Region Skåne
HTA Syd

Health Technology Assessment (HTA)

Sonderande litteraturöversikt med enkel analys

CARDIAC CONTRACTILITY MODULATION: EN MÖJLIG TILLÄGGS-BEHANDLING VID ALLVARLIG HJÄRTSVIKT

Datum: 210901

Innehållsdeklaration

Detta HTA Syd-dokument är baserat på följande delmoment:

☒ Metodbeskrivning

☐ Fokuserad klinisk frågeställning, PICO och avgränsningar

☒ Sonderande litteratursökning

☐ Uttömmande litteratursökning

☒ Flödesschema

☒ Artikelsållning

☐ Relevansbedömning

☐ Kvalitetsgranskning

☒ Översiktlig tabellering

☒ Enkel analys

☐ Sammanvägning av resultat

☐ Narrativ analys

☐ Metaanalys

☐ Tillförlitlighetsbedömning enligt GRADE

☒ Sammanfattning

☐ Hälsoekonomi

☐ Organisation

☐ Etik

☒ Pågående studier

☒ Exkluderade artiklar

☐ Expertgrupp deltar

☐ Extern granskning

☐ Kunskapsluckor identifierade

☐ Godkänd jävsdeklaration

Använda förkortningar

CCM	Cardiac Contractility Modulation
PICO	Patient, intervention, comparison, outcome
HF	Heart Failure
CHF	Chronic Heart Failure
RCT	Randomized Controlled Trial
QRS	Q-, R- och S- våg
ESC	European Society of Cardiology
NICE	National Institute for health and Care Excellence
HFrEF	Heart Failure with reduced Ejection Fraction
NYHA	New York Heart Association
VAT	Ventilatory Anaerobic Threshold
VO2 (VO_2)	Volume Oxygen
HrQoL	Health-related Quality of Life
MACE	Major Adverse Cardiovascular Events
FIX-HF	Akronym-Heart Failure
LVEF	Left Ventricular Ejection Fraction
S-ICD	Subcutaneous Implantable Cardioverter-Defibrillator

Sammanfattning

En bred och sonderande sökning för behandling med Cardiac Contractility Modulation (CCM) vid hjärtinsufficiens har gjorts utifrån frågeställningen kring möjligheterna att göra en konventionell och fullständig HTA-rapport i ämnet.

Sökningen resulterade totalt i knappt 1200 träffar, varav 28 studier gallrades ut som intressanta. Detta inkluderade 6 RCT:er, 7 systematiska översikter och 15 originalartiklar från 2004 och framåt. Totalt ingick knappt 3000 patienter i studierna, som var från USA, Tyskland och Kina samt gränsöverskridande samarbetsstudier. I mer än 60 % av studierna var det tillverkande företaget inblandad, huvudsakligen som finansiär.
Aktuella riktlinjer är inte entydiga men påtalar behovet av mer forskning.

HTA Syds enkla analys av ovan talar för, men garanterar inte, att en fullständig HTA-rapport skulle kunna leda till konklusiva resultat.

En fullständig HTA-rapport skulle vara till gagn för den aktuella patientkategorin i Region Skåne och i Södra Sjukvårdsregionen samt sannolikt även nationellt via kunskapsstyrningsorganisationen och tillika vara till nytta för såväl patientansvariga kliniker som beslutsfattare i andra delar av regionens organisation.

För HTA Syd;
Erik Wikström, informationsspecialist
Ylva Sundin, fil mag, informationsspecialist
Jan Holst, docent, överläkare, HTA handledare

Introduktion, Frågeställning och Bakgrund

Det har inkommit en fråga till HTA Syd (se Appendix 1) från verksamhetsområde Hjärt- och Lungmedicin (sektionschef, doc Rasmus Borgquist och verksamhetschef, doc Patrik Tydén) om möjligheterna att genomföra en regelrätt HTA-analys kring huruvida Cardiac Contractility Modulation (CCM, på svenska ungefär: modulering av hjärtmuskelns sammandragande förmåga) har en evidensbaserad plats i arsenalen som tilläggsbehandling vid allvarlig hjärtsvikt.

Frågan inkom initialt från kollegorna ovan redan i augusti 2020. Vid en muntlig diskussion då togs beslut om att avvakta tills mer utvärderingsbara data blivit tillgängliga. Frågan har nu ånyo aktualiserats. Den aktuella frågan att nu besvara är således: Finns det en rimlig och tillräcklig mängd publicerad vetenskap för att HTA-mässigt kunna utvärdera den kliniska effekten av CCM som tilläggsbehandling vid avancerad hjärtsvikt? De patientnära effektmått som konventionellt studeras i dessa sammanhang är: total och kardiovaskulär mortalitet samt morbiditet mätt som återinläggning för hjärtsvikt; hälsorelaterad livskvalitet; funktionstester som 6 minuters gångtest och VO_2-max samt farmakologisk modifiering och hjärtsviktsklassificering m.fl. Vidare studeras även andelen tekniskt framgångsrika inläggningar och komplikationsfrekvensen för CCM.

Hjärtsvikt är en vanlig och progredierande sjukdom; en uppskattning utifrån publicerade moderna västerländska prevalensdata hos vuxna ger ett estimat på 1-2 %[1]. Prevalensen är stigande med ålder och så hög som >10 % hos populationer >70 år[2,3]. Enligt SCB och Regionfakta skulle absoluta antalet vuxna hjärtsviktspatienter i Sverige och Skåne kunna uppskattas till 120 000 respektive knappt 17 000 för vår region. Av dessa patienter anses prevalensen för allvarlig hjärtsvikt vara 15-30 %. Teoretiskt skulle därmed 3 400 patienter i Skåne ha en avancerad hjärtsvikt (NYHA klass III/IV). Detta trots optimerad farmakologisk behandling, livsstilsmodifiering och interventionella åtgärder. Patienterna erfar ofta upprepade episoder med sjukhusvård; tillika påverkas mortaliteten menligt[4].

Principen för CCM är att man tillför en icke-excitatorisk elektrisk stöt till hjärtmuskeln vid dess absolut refraktära perioden under den elektriska cykeln. Detta motsvaras av perioden från början på Q-vågen till mitten av T-vågen på ett EKG. Grundläggande förutsättningar är bl.a. att patienten har sinusrytm, att QRS-komplexet inte får överstiga ca 120 msek och att vänsterkammarens ejektionsfraktion är uppmätt till 25-45 %[5]. Andelen patienter med allvarlig hjärtsvikt och som innefattas av nämnda inklusionskriterier uppskattas till 30 %[6].

Rent praktiskt för patienten påminner inläggningen och behandlingen om den för en konventionell pacemaker. Den uppladdningsbara dosan är placerad i underhuden strax nedom ena nyckelbenet. 2-3 elektroder är kopplade till dosan. Elektroderna når hjärtat via ytliga och djupa venösa kärl. I hjärtat är en av elektroderna placerad i höger förmak där den första fasen i den elektriska cykeln detekteras. De andra sitter fast i den högra kammarväggen och därifrån kommer den modulerande elektriska stöten.

CCM-apparaten produceras av ett amerikanskt medicintekniskt företag. CCM blev CE märkt år 2016 och godkändes av amerikanska kontrollmyndigheten FDA för 2,5 år sedan. Globalt uppskattas det att 4500 CCM-implantationer är genomförda[7]. Styckpriset är 170 000 kr, vid inköp av flera apparater åt gången är priset på sedvanligt sätt förhandlingsbart.

CCM-behandlingen betraktas för närvarande som högspecialiserad vård. Eventuellt framtida vårdnivå kan i nuläget inte bedömas. Vid Skånes universitetssjukhus har det hittills inte genomförts några behandlingar. Vid Karolinska Sjukhuset har ca tio behandlingar genomförts. Enligt frågeställarna är den kliniska bedömningen, från läkare som prövat den, att behandlingen är till övervägande del välfungerande och positiva effekter har noterats på ovan angivna effektmått[6].

Metodbeskrivning

Utifrån frågeställningen identifierades en enkel sökträng för litteratursökning: cardiac contractility modulation AND heart failure. Eftersom detta var en sonderande sökning användes inget PICO utan sökningen gjordes så bred som möjligt för att finna största möjliga underlag.

I ett första skede värderdes studierna baserat på om studien behandlade korrekt ämne enligt sökträngen utifrån titel och ev. abstrakt. I andra skedet gjordes urval på grundval av studietyp. Systematiska översikter, meta-analyser, RCT, jämförande artiklar med originaldata (prospektiva eller retrospektiva) och observationella longitudinella studier togs med. Djurstudier och icke systematiska översikter valdes bort. I det tredje och sista skedet baserades urvalet på huruvida artikeln redovisade ett patientnära effektmått, hade tillräckligt många deltagare (n>10) och var en studie på enhetliga patientgrupper med en uppföljning på minst 1 mån. Studier med lågt antal deltagare, studieprotokoll, subgruppsstudier samt artiklar utan åtkomlig fulltext sorterades bort.

Litteratursökning gjordes 15-17 juni 2021 i PubMed, Cinahl (via Ebsco) och Cochrane Library. I PubMed och Cinahl filtrerades artiklar som inte var på engelska eller svenska bort.

I databaserna hittas totalt 1147 träffar och efter borttagning av dubbletter återstod 1098 unika referenser. Efter första urvalet återstod 110 artiklar. Av dessa återstod 37 studier ut efter andra urvalet. 9 av studierna valdes bort, så totalt inkluderas 27 studier.

För att hitta pågående studier gjordes 23 juni 2021 en sökning i ClinicalTrials.gov. Då hittades totalt 13 studier, varav 5 pågående.

