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Gesundheitsökonomische und epidemiologische Analysen der kardialen Resynchronisationstherapie

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Abkürzungsverzeichnis

CRT	Kardialen Resynchronisationstherapie
CRT-D	Biventrikulärer Defibrillator
CRT-P	Biventrikulärer Schrittmacher
DRG	Diagnosis-Related-Group
HR	Hazard Ratio
ICD	Implantierbarer Kardioverter-Defibrillator
ICD-10-GM	Internationale statistische Klassifikation der Krankheiten und verwandter Gesundheitsprobleme, 10. Revision, German Modification
ICER	Kosten-Effektivitäts-Verhältnis
KI	Konfidenzintervall
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
OMT	Optimale medikamentöse Therapie
OPS	Operations- und Prozedurenschlüssel
QALYs	Qualitätsadjustierte Lebensjahre
RCT	Randomisierte kontrollierte Studie

1 Einleitung

Die vorliegende kumulative Dissertation untersucht gesundheitsökonomische und epidemiologische Aspekte der kardialen Resynchronisationstherapie (CRT) bei Herzinsuffizienz. Im Zentrum steht die Frage, wie sich CRT-Geräte ohne (CRT-P) und mit Defibrillatorfunktion (CRT-D) hinsichtlich Effektivität und Kosten unterscheiden. In der ersten Studie dieser Dissertation wurde ein literaturbasiertes gesundheitsökonomisches Modell erstellt, um eine Kosten-Nutzwert-Analyse aus der Kostenperspektive der gesetzlichen Krankenkassen in Deutschland durchzuführen. Die zweite Studie analysierte mithilfe von Routinedaten der gesetzlichen Krankenkasse BARMER aus den Jahren 2006 bis 2019 die Laufzeit und Kosten von CRT-Geräten. Die dritte Studie dieser Dissertation nutzte wieder Daten der BARMER, jedoch lediglich aus den Jahren 2014 bis 2019. In dieser Studie wurde untersucht, ob ein Unterschied im Überleben zwischen Patient:innen besteht, denen ein CRT-P- oder ein CRT-D-Gerät implantiert wurde.

1.1 *Epidemiologie der Herzinsuffizienz*

Eine der häufigsten Herz-Kreislauf-Erkrankungen ist die Herzinsuffizienz. Unter chronischer Herzinsuffizienz versteht man die mangelnde Fähigkeit des Herzens, den Körper mit ausreichend Blut und damit mit genügend Sauerstoff für den Stoffwechsel zu versorgen (1). Herzinsuffizienz ist verbunden mit einer hohen Morbidität, verringerten Lebensqualität, häufigen Krankenhauseinweisungen und einer hohen Mortalität (2,3). In Deutschland ist die Herzinsuffizienz die häufigste Einzeldiagnose für eine Hospitalisierung und die Zahl der Hospitalisierungen mit dieser Diagnose ist in den letzten Jahren stetig angestiegen (4). Die Herzinsuffizienz zählt hierzulande zu den häufigsten Todesursachen (5) und ist verbunden mit hohen Ressourcenverbräuchen und Kosten für das Gesundheitswesen (6). Im Jahr 2015 betrugen die Krankheitskosten aufgrund von Herzinsuffizienz 5.3 Milliarden € in Deutschland (7).

Die Prävalenz von Herzinsuffizienz beträgt in Deutschland zwischen 2 und bis zu 4 % (8,9). Mit dem Alter steigt die Prävalenz stark an, so beträgt die Prävalenz nach der Analyse von Routinedaten einer deutschen Krankenkasse bei den 65- bis

69-Jährigen 6,9 % und bei den 80- bis 84-Jährigen 24,3 % (10). Die Krankheits-schwere der Herzinsuffizienz wird auf der Skala der New York Heart Association (NYHA) mit den Klassen I bis IV beschrieben, wobei die NYHA Klasse I eine asymptomatische Herzinsuffizienz beschreibt und die NYHA Klasse IV die schwerste Form darstellt, die mit starken Lebensqualitätseinschränkungen durch Beschwerden bei jeglichen körperlichen Aktivitäten bzw. in Ruhe einhergeht (11).

1.2 Die kardiale Resynchronisationstherapie

Mit Beginn der 1990er Jahre hat sich die CRT zusätzlich zu den medikamentösen Therapien für Herzinsuffizienzpatient:innen mit reduzierter Ejektionsfraktion und ventrikulären Dyssynchronie zu einer der wichtigsten Behandlungssäulen entwickelt (3). Die CRT ist eine Gerätetherapie mit biventrikulären Schrittmachern, die durch gleichzeitige Stimulation eine Resynchronisation beider Herzkammern erreichen soll. CRT-Geräte verlängern das Überleben, verbessern die Lebensqualität und reduzieren die Krankheitsschwere im Vergleich zu einer reinen optimalen medikamentösen Therapie (OMT) oder implantierbaren Kardioverter-Defibrillatoren (ICD) (12,13). Gemäß aktuellen Leitlinien hat die Behandlung mit CRT-Geräten den höchsten Empfehlungsgrad A für Patient:innen mit reduzierter Ejektionsfraktion, Sinusrhythmus, breitem QRS-Komplex und Linksschenkelblock in den NYHA-Klasse II bis IV. Es wird geschätzt, dass nach Leitlinienkriterien 5 bis 10 % der Herzinsuffizienzpatient:innen eine Indikation für eine CRT haben (11).

Bei der kardialen Resynchronisationstherapie kann zwischen reinen biventrikulären Schrittmachern (CRT-P) und solchen mit zusätzlicher Defibrillatorfunktion (CRT-D) unterschieden werden. CRT-D-Geräte haben im Vergleich zu CRT-P-Geräten eine zusätzliche Defibrillatorfunktion, die dazu gedacht ist, Patient:innen vor einem plötzlichen Herztod durch bösartige Herzrhythmusstörungen zu schützen. In den Leitlinien der Europäischen Gesellschaft für Kardiologie (14,15) und in einer aktuellen Stellungnahme von kardiologischen Fachgesellschaften (16) wird eine individuelle Entscheidungsfindung für die Wahl des CRT-Gerätetyps auf Basis der Patientencharakteristika empfohlen. Die Entscheidung sollte auf Kriterien basieren, die sowohl das Risiko des plötzlichen Herztodes als auch das konkurrierende Risiko, an anderen Ursachen zu sterben, berücksichtigen. Im Jahr 2019 wurden in Deutschland 12.586 CRT-Operationen durchgeführt. In 7.708 (61 %) Fällen wurde

ein CRT-D-Gerät implantiert (17). Im europäischen Vergleich werden in Deutschland verhältnismäßig viele CRT-D-Geräte implantiert (18).

1.3 Der Nutzen des zusätzlichen Defibrillators ist umstritten

Ein Überlebensvorteil durch den Defibrillator in CRT-D-Geräten im Vergleich zu CRT-P-Geräten ist umstritten. CRT-Geräte reduzieren bereits per se das Risiko für den plötzlichen Herztod (19). Zusätzlich wird dieses Risiko durch moderne medikamentöse Therapien wie den breiteren Einsatz von Betablockern (20), ACE-Hemmern, Mineralokortikoid-Antagonisten (21) und Angiotensin-Rezeptor-Nep- rilylin-Hemmern (22) weiter gesenkt, was insgesamt zu einer deutlichen Reduktion des plötzlichen Herztodes führt. Der erwartbare Nutzen des Defibrillators hat sich insgesamt verringert (23). Bisher gibt es keine allgemeinaussagekräftige randomisierte kontrollierte Studie (RCT), die CRT-P- und CRT-D-Geräte direkt miteinander vergleicht. Die randomisierte und kontrollierte COMPANION-Studie untersuchte CRT-P- und CRT-D-Geräte jeweils mit einer optimalen medizinischen Therapie, aber die Studie verfügte jedoch nicht über ausreichend statistische Power, um die Geräte untereinander zu vergleichen (13). In der randomisierten und kontrollierten DANISH-Studie konnte kein Überlebensvorteil für CRT-D-Geräte im Vergleich zu CRT-P-Geräten bei Patient:innen mit nicht-ischämischer Kardiomyopathie nachgewiesen werden (24). Eine systematische Übersichtsarbeit zeigte, dass insgesamt die Raten des plötzlichen Herztodes in den randomisiert kontrollierten Studien über die Jahre gesunken sind (25).

Die Behandlung mit CRT-D-Geräten ist gegenüber CRT-P-Geräten mit Nachteilen assoziiert. Aufgrund des zusätzlichen Defibrillators ist das Design von CRT-D-Geräten komplexer und mit einer höheren Rate von Infektionen und Komplikationen assoziiert (26). Es wird angenommen, dass die Gerätelauzeit von CRT-D-Geräten kürzer ist, was auf die zusätzliche Defibrillator-Funktion zurückzuführen ist, wobei das Infektionsrisiko mit jedem Eingriff und zunehmenden Alter steigt (27). Durch den Defibrillator kann es auch zu unnötigen Schocks kommen, die von Einschränkungen der Lebensqualität bis zu depressiven Störungen oder Angststörungen führen können (28,29).

1.4 CRT-P-Geräte im Vergleich zu CRT-D-Geräten – die Perspektive der Evaluation

Aus der Perspektive des Gesundheitswesens stellt sich die Evaluation von CRT-P- und CRT-D-Geräten als ein komplexes Entscheidungsproblem dar. Es gibt noch keine aussagekräftige klinische randomisierte kontrollierte Studie, die die beiden Geräte hinsichtlich des Überlebens untersucht. Die verfügbaren Beobachtungsstudien liefern widersprüchliche Ergebnisse. Manche Studien finden einen Überlebensvorteil für CRT-D-Geräte (30,31) und andere Studien finden keinen Überlebensunterschied zwischen den beiden Gerätetypen (32–34).

Es gehört darüber hinaus zu einer umfassenden Betrachtung der Geräte, dass die Kosten für das Gesundheitssystem bei der Gerätewahl berücksichtigt werden. Die Kosten, die durch den Einbau eines CRT-Geräts für die gesetzliche Krankenkasse in Deutschland entstehen, sind bei CRT-D-Geräten höher. Im Jahr 2021 betrug die Fallpauschale für CRT-D-Geräte 13.339 € (Diagnosis-Related-Group (DRG): F01C) und 9.459 € (DRG: F12B) für CRT-P-Geräte, was einem Kostenunterschied von rund 3.880 € oder 41 % entspricht. Des Weiteren haben unerwünschte Ereignisse wie Infektionen oder Krankenhauseinweisungen aufgrund von Gerätefunktionsstörungen oder Batterieerschöpfung einen Einfluss auf die Lebensqualität von Patient:innen wie auch auf die Kosten für das Gesundheitssystem.

In diesem Zusammenhang sind gesundheitsökonomische Analysen eine wichtige Quelle für die Information von Entscheidungsträger:innen. Ziel ist es, Informationen zur Kosteneffektivität einer neuen Intervention bereitzustellen. Dabei werden die Differenzen der Kosten und Effekten von alternativen Interventionen zueinander ins Verhältnis gesetzt (35). In entscheidungsanalytischen Modellen können die Ergebnisse aus unterschiedlichen klinischen Studien miteinander verbunden und, wenn nötig, über den Beobachtungszeitraum extrapoliert werden. Zusätzlich können beim Einsatz von Modellen nicht nur die Kosten der Therapie berücksichtigt werden, sondern zum Beispiel auch unerwünschte Ereignisse.

Vor dem Hintergrund dieser allgemeinen Problemstellung ergaben sich folgende konkrete Forschungsfragen für die drei Einzelpublikationen dieser Dissertation:

1. Wie verhalten sich die langfristigen inkrementellen Kosten im Verhältnis zur inkrementellen Effektivität zwischen den Therapien mit CRT-D- oder CRT-P-Geräten?
2. Wie lang sind die durchschnittlichen Laufzeiten von CRT-P- und CRT-D-Geräten und wie hoch sind die Implantationskosten der Geräte?
3. Gibt es einen Überlebensunterschied zwischen Patient:innen nach einer CRT-P oder einer CRT-D *de novo* Implantation?

2 Kardiale Resynchronisationstherapie bei Patient:innen mit Herzinsuffizienz in Deutschland: Eine Kosten-Nutzwert-Analyse

2.1 *Hintergrund*

Modellierungen eignen sich dafür, medizinische Interventionen miteinander zu vergleichen, für die es noch keinen direkten Vergleich gibt. Dafür werden Ergebnisse aus mehreren Studien in einem literaturbasierten Modell zusammengeführt. Zudem können bei chronischen Erkrankungen die Effekte und die Kosten einer medizinischen Intervention über den Zeitraum einer klinischen Studie hinaus extrapoliert werden, um alle relevanten medizinischen und ökonomischen Ereignisse und Ergebnisse zu berücksichtigen.

