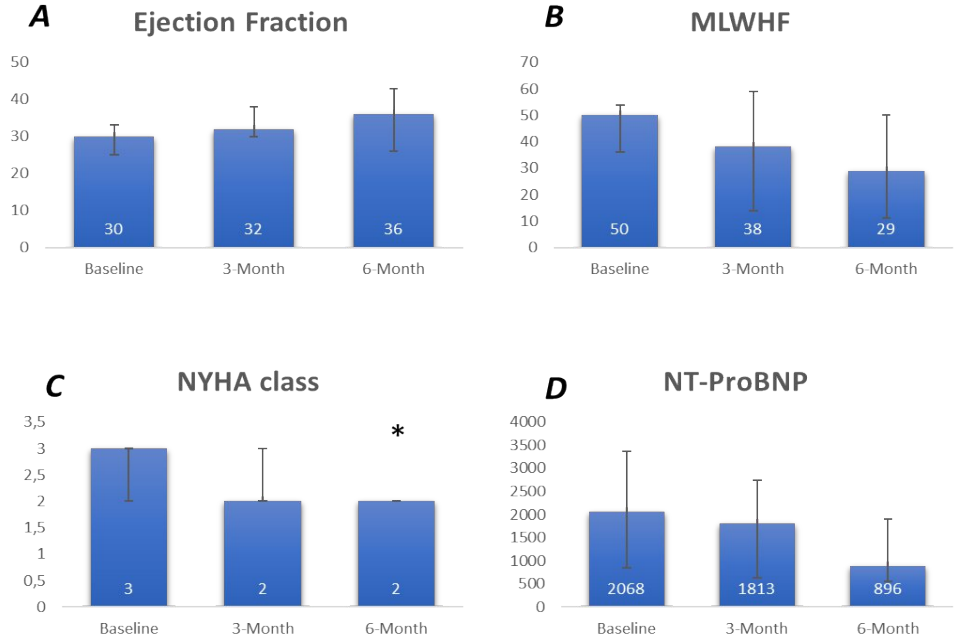


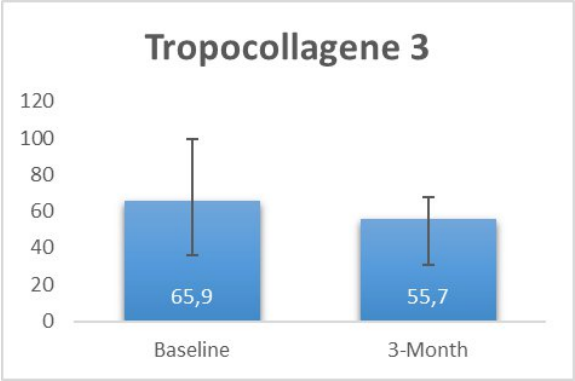
ClinicalTrials.gov PRS
Protocol Registration and Results System

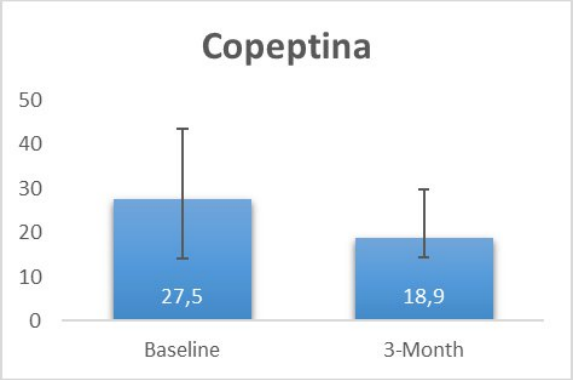
Contact ClinicalTrials.gov PRS
Org: MonaldiH User: ADOnofrio Logout

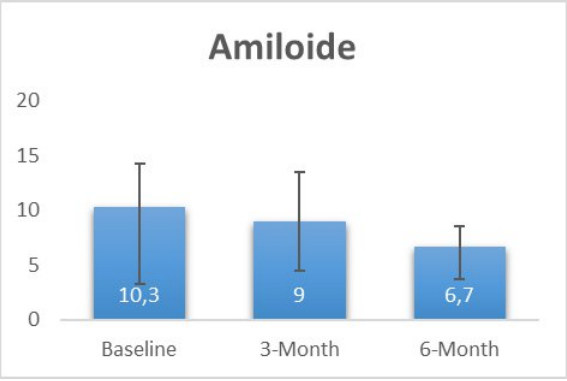
Home > Record Summary

ID: CCM-001Mon Observational and Prospective Registry on Cardiac Contractility Modulation (CCM) Therapy NCT04902079

Valutazione nuovi marker per lo scompenso cardiaco







Attività sulla terapia CCM
Monaldi UOSD Elettrofisiologia Studio e Terapie delle aritmie

ODOCOR II Study (Studio sponsorizzato):

- Valutazione dei primi elettrocateteri dedicati per la terapia CCM (studio Europeo);

- Primo impianto in Italia effettuato il 13.5.2021 al Monaldi – UOSD Elettrofisiologia Studio e Terapie delle Aritmie