En kompletterande sökning gjordes 13 augusti. Då hittades 12 nya träffar (i PubMed). Av dessa återstod 2 efter första urvalet, och 1 efter granskning Denna inkluderades i de utvalda studierna (så totalt blev det 28). Eftersom inga nya träffar hittades i Cinahl eller Cochrane uppdaterades inte sökstrategierna för dessa.

För sökstrategier och urvalsprocess se Appendix 2.

Resultat

Av de ingående studierna var 6 RCT; 7 systematiska översikter och 15 artiklar med annan patientnära originaldata (observationsstudier, pilotstudier eller retrospektiva jämförande studier). De systematiska översikterna publicerades från 2012 fram till 2020; RCT:erna mellan 2006 och 2018 och artiklar med originaldata från 2004.

Totalt ingick 2851 patienter i de utvalda studierna, varav 849 i RCT (varav 206 som ingick i en delstudie från en annan RCT) och 2002 i kohortstudier (longitudinella observationsstudier och retrospektiva jämförande studier). Patientgrupperna som studerades fanns i USA (7); Tyskland (5) och Kina (3, varav 1 Hongkong); i kollaborationsstudier i USA/Tyskland/Israel (1), USA/Tyskland (1), Tyskland/Israel (1), Italien/Österrike (1) och USA/Pakistan (1); samt en multicenterstudie i Europa och USA. I vissa fall angavs inte demografiskt vilka grupper som studerades. De dominerande patientnära effektmåtten i studierna var: ändring av klinisk hjärtinsuffiens-klassificering, livskvalitet, funktionsprov med 6-minutersgångprov, olika varianter på syreupptagningsförmåga, sjukhusinläggning samt total och kardiovaskulär dödlighet.

Eftersom CCM är en metod som i stort sett alltid använder ett implanterbart Optimizer™ system, som tillverkas av Impulse Dynamics, gjordes även en undersökning om artiklarna hade någon koppling till företaget. Detta var fallet i totalt 17 av 28 artiklar. 11 av studierna fick forskningsanslag och 1

ospecificerat stöd. 9 av artiklarna hade medförfattare som var anställda på Impulse Dynamics och ytterligare 6 hade medförfattare som var konsulter åt företaget. Impulse Dynamics var involverade i 5 av 6 RCT, i samtliga fall genom att ge forskningsanslag.

För mer utförlig information se tabell 1 nedan.

Det finns endast ett fåtal rekommendationer kring CCM som vi identifierat. Den första från European Society of Cardiology (ESC) från 2016[5] nämner bara CCM helt kort och säger att:

> *CCM has been evaluated in patients with HFrEF in NYHA Classes II–III with normal QRS duration (120 ms) An individual patient data meta-analysis demonstrated an improvement in exercise tolerance (peak VO_2) and quality of life (Minnesota Living with Heart Failure questionnaire). Thus CCM may be considered in selected patients with HF. The effect of CCM on HF morbidity and mortality remains to be established.*

I ESC-dokumentet ges ingen graderad rekommendation (I, IIa, IIb eller III), ej heller ges någon evidensgradering (A, B eller C) av befintlig data, bara att ytterligare forskning behövs (s. 2154). När eventuell revison av ovan kan förväntas från ESC och publiceras är inte känt.

Den andra rekommendationen från brittiska NICE från 2019[8], uppger att CCM enbart bör användas för forskning och inte i klinisk medicin.

> *The evidence on cardiac contractility modulation device implantation for heart failure raises no major safety concerns. However, the evidence on efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.*

men kan användas som behandling när normala behandlingsmetoder inte fungerar (s. 2):

> *Cardiac contractility modulation device implantation may be an option for people with advanced heart failure that hasn't responded to conventional therapy.*

Enligt uppgift kommer NICE-rekommendationen att uppdateras juni 2022.

För mer information om inkluderade, exkluderade och pågående studier se Appendix 3

Sammanfattande tabell

Referens	Ursprung	Studietyp	Pat-nära effektmått	Redovisade pat-nära effektmått	Uppföljningstid >1 mån	Kopplingar till Impulse Dynamics
Abraham (2011)	USA	RCT; subgruppsanalys i FIX-HF 5 studien	ja	VAT	ja	Forskningsanslag; medförfattare konsult
Abraham (2018)	USA	RCT, redovisning av FIX-HFC	ja	VO2, 6min-gångtest, HrQoL, mortalitet och återinläggning	ja	Forskningsanslag; medförfattare konsult
Anker (2015)	Tyskland	longitudinell obs-studie, registerstudie	ja	Kardiovaskulär sjukhusinläggning; NYHA, mortalitet	ja	Forskningsanslag; medförfattare anställd forskare
Borggrefe (2008)	USA	RCT m cross-over	ja	VO_2 peak (VO_2 max) HrQoL	ja	Forskningsanslag; medförfattare anställd forskare

Cappannoli (2021)	USA	systematisk översikt	/		/	inga
Fastner (2021)	multicenter, Europa o USA	retrospektiv jämförande studie	ja	mortalitet, NYHA	ja	medförfattare konsult
Giallauria (2014)		systematisk översikt	/		/	inga
Giallauria (2020)		systematisk översikt	/		/	medförfattare konsult
Kadish (2011)		RCT	ja	VO_2 max, 6min-gångtest, HrQoL, total mortalitet	ja	Forskningsanslag
Kloppe (2016a)	Tyskland	single center pilotstudie	ja	HrQoL, träningstolerans, kardiell funktion	ja	Forskningsanslag; medförfattare anställd forskare
Kloppe (2016b)		longitudinell obs-studie i grunden, men man jfr mot ett vedertaget scoringsystem för tot mortalitet	ja	total mortalitet	ja	inga
Kuschyk (2015)		longitudinell retrospektiv-studie	ja	mortalitet, livskvalitet m. fl.	ja	medförfattare anställd forskare
Kuschyk (2021)		longitudinell obs-studie	ja	kardiovaskulär mortalitet, LVEF, NYHA-klass, HrQoL, mfl	ja	medförfattare anställd forskare
Kwong (2012)	USA	systematisk översikt	ja	total mortalitet, total sjukhusinläggning	ja	inga
Liu (2016)	Hongkong	longitudjämförande studie	ja	total mortalitet	ja	Forskningsanslag; medförfattare anställd forskare
Liu (2017)	Tyskland, Israel	systematisk översikt	ja	total mortalitet, total sjukhusinläggning, MACE, VO_2 max, 6 min-gångtest	ja	inga
Mando (2019)	Tyskland	systematisk översikt	ja	sjukhusinläggning för HF (+tot), 6min-gångtest, HrQoL, total mortalitet	ja	inga
Müller (2017)	USA, Tyskland	longitudinell obs-studie	ja	VO_2 max, 6min-gångtest, HrQoL, kardiovaskulär och total mortalitet	ja	Ospecificerat stöd; medförfattare anställd forskare
Nadeem (2020)	Kina	systematisk översikt	ja	total mortalitet	ja	inga

Neelagaru (2006)	Kina (Wuhan)	RCT	ja	NYHA-klass, 6min-gångtest, kardiovaskulär inläggning	ja	inga
Pappoe (2004)	Italien, Österrike	longitudinell obs-studie	ja	LVEF, NYHA-klass, VO_2 max, 6min-gångtest	ja	Forskningsanslag; medförfattare anställd forskare
Pilecky (2021)	USA	longitudinell obs-studie	ja	LVEF, NYHA mfl	ja	inga
Röger (2014)	Tyskland, Israel, USA	longitudinell obs-studie	nej		/	inga
Röger (2017)	USA, Pakistan	RCT	ja	LVEF, NYHA mfl	ja	Forskningsanslag; medförfattare anställd forskare
Röger (2018)	Tyskland	longitudinell obs-studie	ja	NYHA, LVEF	ja	medförfattare konsult
Schau (2011)	Tyskland	longitudinell obs-studie	ja	total mortalitet	ja	inga
Stix	USA?	longitudinell obs-studie	ja	LVEF, 6min-gångtest	ja	Forskningsanslag; medförfattare konsult
Yu (2009)	USA	longitudinell obs-studie	ja	LVEF, NYHA mfl	ja	Forskningsanslag

Tabell 1: Jämförelse mellan olika studier

Enkel analys

Föreliggande dokument är inte en fullständig HTA-analys, essentiella delar för en sådan saknas, vg se innehållsdeklarationen på sidan 2.

HTA Syds enkla analys av den genomförda sonderande litteratursökningen talar för, men garanterar inte, att en fullständig HTA-rapport skulle kunna leda till konklusiva resultat.

En sådan fullständig HTA-rapport skulle kunna vara till gagn för den aktuella patientkategorin i lokalt i Skåne och regionalt för Södra Sjukvårdsregionen samt sannolikt även nationellt via kunskapsstyrningsorganisationen. Vidare kan en HTA-rapport i ämnet vara till nytta för såväl patientansvariga kliniker som beslutsfattare i andra delar av organisationen.

HTA-Syd önskar dock poängtera att en fullständig HTA-rapport med vårt verksamhetsnära tillvägagångssätt förutsätter:

a) att tid avsätts för sakkunniga från kliniken på sedvanligt sätt,
b) att Region Skånes Metod- och prioriteringsråd ger sitt godkännande till projektet,
c) att HTA Syds resurser kan prioriteras till projektet.