International gibt es verschiedene gesundheitsökonomische Evaluationen der Therapie mit CRT-D-Geräten im Vergleich zu CRT-P-Geräten. Für den deutschen Versorgungskontext wurden jedoch bisher nur gesundheitsökonomische Evaluationen durchgeführt, die CRT-D-Geräte mit OMT vergleichen oder CRT-P-Geräte mit OMT. Zur Beantwortung der Fragestellung dieser Studie, wie sich die langfristigen inkrementellen Kosten im Verhältnis zu der entstehenden inkrementellen Effektivität zwischen einer Therapie mit CRT-D- oder CRT-P-Geräten unterscheiden, wurde eine Kosten-Nutzwert-Analyse von CRT-D-Geräten im Vergleich zu CRT-P-Geräten erstellt. Um alle potenziellen Behandlungsoptionen abzudecken, wurde auch die alleinige Therapie mit OMT berücksichtigt.

2.2 *Methode*

Für die Kosten-Nutzwert-Analyse wurde ein Kohorten-Markov-Modell erstellt. Bei einem Kohorten-Modell haben alle hypothetischen Patient:innen die gleichen Eigenschaften. Die Outcomes des Modells waren qualitätsadjustierte Lebensjahre (QALYs) und Kosten aus der Perspektive der deutschen gesetzlichen Krankenkassen. Aus diesen beiden Outcomes wurde das inkrementelle Kosten-Effektivitäts-Verhältnis (ICER) berechnet. Bei der Berechnung des ICER wird die Differenz aus den entstehenden Kosten (inkrementelle Kosten) von der Therapie mit CRT-D-Geräten im Vergleich zur Therapie mit CRT-P-Geräten durch die Differenz der entstehenden QALYs (inkrementeller Effekt) der beiden Therapien geteilt. Der ICER

gibt die durchschnittlichen inkrementellen Kosten an, die mit einem zusätzlichen QALY verbunden sind. Die simulierten Patient:innen waren 66 Jahre alt und die Modelllaufzeit betrug 20 Jahre. Die Outcomes wurden mit 3 % pro Jahr diskontiert.

Das Markov-Modell bestand aus sechs Markov-Zuständen (siehe Abbildung 1). Es wurden 1.000 Patient:innen simuliert. Alle Patient:innen betraten das Modell durch die initiale CRT-Implantation. Wenn die Implantation gelang, wurden die Patient:innen dem Markov-Zustand „Stable“ im CRT-Bereich zugewiesen. Falls die Implantation misslang, kamen die Patient:innen in den Zustand „Stable“ im OMT-Bereich. In jedem Zyklus bestand die Chance, dass Patient:innen aufgrund von Herzinsuffizienz, Geräteinfektion, Sondendysfunktion oder einer ventrikulären Arrhythmie hospitalisiert wurden. Der absorbierende Zustand war Tod.

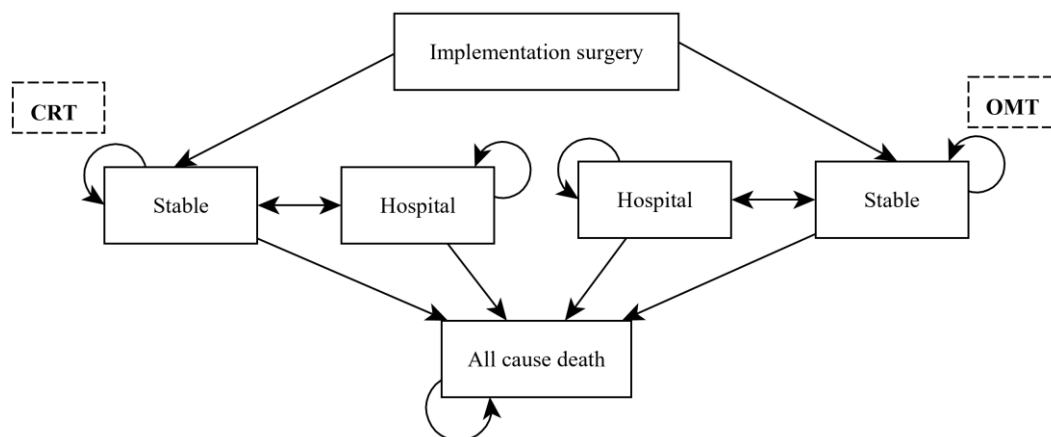


Abbildung 1: Markov-Modell Struktur

CRT: kardiale Resynchronisationstherapie, **OMT:** optimale medikamentöse Therapie

Die Inputparameter für das Modell bestanden aus dem Risiko zu versterben, der Wahrscheinlichkeit hospitalisiert zu werden, Kosten für die jeweiligen Ereignisse und Werte für die Lebensqualität in dem jeweiligen Zustand. Studien für die Inputparameter wurden systematisch über die Datenbank „Medline“ gesucht. Falls es mehrere Studien pro Inputparameter gab, wurden diese mit einem Random-Effects-Modell gepoolt. Es wurden deterministische Sensitivitätsanalysen und probabilistische Sensitivitätsanalysen mit einer Monte-Carlo-Simulation durchgeführt, um die Unsicherheit in den Inputparametern auf die Modellergebnisse abschätzen zu können.

Für die Modellierung der Überlebenszeit wurden die Kaplan-Meier-Kurven für die Therapie mit CRT-P-Geräten und OMT aus der CARE-HF-Studie digitalisiert

und rekonstruiert, um damit parametrische Überlebensfunktionen schätzen zu können und das Überleben über die berichteten Zeiträume hinaus zu extrapolieren. Die CARE-HF-Studie hatte ein Patientenkollektiv, das mit den heutigen Leitlinienempfehlungen vergleichbar ist, und berichtete in weiteren Veröffentlichungen Follow-up-Daten zu Überlebensraten. Die Wahl der passenden parametrischen Verteilung basierte auf dem Akaike-Informationskriterium, der visuellen Übereinstimmung mit der ursprünglichen Kaplan-Meier-Überlebenskurve und der plausiblen langfristigen Entwicklung. Für CRT-P und OMT wurden Gompertz-Verteilungen gewählt. Um eine Überlebenskurve für die Behandlung mit CRT-D-Geräten zu erstellen, wurde auf die Überlebenskurve von CRT-P ein Hazard Ratio (HR) multipliziert. Das HR stammt aus einer Netzwerk-Metaanalyse mit individuellen Patientendaten, welche die wichtigsten RCTs für Patient:innen mit Herzinsuffizienz und reduzierter Ejektionsfraktion umfasst. Angaben für die Gerätelauzeit wurden aus einer Veröffentlichung des National Institute for Health and Care Excellence (NICE) entnommen. Für die Lebensqualität wurde der Nutzwert von deutschen Herzinsuffizienzpatient:innen, unterteilt nach NYHA Klasse, verwendet. Für Hospitalisierungen wurde ein Dekrement auf die Lebensqualität hinzugefügt.

Alle Kosten, die im stationären Kontext angefallen sind, wurden anhand des DRG-Fallpauschalkatalogs berechnet. Jeder Grund für eine Hospitalisierung konnte im Modell einem oder mehreren DRG-Codes zugeordnet werden. Alle weiteren Kosten wie ambulante Kosten und Medikamentenkosten nach Abhängigkeit der NYHA Klasse wurden aus anderen Studien übernommen.

2.3 Ergebnisse

Das prädizierte mediane Überleben von Patient:innen mit CRT-D-Geräten betrug 7,8 Jahre und mit CRT-P-Geräten 6,5 Jahre. Das mediane Überleben mit OMT betrug 4,1 Jahre. Die Behandlung der Patient:innen mit CRT-D-Geräten verursachte im Mittel Kosten in Höhe von 32.447 €, die Behandlung mit CRT-P-Geräten in Höhe von 18.502 € und mit OMT in Höhe von 5.472 €. Somit verursachte die CRT-D-Geräte im Vergleich zur CRT-P 13.945 € zusätzlich inkrementelle Kosten pro Patient:in. Die inkrementellen Kosten von CRT-P-Geräten im Vergleich zur OMT betrugen 13.029 €. Bei der Nutzung von CRT-D verglichen mit CRT-P wurden 0,57 inkrementelle QALYs über den Zeithorizont gewonnen. Beim Einsatz von

CRT-P verglichen mit OMT wurden 2,23 inkrementelle QALYs gewonnen. Die ICER betrug 24.659 € pro zusätzlichem QALY für CRT-D-Geräte im Vergleich zu CRT-P-Geräten und 5.837 € für CRT-P-Geräte im Vergleich zu OMT.

In der deterministischen Sensitivitätsanalyse hatte das HR, das den Überlebensvorteil von CRT-D zu CRT-P angibt, den mit Abstand stärksten Einfluss, gefolgt von der angenommenen CRT-D-Geräteaufzeit. In 96 % aller simulierten Fälle in der Monte-Carlo Simulation ergab sich eine Konstellation aus positiven inkrementellen Kosten und positiven inkrementellen QALYs. Im Umkehrschluss war in 4 % der simulierten Fälle die Therapie mit CRT-P günstiger und effizienter. Der durchschnittliche ICER der Monte-Carlo Simulation betrug 22.477 €.

2.4 Diskussion

Das Ergebnis dieser Studie war, dass die Therapie mit CRT-D-Geräten mit einem Zugewinn von inkrementellen QALYs von 0,57 und einem gleichzeitigen Anstieg der inkrementellen Kosten von 13.945 € verbunden ist. Das ICER betrug 24.659 €. Das bedeutet, dass ein zusätzliches qualitätsadjustiertes Lebensjahr mit der Therapie von CRT-D- im Vergleich zu CRT-P-Geräten mit Investitionen von 24.659 € verbunden ist. Der berechnete ICER in dieser Modellierungsstudie ist geringer als in vergleichbaren Publikationen. In der Literatur beträgt die Spanne der berechneten ICER 30.377 € bis 56.719 € in Preisen von 2014. Ein Grund für die unterschiedlichen Ergebnisse könnte der Unterschied zwischen den verwendeten deutschen Nutzwengewichten und dem HR von CRT-D zu CRT-P in den anderen Studien sein. Weitere Gründe für unterschiedliche Ergebnisse können ungleichen Modellstrukturen sein oder eine Verringerung des Kostenunterschieds von CRT-D und CRT-P-Geräten über die Jahre.

In Bezug auf die Sensitivitätsanalyse war das Modell robust. Allerdings reagierten die Modellergebnisse empfindlich auf Änderungen des Überlebensvorteils. Dieser hatte bei Weitem den stärksten Einfluss auf die Modellergebnisse. Es gibt eine anhaltende Debatte über den potenziellen Zusatznutzen des Defibrillators in CRT-D-Geräten. So würde beispielsweise eine Verringerung des plötzlichen Herztodes infolge einer verbesserten medikamentösen Therapie, wie z.B. mit Sacubitril/Valsartan, voraussichtlich den Überlebensvorteil von CRT-D verringern und damit die ICER erhöhen.

Ein weiterer einflussreicher Eingangsparameter war die Laufzeit der Geräte. Gerätelaufzeit und Gerätewechselkosten stehen in einem engen Zusammenhang. Mit höherer Batteriekapazität fallen die hohen Kosten für den Gerätewechsel weniger häufig an. Ein technologischer Fortschritt bei der Batteriekapazität würde die ICER zugunsten von CRT-D verändern.

Die zentrale Limitation der Studie war, dass die Inputparameter für das Modell aus älteren Studien abgeleitet wurden. Die für die das Modell verwendete Evidenz kann veraltet sein und somit könnten signifikante Fortschritte in der Behandlung von Herzinsuffizienz nicht ausreichend berücksichtigt worden sein. Eine Stärke der Analyse war, dass soweit möglich, gepoolte Effektschätzer für die Inputparameter verwendet wurden.

3 Gerätelaufzeit und Kosten in der kardialen Resynchronisationstherapie

3.1 Hintergrund

Neben dem Überlebensvorteil sind die Laufzeit eines CRT-Geräts und seine Kosten entscheidende Faktoren für die Bewertung der Kosteneffektivität. In gesundheitsökonomischen Modellierungsansätzen kann eine hohe Variabilität der angenommenen CRT-Gerätelaufzeit beobachtet werden. Die CRT-Gerätelaufzeit ist jedoch einer der wichtigsten Eingangsparameter für die Bewertung der Kosteneffektivität, da CRT-D-Geräte teurer sind als CRT-P-Geräte und die Kosten für den Geräte austausch und die Gerätelaufzeit miteinander zusammenhängen. Darüber hinaus ergab eine Modellierungsstudie, dass eine längere Akkulaufzeit unerwünschte Ereignisse, wie Infektionen und Geräte revisionen, reduziert und damit auch Kosten reduziert.