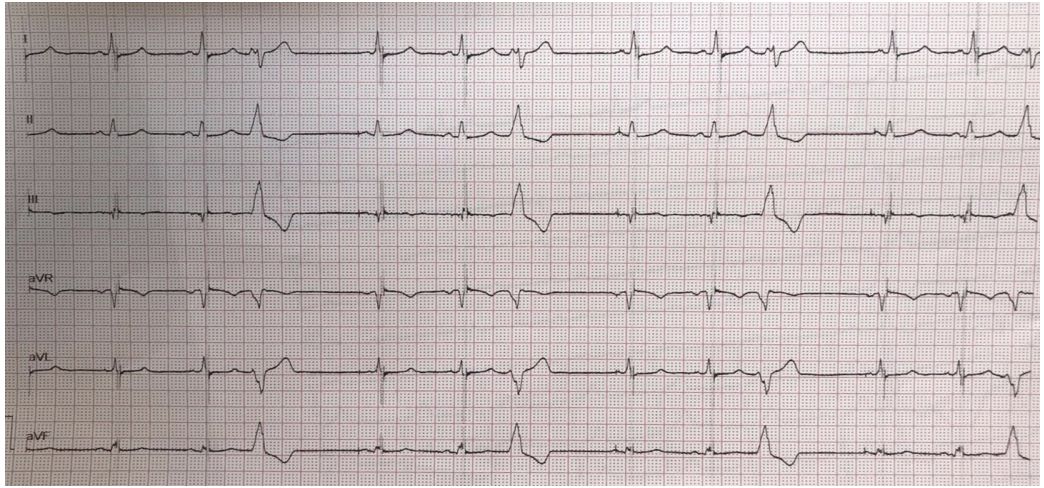
- Ad oggi arruolati 12 pazienti

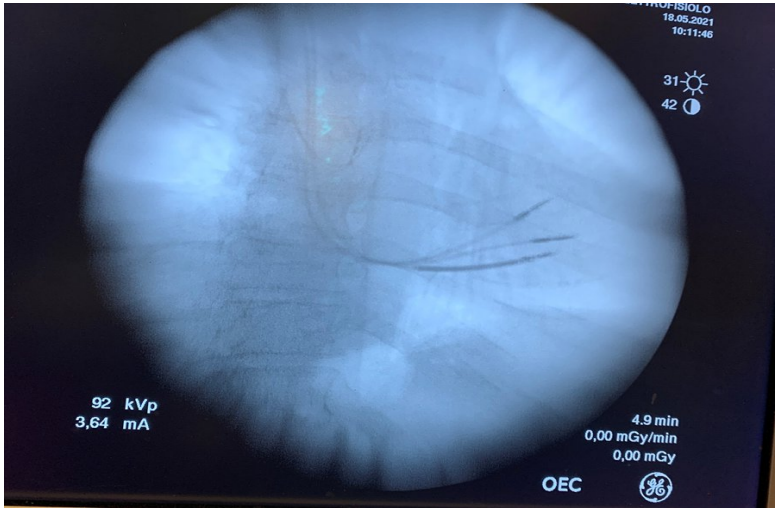
Case report

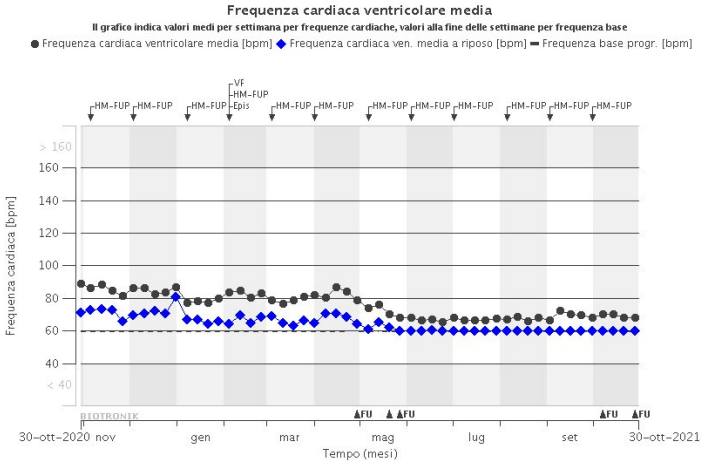
Paziente M, 52 anni, Peso 114 kg Altezza 170 cm
Cardiopatia dilatativa non ischemica
Portatore di ICD DR dal 2017 in prevenzione primaria
Nel 2020 n 2 ricoveri per riacutizzazione per scompenso cardiaco

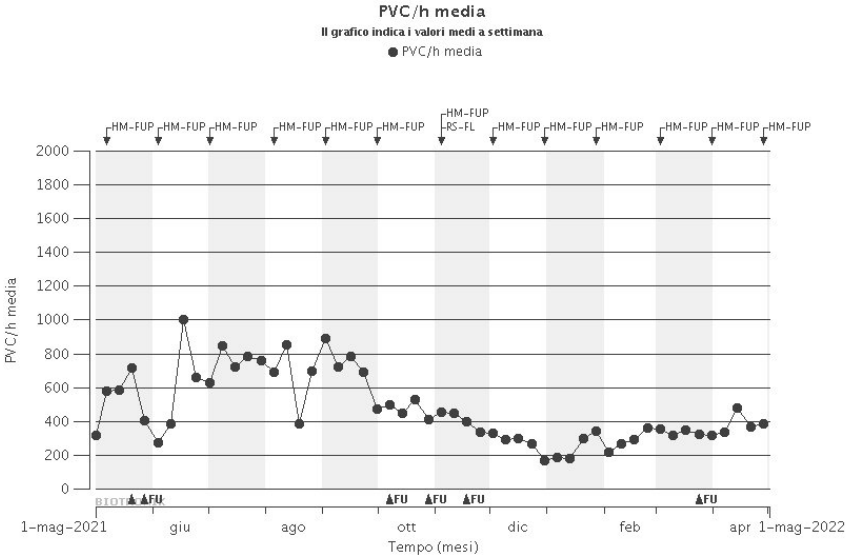
Dispnea per sforzi lievi e importante ortopnea, FE 35 % NYHA III (MLWHFQ= 55; KCCQ= 39,1)
PA 100/60 mmHg Fc 70 bpm
Terapia domiciliare:
IPP, carvedilolo 25 mg BID; furosemide 25 mg OD, spironolattone 100 mg OD, amiodarone 200 mg OD, Sacubitril/Valsartan 49/51 mg BID

Impianto dispositivo per la modulazione della contrattilità cardiaca (05/2021)



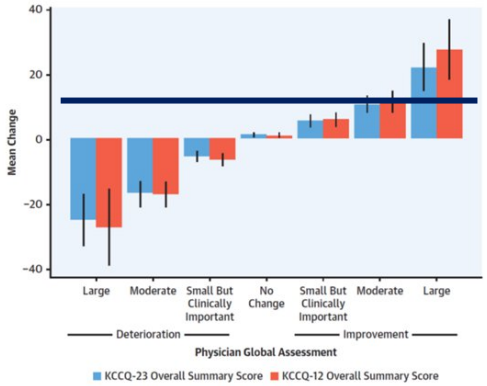



Frequenza cardiaca ventricolare media
Il grafico indica valori medi per settimana per frequenze cardiache, valori alla fine delle settimane per frequenza base
Frequenza cardiaca ventricolare media [bpm]
Frequenza cardiaca ven. media a riposo [bpm]
Frequenza base progr. [bpm]
HM-FUP
VF
HM-FUP
Episi
> 160
160
140
120
100
80
60
40
< 40
Frequenza cardiaca [bpm]
BIOTRONIK
FU
30-ott-2020
nov
gen
mar
mag
lug
set
30-ott-2021
Tempo (mesi)


PVC/h media
Il grafico indica i valori medi a settimana
PVC/h media
HM-FUP
RS-FL
2000
1800
1600
1400
1200
1000
800
600
400
200
0
PVC/h media
BIOTRONIK
FU
1-mag-2021
giu
ago
ott
dic
feb
apr
1-mag-2022
Tempo (mesi)

FU 6 mesi

Parametro	Basale	FU 3 Mesi	Fu 6 mesi	Fu 12 mesi
NT-ProBNP	814	852	512	256
FE	35	37	43	43
MLWHFQ	55	52	34	34
KCCCQ	39,1	39,1	49,1	49,1