Appendix 1

HTA Skåne

Fråga till HTA Skåne
Projektnamn Cardiac Contractility Modulation therapy mot hjärtsvikt Namnge projektet.
Klinisk frågeställning Kan CCM hjälpa patienter med systolisk hjärtsvikt avseende minskad risk för hospitalisering och/eller mortalitet. Frågan kan med fördel formuleras enligt den här modellen: Har metod XX fördelar jämfört med metod YY (nuvarande standardbehandling) för att bota, behandla, lindra eller förebygga sjukdom ZZ i patientgruppen ÅÅ?
Beskriv kortfattat (max 100 ord) varför denna fråga är aktuell just nu Patienter med hjärtsvikt och nedsatt vänsterkammarfunktion som står på optimal medicinsk terapi men fortfarande har symtom, har fortsatt en relativt dålig prognos och ofta behov av inneliggande vård. För patienter med breda QRS komplex finns Cardiac Resynchronization Therapy som kan bättra prognos och symtom. För dem med normala (smala) QRS komplex har motsvarande alternativ inte funnits tidigare. Nu finns nya kliniska data för CCM som talar för att denna behandling ev. har samma gynnsamma effekter som CRT. För vem och varför är frågan viktig? Vad har aktualiserat frågan?
Aktuell patientvolym Prevalensen för hjärtsvikt är cirka 2% totalt sett i Sverige. Av dessa uppfyller potentiellt cirka 5% indikationerna för CCM, enligt en brittisk studie publicerad nyligen. Det innebär att cirka 8-10 000 patienter skulle kunna vara aktuella för behandlingen på sikt. Ange årsvolym patienter som erhåller nuvarande standardbehandling/diagnostik.
Finns det riktlinjer/guidelines från myndigheter eller sakkunniga organisationer? I Europeiska kardiologföreningens riktlinjer finns behandlingen nämnd med orden ”Cardiac contractility modulation (CCM) may be considered in patients with HFrEF (LVEF 25–45%) and a narrow QRS complex (<130 ms) in order to improve exercise capacity, quality of life and alleviate HF symptoms.” Ange referens för eventuella internationella, nationella, regionala eller lokala riktlinjer.
Ange 2-5 nyckelreferenser för projektet Se separat wordfil och en pdf Referenser som bedöms belysa frågeställningen.
Verksamhet SUS arytmisektionen, devicedelen. Ange vilken verksamhet som ställer frågan. Ange förvaltning och ort.
Vem ställer frågan? Rasmus Borgquist, EAL. Namn, titel, kontaktinformation.
Verksamhetschef(-er) **Pia Malmkvist** Undertecknad stödjer projektet och frigör tid för medarbetare att delta i projektet, 60-100 timmar per deltagare. Signatur och namnförtydligande.
Läkare som är medicinskt ansvarig för området frågan berör **Rasmus Borgquist** Undertecknad stödjer projektet. Signatur och namnförtydligande.
Ort och datum Lund, 19 aug 2020 Datum för inskickande.

Appendix 2

Litteratursökning

Sökstrategier

1. **PubMed**
   Datum: 2021-08-13
   Antal träffar: 1063

	Söktermer	Antal träffar
#1	cardiac contractility modulation AND heart failure AND english[Filter]	1063

2. **CINAHL with Full Text (via Ebsco)**
   Datum: 2021-06-16
   Limiters – Engelskspråkig
   Antal träffar: 45

	Söktermer	Antal träffar
#1	cardiac contractility modulation	51
#2	heart failure	67781
#3	1 AND 2	45

3. **Cochrane Library**
   Datum: 2021-06-17
   (Word variations have been searched)
   Antal träffar: 51; varav:
   0 Cochrane Reviews
   0 Cochrane Protocols
   51 Trials
   0 Editorials
   0 Clinical Answers

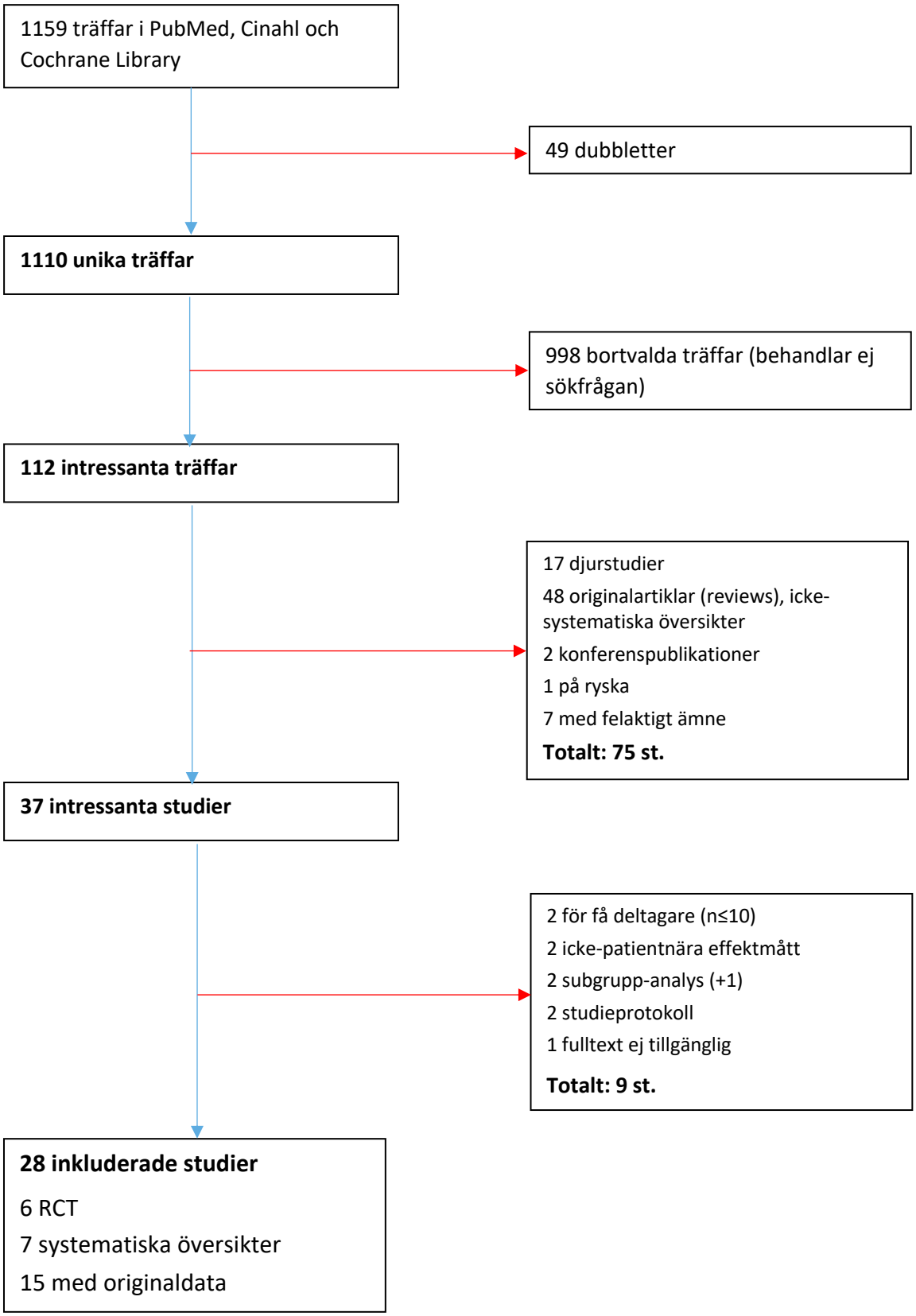
	Söktermer	Antal träffar
#1	(cardiac contractility modulation):ti,ab,kw	66
#2	("heart failure"):ti,ab,kw	30834
#3	1 AND 2	51

4. **ClinicalTrials.gov**
   Datum: 2021-06-23
   Antal träffar: 13

	Söktermer	Antal träffar
#1	cardiac contractility modulation	12
#2	heart failure	4,794
#3	1 AND 2	13*

* inklusive 1 med coronary contractility modulation

Sökningsresultat



Appendix 3

Inkluderade studier

Referens	Abstrakt
Abraham (2011)	Background: Cardiac contractility modulation (CCM) signals are nonexcitatory electrical signals delivered during the absolute refractory period intended to improve contraction. We previously tested the safety and efficacy of CCM in 428 NYHA functional class III/IV heart failure patients with EF ≤35% and narrow QRS randomized to optimal medical treatment (OMT) plus CCM (n = 215) versus OMT alone (n = 213) and found no significant effect on ventilatory anaerobic threshold (VAT), the study's primary end point. In the present analysis, we sought to identify if there was a subgroup of patients who showed a response to CCM. Methods and results: The protocol specified that multiregression analysis would be used to determine if baseline EF, NYHA functional class, pVO(2), or etiology of heart failure influenced the impact of CCM on AT. Etiology and baseline pVO(2) did not affect efficacy. However, baseline NYHA functional class III and EF ≥25% were significant predictors of increased efficacy. In this subgroup (comprising 97 OMT and 109 CCM patients, ∼48% of the entire population) VAT increased by 0.10 ± 2.36 in CCM versus -0.54 ± 1.83 mL kg(-1) min(-1) in OMT (P = .03) and pVO(2) increased by 0.34 ± 3.11 in CCM versus -0.97 ± 2.31 (P = .001) at 24 weeks compared with baseline; 44% of CCM versus 23% of OMT subjects showed improvement of ≥1 class in NYHA functional class (P = .002), and 59% of CCM versus 42% of OMT subjects showed a ≥10-point reduction in Minnesota Living with Heart Failure Questionnaire (P = .01). All of these findings were similar to those seen at 50 weeks. Conclusions: The results of this retrospective hypothesis-generating analysis indicate that CCM significantly improves objective parameters of exercise tolerance in a subgroup of patients characterized by normal QRS duration, NYHA functional class III symptoms, and EF >25%.
Abraham (2018)	Objectives: This study 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%. Background: CCM therapy for New York Heart Association (NYHA) functional class III and IV heart failure (HF) patients consists of nonexcitatory electrical signals delivered to the heart during the absolute refractory period. Methods: A total of 160 patients with NYHA functional class III or IV symptoms, QRS duration <130 ms, and ejection fraction ≥25% and ≤45% were randomized to continued medical therapy (control, n = 86) or CCM (treatment, n = 74, unblinded) for 24 weeks. Peak Vo_2 (primary endpoint), Minnesota Living With Heart Failure questionnaire, NYHA functional class, and 6-min hall walk were measured at baseline and at 12 and 24 weeks. Bayesian repeated measures linear modeling was used for the primary endpoint analysis with 30% borrowing from the FIX-HF-5 subgroup. Safety was assessed by the percentage of patients free of device-related adverse events with a pre-specified lower bound of 70%.