Mehrere klinische Studien untersuchten die Gerätelebensdauer von CRT-D oder implantierbaren ICD-Geräten. Es gibt jedoch nur wenige Informationen über die Lebensdauer von CRT-P-Geräten, die für Modellierungsstudien von entscheidender Bedeutung sind. Häufig wird die Gerätelebensdauer als die Zeit bis zur Erschöpfung der Batterie definiert. Aus der Perspektive des Gesundheitssystems ist aber die Laufzeit eines CRT-Geräts bis zum Wechsel beziehungsweise Ausbau relevant. Dabei ist es zweitrangig, ob der Wechsel durch eine erschöpfte Batterie, durch eine Entzündung oder Fehlfunktion des Geräts hervorgerufen wird. Daher hat diese Studie das Ziel, die Laufzeit und die Kosten von CRT-Geräten von der Implantation bis zu jedwedem Austausch auf Basis von deutschen Routinedaten zu analysieren.

3.2 Methode

Routinedaten deutscher gesetzlicher Krankenkassen beinhalten längsschnittliche personenbezogene Daten zur Inanspruchnahme von Behandlungsanlässen und Leistungsverordnungen. Die BARMER ist die zweitgrößte deutsche gesetzliche Krankenversicherung, die circa 8,8 Million Menschen versichert. Die BARMER-Datenbank enthält anonymisierte Längsschnittinformationen aller Versicherten zu Vitalstatus, Kosten, Inanspruchnahme und Soziodemografie zwischen 2005 und 2019. Für stationäre Behandlungen wird in Deutschland ein DRG-System für die

Erstattung verwendet. Daher müssen alle ICD-10-GM¹-Codes und Operations- und Prozedurenschlüssel-Codes (OPS) gemeldet werden, die für die Behandlungen der Patient:innen relevant sind.

Um die Laufzeit von CRT-Geräten zu bestimmen, wurden alle CRT-Implantationen oder Geräte-Upgrades aus den Jahren 2006 bis 2019 in der Datenbank der BARMER ausgewählt. Die Implantation, der Wechsel und die Entfernung eines CRT-Geräts wurden anhand der OPS-Codes identifiziert. Es wurden alle Patient:innen in der Datenbank ausgewählt, bei denen eine CRT-Geräteimplantation, ein Gerätewechsel oder ein Geräte-Upgrade kodiert wurde (N = 19.899). Nach Anwenden der Ein- und Ausschlusskriterien umfasste die endgültige Stichprobe 17.826 Patient:innen.

Das Indexdatum für die Analyse der Gerätelaufzeit war definiert als das Datum der Implantation des Geräts oder der Aufrüstung auf ein CRT-Gerät. Die Nachbeobachtungszeit wurde definiert als die Zeit zwischen der Implantation und dem Datum des Aggregatwechsels, der Entfernung des Geräts aus einem anderen Grund oder der Zensierung. Gründe für die Zensierung waren u. a. der Tod des Patienten oder der Patientin, ein Wechsel der Krankenkasse oder dass das Gerät am Ende des Beobachtungszeitraums, d.h. am 31. Dezember 2019, noch in Benutzung war. Neben der Laufzeit des Geräts wurden auch die mittleren Kosten in Euro für die Implantation, den Aggregatwechsel und die Entfernung des Geräts berücksichtigt. Um der Preisinflation Rechnung zu tragen, wurden nur Kostendaten für 2019 verwendet. Zusätzlich wurde die mediane Preisentwicklung über die Zeit pro Gerät analysiert.

In der statistischen Auswertung wurde die mediane Laufzeit pro Gerätetyp berechnet (zweiseitiges 95 %-Konfidenzintervall). Die Zeit bis zum Austausch des Geräts wurde anhand von Kaplan-Meier-Kurven dargestellt. Die Unterschiede zwischen CRT-D und CRT-P wurden mit dem Long-Rank-Test analysiert. Ein p-Wert von $< 0,05$ wurde als statistisch signifikant angesehen. Die statistische Analyse wurde mit dem Statistikprogramm R (Version 4.03) durchgeführt.

¹ Internationale statistische Klassifikation der Krankheiten und verwandter Gesundheitsprobleme, 10. Revision, German Modification

3.3 Ergebnisse

Bei 17.826 identifizierten Patient:innen wurden insgesamt 18.246 Geräteimplantationen oder -aufrüstungen, 4.043 Aggregatwechsel und 371 Geräteentfernungen durchgeführt. Von diesen 22.660 Eingriffen entfielen 18.404 auf CRT-D-Geräte und 4.256 auf CRT-P-Geräte. Die mediane Nachbeobachtungszeit pro Patient:in betrug 2,89 Jahre (Interquartilsbereich 1,26 Jahre – 4,79 Jahre). Im Durchschnitt waren CRT-P-Patient:innen bei ihrer ersten CRT-Implantation 6,4 Jahre älter als CRT-D-Patient:innen und häufiger weiblich.

Es wurden insgesamt 4.725 vollständige Laufzeiten beobachtet. Davon waren 4.296 CRT-D-Laufzeiten und 429 CRT-P-Laufzeiten. Die mediane Gerätelaufzeit betrug 6,04 Jahre (95 % Konfidenzintervall (KI) 6,00; 6,10) für CRT-D-Geräte und 8,16 Jahre (95 % KI 7,93; 8,59) für CRT-P-Geräte (Log-Rank-Test $p < 0,0001$) (Abbildung 2). Die Ergebnisse für die Gerätelaufzeit waren in weiteren Sensitivitätsanalysen robust.

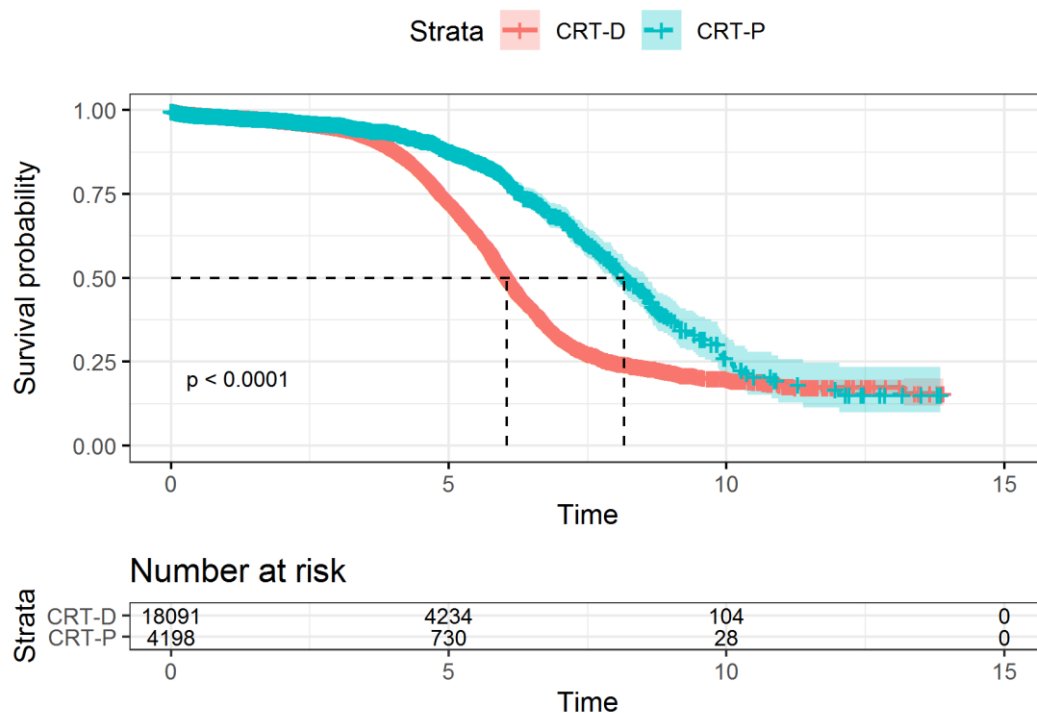


Abbildung 2: Kaplan-Meier-Kurven für die Laufzeit von CRT-Geräten

CRT-P: biventrikuläre Schrittmacher; **CRT-D:** biventrikuläre Defibrillatoren

Im Jahr 2019 betrugen die medianen Kosten für die Implantation eines CRT-D-Geräts 14.270 €, für einen Aggregatwechsel 8.417 € und für eine Geräteentfernung 12.258 €. Für eine CRT-P-Implantation betrugen die medianen Kosten 9.349 €, für einen Aggregatwechsel 5.226 € und für eine Geräteentfernung 13.019 €. Über den Beobachtungszeitraum von 2006 bis 2019 waren die Kosten für CRT-P-Geräte stabil, während die Kosten für eine CRT-D-Implantation stetig sanken.

3.4 Diskussion

Die Studie zeigte, dass die Laufzeit von CRT-P-Geräten länger ist und die Implantation von CRT-P-Geräten im Durchschnitt 5.853 € günstiger ist als die Implantation von CRT-D-Geräten. Die beobachtete Laufzeit für CRT-D-Geräte war ähnlich der berichteten Laufzeit aus anderen Studien. In einer Veröffentlichung von NICE wird die mediane Laufzeit von 10,4 Jahren für CRT-P-Geräte angegeben. In derselben Veröffentlichung werden 5,8 Jahren für CRT-D-Geräte berichtet. Das Ergebnis für CRT-D-Geräte ist vergleichbar mit dem Ergebnis der vorliegenden Analyse. Für CRT-P-Geräten wurde hingegen in der NICE-Veröffentlichung eine erheblich höhere mediane Laufzeit angegeben als in der hier vorliegenden Analyse (10,4 vs. 8,16 Jahre). Die Ergebnisse zur medianen Laufzeit von CRT-P-Geräten unterscheiden sich also um 2,24 Jahre.

Die Gerätekosten sanken im Laufe der Zeit, insbesondere die Implantationskosten der CRT-D-Geräte. Hält man alle anderen Parameter in einer Modellierungsstudie konstant, wirkt sich die geringere Kostendifferenz positiv auf die Kosteneffektivität von CRT-D-Geräten im Vergleich zu CRT-P-Geräten aus. Die dennoch beträchtlichen Kostenunterschiede zwischen den beiden Geräten unterstreichen die Bedeutung von gesundheitsökonomischen Analysen im Bereich der kardialen Resynchronisationstherapie.

Die durchgeführte Studie hatte einige Limitationen. In den Routinedaten sind weder der Hersteller des Geräts noch der Batterietyp erfasst. Aus diesem Grund war es nicht möglich, Unterschiede in der Laufzeit der Geräte zwischen den Herstellern zu untersuchen. Darüber hinaus konnten aufgrund der Nichtverfügbarkeit von Daten keine beeinflussenden Kontrollvariablen, wie der Schrittmachermodus, in die Analyse einbezogen werden.

4 Überleben von Patient:innen bei kardialer Resynchronisationstherapie mit und ohne Defibrillator

4.1 Hintergrund

Bisher gibt es keine aussagekräftige randomisierte kontrollierte Studie, die das Überleben von CRT-P- und CRT-D-Patient:innen vergleicht. Beobachtungsstudien haben das Überleben nach CRT-P- und CRT-D-Implantation analysiert. Die Ergebnisse der Studien sind jedoch widersprüchlich. Einige Studien berichten einen Überlebensvorteil durch CRT-D-Geräte, wohingegen andere keinen Überlebensvorteil finden können. Gründe hierfür können in den unterschiedlichen verwendeten statistischen Methoden, untersuchten Zeiträumen oder beobachteten Populationen liegen. Die Fragestellung der Studie war, hypothesenfrei zu untersuchen, ob bei Herzinsuffizienzpatient:innen nach einer *de novo* CRT-P- oder CRT-D-Implantation ein Überlebensunterschied besteht. Die Datengrundlage bildeten erneut Routinedaten der deutschen gesetzlichen Krankenkasse BARMER aus den Jahren 2014 bis 2019.

4.2 Methode

Für die Überlebensanalyse auf Basis der Routinedaten der BARMER wurde ein retrospektives, nicht-experimentelles, bevölkerungsbasiertes, gewichtetes Kohortenstudien-Design verwendet. Alle in der BARMER-Datenbank erfassten Patient:innen mit CRT-Implantation in den Jahren 2014 bis 2019 wurden für die Studienpopulation berücksichtigt (N = 7.082). Die Ein- und Ausschlusskriterien für die Überlebensanalyse wurden mit Hilfe von Kardiologen, anhand der in der BARMER-Datenbank erfassten ICD-10-GM- und OPS-Codes, operationalisiert. Nach Anwendung der Ein- und Ausschlusskriterien wurden 3.569 Patient:innen mit CRT *de novo* Implantationen in die Analyse aufgenommen. Davon waren 847 CRT-P-Implantationen und 2.722 CRT-D-Implantationen.

Der Endpunkt der Analyse war Tod, der zwischen der CRT-Implantation und dem 31. Dezember 2019 auftrat. Für alle Patient:innen in der Studienkohorte wurde ermittelt, ob sie bis zum Ende des Beobachtungszeitraums verstorben waren, die

BARMER verlassen hatten ($<1,05\%$ der Studienpopulation) oder weiterhin bei der BARMER krankenversichert waren.