Miglioramento moderatamente significativo della qualità della vita

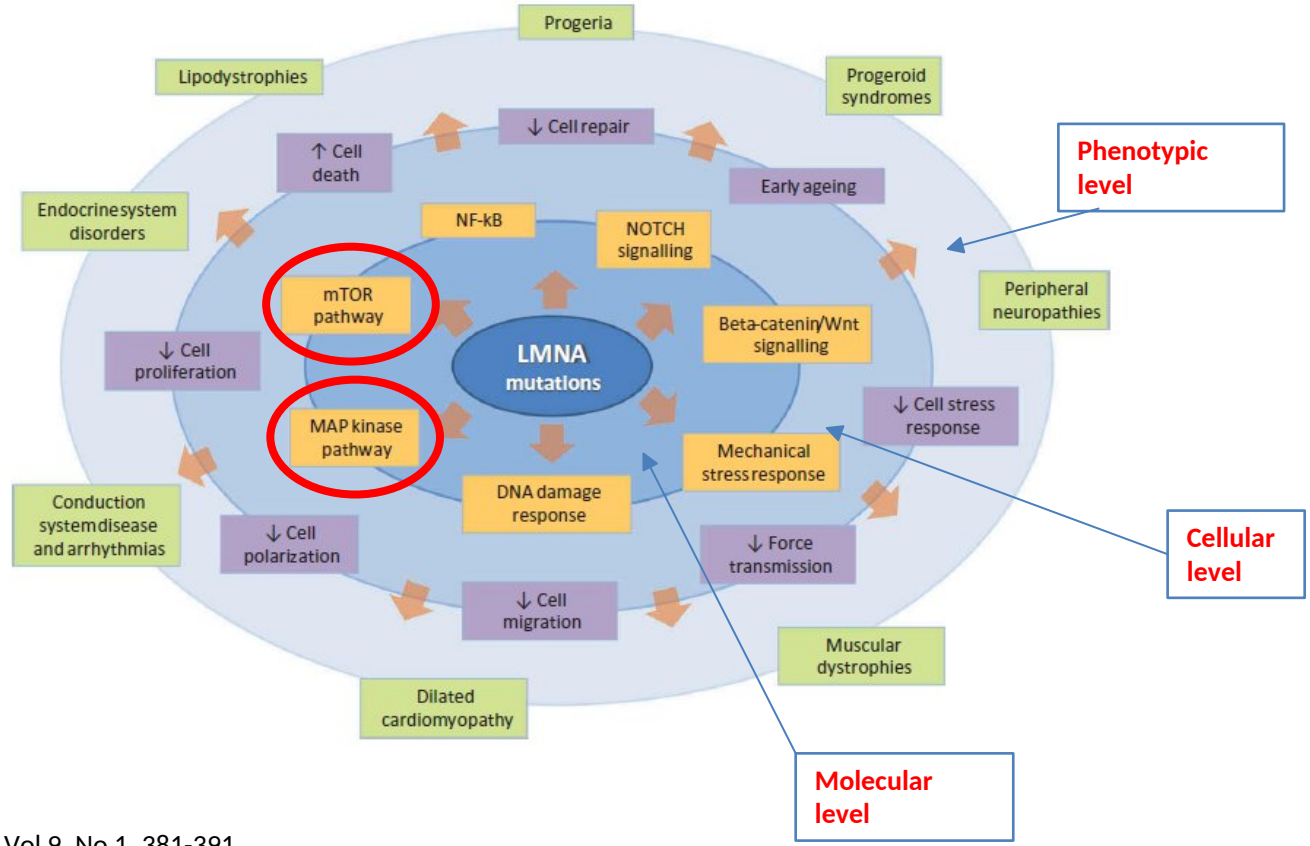
- **- 19 dal MLWHFQ**
- **+10 dal KCCQ**

Introduzione di SLGT2 I

Caso di applicazione CCM su Cardiolaminopatia

Uomo, 48 anni , cardiopatia dilatativa geneticamente determinata da mutazione del gene Lamina A/C forma familiare
Portatore di ICD DR impiantato nel 06/2018 in prevenzione primaria per morte improvvisa familiare e bassa frazione d'eiezione ventricolare sinistra (FE 30 %).
Nel 2020 ha ricevuto 3 episodi di DC shock appropriati.
Un fratello del paziente con la stessa eziologia e portatore di CRTD, è stato sottoposto ad impianto LVAD.

Il paziente è in lista trapianto e segue una terapia farmacologica con Sacubritil/Valsartan 49/51 BID (introdotto prima dell'impianto), bisoprololo 2,5 mg OD, fuorosemide 25mg OD, eplerenore 50 mg OD. In discreto compenso emodinamico. Classe NYHA II
In attesa di trapianto, si è decide in accordo con il paziente di procedere all'impianto di dispositivo per la terapia CCM



Peretto G. – Nucleus 2018; Vol 9, No 1, 381-391

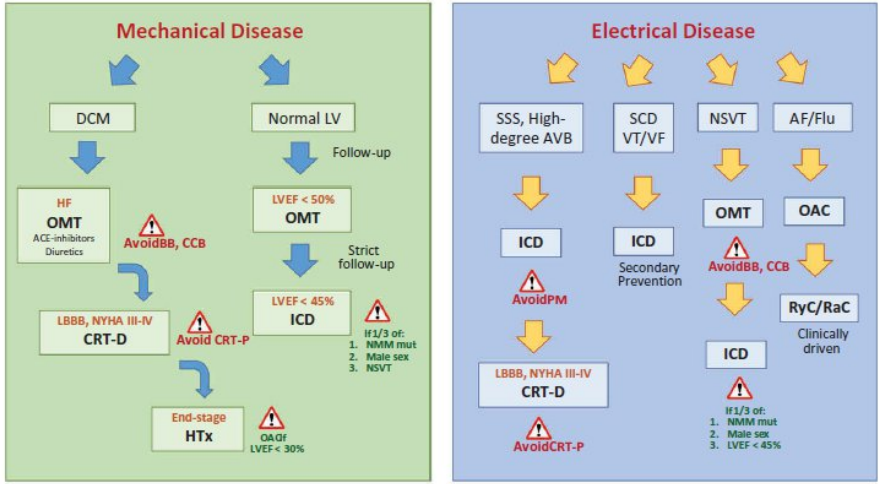
LMNA e scompenso cardiaco

- Le manifestazioni cardiache includono disturbi di conduzione, tachiaritmie atriali e ventricolari, e disfunzioni meccaniche che portano progressivamente a cardiomiopatia dilatativa (DCM) [2].
- La cardiolaminopatia (LMNA-DCM) ha un corso clinico aggressivo con più elevati tassi di aritmie mortali e insufficienza cardiaca rispetto alla maggior parte di altre malattie cardiache.
- Pertanto, i portatori di mutazioni LMNA con anomalie cardiache hanno un alto rischio di morte cardiaca improvvisa e grave insufficienza cardiaca (HF).
- La mutazione LMNA sono state riscontrate nel 6% dell'intera popolazione dei pazienti con DCM[3,4] , nel 7,5 di forme familiari e 3,6-11% di forme sporadiche. Secondo i dati presi da una metanalisi di 299 pazienti [5] , il 12% della mortalità è dovuta alla disfunzione della funzione pompa del cuore e i segni dello scompenso cardiaco diventano apparenti 15-20 anni dopo la insorgenza di aritmie.
- L'età di insorgenza dello scompenso cardiaco è stato trovato al 10% in pazienti fino a 30 anni di età e nel 64% dei pazienti dai 50 anni di età.
- Similarmente alle altre DCM, LMNA-DCM è caratterizzata da un aumento delle camere cardiache e dalla disfunzione sistolica di uno o entrambi i ventricoli [1]
- Il Network Italiano sulle Laminopatie (NIL) ha trovato che il tempo mediano dalla diagnosi è 13 anni entrambi per LVEF ˂45% (sviluppato nel 26% della popolazione) e dilatazione del ventricolo sinistro (sviluppato nel 37% della popolazione). Il 9% di essi vanno a trapianto cardiaco [6]