	Results: The difference in peak Vo_2 between groups was 0.84 (95% Bayesian credible interval: 0.123 to 1.552) ml O_2/kg/min, satisfying the primary endpoint. Minnesota Living With Heart Failure questionnaire ($p < 0.001$), NYHA functional class ($p < 0.001$), and 6-min hall walk ($p = 0.02$) were all better in the treatment versus control group. There were 7 device-related events, yielding a lower bound of 80% of patients free of events, satisfying the primary safety endpoint. The composite of cardiovascular death and HF hospitalizations was reduced from 10.8% to 2.9% ($p = 0.048$). Conclusions: CCM is safe, improves exercise tolerance and quality of life in the specified group of HF patients, and leads to fewer HF hospitalizations. (Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects With Moderate-to-Severe Heart Failure; NCT01381172).
Anker (2015)	Aims: Cardiac contractility modulation (CCM) improves symptoms and exercise tolerance and reduces heart failure (HF) hospitalizations over 6-month follow-up in patients with New York Heart Association (NYHA) class III or IV symptoms, QRS < 130 ms and 25% ≤ left ventricular ejection fraction (LVEF) ≤ 45% (FIX-HF-5C study). The current prospective registry study (CCM-REG) aimed to assess the longer-term impact of CCM on hospitalizations and mortality in real-world experience in this same population. Methods and results: A total of 140 patients with 25% ≤ LVEF ≤ 45% receiving CCM therapy ($CCM\text{-}REG_{25\text{-}45}$) for clinical indications were included. Cardiovascular and HF hospitalizations, Minnesota Living with Heart Failure Questionnaire (MLHFQ) and NYHA class were assessed over 2 years. Mortality was tracked through 3 years and compared with predictions by the Seattle Heart Failure Model (SHFM). A separate analysis was performed on patients with 35% ≤ LVEF ≤ 45% ($CCM\text{-}REG_{35\text{-}45}$) and 25% ≤ LVEF < 35% ($CCM\text{-}REG_{25\text{-}34}$). Hospitalizations decreased by 75% (from 1.2/patient-year the year before, to 0.35/patient-year during the 2 years following CCM, $P < 0.0001$) in $CCM\text{-}REG_{25\text{-}45}$ and by a similar amount in $CCM\text{-}REG_{35\text{-}45}$ ($P < 0.0001$) and $CCM\text{-}REG_{25\text{-}34}$. MLHFQ and NYHA class improved in all three cohorts, with progressive improvements over time ($P < 0.002$). Three-year survival in $CCM\text{-}REG_{25\text{-}45}$ (82.8%) and $CCM\text{-}REG_{24\text{-}34}$ (79.4%) were similar to those predicted by SHFM (76.7%, $P = 0.16$; 78.0%, $P = 0.81$, respectively) and was better than predicted in $CCM\text{-}REG_{35\text{-}45}$ (88.0% vs. 74.7%, $P = 0.046$). Conclusion: In real-world experience, CCM produces results similar to those of previous studies in subjects with 25% ≤ LVEF ≤ 45% and QRS < 130 ms; cardiovascular and HF hospitalizations are reduced and MLHFQ and NYHA class are improved. Overall mortality was comparable to that predicted by the SHFM but was lower than predicted in patients with 35% ≤ LVEF ≤ 45%.
Borggrefe (2008)	Aims: We performed a randomized, double blind, crossover study of cardiac contractility modulation (CCM) signals in heart failure patients. Methods and results: One hundred and sixty-four subjects with ejection fraction (EF) < 35% and NYHA Class II (24%) or III (76%) symptoms received a CCM pulse generator. Patients were randomly assigned to Group 1 (n = 80, CCM treatment 3 months, sham treatment second 3 months) or Group 2 (n = 84, sham treatment 3 months, CCM treatment second 3 months). The co-primary endpoints were changes in peak oxygen consumption (VO2,peak) and Minnesota Living with Heart Failure Questionnaire (MLWHFQ). Baseline EF (29.3 +/- 6.7% vs. 29.8 +/- 7.8%), VO2,peak (14.1 +/- 3.0 vs. 13.6 +/- 2.7 mL/kg/min), and MLWHFQ (38.9 +/- 27.4 vs. 36.5 +/- 27.1) were similar between the groups. VO2,peak increased similarly in both groups during the first 3 months (0.40 +/- 3.0 vs. 0.37 +/- 3.3 mL/kg/min, placebo effect). During the next 3 months, VO2,peak decreased in the group switched to sham (-0.86 +/- 3.06 mL/kg/min) and increased in patients switched to active treatment (0.16 +/- 2.50 mL/kg/min). MLWHFQ trended better with treatment (-12.06 +/- 15.33 vs. -9.70 +/- 16.71) during the first 3 months, increased during the second 3 months in the group switched to sham (+4.70 +/- 16.57), and decreased further in patients switched to active treatment (-0.70 +/- 15.13). A comparison of values at the end of active treatment periods vs. end of sham treatment periods indicates statistically significantly improved VO2,peak and MLWHFQ ($P = 0.03$ for each parameter).

	Conclusion: In patients with heart failure and left ventricular dysfunction, CCM signals appear safe; exercise tolerance and quality of life (MLWHFQ) were significantly better while patients were receiving active treatment with CCM for a 3-month period.
Cappannoli (2021)	Heart failure is the cardiovascular epidemic of the twenty-first century, with poor prognosis and quality of life despite optimized medical treatment. Despite over the last decade significant improvements, with a major impact on morbidity and mortality, have been made in therapy for heart failure with reduced ejection fraction, little progress was made in the development of devices, with the implantable defibrillator indicated for patients with left ventricle ejection fraction ≤ 35% and cardiac resynchronization therapy for those with QRS ≥ 130 ms and evidence of left bundle branch block. Nevertheless, only a third of patients meet these criteria and a high percentage of patients are non-responders in terms of improving symptoms. Nowadays, in patients with symptomatic heart failure with ejection fraction between 25% and 45% and QRS < 130 ms, not eligible for cardiac resynchronization, the cardiac contractility modulation (CCM) represents a concrete therapeutic option, having proved to be safe and effective in reducing hospitalizations for heart failure and improving symptoms, functional capacity, and quality of life. The aim of this review is therefore to summarize the pathophysiological mechanisms, the current indications, and the recent developments regarding the new applications of the CCM for patients with chronic heart failure.
Fastner (2021)	Background: Cardiac contractility modulation (CCM) is an FDA-approved device-based therapy for patients with systolic heart failure and normal QRS complex who are symptomatic despite optimal drug therapy. The purpose of this study was to compare the long-term therapeutic effects of CCM in patients with ischemic (ICM) compared to non-ischemic cardiomyopathy (NICM Changes in NYHA class, left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), NT-proBNP and KDIGO CKD stage, were compared as functional parameters. Moreover, observed mortality rates at one and three years were compared to those predicted by the MAGGIC heart failure risk score and compared between groups. Results: One hundred and seventy-four consecutive patients with chronic heart failure were included in this retrospective analysis of patients implanted with a CCM device between 2002 and 2019. LVEF improved after three years of CCM treatment (35 ± 9 vs. 30 ± 9%; p = 0.0211) and after five years, TAPSE of NICM patients was significantly higher than that of ICM patients (21 ± 5 vs. 18 ± 5%; p = 0.0437). There were no differences in other effectiveness parameters. Over the entire follow-up period, 35% of all patients died (p = 0.81); only in ICM patients, mortality was lower than predicted at 3 years (35 vs. 43%, p = 0.0395). Conclusions: Regarding improvement of biventricular systolic function, patients with NICM appear to benefit particularly from CCM.
Giallauria (2014)	Background: Although cardiac contractility modulation (CCM) has emerged as a promising device treatment for heart failure (HF), the effect of CCM on functional capacity and quality of life has not been the subject of an individual patient data meta-analysis to determine its effect on measures of functional capacity and life quality. This meta-analysis is aimed at systematically reviewing the latest available randomized evidence on the effectiveness of CCM on functional capacity and quality of life indexes in patients with HF. Methods: The Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE were searched in May 2013 to identify eligible randomized controlled trials comparing CCM with sham treatment or usual care. Primary outcomes of interest were peak oxygen consumption, 6-minute walk test distance and quality of life measured by Minnesota Living With Heart Failure Questionnaire. There was no sufficient information to address safety. Mean difference and 95% confidence intervals (C.I.s) were calculated for continuous data using a fixed-effects model.