Als demografische Merkmale wurden Alter und Geschlecht berücksichtigt. Als medizinische Charakteristika wurden die Anzahl der Krankenhausaufenthalte ein Jahr vor der CRT-Implantation (0, 1, 2, >2), die NYHA-Klasse (II, III, IV) und die Ätiologie der Herzinsuffizienz (ischämisch/nicht-ischämisch) mit aufgenommen. Als weitere Komorbiditäten wurden Nierenfunktionsstörungen (Stadien III und IV), Diabetes und Vorhofflimmern berücksichtigt. Außerdem wurden alle Komorbiditäten der Elixhauser-Komorbiditätsgruppen, die nicht bereits in der Analyse enthalten waren, mit aufgenommen.

Die statistische Analyse bestand aus drei aufeinander aufbauenden Schritten. Erstens wurde eine unadjustierte Analyse zum Überleben von CRT-P- und CRT-D-Patient:innen ausgeführt. Patient:innen, die am Ende des Beobachtungszeitraums (31. Dezember 2019) noch am Leben waren, wurden zensiert. Für Patienten, die die BARMER verließen, wurde das Austrittsdatum zur Zensierung herangezogen. Die Nachbeobachtungszeit war definiert als die Zeit zwischen der Implantation des CRT-Geräts (Indexdatum) und dem Tod oder der Zensierung. Patient:innen, denen ein CRT-D-Gerät implantiert wurde, bildeten die Kontrollgruppe.

Zweitens wurde eine altersadjustierte Analyse für die Gesamtstichprobe durchgeführt. Zusätzlich wurde die Stichprobe in drei Altersgruppen eingeteilt und in jeder Altersgruppe eine unadjustierte Analyse durchgeführt, um zu testen, ob es in unterschiedlichen Altersgruppen der CRT-Patient:innen einen potentiellen Überlebensunterschied gab.

Drittens wurde in einer gewichteten Analyse mit Entropy Balancing das Überleben untersucht. Entropy Balancing ist eine Gewichtungsmethode, die darauf abzielt, eine exakte Balance der Kovariaten von CRT-P- und CRT-D-Patient:innen herzustellen. Entropy Balancing, das als eine Verallgemeinerung der Propensity-Score-Weighting angesehen werden kann, verwendet einen Optimierungsalgorithmus, in dem allen Patient:innen in der Kontrollgruppe ein skalares Gewicht zugewiesen wird, um Mittelwerte und Varianzen zwischen den Daten der CRT-P-Patient:innen und den neu gewichteten CRT-D-Patient:innen auszugleichen. Ein

p-Wert von $<0,05$ wurde als statistisch signifikant angesehen. Die statistischen Analysen wurden mit dem Statistikprogramm "R" (Version 4.03) erstellt.

4.3 Ergebnisse

Die mediane Follow-up Zeit betrug 2,35 Jahre (Interquartilsbereich 1,09 Jahre – 3,92 Jahre). CRT-P-Patient:innen waren im Durchschnitt 6,7 Jahre älter und häufiger weiblich. Die Ätiologie der Herzinsuffizienz (ischämisch/nicht ischämisch) war zwischen den beiden Gruppen vergleichbar. Die Unterschiede in den NYHA-Klassen und den Hospitalisierungen vor der CRT-Implantation waren gering. CRT-D-Patient:innen hatten häufiger Diabetes, während Nierenfunktionsstörungen im Stadium III und IV und Vorhofflimmern häufiger bei CRT-P-Patient:innen auftraten.

Über die gesamte Nachbeobachtungszeit wurden 203 (24 %) Todesfälle bei CRT-P-Patient:innen und 511 (19 %) Todesfälle bei CRT-D-Patient:innen beobachtet. In den unadjustierten Analyse war das Risiko zu versterben für CRT-P-Patient:innen signifikant höher als für CRT-D-Patient:innen (HR: 1,63; 95 % KI 1,38-1,92) (Abbildung 3).

Wenn für Alter adjustiert wurde, lag das HR bei 1,13 (95 % KI 0,95-1,35). In keiner der drei unadjustierten Analysen in den drei Altersgruppen wurde ein signifikanter Überlebensunterschied zwischen den beiden Gerätegruppen beobachtet.

Nach Verwendung der Gewichtung aus dem Entropy Balancing war der gewichtete Durchschnitt der Baseline-Charakteristika der CRT-D-Patient:innen der gleiche wie der Durchschnitt der Baseline-Charakteristika der CRT-P-Patient:innen. In der gewichteten Analyse wurde kein signifikanter Unterschied im Überleben beobachtet. Das HR lag nahe 1 (HR: 0,99; 95 % KI 0,81-1,20). Das Ergebnis war robust in zwei Sensitivitätsanalysen.

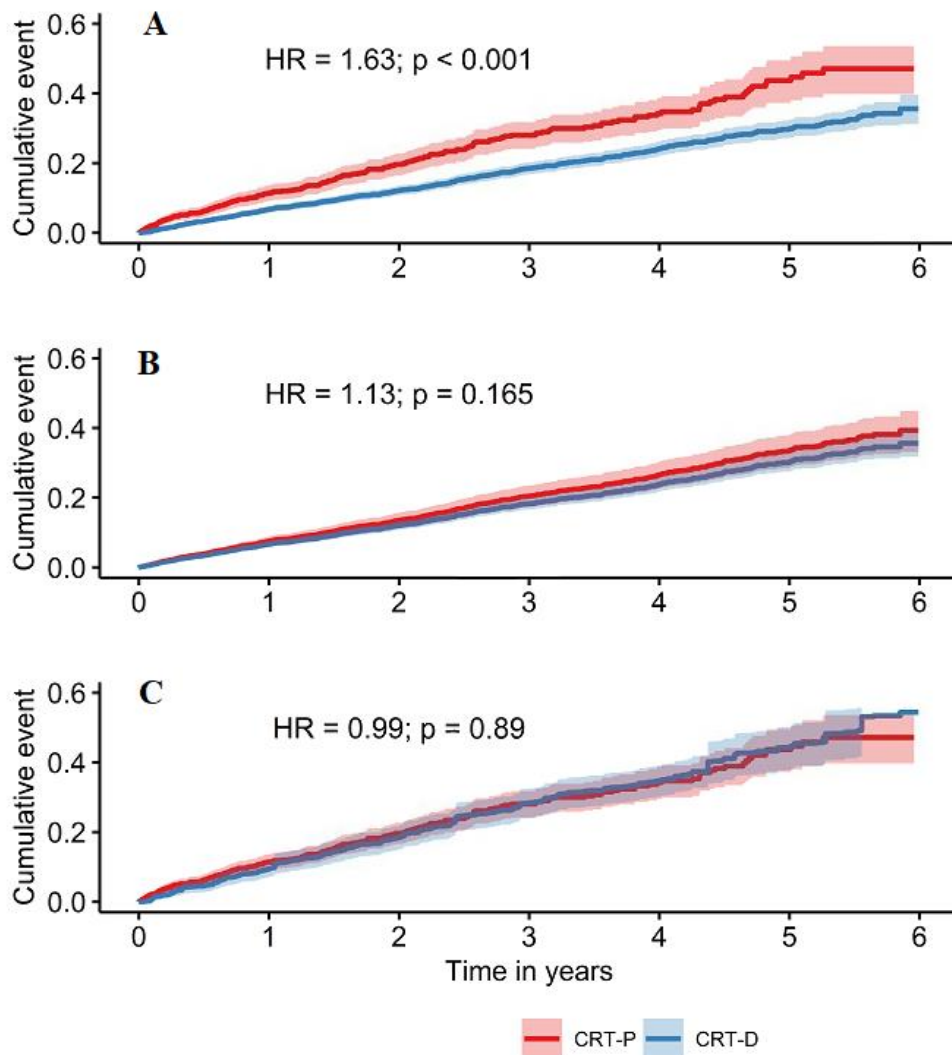


Abbildung 3: Überlebensanalyse CRT-P zu CRT-D

A: unadjustierte Kaplan-Meier-Kurven für die kumulative Inzidenz von Tod; B: Altersadjustierte kumulative Inzidenz auf der Grundlage des Cox-Proportional-Hazard-Modells; C: Analyse mit Gewichtung aus Entropy Balancing.

CRT-P: biventrikuläre Schrittmacher; CRT-D: biventrikuläre Defibrillatoren; HR: hazard ratio

4.4 Diskussion

In der Analyse von Routinedaten wurde nach Adjustierung für Confounder kein Überlebensvorteil zwischen CRT-P- und CRT-D-Geräte identifiziert. Das heißt zwar nicht, dass die beiden Methoden hinsichtlich des Überlebens identisch sind, aber mögliche Unterschiede sind als eher klein und klinisch nicht relevant einzustufen. Studien, die große Stichproben aus dem Vereinigten Königreich analysierten, berichteten jedoch einen Überlebensvorteil von CRT-D-Geräten im Vergleich zu CRT-P-Geräten. Die Ergebnisse einer *Post-hoc*-Analyse der COMPANION-

Studie stützt das Ergebnis dieser Analyse. Es wurde kein Überlebensunterschied gefunden. Zusätzlich ergab eine große multinationale Analyse von Patient:innen, welche die ersten fünf Jahre nach der Implantation überlebten, ein identisches späteres Überleben von CRT-P- und CRT-D-Patient:innen. In Übereinstimmung mit unseren Ergebnissen fand eine Analyse von 5 % der Medicare-Versicherten in den USA keine signifikanten Unterschiede im Überleben von CRT-P-Patient:innen im Vergleich zu CRT-D-Patient:innen bei nicht-ischämischen Patient:innen.

Die Studie hatte mehrere Limitationen, die typisch für retrospektive Analysen von Gesundheitsdaten sind. Erstens basierten die Schlussfolgerungen der nach Entropy Balancing gewichteten Analyse auf der Annahme, dass alle relevanten Baseline-Charakteristika eingeschlossen wurden und dass keine unbeobachteten Confounder existieren. Zweitens fehlten detaillierte Informationen über weitere klinische Parameter, die für das Überleben essenziell sind, wie QRS-Dauer oder Ejektionsfraktion. Drittens können, da die Analyse auf Krankenkassendaten basierte, mögliche Fehlkodierungen, z. B. bei ICD-10-GM-Codes, nicht ausgeschlossen werden.

Die Analyse unterscheidet sich von früheren Beobachtungsstudien in dem wichtigen Punkt, dass sie auf den Zeitraum von 2014 bis 2019 beschränkt wurde, um die aktuelle klinische Praxis widerzuspiegeln und somit den aktuellen technologischen und medizinischen Behandlungsstandard berücksichtigte. Die Wahl des Beobachtungszeitraums ist wichtig, weil die Raten des plötzlichen Herztodes in Studien zur Herzinsuffizienz im Laufe der Zeit gesunken sind.²

² z. B. durch den konsequenten Einsatz einer optimalen medizinischen Therapie und neuer Medikamente wie Sacubitril/Valsartan.

5 Diskussion und Ausblick

Die vorliegende kumulative Dissertation befasst sich mit der gesundheitsökonomischen und epidemiologischen Bewertung der kardialen Resynchronisationstherapie bei Herzinsuffizienz. Mit den durchgeführten Studien wurden die Therapie mit den beiden Geräteoptionen CRT-P und CRT-D untersucht. Es wurde eine literaturbasierte gesundheitsökonomische Modellierungsstudie erstellt, welche die Therapie mit CRT-P- und CRT-D-Geräten evaluiert. Die Gerätelaufzeit von CRT-Geräten wurde bestimmt und das Überleben nach einer *de novo* CRT-P oder CRT-D-Implantation analysiert.

5.1 Diskussion der Ergebnisse der drei Studien

Es gibt eine Vielzahl von klinischen Studien im Bereich der kardialen Resynchronisationstherapie. Auf diesen Studien basieren diverse internationale gesundheitsökonomische Analysen, die CRT-D- und CRT-P-Geräte miteinander vergleichen und evaluieren. Für den deutschen Versorgungskontext fehlte jedoch bisher eine solche Analyse, die die Kosten und Nutzwerte für das deutsche Gesundheitssystem berücksichtigt. Bei der ersten durchgeführten Studie zeigte sich, dass der Faktor Überleben zentral für die Beurteilung der Kosteneffektivität war. In der Modellierung war die Therapie mit CRT-D-Geräten effektiver, aber auch kostenintensiver. Die Nichtverfügbarkeit aktueller Daten limitierte die Analyse. Die Daten aus den klinischen Studien waren teils bis zu 17 Jahre alt und bildeten deswegen die heutigen Therapiemöglichkeiten nicht mehr ab. Dies könnte zu einer Überschätzung der Effektivität der Therapie mit CRT-D-Geräten geführt haben.