1. Lu - Disease Model & Mechanisms 4, 562-568 (2011) doi:10.1241/dmm.006346;
2. Taylor MR - J. Am. Coll. Cardiol. 2003 41, 771-780;
3. Hershberger RE - J Am Coll Cardiol 2011; 57:1641–1649;
4. Parks S B- Am Heart J 2008; 156:161–169;
5. Van Berlo JH - J Mol Med (Berl) 2005; 5. 83:79–83;
6. Peretto G - Ann Intern Med. 2019; 171:458-463. doi:10.7326/M18-2768;

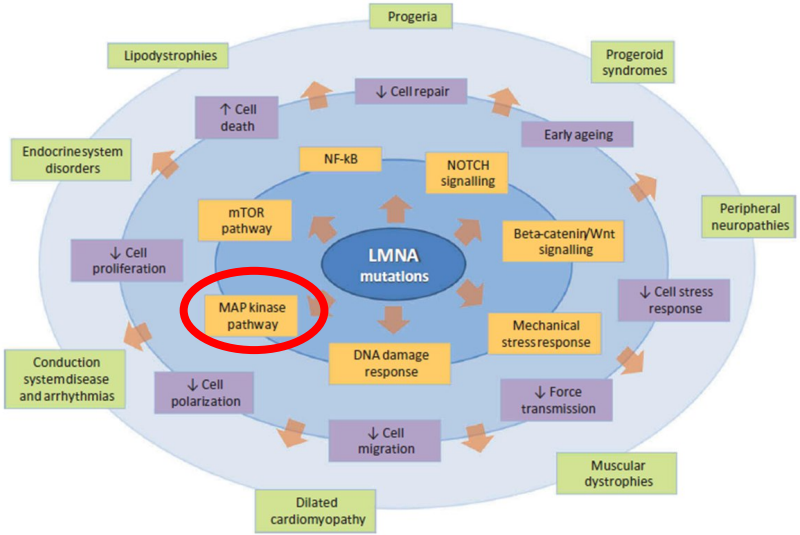
Trattamento delle Cardiolaminopatie

- Nelle cardiolaminopatie, in genere, i segni dello scompenso cardiaco diventano apparenti 15-20 anni dopo la insorgenza di aritmie.
- Al momento non c'è un trattamento specifico per le cardiolaminopatie.
- La terapia farmacologica è conforme allo stato dell'arte del trattamento di altre forme di Cardiomiopatie dilatative, ma non è chiaro se l'uso dei farmaci standard per rallentare la progressione della malattia è giustificato nei portatori sintomatici



Cabanelas N - Rev Port Cardiol. 2015; 34(2): 139.e1-139.e5;
Peretto G. – Nucleus 2018; Vol 9, No 1, 381-391

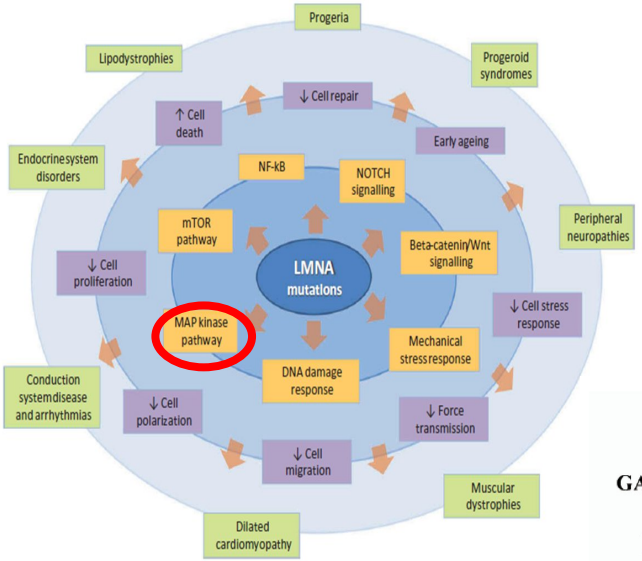
Sviluppo della LMNA-DCM : Ipotesi della espressione genica



- La somministrazione di inibitori di MEK1/2 (la chinasi MAPK che fosforila ERK1/2), o percorsi JNK, sia **prima o dopo lo sviluppo della Cardiomiopatia dilatativa, previene o ritarda la dilatazione ventricolare sinistra, il decremento della frazione di eiezione e lo sviluppo della fibrosi miocardica rispetto al gruppo topi placebo.**
- Risultati analoghi sono stati ottenuti con la somministrazione di un inibitore p38 in questi topi, dal momento che questo approccio farmacologico è stato in grado di prevenire dilatazione cardiaca e il deterioramento dell'accorciamento frazionario, ma non ha migliorato la fibrosi cardiaca.

Tsikitis – Biophysical Reviews (2018) 10:1007-1031

Cardiac Contractility Modulation Electrical Signals Improve Myocardial Gene Expression in Patients With Heart Failure



Vol. 51, No. 18, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.01.036

Sono stati valutate biopsie su 11 pazienti con DCM partecipanti allo studio FIX-HF-4 che ricevevano la terapia in cross-over (3 mesi con terapia CCM ON e 3 mesi con terapia CCM OFF). I pazienti sono stati sottoposti a biopsia cardiaca destra in basale, alla fine del 3 mese e del 6 mese di trattamento per la valutazione della modifica dell'espressione genica di alcuni enzimi e proteine, inclusa la **p38MAPK.**

È stato dimostrato che nei periodi in cui la terapia CCM veniva erogata, si verificava la riduzione dell'espressione genica del p38MAPK, cosa auspicabile perché una sua inibizione va ad impattare positivamente sulla progressione della cardiopatia e sul aumento della frazione di eiezione.

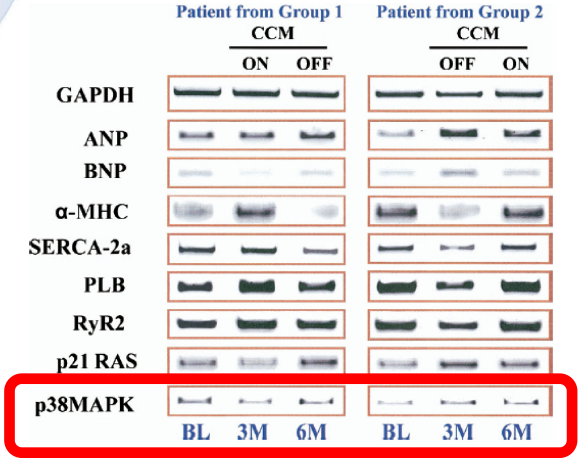
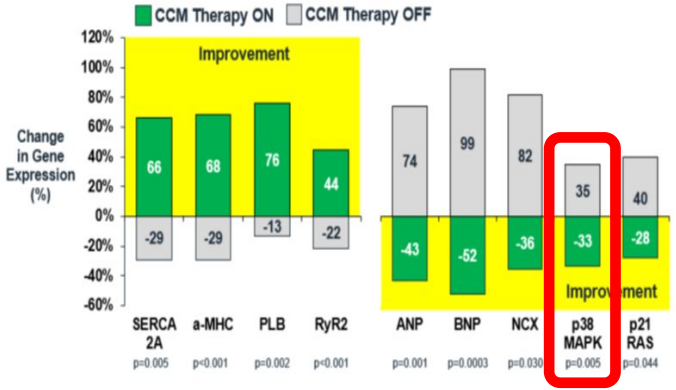