	Results: Three studies enrolling 641 participants were identified and included. Pooled analysis showed that, compared to control, CCM significantly improved peak oxygen consumption (mean difference +0.71, 95% C.I. 0.20 to 1.21 mL/kg/min, p=0.006), 6-minute walk test distance (mean difference +13.92, 95% C.I. -0.08 to 27.91 m, p=0.05) and quality of life measured by Minnesota Living With Heart Failure Questionnaire (mean difference -7.17, 95% C.I. -10.38 to -3.96, p<0.0001). Conclusions: Meta-analysis of individual patient data from randomized trials suggests that CCM has significant if somewhat modest benefits in improving measures of functional capacity and quality of life.
Giallauria (2020)	Aims: Cardiac contractility modulation, also referred to as CCM™, has emerged as a promising device treatment for heart failure (HF) in patients not indicated for cardiac resynchronization therapy. We performed a comprehensive individual patient data meta-analysis of all non-confounded prospective randomized controlled trials of CCM vs. control that have measured functional capacity and/or quality of life questionnaires in patients with HF. Methods and results: The Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE were searched in January 2020 to identify eligible randomized controlled trials. We also asked the sole manufacturer of the device for their list of known trials. Primary outcomes of interest were peak oxygen consumption (peak VO2), 6 min walk test distance, and quality of life measured by Minnesota Living with Heart Failure Questionnaire (MLWHFQ), and all data were received as individual patient and individual time point data-points. Mean differences and 95% confidence intervals (CIs) were calculated for continuous data using a fixed-effects model. Five trials were identified, four randomized studies enrolling 801 participants for all endpoints of interest, and for peak VO2 alone (n = 60), there was an additional single arm non-randomized trial (FIX-HF-5C2) with a prospective comparison of its 24 week peak VO2 data compared with the control group of the FIX-HF-5C control patients. Pooled analysis showed that, compared with control, CCM significantly improved peak VO2 (mean difference +0.93, 95% CI 0.56 to 1.30 mL/kg/min, P < 0.00001), 6 min walk test distance (mean difference +17.97, 95% CI 5.48 to 30.46 m, P = 0.005), and quality of life measured by MLWHFQ (mean difference -7.85, 95% CI -10.76 to -4.94, P < 0.00001). As a sensitivity analysis, we excluded the FIX-HF-5C2 trial (only relevant for peak VO2), and the result was similar, mean difference +0.65, 95% CI 0.21 to 1.08 mL/kg/min, P = 0.004. Conclusions: This comprehensive meta-analysis of individual patient data from all known randomized trials has shown that CCM provides statistically significant and clinically meaningful benefits in measures of functional capacity and HF-related quality of life.
Kadish (2011)	Background: Cardiac contractility modulation (CCM) delivers nonexcitatory electrical signals to the heart during the absolute refractory period intended to improve contraction. Methods: We tested CCM in 428 New York Heart Association class III or IV, narrow QRS heart failure patients with ejection fraction (EF) ≤ 35% randomized to optimal medical therapy (OMT) plus CCM (n = 215) versus OMT alone (n = 213). Efficacy was assessed by ventilatory anaerobic threshold (VAT), primary end point, peak Vo_2 (pVo_2), and Minnesota Living with Heart Failure Questionnaire (MLWFQ) at 6 months. The primary safety end point was a test of noninferiority between groups at 12 months for the composite of all-cause mortality and hospitalizations (12.5% allowable delta). Results: The groups were comparable for age (58 ± 13 vs 59 ± 12 years), EF (26% ± 7% vs 26% ± 7%), pVo_2 (14.7 ± 2.9 vs 14.8 ± 3.2 mL kg^{-1} min^{-1}), and other characteristics. While VAT did not improve at 6 months, CCM significantly improved pVo_2 and MLWHFQ (by 0.65 mL kg^{-1} min^{-1} [P = .024] and -9.7 points [P < .0001], respectively) over OMT. Forty-eight percent of OMT and 52% of CCM patients experienced a safety end point, which

	satisfied the noniferiority criterion (P = .03). Post hoc, hypothesis-generating analysis identified a subgroup (characterized by baseline EF ≥ 25% and New York Heart Association class III symptoms) in which all parameters were improved by CCM. Conclusions: In the overall target population, CCM did not improve VAT (the primary end point) but did improve pVo_2 and MLWHFQ. Cardiac contractility modulation did not have an adverse affect on hospitalizations or mortality within the prespecified boundaries. Further study is required to clarify the role of CCM as a treatment for medically refractory heart failure.
Kloppe (2016a)	Background: Cardiac contractility modulation (CCM) signals are non-excitatory electrical signals delivered during the absolute refractory period intended to improve contraction and cardiac function. Clinical trials have shown that CCM treatment significantly improves exercise tolerance and quality of life in symptomatic heart failure patients. Studies with CCM therapy typically include CCM delivery for 3, 5 or 7 h per day, although other configurations are also commonly used. Each has been associated with improved outcomes in heart failure, but it is not clear whether different application durations are associated with the various degrees of benefit. The purpose of the current pilot evaluation study was to evaluate the quality of life, exercise tolerance, and cardiac function, over a 6-month period when CCM was delivered for 5 h/day vs. 12 h/day. Increasing the daily CCM therapy duration is safe and as good as the standard CCM periods of application per day. Methods: This single center pilot evaluation study involved 19 medically refractory symptomatic patients with heart failure and reduced left ventricular function who underwent implantation of an Optimizer™ system (Impulse Dynamics, Orangeburg, NY, USA). Patients were randomized into one of two treatment groups; 5 h/day CCM treatment or 12 h/day CCM treatment. Subjects and evaluating physicians were blinded to the study group. Subjects returned to the hospital after 12 and 24 weeks. Efficacy evaluations included changes from baseline to 24 weeks in Minnesota Living With Heart Failure Questionnaire score (MLWHFQ), maximal oxygen consumption in the cardio-pulmonary stress test (peak VO2), New York Heart Association classification (NYHA), 6-min walk distance (6MWD), and ejection fraction (EF). Results: At the end of 24 weeks, clinical improvement was observed in the entire cohort in all efficacy measures (mean change from baseline of -17.1 in MLWHFQ, -0.86 in NYHA, and improvement trend of 1.48 mL O2/kg/min in peak VO2, 31.3 m in 6MWD, and 2.25% in EF). There were no significant differences, either clinically or statistically, between the groups receiving CCM for 5 h/day vs. 12 h/day. Three subjects were voluntarily withdrawn before completing the study. One subject died from pneumonia after 125 days, and 6 serious adverse events were reported, none of which was classified as related to either the device or the procedure. Conclusions: Together with previously reported experience with CCM, delivery of CCM therapy is equally safe and appears similarly effective over the range of shorter (5 h) to longer (12 h) daily periods of application. Given the small sample size, further studies are warranted.
Kloppe (2016b)	Aims: Cardiac Contractility Modulation (CCM) is a treatment for heart failure based on electrical signals applied during the absolute refractory period. CCM improves myocardial molecular and biochemical characteristics of heart failure and improves exercise tolerance and quality of life. However, the long term impact on survival has not been described. Methods and results: Survival was determined retrospectively from a cohort of 68 consecutive heart failure cases with NYHA II or III symptoms and QRS duration ≤130ms, implanted with a CCM device between May 2002 and July 2013 in either Bochum or Ludenscheid, Germany. Results were compared with predicted survival (Seattle Heart Failure Model; SHFM) pre-implant for each patient. Mean follow-up was 4.5years (range 0.25-10.3years). Baseline characteristics were as follows: mean age 61years, 88% male, 68% with ischemic heart disease, 78% with an ICD, mean NYHA class 2.9±0.3, LVEF 26%±6% (range 15-40%) and mean QRS duration 106±11ms. Mortality rates (Kaplan-Meier analysis) at 1-, 2- and 5-years were

	lower with CCM than predicted by SHFM for the cohort (0% with CCM vs. 6.1% per SHFM, 3.5% vs. 11.8%, and 14.2% vs. 27.7%, respectively, p=0.007). Conclusions: Long-term mortality rates in heart failure patients with NYHA (II-III) and QRS≤130ms are lower when treated by CCM than predicted for the cohort. These findings warrant substantiation in a prospective study.
Kuschyk (2015)	Aims: To analyze long-term efficacy and survival in patients with chronic heart failure treated with cardiac contractility modulation. Methods: 81 patients implanted with a CCM device between 2004 and 2012 were included in this retrospective analysis. Changes in NYHA class, ejection fraction (EF), Minnesota Living with Heart Failure Questionnaire, NT-proBNP and peak VO_2 were analyzed during a mean follow up of 34.2 ± 28 months (6-123 months). Observed mortality rate was compared with that predicted by the MAGGIC Score. Results: Patients were 61 ± 12 years old with EF 23 ± 7%. Heart failure was due to ischemic (n=48, 59.3%) or idiopathic dilated (n=33, 40.7%) cardiomyopathy. EF increased from 23.1 ± 7.9 to 29.4 ± 8.6% (p<0.05), mean NT-proBNP decreased from 4395 ± 3818 to 2762 ± 3490 ng/l (p<0.05) and mean peak VO2 increased from 13.9 ± 3.3 to 14.6 ± 3.5 ml/kg/min (p=0.1). The overall clinical responder rate (at least 1 class improvement of NYHA within 6 months or last follow-up) was 74.1%. 21 (25.9%) patients died during follow up, 11 (52.4%) due to cardiac conditions and 10 (47.6%) due to non-cardiac conditions. Mortality rates at 1 and 3 years were 5.2% and 29.5% compared to mortality rates estimated from the MAGGIC risk score of 18.4% (p<0.001) and 40% (p=ns), respectively. Log-Rank analysis of all events through 3 years of follow-up, however, was significantly less than predicted (p=0.022). Conclusions: CCM therapy improved quality of life, exercise capacity, NYHA class, EF and NT-proBNP levels during long-term follow up. Mortality rates appeared to be lower than estimated from the MAGGIC score.
Kuschyk (2021)	Aims: We assessed long-term effects of cardiac contractility modulation delivered by the Optimizer Smart system on quality of life, left ventricular ejection fraction (LVEF), mortality and heart failure and cardiovascular hospitalizations. Methods and results: CCM-REG is a prospective registry study including 503 patients from 51 European centres. Effects were evaluated in three terciles of LVEF (≤25%, 26-34% and ≥35%) and in patients with atrial fibrillation (AF) and normal sinus rhythm (NSR). Hospitalization rates were compared using a chi-square test. Changes in functional parameters of New York Heart Association (NYHA) class, Minnesota Living with Heart Failure Questionnaire (MLWHFQ) and LVEF were assessed with Wilcoxon signed-rank test, and event-free survival by Kaplan-Meier analysis. For the entire cohort and each subgroup, NYHA class and MLWHFQ improved at 6, 12, 18 and 24 months (P < 0.0001). At 24 months, NYHA class, MLWHFQ and LVEF showed an average improvement of 0.6 ± 0.7, 10 ± 21 and 5.6 ± 8.4%, respectively (all P < 0.001). LVEF improved in the entire cohort and in the LVEF ≤25% subgroup with AF and NSR. In the overall cohort, heart failure hospitalizations decreased from 0.74 [95% confidence interval (CI) 0.66-0.82] prior to enrolment to 0.25 (95% CI 0.21-0.28) events per patient-year during 2-year follow-up (P < 0.0001). Cardiovascular hospitalizations decreased from 1.04 (95% CI 0.95-1.13) events per patient-year prior to enrolment to 0.39 (95% CI 0.35-0.44) events per patient-year during 2-year follow-up (P < 0.0001). Similar reductions of hospitalization rates were observed in the LVEF, AF and NSR subgroups. Estimated survival was significantly better than predicted by MAGGIC at 1 and 3 years in the entire cohort and in the LVEF 26-34% and ≥35% subgroups. Conclusions: Cardiac contractility modulation therapy improved functional status, quality of life, LVEF and, compared to patients' prior history, reduced heart failure hospitalization rates. Survival at 1 and 3 years was significantly better than predicted by the MAGGIC risk score.