Sowohl aus Sicht der Patient:innen als auch hinsichtlich der Kosten im deutschen Gesundheitssystem ist eine lange Laufzeit eines CRT-Geräts wünschenswert. Jede Operation oder Einweisung in ein Krankenhaus ist mit dem Risiko einer Infektion oder dem Risiko anderer Komplikationen sowie zusätzlichen Kosten verbunden. Die Studie zur Analyse der Gerätelaufzeit ergab, dass CRT-P-Geräte eine signifikant längere Laufzeit aufweisen. Eine Gerätelaufzeit, die der Lebenserwartung der Patient:innen entspräche, könnte den Patient:innen zusätzliche Krankenhauseinweisungen aufgrund von Komplikationen mit dem implantierten Gerät ersparen. Die Verwendung von Routinedaten hatte in der Studie den Vorteil, dass

Daten für einen langen Zeitraum zur Verfügung standen und bei der Analyse nicht die Batterielebensdauer untersucht wurde, sondern die gesamte Gerätelauzeit einschließlich des Austauschs aufgrund von Gerätefehlfunktionen und anderen Gründen, was für Patient:innen, Ärzt:innen und Krankenkassen den wichtigeren Parameter darstellt.

In der Literatur ist ein möglicher Überlebensvorteil von CRT-D-Geräten durch den zusätzlichen Defibrillator umstritten. Da es bis heute keine aussagekräftige klinische randomisierte kontrollierte Studie gibt, die CRT-D-Geräte mit CRT-P-Geräten vergleicht, beschränkt sich die Evidenz auf konfligierende Ergebnisse aus Beobachtungsstudien, die generell ein niedrigeres Evidenzlevel als RCTs aufweisen. In der Überlebensanalyse mit deutschen Routinedaten aus den Jahren 2014 bis 2019, welche die aktuelle Therapieform abdecken, war in der dritten Studie kein signifikanter und klinisch relevanter Überlebensunterschied zwischen den beiden CRT-Geräten nachweisbar.

5.2 Eine gezieltere Auswahl von CRT-D-Empfänger:innen

In Deutschland werden im europäischen Vergleich überproportional viele CRT-D-Geräte implantiert. Die erste Studie zeigte, dass das Überleben bei der Evaluation von CRT-Geräten zentral für die Kosteneffektivität ist. Zusätzlich zeigte sowohl die zweite Studie als auch die dritte Studie, die jeweils Routinedaten analysierten, dass ein möglicher Überlebensvorteil von CRT-D-Geräten gering zu sein scheint und die Gerätelauzeit von CRT-D-Geräten signifikant geringer ist.

Risiko-Scores können prädiktieren, ob Patient:innen von einem CRT-D-Gerät profitieren würden (36). Bei einer gezielteren Auswahl der Patient:innen anhand ihrer Eigenschaften wie Alter, Geschlecht, Erkrankungsschwere oder Komorbiditäten, die von dem zusätzlichen Defibrillator bei CRT-D-Geräten in Zukunft wahrscheinlich profitieren, sind Einsparungen für das Gesundheitssystem möglich. Die begrenzten Ressourcen im Gesundheitssystem könnten effizienter verteilt werden.

5.3 Potential von Routinedaten

Die zwei Studien dieser Dissertation, in denen Routinedaten ausgewertet wurden, zeigten das Potential von Routinedaten auf. Eine große Stärke liegt in der zeit-

nahen Verfügbarkeit der Daten im Vergleich zu Ergebnissen aus klinischen randomisierten kontrollierten Studien. Die schnelle Verfügbarkeit der Daten ist auch deshalb von hoher Relevanz, da die Wahl des Untersuchungszeitraums bei dem Vergleich von CRT-P- und CRT-D-Geräten elementar ist. Der Untersuchungszeitraum sollte die aktuellen Therapiemöglichkeiten abbilden, da die medikamentöse Therapie der Patient:innen sich über die Zeit deutlich verbessert hat und die Raten des plötzlichen Herztodes gesunken sind. Dieser Aspekt ist wichtig zu berücksichtigen, da der zusätzliche Defibrillator bei CRT-D-Geräten dafür intendiert ist, Patient:innen vor dem plötzlichen Herztod zu schützen. Es bleibt abzuwarten, ob durch neue medikamentöse Therapieformen die Wahrscheinlichkeit eines plötzlichen Herztodes weiter verringert werden kann.

In Routinedaten wird ein langer Beobachtungszeitraum abgebildet, der dazu genutzt werden kann, Änderungen über die Zeit, Prävalenzen von Erkrankungen oder Kosten, die durch bestimmte Erkrankungen entstehen, zu analysieren. Von hoher Relevanz bei der Analyse von Routinedaten ist es, dass medizinische Expert:innen klare Selektionskriterien für die Identifikation der Patient:innen in der Datenbank bereitstellen. Bei Beobachtungsstudien, die sich auf Sekundärdaten stützen, ist eine sorgfältige Selektion der Patientenpopulation wesentlich, um eine Vergleichbarkeit der Gruppen zu gewährleisten. Bei der Analyse von Routinedaten ist es jedoch wichtig zu beachten, dass keine klinischen Parameter verfügbar sind.

5.4 Das RESET-CRT Projekt und die Notwendigkeit einer randomisierten kontrollierten Studie

Die randomisierte kontrollierte Studie „Re-evaluation of optimal re-synchronisation therapy in patients with chronic heart failure“ (RESET-CRT, NCT03494933), an der die Lübecker Arbeitsgruppe beteiligt ist, untersucht, ob die Behandlung mit CRT-P-Geräten der Behandlung mit CRT-D-Geräten nicht unterlegen ist (37). Die Studie wird zurzeit noch durchgeführt. Das Ergebnis der dritten Studie dieser Dissertation unterstützt die Hypothese der klinischen Studie.

In der Modellierungsstudie war das Überleben der maßgebliche Parameter, deshalb ist das Ergebnis von RESET-CRT auch zentral für die weitere Beurteilung der Kosteneffektivität von CRT-P-Geräten zu CRT-D-Geräten. Darüber hinaus wäre es wichtig zu evaluieren, inwiefern adverse Ereignisse wie Hospitalisierungen oder

Tod sich zwischen Routinedaten und den Ergebnissen der klinischen Studie unterscheiden. Eine abschließende Beurteilung zum Überleben der Patient:innen mit implantierten CRT-P- oder CRT-D-Geräten und zur Kosteneffektivität kann nur durch eine klinische randomisierte kontrollierte Studie getroffen werden.

5.5 *Ausblick*

Die Studien der vorliegenden Dissertation zeigen wie zentral die Begleitung von klinischen Studien durch Analysen von Routinedaten sind. Durch die schnelle Verfügbarkeit von Routinedaten und das breite Methodeninstrumentarium zur Analyse von Sekundärdaten können Hypothesen getestet werden und im Sinne von Real-World-Evidence hinsichtlich der Übertragbarkeit auf den realen Versorgungskontext überprüft werden. Zusammengefasst bieten die drei vorgestellten Studien die Grundlage für eine erneute Modellierung der CRT-Therapie. Die erste Studie bietet Modellierungsansätze, die zweite und dritte Studie stellen aktuellere Inputparameter für das Modell bereit, die zentral für die Beurteilung der Kosteneffektivität von CRT-Geräten sind.

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Anhang



Cardiac Resynchronisation Therapy in Patients with Moderate to Severe Heart Failure in Germany: A Cost-Utility Analysis of the Additional Defibrillator

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Abstract

Background Cardiac resynchronisation therapy (CRT) is a well-established form of treatment for patients with heart failure and cardiac dyssynchrony. There are two different types of CRT devices: the biventricular pacemaker (CRT-P) and the biventricular defibrillator (CRT-D). The latter is more complex but also more expensive. For the majority of patients who are eligible for CRT, both devices are appropriate according to current guidelines. The purpose of this study was to conduct a cost-utility analysis for CRT-D compared to CRT-P from a German payer's perspective.

Methods A cohort Markov-model was developed to assess average costs and quality-adjusted life-years (QALY) for CRT-D and CRT-P. The model consisted of six stages: one for the device implementation, one for the absorbing state death, and two stages ("Stable" and "Hospital") for either a CRT device or medical therapy. The time horizon was 20 years. Deterministic and probabilistic sensitivity analyses and scenario analyses were conducted.

Results The incremental cost-effectiveness ratio (ICER) of CRT-D compared with CRT-P was €24,659 per additional QALY gained. In deterministic sensitivity analysis, the survival advantage of CRT-D to CRT-P was the most influential input parameter. In the probabilistic sensitivity analysis 96% of the simulated cases were more effective but also more costly.

Conclusions Therapy with CRT-D compared to CRT-P resulted in an additional gain of QALYs, but was more expensive. In addition, the ICER was subject to uncertainty, especially due to the uncertainty in the survival benefit. A randomised controlled trial and subgroup analyses would be desirable to further inform decision making.

Key Points for Decision Makers

Treatment with the biventricular pacemaker (CRT-P) is less expensive than treatment with the biventricular defibrillator (CRT-D). But treatment with CRT-D resulted in a higher expected median survival.

The cost difference between CRT-D and CRT-P is largely influenced by device costs, more frequent hospitalisations and shorter device longevity.

The uncertainty in the cost-effectiveness ratio is mainly driven by uncertainty in the survival benefit of CRT-D compared to CRT-P.

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1 Background

Heart failure is one of the leading causes of death in Germany [1]. It reduces survival and impairs quality of life [2–4]. Healthcare resource utilisation is high in heart failure—especially due to hospitalisations [5]. The prevalence of heart failure in Germany ranges between 2% and 4%, and rises with age [6, 7]. Cardiac resynchronisation therapy (CRT) is indicated, with the highest recommendation level for patients with symptomatic heart failure in New York Heart Association (NYHA) classes II–IV, reduced ejection fraction $\leq 35\%$ and broad QRS complex, according to the current corresponding European guideline [8].

CRT is a well-established form of treatment that relies on two different treatment options: the biventricular pacemaker (CRT-P) and the cardiac biventricular defibrillator (CRT-D). The additional defibrillator is intended to protect patients from sudden cardiac death. However, CRT-D devices are more complex and costly, with a higher hospitalisation rate due to lead failure, infections or inappropriate shocks, which impairs quality of life [9, 10]. In Germany, 21,479 CRT procedures were performed in 2015, of which about 80% were CRT-D implementations. The relative share of CRT-D on all CRT devices is considerably higher in Germany compared to other European countries [2].

Several RCTs have shown that patients with CRT devices have significantly better outcomes compared to patients solely treated with optimal medical therapy (OMT) or an implantable cardioverter defibrillator [11–13]. However, there has been no sufficiently powered head-to-head trial of CRT-D and CRT-P to date. For the majority of patients who are eligible for CRT, both devices are appropriate according to the current guideline [8].

Two studies conducted a health economic evaluation for the German healthcare system, either for CRT-P versus OMT [14] or for CRT-D versus OMT [15]. Therefore, this study aimed to evaluate cost-effectiveness of CRT-D versus CRT-P by an indirect comparison from a German statutory health insurance (SHI) perspective. Since survival is the crucial parameter in this evaluation, a long-term perspective was applied by extrapolating the survival of Kaplan–Meier curves.

2 Methods

A Markov-model was developed to analyse the cost-effectiveness of CRT-D + OMT compared to CRT-P + OMT. To perform a comprehensive analysis the results of CRT-P + OMT compared to OMT are reported as well,

as OMT is the low-cost alternative to treat this patient cohort. The model outcomes were quality-adjusted life-years (QALYs) and costs from a German SHI payer's perspective.

Heart failure is a chronic disease and most common in older people; therefore extrapolation beyond the follow-up was necessary. After 20 years, the model predicted that 13% of CRT-D patients, 10% of CRT-P patients and 0% of OMT patients were still alive. For this reason, a time horizon of 20 years was chosen because a longer life model would add unnecessary uncertainty and the major health and economic outcomes could be captured. In addition, the model converged from that time onwards. Model results for 9 years, the maximum follow-up time of CARE-HF and for 15 years are reported as well. The cycle length was 1 month. The model was conducted for three identical and homogeneous cohorts, differing only in the three treatment strategies: (1) CRT-P + OMT, (2) CRT-D + OMT or (3) OMT. The model was run for a cohort of 1000 hypothetical patients for each strategy. Using a cohort simulation, expected costs and expected survival were calculated [16]. Costs and QALYs were discounted by 3% per year [17]. The outcomes were used to calculate the incremental cost-effectiveness ratio (ICER), which indicates the amount to be spent for an additional QALY. The model was set up in “R” [18] with the package “heemod” [19].

2.1 Target Population

In the European guideline, CRT is recommended for patients with reduced ejection fraction $\leq 35\%$, broad QRS complex and symptomatic heart failure in NYHA classes II–IV despite OMT [8]. Three treatment options are available for this patient group: OMT, CRT-P and CRT-D. The patients face three different causes of death: heart failure death, sudden cardiac death and non-cardiac death. The additional defibrillator of a CRT-D device should reduce sudden cardiac death. There are two RCTs that cover this patient collective: COMPANION [20] and CARE-HF [21]. The CARE-HF trial was chosen for the analysis of survival because it comprises the longest follow-up of a patient heart-failure collective due to left ventricular systolic dysfunction and cardiac dyssynchrony, which is the relevant patient cohort for researching cost-effectiveness of CRT-D compared to CRT-P. The initial age (66 years) of the hypothetical cohort was set according to the median age of CARE-HF patients at baseline.