Figure 12. Impact of CCM therapy on expression of gene programs

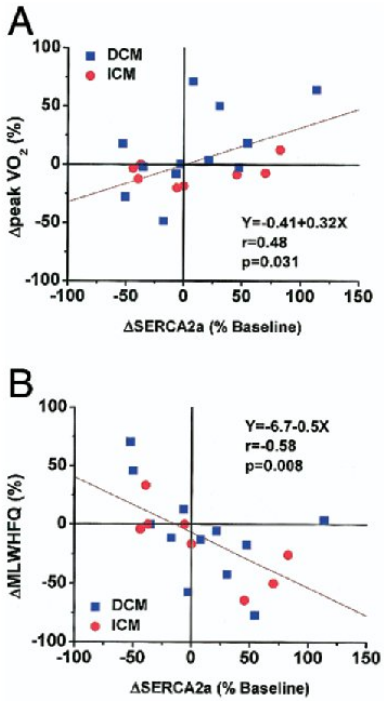


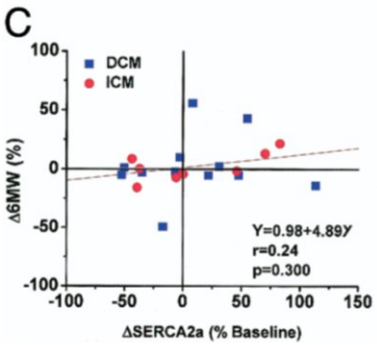
Adapted from Butter et al. Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure. J Am Coll Cardiol 2008;51:1784-1789.

Cardiac Contractility Modulation Electrical Signals Improve Myocardial Gene Expression in Patients With Heart Failure

Christian Butter, MD,* Sharad Rastogi, MD,† Hans-Heinrich Minden, MD,* Jürgen Meyhöfer, MD,* Daniel Burkhoff, MD, PHD,‡ Hani N. Sabbah, PHD†

Bernau/Berlin, Germany; Detroit, Michigan; and New York, New York





However, rather than invoking a direct effect of CCM signal treatment on gene expression, it is also possible that the changes in gene expression are secondary to alleviation of mechanical stresses brought about by local and global changes in myocardial function. For example, decreases in A- and B-type natriuretic peptides, p21 Ras, and p38 mitogen activated protein kinase are typically interpreted as indicating reduced mechanical stresses. Thus, alleviating excessive myocardial stretch may be responsible for down-regulation of stretch response proteins and block an important signaling pathway for HF progression. Nevertheless, it

L'impatto positivo sul programma genico è correlato ad un miglioramento delle capacità funzionali dei pazienti

Vol. 51, No. 18, 2008
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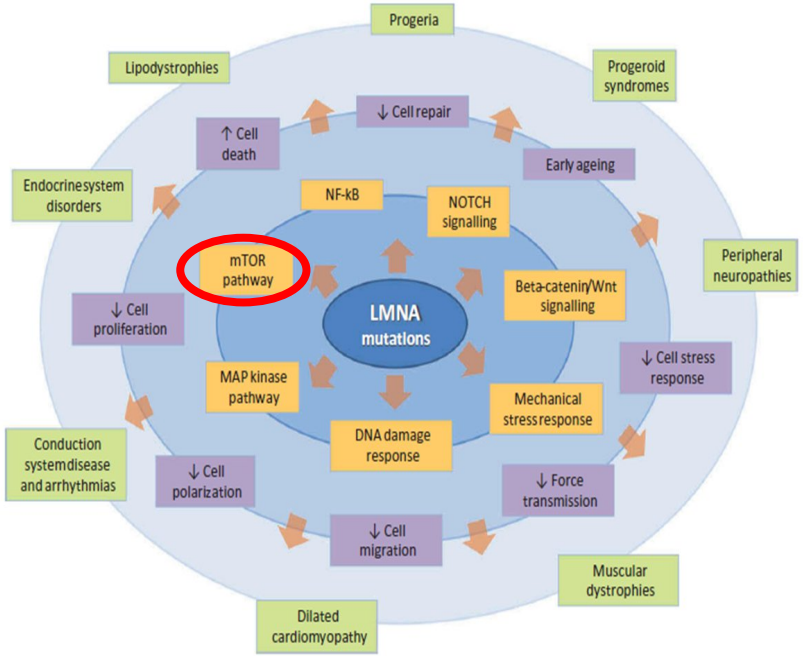
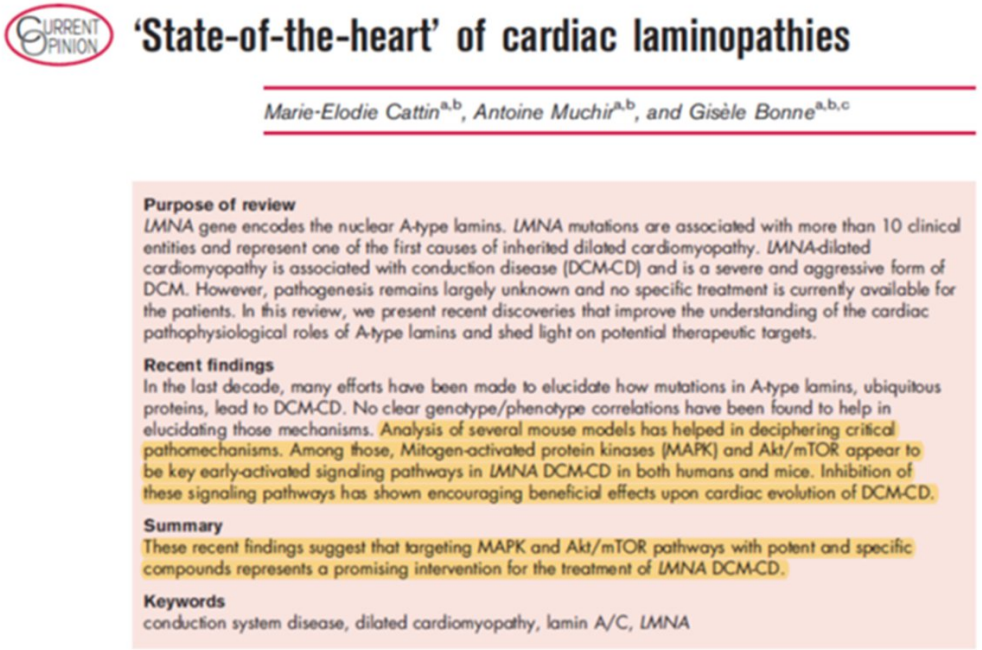




CURRENT OPINION

'State-of-the-heart' of cardiac laminopathies

Marie-Elodie Cattin[a,b], Antoine Muchir[a,b], and Gisèle Bonne[a,b,c]

Purpose of review
LMNA gene encodes the nuclear A-type lamins. *LMNA* mutations are associated with more than 10 clinical entities and represent one of the first causes of inherited dilated cardiomyopathy. *LMNA*-dilated cardiomyopathy is associated with conduction disease (DCM-CD) and is a severe and aggressive form of DCM. However, pathogenesis remains largely unknown and no specific treatment is currently available for the patients. In this review, we present recent discoveries that improve the understanding of the cardiac pathophysiological roles of A-type lamins and shed light on potential therapeutic targets.