Kwong (2012)	Background: Cardiac contractility modulation (CCM) emerges as a promising device treatment for heart failure (HF). This meta-analysis aimed to systematically review the latest available randomized evidence on the effectiveness and safety of CCM in HF. Methods: The Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE were searched in November 2011 to identify eligible randomized controlled trials comparing CCM with sham treatment or usual care. Primary outcomes of interest were all-cause mortality, all-cause hospitalizations, and adverse effects. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous data using a random-effects model. Results: Three studies enrolling 641 participants were included. Pooled analysis showed that, compared to control, CCM did not significantly improve all-cause mortality (n = 629, RR 1.19, 95% CI 0.50-2.86, P = 0.69), nor was there a favorable effect in all-cause hospitalizations. No increase in adverse effects with CCM was observed. Conclusions: Meta-analysis of data from small randomized trials suggests that CCM, although with no clear benefits in improving clinical outcomes, is not associated with worsening prognosis. Large, well-designed trials are needed to confirm its role in HF patients for whom cardiac resynchronization therapy is contraindicated or unsuccessful.
Liu (2016)	Introduction: Cardiac contractility modulation (CCM) has been shown to be effective in improving symptoms and cardiac function in heart failure (HF). However, there is limited data on the role of CCM on long-term survival, which was explored in the present study. Methodology: Forty-one consecutive HF patients with left ventricular ejection fraction (EF) <40% received CCM and were followed for approximately 6 years. They were compared with another 41 HF patients who were enrolled into the HF registry in the same period, and had similar age, gender, EF and etiology of HF. The primary end-point was all cause-mortality. This was stratified by EF. Secondary end-points included HF hospitalization, cardiovascular death, and the composite outcome of death or heart failure hospitalization. Results: The CCM and control groups were well balanced for demographic data, medications and baseline left ventricular EF (27 ± 6 vs 27 ± 7%, p=NS). The mean follow-up duration was 75 ± 19 months in the CCM group and 69 ± 17 months in the control group. All-cause mortality was lower in the CCM group than the control group (39% vs. 71%, respectively; Log-rank $\chi(2)=11.23$, p=0.001). Of note, the improvement of all-cause mortality is more dramatic in patients with EF ≥ 25-40% (36% vs. 80%, Log-rank $\chi(2)=15.8$, p<0.001) than those with EF<25% (50% vs. 56%, p=NS), CCM vs. control respectively. Similar results were shown for the benefit of CCM in the secondary endpoints of cardiovascular death, and the composite outcome of death or heart failure hospitalization. The occurrence of HF hospitalization showed no significant difference between CCM and control groups in the whole cohort (41% vs. 49%, p=NS), but was significantly lower with CCM in subjects with EF ≥ 25-40% at baseline (36% vs. 64%, Log-rank $\chi(2)=7.79$, p=0.005). Conclusion: CCM resulted in significant improvement of long-term survival, in particular in those with EF ≥ 25-40%. A reduction in heart failure hospitalizations was also seen in this group of patients with less severely reduced EF.
Liu (2017)	Background: Cardiac contractility modulation (CCM) has developed as a promising treatment device for heart failure (HF). This meta-analysis aimed at systematically reviewing the latest available published trials to provide evidence on the safety and efficacy of CCM in patients with HF. Methods: We searched the Cochrane Central Resister of Controlled Trials, PubMed, and EMBASE in May 2016 to identify eligible clinical trials comparing CCM with sham treatment or with usual care. All-cause mortality, all-cause hospitalization, and serious cardiopulmonary adverse effects were considered to be the primary outcomes of interest in evaluating the safety of CCM for patients with HF. Peak oxygen consumption and 6-min

	walk tests were performed as the second outcomes of interest to assess efficacy. Risk ratio (RR), standard mean difference (SMD), and 95% confidence intervals (CIs) were calculated. Results: Four studies enrolling 723 participants were included. Compared with the control arm, CCM did not significantly improve all-cause mortality or all-cause hospitalizations. No differences were observed for adverse effects of CCM, possibly due to the low number of studies. By contrast, CCM significantly improved peak oxygen consumption (standard mean difference 0.233, 95% CI, 0.065-0.401 ml/kg/min, p = 0.006) and the 6-min walk test distance (standard mean difference 0.924, 95% CI, 0.001-0.334 m, p = 0.049). Conclusion: In our meta-analysis of published clinic trials we found that CCM did not lower the risk of severe cardiovascular adverse events; however, it was associated with remarkable improvements in functional cardiopulmonary capacity. Therefore, CCM may serve as an alternative option for patients with advanced HF.
Mando (2019)	Background: Cardiac contractility modulation (CCM) is a device therapy for systolic heart failure (HF) in patients with narrow QRS. We aimed to perform an updated meta-analysis of the randomized clinical trials (RCTs) to assess the efficacy and safety of CCM therapy. Methods: We conducted a systematic review and meta-analysis of randomized clinical trials (RCTs) between January 2001 and June 2018. Outcomes of interest were peak oxygen consumption (peak VO2), 6-Minute Walk Distance (6MWD), Minnesota Living with Heart Failure Questionnaire (MLHFQ), HF hospitalizations, cardiac arrhythmias, pacemaker/ICD malfunctioning, all-cause hospitalizations, and mortality. Data were expressed as standardized mean difference (SMD) or odds ratio (OR). Results: Four RCTs including 801 patients (CCM n = 394) were available for analysis. The mean age was 59.63 ± 0.84 years, mean ejection fraction was 29.14 ± 1.22%, and mean QRS duration was 106.23 ± 1.65 msec. Mean follow-up duration was six months. CCM was associated with improved MLWHFQ (SMD -0.69, p = 0.0008). There were no differences in HF hospitalizations (OR 0.76, p = 0.12), 6MWD (SMD 0.67, p = 0.10), arrhythmias (OR 1.40, p = 0.14), pacemaker/ICD malfunction/sensing defect (OR 2.23, p = 0.06), all-cause hospitalizations (OR 0.73, p = 0.33), or all-cause mortality (OR 1.04, p = 0.92) between the CCM and non-CCM groups. Conclusions: Short-term treatment with CCM may improve MLFHQ without significant difference in 6MWD, arrhythmic events, HF hospitalizations, all-cause hospitalizations, and all-cause mortality. There is a trend towards increased pacemaker/ICD device malfunction. Larger RCTs might be needed to determine if the CCM therapy will be beneficial with longer follow-up.
Müller (2017)	Introduction: Heart failure is a major cause of morbidity and mortality throughout the world. Despite advances in therapy, nearly half of patients receiving guideline-directed medical therapy remain limited by symptoms. Cardiac contractility modulation (CCM) can improve symptoms in this population, but efficacy and safety in prospective studies has been limited to 12 months of follow-up. We report on the first 2 year multi-site evaluation of CCM in patients with heart failure. Methods: One hundred and forty-three subjects with heart failure and reduced ejection fraction were followed via clinical registry for 24 months recording NYHA class, MLWHFQ score, 6 min walk distance, LVEF, and peak VO_2 at baseline and 6 month intervals as clinically indicated. Serious adverse events, and all cause as well as cardiovascular mortality were recorded. Data are presented stratified by LVEF (all subjects, LVEF <35%, LVEF ≥35%). Results: One hundred and six subjects from 24 sites completed the 24 month follow-up. Baseline parameters were similar among LVEF groups. NYHA and MLWHFQ improved in all 3 groups at each time point. LVEF in the entire cohort improved 2.5, 2.9, 5.0, and 4.9% at 6, 12, 18, and 24