2.2 Model Structure

The model consists of six Markov-states (Fig. 1). All patients entered the model via the implementation surgery, which could either be successful or fail. The main part was

Fig. 1 Markov-model for cardiac resynchronisation therapy; *CRT* cardiac resynchronisation therapy, *OMT* optimal medical therapy, *NYHA* New York Heart Association

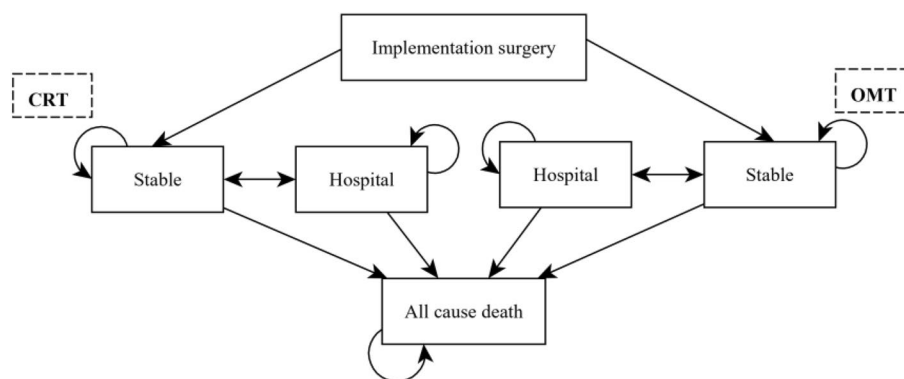


Table 1 Distribution of New York Heart Association (NYHA) classes over time

NYHA class	Mean	Lower 95% confidence interval	Upper 95% confidence interval	Probability distribution	Reference
<i>OMT proportion at baseline</i>					
III	0.938	0.7542	1	Beta ($\alpha=3.48, \beta=43.45$)	[11]
IV	0.062	0.0498	0.0742	Beta ($\alpha=3.48, \beta=43.45$)	
<i>OMT proportion at 90 days</i>					
I	0.101	0.812	0.1208	Multinomial (101, 299, 548,52)	[11]
II	0.299	0.2404	0.3576		
III	0.548	0.4406	0.6554		
IV	0.052	0.0418	0.0622		
<i>OMT proportion at 18 months</i>					
I	0.127	0.1021	0.1519	Multinomial (127, 373, 457,43)	[11]
II	0.373	0.2999	0.4461		
III	0.457	0.3674	0.5466		
IV	0.043	0.0346	0.0514		
<i>CRT proportion at baseline</i>					
III	0.938	0.7542	1	Beta ($\alpha=3.48, \beta=43.45$)	[11]
IV	0.062	0.0498	0.0742	Beta ($\alpha=3.48, \beta=43.45$)	
<i>CRT proportion at 90 days</i>					
I	0.295	0.2372	0.2628	Multinomial (295, 415, 272,18)	[11]
II	0.415	0.3337	0.4963		
III	0.272	0.2187	0.3253		
IV	0.018	0.0145	0.0215		
<i>CRT proportion at 18 months</i>					
I	0.315	0.2533	0.3767	Multinomial (315, 444, 225,15)	[11]
II	0.444	0.3570	0.5310		
III	0.225	0.1809	0.2691		
IV	0.015	0.0121	0.0179		

CRT cardiac resynchronisation therapy, *OMT* optimal medical therapy

divided into a CRT section and an OMT section. In case the implementation surgery failed, patients were solely treated with OMT. Each subsection of the model comprised a Markov state “Stable” and a Markov state “Hospital”, which included hospitalisations due to heart failure, lead failure, a device infection or ventricular arrhythmia. The distribution of NYHA classes over time was taken from Colquitt et al. [11] (see Table 1). The absorbing state was all-cause death.

The possibility of device upgrades was excluded. The same events could occur in the OMT section, except for hospitalisations due to device malfunctions or infections.

2.3 Model Parameters

The model parameters for the chosen model structure consisted of the mortality risk, the probability of adverse events,

costs that occur for specific events and health-related quality-of-life (HRQoL) values for the health states in the model. The main model was deterministic. Mortality was the crucial parameter in this modelling. To date there has been no randomised, controlled trial (RCT) that directly compared CRT-D to CRT-P, but many meta-analyses comparing CRT devices have already been performed. Therefore, meta-analyses have been systematically searched via PubMed to investigate the effect of the devices on mortality. We chose the analysis of Woods et al. [12] because they were the only ones who performed a network meta-analysis of RCTs with individual patient data of CRT-D, CRT-P, OMT and ICD trials. More recent meta-analyses such as Barra et al. [13] have not included other relevant RCTs.

Input parameters for the transition probabilities and device longevity calculations are based on single RCTs used by six meta-analyses [11–13, 22–24]. Two additional references [9, 25] were found by literature search via PubMed. With the exception of one observational study [9], only RCTs were used to compute transition probabilities, as these generally have a higher level of evidence. The probabilities were transformed to the cycle length of 1 month [16] and were pooled with a random-effects model [26] (see Table 2).

One-way deterministic sensitivity analyses were conducted (see Table 2). For the probabilistic sensitivity analysis, a Monte Carlo simulation with 10,000 iterations was applied, where the values of the input parameters were assumed to follow certain probability distributions. Based on the recommendations by the ISPOR guideline, distributions for the input parameters were chosen [27]. The input parameters for all three treatment strategies are listed in Table 2.

2.3.1 Effectiveness Data

To estimate survival, the Kaplan–Meier curves for all-cause mortality in the CARE-HF [28, 29] trial for patients with either CRT-P or OMT were digitalised with DigitizeIt [30]. For OMT the publication with the shorter follow-up was chosen because in the subsequent publication a lot of treatment cross-overs were reported. In the CARE-HF study CRT-P was compared to OMT with a maximum follow-up of 9 years. The individual patient data were reconstructed using the R-code by Guyot et al. [31]. We plotted cumulative hazard functions for OMT and CRT-P. In both plots the hazard is monotonically increasing, which indicates a distribution that enables increasing hazards. Afterwards parametric survival curves were fitted (exponential, Weibull, Gompertz, gamma, log-logistic, lognormal). The differences in the Akaike Information Criterion (AIC) indicated a similarly good fit for all curves, except maybe for lognormal and log-logistic. Thus, the parametric survival distributions

were selected according to visual conformity to the original Kaplan–Meier survival curve and plausibility in the long run. A Gompertz distribution was chosen for CRT-P and for OMT.

To construct a survival curve for CRT-D, a hazard ratio of 0.81 was applied to the parametric survival curve of CRT-P in order to derive device-dependent mortality rates. This value for the hazard ratio [95% confidence interval (CI) 0.67–0.99] was reported by Woods et al. in an individual patient data network meta-analysis [12], which incorporates the major RCTs for patients with heart failure and reduced ejection fraction who received an OMT, ICD, CRT-P or CRT-D, and is therefore considered the highest available evidence. In total, the meta-analysis included 12,638 patients with 2422 deaths. Mean follow-up was 2.5 years (range 0–7.5 years). For ten trials individual patient data were available. An unadjusted network meta-analysis was performed to determine the overall efficacy of the devices throughout all RCTs. An adjusted analysis was performed for different baseline characteristics to evaluate whether these subgroups experienced different treatment effects. In line with Mealing et al. [32], we assumed that the hazard ratio started to increase after 7.5 years, which was the maximum follow-up in the meta-analysis by Woods et al. [12], until it was 1 after 20 years. The observed survival curves for OMT and CRT-P were based on data from patients aged on average 66 years and the parametric survival curves were then extrapolated over the model time horizon (maximum follow-up 9 years, extrapolation for 20 years). The extrapolation of survival curves over such a long time period is subject to uncertainty. Thus, three scenario analyses were run for that input parameter.

The reported device longevity for CRT-P and CRT-D varied between the cost-effectiveness studies. Therefore, the median device longevity was taken from a National Institute for Health and Care Excellence (NICE) report calculated from approximately 40,000 implementations from 2000 to 2011 [33]. Lower and higher device longevity estimates were taken from cost-effectiveness studies for the sensitivity analysis [30–32] (see Table 2). In the case of battery depletion the whole CRT system has to be replaced.

2.3.2 Quality of Life

Beside the importance of survival, heart failure is characterised by decreased quality of life and frequent hospitalisations, which were assumed to also impair quality of life. Quality of life decreases with progress of heart failure. Boczor estimated HRQoL weights for German patients with chronic heart failure ($n=3387$) with the EQ-5D-5L questionnaire [34]. HRQoL weights were reported for each

Table 2 Input parameters

Input parameter (SE)	Baseline value	DSA values		PSA distribution	References
		Lower	Upper		
Costs in €					
Implementation					
CRT-D	15,223.29	14,566.13	22,273.94	Beta ^a ($\alpha=579$, $\beta=54$)	[38, 39]
CRT-P	10,054.07	9,160.61	14,555.73	Beta ^a ($\alpha=109$, $\beta=22$)	[38, 39]
CRT change					
CRT-D	10741.21	–	–	Multinomial ^a (547,118,11)	[38, 39]
CRT-P	4687.789	–	–	Beta ^a ($\alpha=42$, $\beta=14$)	[38, 39]
Hospitalisation					
Heart failure	2,926.43	–	–	Multinomial ^a (4,13,929,54)	[38, 39]
Lead failure	5,099.95	–	–	Multinomial ^a (54,40,444,267,21,13,14,120,27)	[38, 39]
CRT infection	8,982.64	–	–	Multinomial ^a (327,76,170,152,135,58,47,35)	[38, 39]
Ventricular arrhythmia	4,033.69	–	–	Multinomial ^a (37, 666,116,137,4,40)	[38, 39]
Monthly NYHA Management					
NYHA I	56.35	–	–	Gamma (mean=56, SD=7.48)	[40]
NYHA II	99.50	–	–	Gamma (mean=99, SD=9.95)	[40]
NYHA III	98.12	–	–	Gamma (mean=98, SD=9.98)	[40]
NYHA IV	105.467	–	–	Gamma (mean=105, SD=10.24)	[40]
Utilities					
NYHA I	0.834 (0.0077)	0.815	0.93	Beta ($\alpha=646$, $\beta=129$)	[34, 35, 55, 57]
NYHA II	0.789 (0.0056)	0.72	0.78	Beta ($\alpha=1253$, $\beta=335$)	[23, 34, 35, 37]
NYHA III	0.683 (0.0077)	0.59	0.74	Beta ($\alpha=497$, $\beta=224$)	[35–37, 58]
NYHA IV	0.564 (0.0219)	0.44	0.6	Beta ($\alpha=49$, $\beta=38$)	[36, 55–57]
Decrement due to hospitalisation					
NYHA I	–0.070	–	–	–	[35]
NYHA II	–0.030	–	–	–	[35]
NYHA III	–0.080	–	–	–	[35]
NYHA IV	–0.210	–	–	–	[35]
Probabilities (per cycle)					
Death					
Shape ^b CRT-P	3.6e–05 (6.6e–05)	–9.49e–05	0.00016	Log-normal (mean=0.000036, SD=0.000067)	[29]
Rate ^b CRT-P	2.6e–04 (3.2e–05)	0.0002	0.00033	Log-normal (mean=0.00026, SD=0.00032)	[29]
Hazard ratio CRT-D	0.81 (0.0996)	0.67	0.99	Log-normal (mean=0.81, SD=0.00014)	[12]
Shape ^b OMT	3.8e–04 (2.0e–04)	0.000046	0.000153	Log-normal (mean=0.00039, SD=0.0002)	[28]
Rate ^b OMT	3.4e–04 (5.0e–05)	0.00046	0.0005	Log-normal (mean=0.000343, SD=0.000051)	[28]
Events					
CRT-D implementation success	0.9126 (0.0167)	0.8798	0.9453	Beta ($\alpha=1876$, $\beta=180$)	[20, 59, 60]
CRT-P implementation success	0.9167 (0.0185)	0.8804	0.9529	Beta ($\alpha=1523$, $\beta=138$)	[20, 21, 61, 62]
CRT-D heart failure hospitalisation	0.0295 (0.0119)	0.0062	0.0529	Beta ($\alpha=51$, $\beta=1666$)	[63–65]
CRT-P heart failure hospitalisation	0.0222 (0.0076)	0.0072	0.0371	Beta ($\alpha=32$, $\beta=1424$)	[21, 61–64]
OMT heart failure hospitalisation	0.0662 (0.0228)	0.0216	0.1109	Beta ($\alpha=64$, $\beta=902$)	[21, 61–63]
CRT-D lead failure hospitalisation	0.0020 (0.0008)	0.0003	0.0036	Beta ($\alpha=5$, $\beta=2735$)	[9, 64, 65]
CRT-P lead failure hospitalisation	0.0021 (0.0012)	0.0000	0.0044	Beta ($\alpha=5$, $\beta=2258$)	[9, 21, 61, 64]
CRT-D infection hospitalisation	0.0008 (0.0004)	0.0000	0.0016	Beta ($\alpha=4$, $\beta=4664$)	[9, 59, 64–67]