Recent findings
In the last decade, many efforts have been made to elucidate how mutations in A-type lamins, ubiquitous proteins, lead to DCM-CD. No clear genotype/phenotype correlations have been found to help in elucidating those mechanisms. Analysis of several mouse models has helped in deciphering critical pathomechanisms. Among those, Mitogen-activated protein kinases (MAPK) and Akt/mTOR appear to be key early-activated signaling pathways in *LMNA* DCM-CD in both humans and mice. Inhibition of these signaling pathways has shown encouraging beneficial effects upon cardiac evolution of DCM-CD.

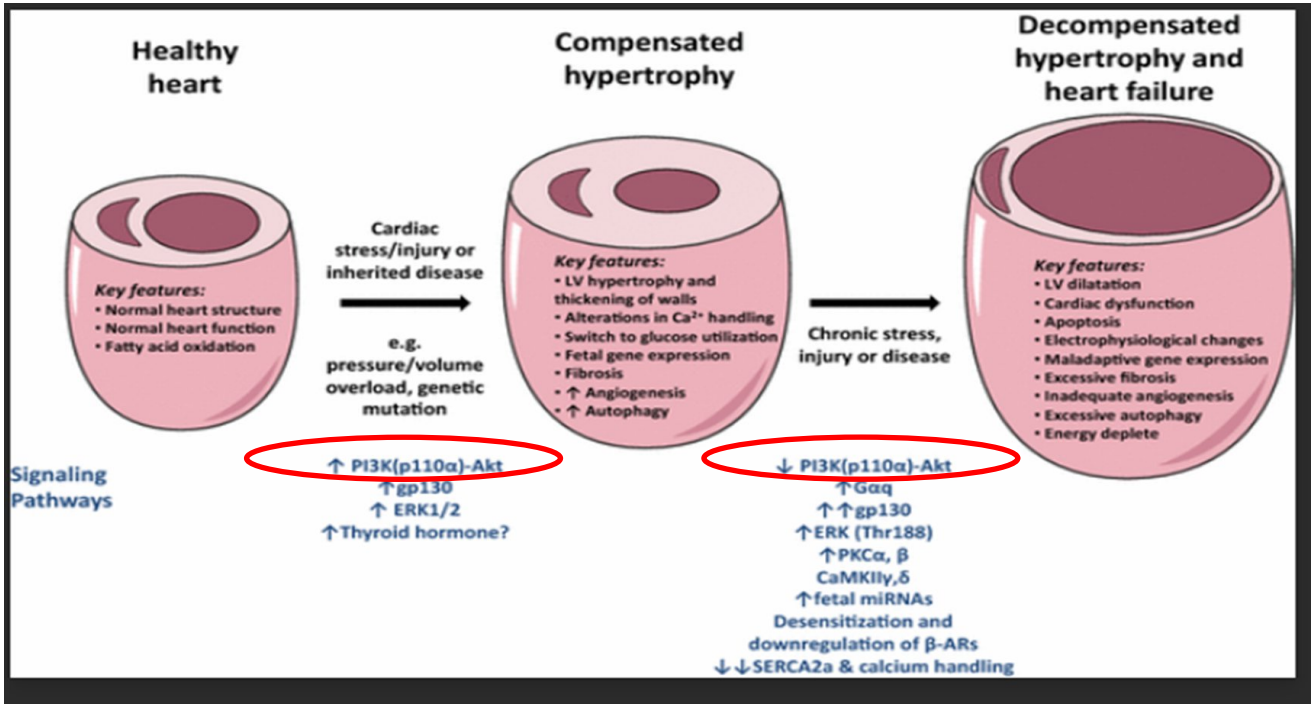
Summary
These recent findings suggest that targeting MAPK and Akt/mTOR pathways with potent and specific compounds represents a promising intervention for the treatment of *LMNA* DCM-CD.

Keywords
conduction system disease, dilated cardiomyopathy, lamin A/C, *LMNA*

Oltre alla MAPK, anche il pathway Akt/mTOR sembra contribuire allo sviluppo precoce della Cardiomiopatia nei pazienti con LMNA (dimostrato in modelli umani e di topi).

La inibizione anche del pathway Akt/mTOR ha mostrato incoraggianti effetti benefici sulla evoluzione della Cardiomiopatia.

Cattin M-E - Current Opinion in Cardiology. 28(3):297-304, MAY 2013.



L'attivazione a breve termine di AKT promuove l'ipertrofia fisiologica e la protezione dal danno miocardico; mentre la sua attivazione a lungo termine causa ipertrofia patologica e insufficienza cardiaca.

Cardiac Contractility Modulation Attenuates Chronic Heart Failure in a Rabbit Model via the PI3K/AKT Pathway

Qingqing Hao,[1,2] Feifei Zhang,[2] Yudan Wang,[1] Yingxiao Li,[2] and Xiaoyong Qi[1,2]

[1]School of Graduate, Hebei Medical University, Shijiazhuang, 050017, Hebei, China
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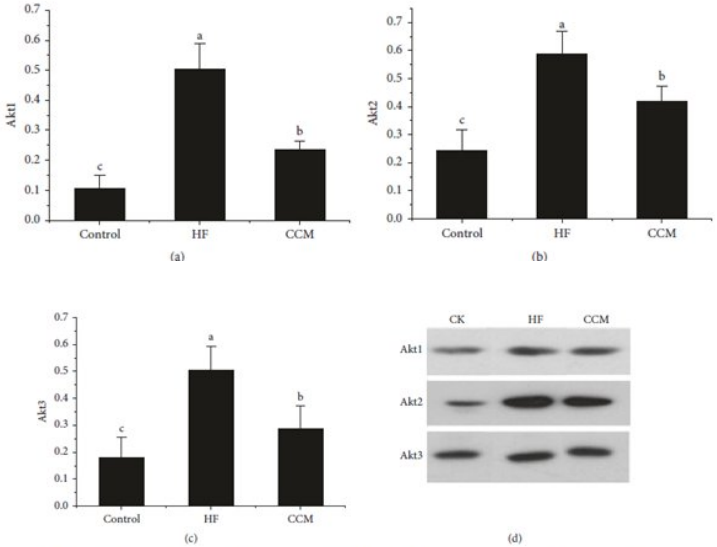

Figure 2: Effects of cardiac contractility modulation (CCM) on Akt1, Akt2, and Akt3 expression in different rabbit myocardial tissues under different treatments. (a) Akt1 expression; (b) Akt2 expression; (c) Akt3 expression; and (d) western blot images of Akt1, Akt2, and Akt3. CK, control group; HF, heart failure. Different lower letters above each boxplot showed the significant differences at $p < 0.05$.

Hindawi
BioMed Research International
Volume 2020, Article ID 1625362, 8 pages
https://doi.org/10.1155/2020/1625362

Akt is a citosolic protein which regulates cardiac growth, myocardial angiogenesis, glucose metabolism, and cell death in cardiac myocites.