	months, respectively. Insufficient numbers of subjects had follow-up data for 6 min walk or peak VO_2 assessment, precluding comparative analysis. Serious adverse events (n = 193) were observed in 91 subjects and similarly distributed between groups with LVEF <35% and LVEF ≥35%, and similar to other device trials for heart failure. Eighteen deaths (7 cardiovascularly related) over 2 years. Overall survival at 2 years was 86.4% (95% confidence intervals: 79.3, 91.2%). Conclusion: Cardiac contractility modulation provides safe and effective long-term symptomatic and functional improvement in heart failure. These benefits were independent of baseline LVEF and were associated with a safety profile similar to published device trials.
Nadeem (2020)	Introduction: Dilated cardiomyopathy has been associated with remarkably high mortality despite guideline-directed therapy. This study compares the all-cause mortality rate between a cardiac contractility modulation group and a standard therapy group in patients with dilated cardiomyopathy who were monitored via follow-up for 12 weeks or more. Materials and methods: We conducted a systematic search of Medline (PubMed) and Cochrane Central Register of Controlled Trials for abstracts and fully published studies (from inception to October 2018). We searched for articles comparing cardiac contractility modulation device therapy with standard therapy for patients with dilated cardiomyopathy between September 1, 2018, and October 30, 2018. Only fully published randomized clinical trials comparing all-cause mortality outcomes of device therapy and standard therapy for patients with dilated cardiomyopathy were included in our meta-analysis. A total of 673 studies were identified. Studies that were systematic reviews or meta-analyses, study designs or protocols, trials on other regimens, wherein medical therapy was not compared, or wherein the primary outcome of mortality was not assessed, were excluded. Data were abstracted by two independent reviewers. A random-effect model using the Mantel-Haenszel method calculated the weighted risk ratio (RR). Statistical analyses were performed using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration; Copenhagen). The primary outcome of interest was a comparison of all-cause mortality between the two groups when patients were monitored via follow-up for 12 weeks or more. Results: Four fully published randomized clinical trials met the inclusion criteria of our analysis. A random-effect model using the Mantel-Haenszel method calculated the weighted RR. Our analysis included a total of 930 patients. The cardiac contractility modulation therapy group showed no significant reduction in all-cause mortality compared to the standard therapy group (RR, 0.63; 95% CI, 0.29-1.35; P = .23). However, the trend was toward device therapy. Tests for statistical heterogeneity did not show any significant heterogeneity (P = .82, I^2 = 0%). Conclusions: Cardiac contractility modulation device therapy is not associated with significant all-cause mortality reduction in patients with dilated cardiomyopathy. Our meta-analysis underscores the need for a large randomized controlled trial on the efficacy of cardiac contractility modulation in a population with dilated cardiomyopathy who are ineligible for cardiac resynchronization therapy.
Neelagaru (2006)	Background: Cardiac contractility modulation signals are associated with acutely improved hemodynamics, but chronic clinical impact is not defined. Objectives: The purpose of this randomized, double-blind, pilot study was to determine the feasibility of safely and effectively delivering cardiac contractility modulation signals in patients with heart failure. Methods: Forty-nine subjects with ejection fraction <35%, normal QRS duration (105 +/- 15 ms), and New York Heart Association (NYHA) class III or IV heart failure despite medical therapy received a cardiac contractility modulation pulse generator. Patients were randomized to have their devices programmed to deliver cardiac contractility modulation signals (n = 25, treatment group) or to remain off (n = 24, control group) for 6

	months. Evaluations included NYHA class, 6-minute walk, cardiopulmonary stress test, Minnesota Living with Heart Failure Questionnaire, and Holter monitoring. Results: Although most baseline features were balanced between groups, ejection fraction (31.4% +/- 7.4% vs 24.9% +/- 6.5%, P = .003), end-diastolic dimension (52.1 +/- 21.4 mm vs 62.5 +/- 6.2 mm, P = .01), peak VO(2) (16.0 +/- 2.9 mL O(2)/kg/min vs 14.3 +/- 2.8 mL O(2)/kg/min, P = .02), and anaerobic threshold (12.3 +/- 2.5 mL O(2)/kg/min vs 10.6 +/- 2.4 mL O(2)/kg/min, P = .01) were worse in the treatment group than in the control group. Nevertheless, one death occurred in the control group, and more patients in the treatment group were free of hospitalization for any cause at 6 months (84% vs 62%). No change in ectopy was observed. Compared with baseline, 6-minute walk (13.4 m), peak VO(2) (0.2 mL O(2)/kg/min), and anaerobic threshold (0.8 mL O(2)/kg/min) increased more in the treatment group than in control. None of these differences were statistically significant (small sample size). NYHA and Minnesota Living with Heart Failure Questionnaire changed similarly in the two groups. Conclusion: Despite a sicker population in the treatment group, no specific safety concerns emerged with chronic cardiac contractility modulation signal administration. Further study is required to definitively define the safety and efficacy of cardiac contractility modulation signals.
Pappone (2004)	Introduction: Conventional electrical therapies for heart failure (HF) encompass defibrillation and ventricular resynchronization for patients at high risk for lethal arrhythmias and/or with inhomogeneous ventricular contraction. Cardiac contractility modulation (CCM) by means of nonexcitatory electrical currents delivered during the action potential plateau has been shown to acutely enhance systolic function in humans with HF. The aim of this multicenter study was to assess the chronic safety and preliminary efficacy of an implantable device delivering this novel form of electrical therapy. Methods and results: Thirteen patients with drug-resistant HF (New York Heart Association [NYHA] class III) were consecutively implanted with a device (OPTIMIZER II) delivering CCM biphasic square-wave pulses (20 ms, 5.8-7.7 V, 30 ms after detection of local activation) through two right ventricular leads screwed into the right aspect of the interventricular septum. CCM signals were delivered 3 hours daily over 8 weeks (3-hour phase) and 7 hours daily over the next 24 weeks (7-hour phase). Safety and feasibility of this novel therapy were regarded as primary endpoints. Preliminary clinical efficacy, -as expressed by changes in ejection fraction (EF), NYHA class, 6-minute walking test (6-MWT), peak O(2) uptake (peak VO(2)), and Minnesota Living with HF Questionnaire (MLWHFQ), was assessed at baseline and at the end of each phase. At the end of follow-up (8.8 +/- 0.2 months), all patients were alive, without heart transplantation or need for left ventricular assist device. Serial 24-hour Holter analysis revealed no proarrhythmic effect. No devices malfunctioned or failed for any reason other than end-of-battery life. Throughout the two study phases, EF improved from 22.7 +/- 7% to 28.7 +/- 7% and 37 +/- 13% (P = 0.004), 6-MWT from 418 +/- 99 m to 477 +/- 96 m and 510 +/- 107 m (P = 0.002), MLWHFQ from 36 +/- 21 to 18 +/- 12 and 7 +/- 6 (P = 0.002), peak VO(2) from 13.7 +/- 1.1 to 14.9 +/- 1.9 to 16.2 +/- 2.4 (P = 0.037), and NYHA class from 3 to 1.8 +/- 0.4 to 1.5 +/- 0.7 (P < 0.001). Conclusion: CCM therapy appears to be safe and feasible. Proarrhythmic effects of this novel therapy seem unlikely. Preliminary data indicate that CCM gradually and significantly improves systolic performance, symptoms, and functional status. CCM therapy for 7 hours per day is associated with greater dispersion near the mean, emphasizing the need to individually tailor CCM delivery duration. The technique appears to be attractive as an additive treatment for severe HF. Controlled randomized studies are needed to validate this novel concept.
Pilecky (2021)	Introduction: Based on recently published randomized controlled trials, cardiac contractility modulation (CCM) seems to be an effective device-based therapeutic option in symptomatic chronic heart failure (HF) (CHF). The aim of the current study was to estimate what proportion of patients with CHF and left ventricular ejection fraction (LVEF) <50% could be eligible for CCM based on the inclusion criteria of the FIX-HF-5C trial.

	Methods: Consecutive patients referred and followed up at our HF clinic due to HF with reduced or mid-range LVEF were retrospectively assessed. After a treatment optimization period of 3-6 months, the inclusion criteria of the FIX-HF-5C trial (New York Heart Association (NYHA) class III/IV, 25% ≤ LVEF ≤45%, QRS <130 ms, and sinus rhythm) were applied to determine the number of patients eligible for CCM. Results: Of the 640 patients who were involved, the proportion of highly symptomatic patients in NYHA class III/IV decreased from 77.0% (n = 493) at baseline to 18.6% (n = 119) after the treatment optimization period (p < 0.001). Mean LVEF increased significantly from 29.0 ± 7.9% to 36.3 ± 9.9% (p < 0.001), while the proportion of patients with 25% ≤ LVEF ≤45% increased from 69.7% (n = 446) to 73.3% (n = 469) (p < 0.001). QRS duration was below 130 ms in 63.1% of patients, while 30.0% of patients had persistent or permanent atrial fibrillation. We found that the eligibility criteria for CCM therapy based on the FIX-HF-5C study were fulfilled for 23.0% (n = 147) of patients at baseline and 5.2% (n = 33) after treatment optimization. Conclusion: This single-center cohort study showed that 5% of patients with CHF and impaired LVEF immediately after treatment optimization fulfilled the inclusion criteria of the FIX-HF-5C study and would be candidates for CCM.
Röger (2014)	Background and purpose: Cardiac contractility modulation (CCM) is an implantable device treatment for heart failure with reduced ejection fraction. CCM therapy improves patient functional status but its effect on intra-ventricular conduction remains unknown. Methods: 70 patients treated with CCM between 12/2002 and 5/2013 had 12-vector-ECG recordings made at baseline and final follow-up visits. QRS complex duration was measured at each time point. Results: Mean follow-up was 2.8 years. Mean QRS duration was unchanged from baseline (112.0 ms) to last follow up (112.9 ms, p=n.s.). These results are strikingly different from comparative published data of several studies with heart failure patients without CCM, consistently indicating an increase in QRS duration (6.0-23.4 ms) over a similar time period. Conclusions: CCM prevents chronic ventricular depolarization delay that occurs in heart failure and that is associated with poorer outcomes. This supports the safety of long-term CCM therapy and suggests a possible long-term benefit in maintaining QRS duration.
Röger (2017)	Background: Cardiac contractility modulation (CCM) is an electrical stimulation treatment for symptomatic heart failure (HF) patients. The procedure involves implantation of two ventricular leads for delivery of CCM impulses. The purpose of this study is to compare the efficacy and safety of CCM when the signal is delivered through one vs. two ventricular leads. Methods: This prospective blinded randomized trial enrolled 48 patients. Eligible subjects had symptoms despite optimal HF medications, left ventricular ejection fraction <40% and peakVO_2≥9ml O_2/kg/min. All patients received a CCM system with two ventricular leads, and were randomized to CCM active through both or just one ventricular lead; 25 patients were randomized to receive signal delivery through two leads (Group A) and 23 patients to signal delivery through one lead (Group B). The study compared the mean changes from baseline to 6 months follow-up in peakVO_2, New York Heart Association (NYHA) classification, and quality of life (by MLWHFQ). Results: Following 6 months, similar and significant (p<0.05) improvements from baseline in NYHA (-0.7±0.5 vs. -0.9±0.7) and MLWHFQ (-14±20 vs. -16±22) were observed in Group A and in Group B. PeakVO_2 showed improvement trends in both groups (0.34±1.52 vs. 0.10±2.21ml/kg/min; p=ns). No patient died. Serious adverse event rates (20 events in 10 subjects) were not different between groups. No statistically significant difference was found in any of the study endpoints.