Table 2 (continued)

Input parameter (SE)	Baseline value	DSA values		PSA distribution	References
		Lower	Upper		
CRT-P infection hospitalisation	0.0006 (0.0005)	0.0000	0.0015	Beta ($\alpha = 1.47$, $\beta = 2612$)	[9, 21, 61, 64, 67]
Arrhythmia hospitalisation	0.0073 (0.0021)	0.0032	0.0114	Beta ($\alpha = 12$, $\beta = 1634$)	[25, 65]
Device longevity in months					
CRT-D	70	48	83	Poisson (mean = 70)	[33, 55, 57]
CRT-P	125	60	127	Poisson (mean = 125)	[31–33]

DSA deterministic sensitivity analysis, PSA probabilistic sensitivity analysis, CRT cardiac resynchronisation therapy, CRT-D cardiac biventricular defibrillator, CRT-P biventricular pacemaker, NYHA New York Heart Association, OMT optimal medical therapy, SE standard error, SD standard deviation

^aCosts for CRT implementation and hospitalisations were varied by distribution of DRG case severities

^bGompertz survival curve

NYHA class (range 0.834–0.564). We assumed that patients in Markov-state “Hospital” have a reduced quality of life because hospitalisation itself can negatively affect a patient’s quality of life and, moreover, a worsened health condition has led to hospitalisation that has affected the quality of life as well. HRQoL decrements for a hospitalisation were taken from Griffiths et al. [35] according to the severity of the NYHA class (range – 0.07 to – 0.21). We applied values from other CRT cost-effectiveness studies from 0.93 to 0.6 [23, 36] and 0.815–0.44 [23, 37] as upper and lower bounds within the deterministic sensitivity analysis.

2.3.3 Costs

All costs associated with hospitalisation were calculated using the reimbursement catalogue for hospital admissions (G-DRG flat rate catalogue) [38]. Each hospitalisation could be matched to one or more diagnoses-related group (DRG) codes and each DRG code is graded in ascending case severity. The costs for a hospitalisation event were estimated from these different DRG codes and their severity grades. This was achieved by weighting the DRGs with their distribution of case severities from the G-DRG Report Browser 2018, depending on ICD and OPS (operation and procedure keys) codes [39].

For instance inpatient treatment for heart failure is grouped into four DRGs (F62A: €10,894.26; F62B: €8,058.05; F62C: €2,943.74; F62D: €794.01). Weighting these DRGs with the G-DRG-Report Browser 2018 resulted in a hospitalisation cost for heart failure of €2,926.43. All other costs related to the management of heart failure such as outpatient, rehabilitation and medication costs subject to the NYHA class were derived from Biermann et al. [40] and inflated to 2018 prices (GDP inflation rate 1.38 [41]).

Costs incurred as a result of the implementation surgery were not considered because in Germany all additional

hospital stays within 30 days are covered by one single DRG (case consolidation) and thus do not differ between CRT-D and CRT-P [42]. In the base-case analysis, we did not consider future costs that are not related to heart failure.

3 Results

The predicted median survival of CRT-D was 7.8 years and of CRT-P was 6.5 years (see Fig. 2). The median survival with OMT was 4.1 years. Treatment of patients with CRT-D caused an average cost of €32,447, treatment with CRT-P an average cost of €18,502 and with OMT €5,472. Hence, CRT-D compared to CRT-P resulted in €13,945 incremental costs per patient. The incremental cost of CRT-P compared to OMT was €13,029. When comparing CRT-D to CRT-P, 0.57 incremental QALYs were gained over the time horizon. Comparing CRT-P to OMT, 2.23 incremental QALYs were gained. The ICER was €24,659 per additional QALY for CRT-D compared to CRT-P and €5,837 for CRT-P versus to OMT respectively. Table 3 shows the disaggregated results for CRT-D to CRT-P and CRT-P to OMT for different model runtimes.

3.1 Sensitivity Analysis

The top ten most influential input parameters on the ICER are depicted in a tornado diagram in Fig. 3a. The survival benefit (hazard ratio) of CRT-D compared to CRT-P was the input parameter with the most influence on the ICER. As an illustration of how strongly the survival benefit influenced the ICER, Fig. 3b shows the ICER as a function of the survival benefit, using the CI of the hazard ratio (0.67–0.99) as limits. Even small changes in the survival benefit had a major influence. Other influential parameters were the device cost of a CRT-D, the device longevity for CRT-D and probability of the implementation success. In

Fig. 2 Model predicted survival curves; *RCT* randomised control trial, *CRT-D* cardiac biven- tricular defibrillator, *CRT-P* biventricular pacemaker, *OMT* optimal medical therapy

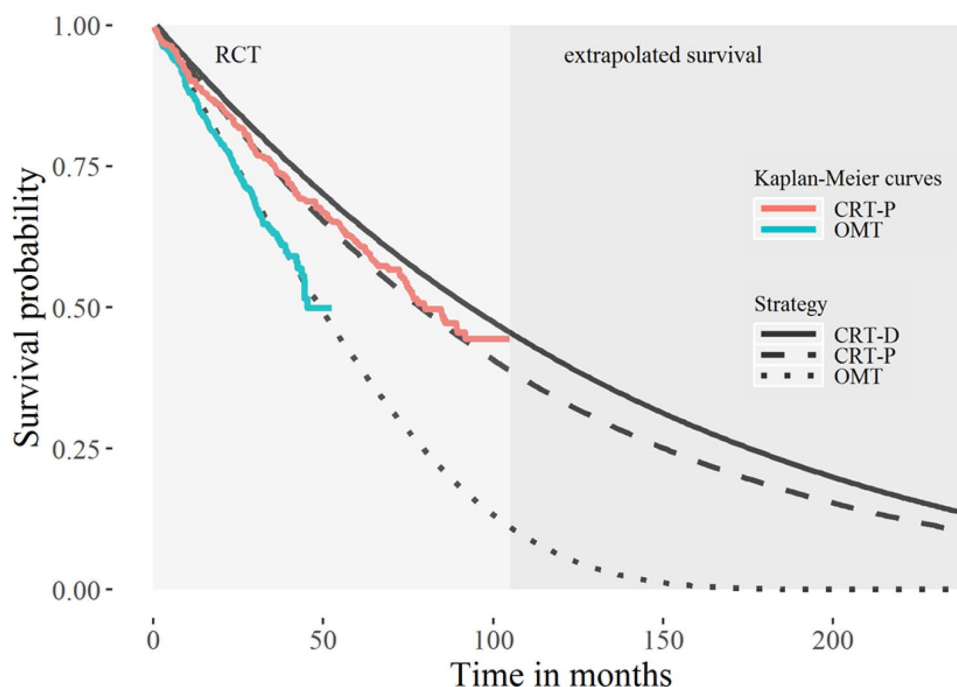


Table 3 Model results

Time horizon	Variable	CRT-D	CRT-P	Difference (CRT-D – CRT-P)	OMT	Difference (CRT-P – OMT)
<i>Base-case (20 years)</i>						
	Costs (€)	32,446.56	18,502.03	13,944.52	5472.45	13,029.58
	QALYs	5.787	5.222	0.565	2.989	2.232
	ICER			24,659.21		5837.03
<i>15 years</i>						
	Costs (€)	30,685.35	18,050.36	12,634.99	5471.65	12,578.71
	QALYs	5.363	4.895	0.468	2.989	1.906
	ICER			27,016.15		6599.15
<i>Maximum follow-up (9 years)</i>						
	Costs (€)	26,559.03	15,727.07	10,831.96	5308.39	10,418.67
	QALYs	4.269	4.005	0.264	2.899	1.106
	ICER			41,019.68		9,422.85

CRT-D cardiac biventricular defibrillator, *CRT-P* biventricular pacemaker, *OMT* optimal medical therapy, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

further sensitivity analyses other HRQoL estimates did not greatly alter the model result. With regard to different time horizons, the ICER per additional QALY for 9 years was €41,020 and for 15 years €27,016. The results of the Monte Carlo simulation are presented in the cost-effectiveness plane (Fig. 3c). In total, 96% of all simulated cases were in the north-east quadrant with positive incremental costs and positive incremental QALYs. In 4% of the simulated cases CRT-P was dominant. The average ICER of the Monte Carlo simulation was €22,477 for an additional QALY. In the probabilistic sensitivity analysis, not the costs for

hospitalisations were varied, but the distributions of the DRG severity. In Fig. 3d the cost-effectiveness acceptability curve (CEAC) is illustrated. It displays the probability of being cost-effective at a given willingness-to-pay.

3.2 Scenario Analysis

Five scenario analyses were conducted for the cost-utility analysis of CRT-D compared to CRT-P. First, life-years (LY) were chosen as an outcome parameter. The ICER was €18,945 per additional LY. Second, to capture overall digitalisation and

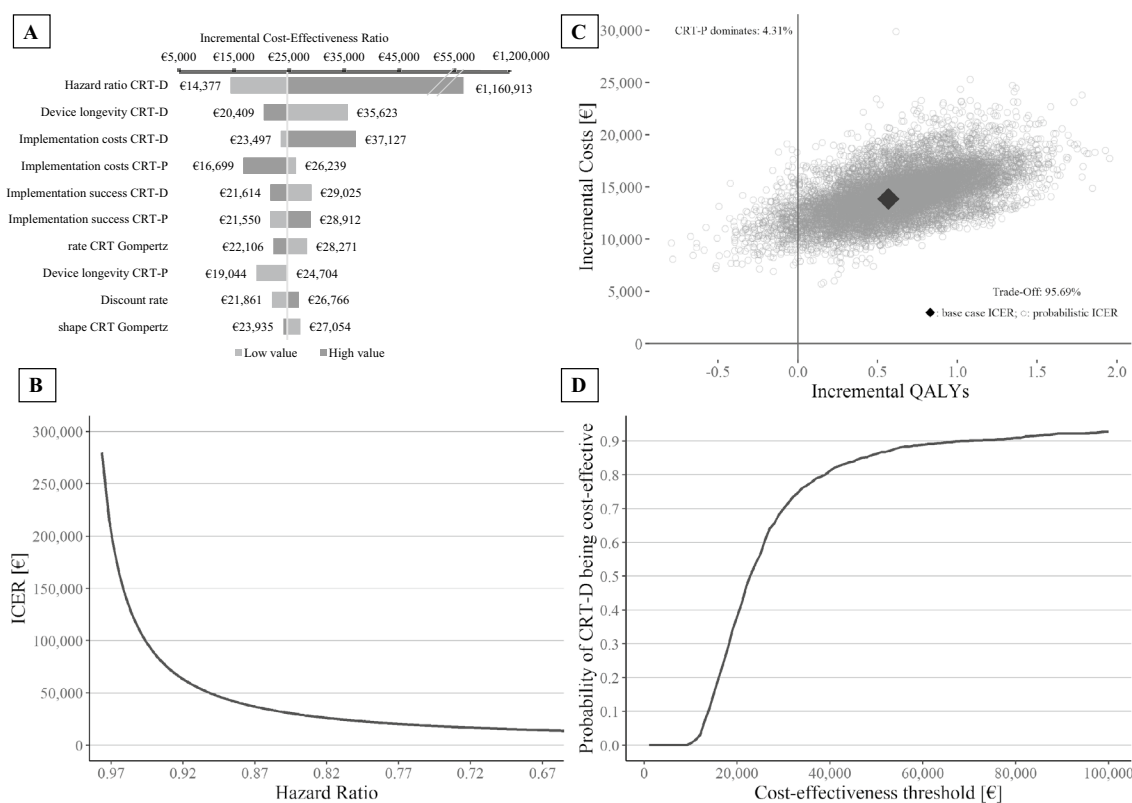


Fig. 3 Results of sensitivity analysis of the cost-utility analysis. **a** Tornado diagram; **b** incremental cost-effectiveness ratio as a function of the hazard ratio; **c** Monte-Carlo simulation; **d** cost-effectiveness

acceptability curve. *CRT-D* cardiac biventricular defibrillator, *CRT-P* biventricular pacemaker, *ICER* incremental cost-effectiveness ratio

parametrisation uncertainty, the parametrisation of the CARE-HF trial by Colquitt et al. [11] was used to model survival. Using these data the ICER yielded €21,597 per additional QALY. Since the CARE-HF study is older it can be assumed that the treatment of heart failure has changed over time. Third, to account for possible treatment changes, the Kaplan–Meier curve for CRT-P of a long-term observational study was parametrised [43] and for CRT-D the hazard ratio was applied. This scenario yielded an ICER of €22,073 per additional QALY. This is just a rough estimate because the digitalised Kaplan–Meier curve was a little imprecise (only 550 of 580 deaths could be reconstructed). The estimated median survival varied only slightly between the different parametrisations. Corrao et al. [44] estimated the probability of death within 30 days of hospital discharge (0.047). As a fourth scenario analysis, this estimate was used to correct the probability of hospital mortality upwards for the period after the maximum follow-up. The ICER was €26,006 per additional QALY. Fifth, we calculated the ICER for additional future costs that were unrelated to heart failure. Applying an additional €7,275 per year for individuals aged 65–84 years and €16,616 for individuals over 85 years [45] resulted in an ICER of €34,460 per additional QALY.