Generally Akt contains three isoforms of Akt, including Akt1, Akt2, and Akt3, were investigated and they showed similar tendency after CCM application.

Akt1 and Akt3 overexpression in the heart results in progression from adaptive to maladaptive hypertrophy. In this study CCM operation significantly decreased the Akt1 and Akt3 levels, which are significantly lower than those in the HF group and higher than those in the control group.

Akt2 overexpression enhanced the murine sensitivity to cardiomyocyte apoptosis in response to ischemic injury. In this results, CCM application slightly decreased the Akt2 expression when compared with the HF group.

Per quanto riguarda gli effetti della terapia CCM sul pathway AKT/mTor, di recente è stato pubblicato un articolo da parte di un gruppo cinese sull'argomento studiandolo in modelli di conigli

È stato dimostrato che la CCM porta il livello di attività del pathway Akt/mTOR a quello dei soggetti sani (nel gruppo con scompenso la loro attività è overespressa).

Il pathway AKT/mTor regola il metabolismo cellulare, la sopravvivenza cellulare e controlla la traduzione del mRNA.

Una inibizione del pathway Akt/mTOR è associata ad una riduzione della fibrosi del miocardio nei pazienti con scompenso e contribuisce al rimodellamento inverso cardiaco.

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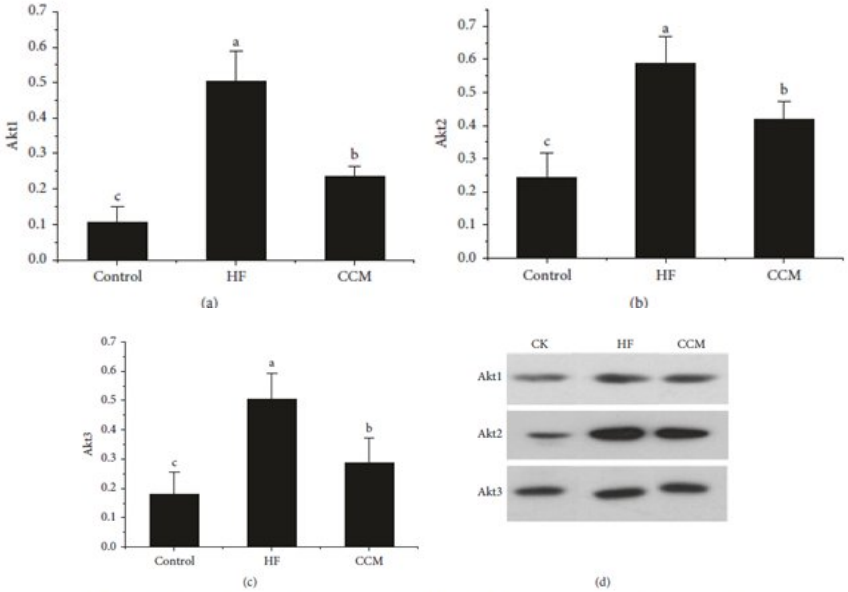

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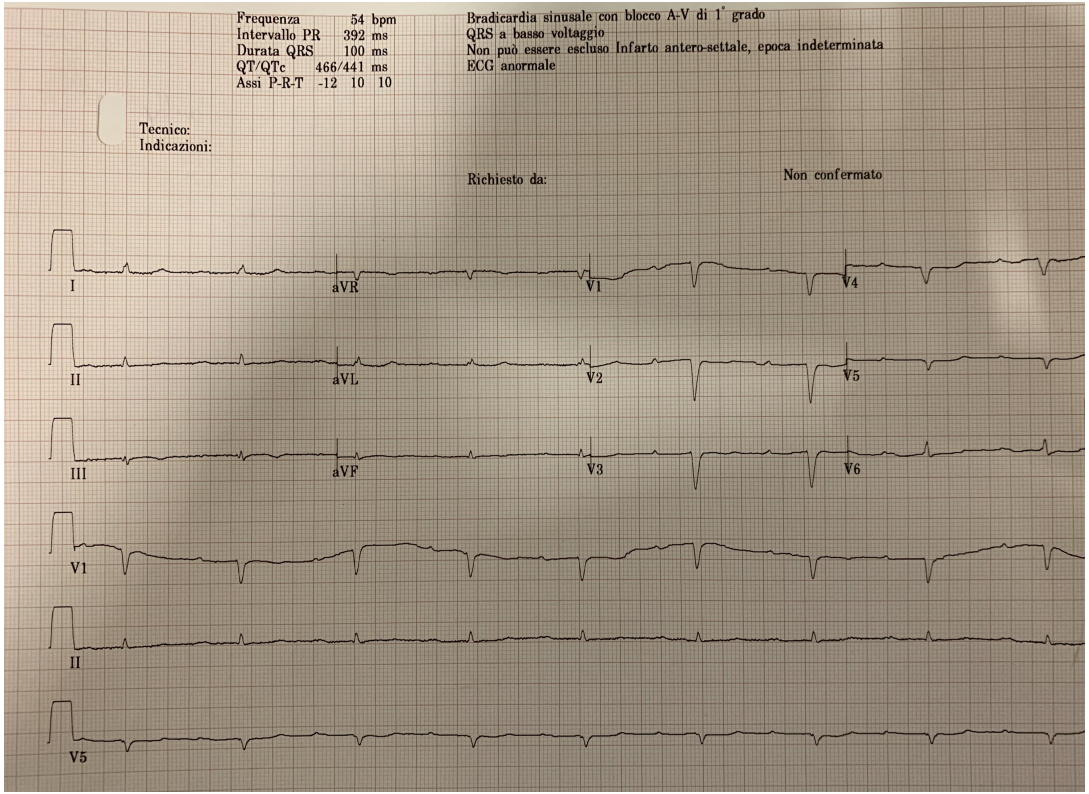
Caso di applicazione CCM su Cardiolaminopatia

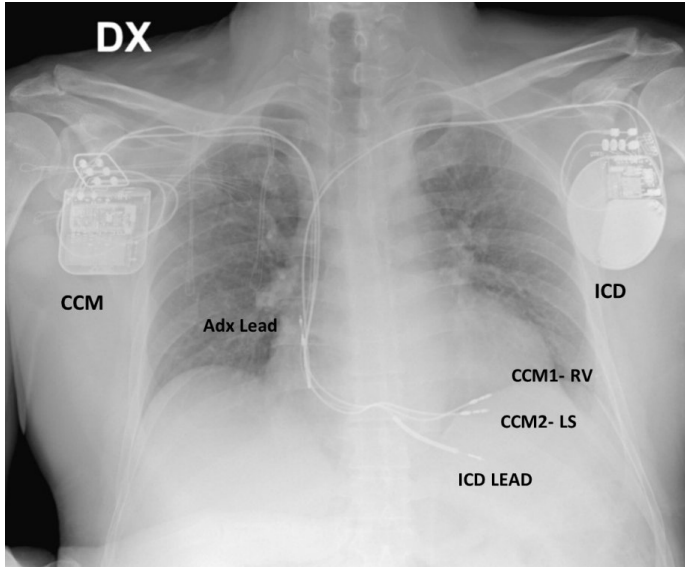


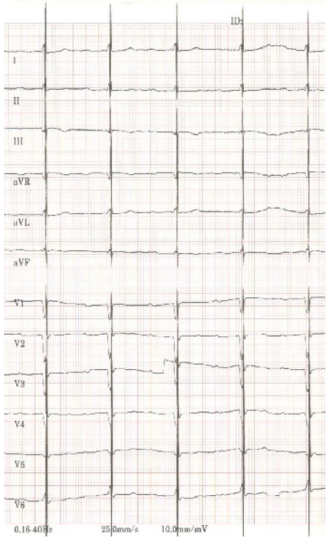
	Baseline
KCCQ	75,5
VTD [ml]	133
VTS [ml]	80
FE [%]	40
GLS	-11,3
RVD1 [mm]	46
RVD2 [mm]	42
RVD3 [mm]	75