	Conclusions: The efficacy and safety of CCM in this study were similar when the signal was delivered through either one or two ventricular leads. These results support the potential use of a single ventricular lead for delivery of CCM.
Röger (2018)	Background: Cardiac contractility modulation (CCM) is an electrical-device therapy for patients with heart failure with reduced ejection fraction (HFrEF). Patients with left ventricular ejection fraction (LVEF) ≤35% also have indication for an implantable cardioverter-defibrillator (ICD), and in some cases subcutaneous ICD (S-ICD) is selected. Hypothesis: CCM and S-ICD can be combined to work efficaciously and safely. Methods: We report on 20 patients with HFrEF and LVEF ≤35% who received CCM and S-ICD. To exclude device interference, patients received intraoperative crosstalk testing, S-ICD testing, and bicycle exercise testing while CCM was activated. Clinical and QOL measures before CCM activation and at last follow-up were analyzed. S-ICD performance was evaluated while both CCM and S-ICD were active. Results: Mean follow-up was 34.3 months. NYHA class improved from 2.9 ± 0.4 to 2.1 ± 0.7 ($P < 0.0001$), Minnesota Living With Heart Failure Questionnaire score improved from 50.2 ± 23.7 to 29.6 ± 22.8 points ($P < 0.0001$), and LVEF improved from 24.4% ± 8.1% to 30.9% ± 9.6% ($P = 0.002$). Mean follow-up time with both devices active was 22 months. Three patients experienced a total of 6 episodes of sustained ventricular tachycardia, all successfully treated with first ICD shock. One case received an inappropriate shock unrelated to the concomitant CCM. One patient received an LVAD, so CCM and S-ICD were discontinued. Conclusions: CCM and S-ICD can be successfully combined in patients with HFrEF. S-ICD and CCM remain efficacious when used together, with no interference affecting their function.
Schau (2011)	Aims: Cardiac contractility modulation (CCM) is a new form of electrical therapy in patients with congestive heart failure. Recently published clinical studies provide evidence of safety and improvements of exercise tolerance and quality of life. In this study, we investigated the impact of CCM on cardiac and all-cause mortality. Methods and results: Fifty-four consecutive patients (age 63 ± 10 years, 91% male, left ventricular ejection fraction 23 ± 6%, baseline peak oxygen consumption 10.0 ± 4.8 mL/min/kg, N-terminal pro-B-type natriuretic peptide 5194 pg/mL, New York Heart Association III/IV) who underwent implantation of an Optimizer system (IMPULSE Dynamics, Orangeburg, NY, USA) at our centre between June 2003 and June 2010 were analysed retrospectively. Patients were followed every 3 months at our outpatient clinic. This study determined long-term outcomes of patients receiving CCM therapy. Twenty-four (44%) patients died during the follow-up period, which included 19 cardiac deaths (3 sudden cardiac deaths and 16 terminal cardiac pump failure deaths). The Kaplan-Meier analysis calculated a median survival time of 992 days (33.1 months) and a mean death rate of 18.4% per year. All-cause mortality for these patients was precisely predicted by the Seattle Heart Failure Model. Conclusion: Cardiac contractility modulation appears to be a safe therapeutic option for advanced heart failure patients who have no other therapeutic options. Symptomatic improvement by CCM has been shown in earlier studies but our observational study suggests, for the first time, that there is no adverse effect of CCM on long-term survival.
Stix(2004)	Aim: In experimental studies, nonexcitatory electrical stimulation delivered at the time of absolute myocardial refractoriness resulted in cardiac contractility modulation (CCM) with improved systolic function. This study reports the initial experience with CCM in patients with chronic heart failure.

	Methods and results: Twenty-five patients, 23 males, with a mean age of 62+/-9 years and drug-refractory NYHA class III heart failure were assigned to CCM-generator implantation. The underlying heart disease was idiopathic dilated cardiomyopathy in 12 patients and coronary heart disease in 13 patients. Acute efficacy of CCM with 7.73-V stimuli delivered via two right ventricular leads was evaluated by measuring the time derivative of left ventricular pressure (dP/dt). After implantation, the CCM generator was activated for 3 h daily over 8 weeks. In 23/25 patients the CCM system was implanted successfully. Heart failure significantly improved from NYHA class III to class II in 15 patients and to class I in 4 patients ($p < 0.000001$), left ventricular ejection fraction improved from 22+/-7% to 28+/-8% ($p = 0.0002$), and the Minnesota Living with Heart Failure Score improved from 43+/-22 to 25+/-18 ($p = 0.001$). The 6-min walk test increased from 411+/-86 to 465+/-81 m ($p= 0.02$). Nine patients (39%) had intermittent sensations associated with CCM delivery. There were two (8%) non-device-related deaths during follow-up. Conclusions: These preliminary data indicate that CCM by delivery of intermittent nonexcitatory electrical stimuli is a promising technique for improving ventricular systolic function and symptoms in patients with drug-refractory NYHA class III heart failure.
Yu (2009)	Objectives: This study aimed to evaluate the impact of cardiac contractility modulation (CCM) on left ventricular (LV) size and myocardial function. Background: CCM is a device-based therapy for patients with advanced heart failure. Previous studies showed that CCM improved symptoms and exercise capacity; however, comprehensive assessment of LV structure, function, and reverse remodeling is not available. Methods: Thirty patients (60 + or - 11 years, 80% male) with New York Heart Association (NYHA) functional class III heart failure, ejection fraction <35%, and QRS <120 ms were assessed at baseline and 3 months. LV reverse remodeling was measured by real-time 3-dimensional echocardiography. Using tissue Doppler imaging, the peak systolic velocity (Sm) and peak early diastolic velocity (Em) were calculated for LV function, while the standard deviation of the time to peak systolic velocity (Ts-SD) and the time to peak early diastolic velocity (Te-SD) were calculated for mechanical dyssynchrony. Results: LV reverse remodeling was evident, with a reduction in LV end-systolic volume by -11.5 + or - 10.5% and a gain in ejection fraction by 4.8 + or - 3.6% (both $p < 0.001$). Myocardial contraction was improved in all LV walls, including sites remote from CCM delivery (all $p < 0.05$); hence, the mean Sm of 12 (2.2 + or - 0.6 cm/s vs. 2.5 + or - 0.7 cm/s) or 6 basal LV segments (2.5 + or - 0.6 cm/s vs. 3.0 + or - 0.7 cm/s) were increased significantly (both $p < 0.001$). In contrast, CCM had no impact on regional or global Em (2.9 + or - 1.3 cm/s vs. 2.9 + or - 1.1 cm/s), whereas Ts-SD (28.2 + or - 11.2 ms vs. 27.9 + or - 12.7 ms) and Te-SD (30.0 + or - 18.3 ms vs. 30.1 + or - 20.7 ms) remained unchanged (all p = NS). Mitral regurgitation was reduced (22 + or - 14% vs. 17 + or - 15%, $p = 0.02$). Clinically, there was improvement of NYHA functional class ($p < 0.001$) and 6-min hall walk distance ($p = 0.015$). A 24-h Holter monitor showed that premature ventricular contractions were not increased during CCM. Conclusions: CCM improves both global and regional LV contractility, including regions remote from the impulse delivery, and may contribute to LV reverse remodeling and gain in systolic function. Such improvement is unrelated to diastolic function or mechanical dyssynchrony.

Exkluderade studier

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Pågående studier

Titel	Studietyp	Status
Observational and Prospective Registry on Cardiac Contractility Modulation (CCM) Therapy https://clinicaltrials.gov/ct2/show/NCT04902079	Observation	Rekryterande
CCM in Heart Failure With Preserved Ejection Fraction (CCM-HFpEF) https://clinicaltrials.gov/show/NCT03240237	Intervention	Aktiv, icke-rekryterande
Italian Registry on Cardiac Contractility Modulation Therapy https://clinicaltrials.gov/show/NCT04327323	Observation (Registerstudie)	Rekryterande
Subanalysis in Patients With CARDIoLAMinopathy Enrolled to Retrospective and Observational Registry on Cardiac Contractility Modulation Therapy https://clinicaltrials.gov/show/NCT04904393	Observation	Rekryterande
A Prospective, Multi-center, Non-randomized, Single Arm Open Label Study of 620 Subjects Receiving the OPTIMIZER Smart With CCM Therapy as Standard of Care https://clinicaltrials.gov/show/NCT03970343	Observation (Registerstudie)	Rekryterande

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