PR=392 ms
QRS= 100 ms
Fc= 54 bpm

Impianto il 09/03/2021

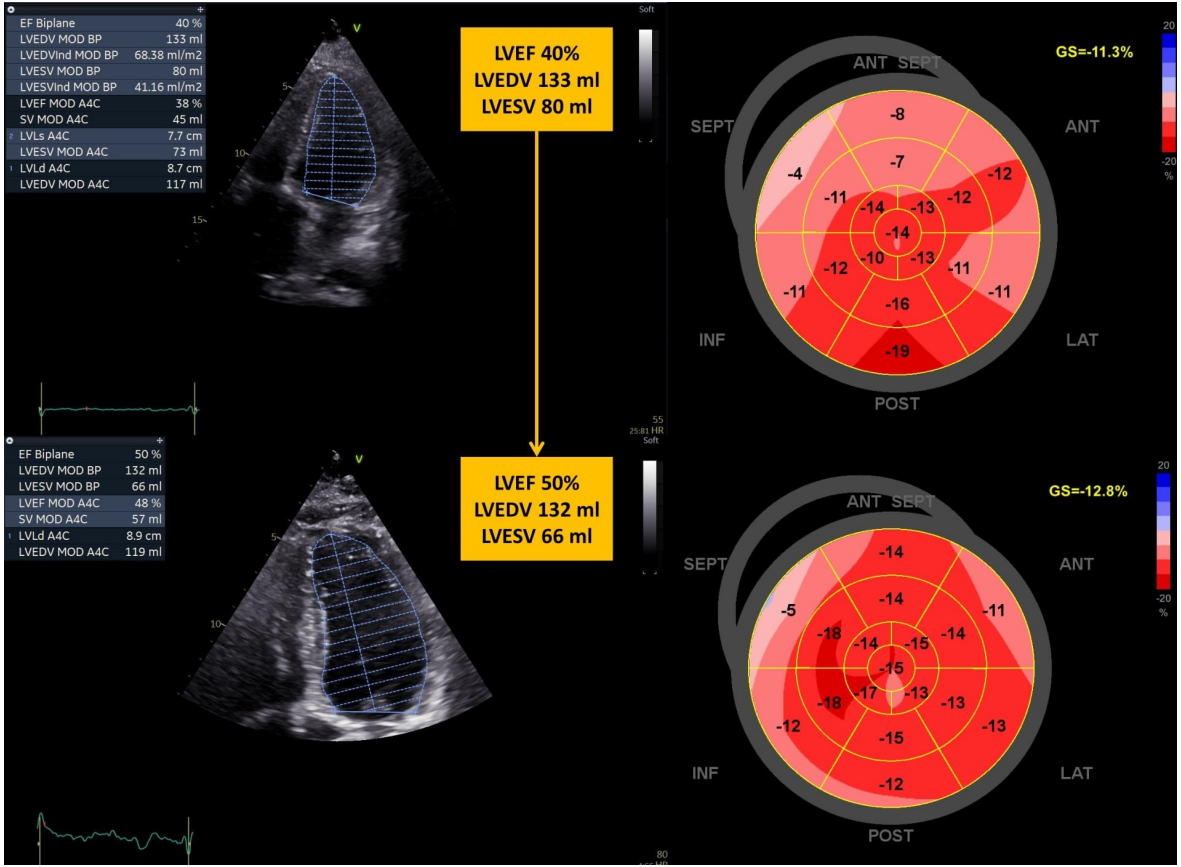
Effettuato impianto di Optimizer Smart il 9 marzo 2021 in sede controlaterale al ICD.
Nessuna evidenza di peggioramento della insufficienza tricuspidalica dall'inserzione dei due elettrocateteri.
Terapia programmata 10 h/giorno.





Follow Up ad 1 anno

	Baseline	6 months	12 months
KCCQ	75,5	87,3	93,6
VTD [ml]	133	133	132
VTS [ml]	80	70	66
FE [%]	40	47	50
GLS	-11,3	-12	-12,8
RVD1 [mm]	46	39	39
RVD2 [mm]	42	42	42
RVD3 [mm]	75	69	69
NtProBNP [pg/mL]	645	527	801
Laminina [ng/mL]	34	28,13	13
Collagene 4 [ng/mL]	33	15,6	21
Collagene3 [ng/mL]	18,1	16,5	21,3
Copeptina [pmol/L]	17,54	14,92	11,32
Cystatina C [mg/L]	1,14	1,01	1,12
Lp-PLA2	1628	26,57	201,5
Interleuchina 6 [pg/mL]	5,1	3,6	< 2


EF Biplane 40 %
LVEDV MOD BP 133 ml
LVEDVInd MOD BP 68.38 ml/m2
LVESV MOD BP 80 ml
LVESVInd MOD BP 41.16 ml/m2
LVEF MOD A4C 38 %
SV MOD A4C 45 ml
LVLs A4C 7.7 cm
LVESV MOD A4C 73 ml
LVLd A4C 8.7 cm
LVEDV MOD A4C 117 ml
LVEF 40%
LVEDV 133 ml
LVESV 80 ml
GS=-11.3%
ANT SEPT
SEPT
ANT
INF
LAT
POST
-8
-7
-4
-12
-11
-14
-13
-12
-14
-12
-10
-13
-11
-11
-11
-16
-19
EF Biplane 50 %
LVEDV MOD BP 132 ml
LVESV MOD BP 66 ml
LVEF MOD A4C 48 %
SV MOD A4C 57 ml
LVLd A4C 8.9 cm
LVEDV MOD A4C 119 ml
LVEF 50%
LVEDV 132 ml
LVESV 66 ml
GS=-12.8%
ANT SEPT
SEPT
ANT
INF
LAT
POST
-14
-14
-5
-11
-18
-14
-15
-14
-15
-17
-13
-18
-13
-12
-13
-15
-12

Take home message

Candidato ideale alla terapia CCM con indicazione primaria :

- NYHA ≥ II nonostante OMT in ritmo sinusale o in fibrillazione atriale
- FE Vsn 25-45 %
- Assenza di significativa disfunzione sistolica ventricolare destra
- Extrasistolia ventricolare < 9000/24 ore
- Clinicamente «stabile» anche se in classe NYHA avanzata
- Assenza di IMA nei 3 mesi precedenti
- Nessuna comorbilità che pregiudichi sopravvivenza a 6 mesi

BACK UP Slide