4 Discussion

Applying a cohort Markov-modelling approach, we aimed to assess evidence on the cost-effectiveness of the CRT-D compared to CRT-P from a payer's perspective. The development of the model was supported by systematic reviews for modelling heart failure, in particular CRT [42–44], various cost-effectiveness CRT studies [11, 36, 37], as well as by feedback from a cardiologist.

In the base case, therapy with CRT-D was more effective but also more costly. For the German healthcare system there was already one study for CRT-D compared to OMT [15] and one study for CRT-P compared to OMT [14]. Both CRTs were found to be more effective than OMT. Our study added the indirect comparison of CRT-D to CRT-P. In addition, we also compared CRT-P to OMT. In the comparison of CRT-D to CRT-P, the resulting ICER was €24,659 per additional QALY and €5,837 for CRT-P to OMT, respectively.

Our estimated ICER is lower than the ICERs reported in other studies investigating the cost-effectiveness of CRT-D to CRT-P. The range of costs per additional QALY reported

in the literature is €30,447–€56,719 in 2014 prices [24]. Most of the studies are based on survival data from COM-PANION or CARE-HF. However, the other analyses differ significantly from ours in utility weights, CRT device runtime, model time horizon, and the hazard ratio used. ICER differences could also be attributed to modelling disparities. A further reason for the lower ICER could be decreased costs for CRT devices over time or the reduced price difference between the CRT devices. The British HTA by Colquitt et al. [11] reported an ICER of €30,420 per additional QALY, which is quite similar to our one [24].

In Germany no official threshold exists for the assessment of cost-effectiveness. If one follows the result of a recent study that surveyed individuals in Germany about their willingness to pay (WTP) per additional QALY, CRT-D would not be cost-effective. In the study, the WTP ranged from €8580 to €18,420 per additional QALY [46]. CRT-P, on the contrary, would be cost-effective compared to OMT in relation to the specific WTP per QALY. According to the NICE guideline, the ICER for an additional QALY would be cost-effective [range €23,600–€35,400; 1.18 as exchange rate (27 March 2019)] [47]. The CEAC (Fig. 3d) can be interpreted as the probability of being cost-effective at a given threshold from a payer's perspective. Taking the upper boundary of the NICE threshold as a hypothetical WTP, CRT-D would be cost-effective with a probability of 77% for an additional QALY.

With respect to the sensitivity analysis the model was robust, only 4% of the probabilistic ICERs were in the North-West quadrant. However, the model results have sensitively responded to changes in the survival benefit. It had by far the strongest influence on the model results. There is an ongoing debate about the additional value of the defibrillator in science [48, 49]. For instance, a reduction of sudden cardiac death as a result of improved medical therapy such as sacubitril/valsartan or improved utilisation of beta blockers, ACE inhibitors and mineralocorticoid antagonists [50], would be expected to decrease the survival benefit of CRT-D and thereby increase the ICER. In addition, Shen et al. [51] reported that the rate of sudden cardiac death in heart failure studies decreases over time. Furthermore, in patients who survived the first 5 years after implementation, the risk of sudden cardiac death was low, and the type of device was not a significant predictor for survival [48]. For this reason, the survival benefit of CRT-D decreased steadily after the maximum follow-up time in the meta-analysis [12]. A reduced survival benefit could be seen as critical in terms of harms aligned with CRT-D devices, such as device malfunctions, increased complication risk or impaired quality of life due to inadequate shocks [52, 53, 54].

Discussions pertaining the impact of survival benefits on cost-utility of CRT-D must be approached with caution, as

the model input data for survival comes with some degree of uncertainty. While we acknowledge that we have used the best available hazard ratio for the survival benefit, there are some restrictions. First, the survival curves of CRT-P and OMT have been extrapolated to a long term scenario. Second, since no direct comparison of CRT-D to CRT-P was available in an RCT, the death probability of CRT-D was estimated with a hazard ratio applied to the survival curve of CRT-P.

Another influential input parameter was the device longevity. Device life and device changing costs are interconnected. With higher battery capacity, the high device changing costs would be incurred less frequently. Technological progress in battery capacity would change the ICER in favour of CRT-D. There are some studies on the longevity of CRT-D devices [55, 56], but there are no studies explicitly researching for CRT-P device longevity [2], and Colquitt et al. [11] noted that the estimates that were reported by NICE [33] could be overestimated. The ICER for a model horizon of 15 years was comparable to the base-case ICER, but if the model horizon was only 9 years, the survival advantage was not so pronounced.

The study has several limitations. First, as already mentioned, the input parameters were derived from older studies. Thus, evidence may be outdated considering the significant progress that has been made in treatment of heart failure patients. To control for this effect in the scenario analysis, the Kaplan–Meier curves of the recent 16-year-long observational study by Leyva et al. [43] were used to model survival, which did not change the results substantially. Second, hospitalisation costs were modelled accurately while outpatient and medication costs were approximated, and costs of sacubitril/valsartan were not included. However, this bias is assumed to be negligible because these parts of the costs were comparatively low. Third, there are more complex approaches to model heart failure that take more possible events into account, but the data basis is partly not sufficient and moreover the survival benefit superimposes most input parameters. Fourth, the probability of hospitalisation or death was not based on time-dependent variables like previous hospitalisations, since no data were available. Fifth, information on NYHA class changes was only available until the 19th month. The cost of monthly NYHA management and utilities depends on NYHA classes. We conducted scenario analyses, assuming the same NYHA class distribution for OMT and CRT for the remaining runtime. Model results were not sensitive to changes in this parameter.

In contrast to Yao et al. [37] and Colquitt et al. [11], this modelling approach did not distinguish between different mortality sub-classifications, because otherwise the hazard ratio by Woods et al. [12] would not have been sufficient to inform the model. The hazard ratio is taken from a patient data network meta-analysis of RCT-CRT studies, and was

therefore assumed to be the best available evidence. Moreover, such a division of mortality could be inaccurate [12], and Cleland et al. [28] only reported number at risk in the Kaplan–Meier curves for all-cause death, which was needed to digitalise the curves with the highest accuracy.

A strength of the modelling is the use of pooled-effect estimators for the input parameters wherever feasible. To check for inaccuracy in the digitalisation process of the Kaplan–Meier curves, the parametrisation of Colquitt et al. [11] was used, which did not change the ICER.

5 Conclusions and Future Research

A literature-based cohort Markov-model was developed to examine cost-effectiveness for CRT-D to CRT-P from a payer's perspective in Germany. CRT-D compared to CRT-P was more effective but also more costly, yielding an ICER of €24,659 for an additional QALY and an ICER of €18,945 for an additional life-year. Future technological changes in device longevity or lower device costs for CRT-D could reduce the ICER. Although results have to be seen in the context of uncertainty especially concerning the survival benefit, our sensitivity analysis shows that our model results were robust. For a reduction of uncertainty a direct comparison under RCT conditions with a longer follow-up would be desirable. It could provide the necessary data to perform subgroup analyses at the patient level to weigh the advantages and disadvantages more properly.

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Author Contributions All authors contributed to the study concept and the critical revision of the manuscript for important intellectual content. Material preparation, data collection, analysis and production of the first draft were performed by MH. Writing, review editing and interpretation of the results were carried out by F-SF, NE, CE, ND, GH and AK.

Data Availability All data used for this study are public and referenced throughout the manuscript. The Excel sheet and the R code are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

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Device runtime and costs of cardiac resynchronization therapy pacemakers – a health claims data analysis

Gerätelaufzeit und Kosten von kardialen Resynchronisationsschrittmachern – eine Routinedatenanalyse

Abstract

Introduction: This study investigates the runtime and costs of biventricular defibrillators (CRT-D) and biventricular pacemakers (CRT-P). Accurate estimates of cardiac resynchronization therapy (CRT) device runtime across all manufactures are rare, especially for CRT-P.

Methods: Health claims data of a large nationwide German health insurance was used to analyze CRT device runtime. We defined device runtime as the time between the date of implantation and the date of generator change or removal. The median costs for implantation, change, and removal of a CRT device were calculated accordingly.

Results: In total, the data set comprises 17,826 patients. A total of 4,296 complete runtimes for CRT-D devices and 429 complete runtimes for CRT-P devices were observed. Median device runtime was 6.04 years for CRT-D devices and 8.16 years for CRT-P devices (log-rank test $p < 0.0001$). The median cost of implantation for a CRT-D device was 14,270 EUR, and for a CRT-P device 9,349 EUR.

Conclusions: Compared to CRT-P devices, CRT-D devices had a significantly shorter device runtime of about two years. Moreover, CRT-D devices were associated with higher cost. The study provides important findings that can be utilized by cost-effectiveness analyses.

Keywords: cardiac resynchronization therapy, device longevity, device runtime, battery runtime, health claims data

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Zusammenfassung

Einleitung: Diese Studie untersucht die Laufzeit und Kosten von biventrikulären Defibrillatoren (CRT-D) und biventrikulären Schrittmachern (CRT-P). Genaue Schätzungen der Laufzeit von Geräten für die kardiale Resynchronisationstherapie (CRT) über alle Hersteller sind selten, insbesondere für CRT-P.

Methoden: Zur Analyse der CRT-Gerätelaufzeit wurden Routinedaten einer großen bundesweiten deutschen Krankenkasse verwendet. Wir definierten die Gerätelaufzeit als die Zeit zwischen dem Datum der Implantation und dem Datum des Generatorwechsels oder der Entfernung. Die medianen Kosten für Implantation, Wechsel und Entfernung eines CRT-Gerätes wurden ebenfalls berechnet.

Ergebnisse: Insgesamt umfasst der Datensatz 17.826 Patienten. Es wurden insgesamt 4.296 komplette Laufzeiten für CRT-D-Geräte und 429 komplette Laufzeiten für CRT-P-Geräte beobachtet. Die mediane Geräte-Laufzeit betrug 6,04 Jahre für CRT-D-Geräte und 8,16 Jahre für CRT-P-Geräte (Log-Rank-Test $p < 0,0001$). Die medianen Implantationskosten betrugen 14.270 EUR für ein CRT-D-Gerät und 9.349 EUR für ein CRT-P-Gerät.

Fazit: Im Vergleich zu CRT-P-Geräten hatten CRT-D-Geräte eine signifikant kürzere Gerätelaufzeit von etwa zwei Jahren. Außerdem waren CRT-D-Geräte mit höheren Kosten verbunden. Die Studie liefert wichtige Ergebnisse, die in Kosten-Effektivitätsanalysen verwendet werden können.

Schlüsselwörter: kardiale Resynchronisationstherapie, Gerätelangzeitigkeit, Gerätelaufzeit, Batterielaufzeit, Routinedaten

1 Introduction

Cardiac resynchronization therapy (CRT) is an established form of treatment for heart failure patients. In addition to the survival benefit, the runtime of a CRT device and its cost are decisive factors in evaluating the cost-effectiveness of CRT devices. Like any surgery, CRT device replacement carries the risk of complications such as infections [1], [2] and puts an economic burden on the healthcare system.

Biventricular defibrillator (CRT-D) or biventricular pacemaker (CRT-P) [3] implantation is indicated for primary prevention in patients with symptomatic heart failure of New York Heart Association (NYHA) classes II–IV, reduced ejection fraction $\leq 35\%$, and broad QRS complex. A CRT-D device combines the functions of a CRT-P device with the addition of a defibrillator [4]. Due to shocks delivered by the defibrillator in the CRT-D device, the battery may be depleted earlier.

In health economic modelling approaches, a high variability of the assumed CRT device runtime could be observed [5]. However, CRT device runtime is one of the most important input parameters for evaluating cost-effectiveness, since CRT-D devices are more expensive than CRT-P devices and the costs of device replacement and device runtime are interrelated. In addition, a modeling study found that longer battery runtime reduces adverse events such as infections, device revisions, and costs [6].

Several clinical studies report the device longevity of CRT-D or implantable cardioverter defibrillators [7], [8], [9], and recent medical publications focus more on runtime differences between device manufacturers [10]. However, to our knowledge, information on CRT-P longevity is scarce [11], yet for cost-effectiveness analysis, valid device runtime estimates are crucial. In addition, device longevity is often defined as the time until battery depletion [8], [9]. However, from a public health perspective, the overall median runtime is relevant regardless of the manufacturer. Therefore, this study aims to evaluate the runtime and costs of CRT devices from implantation to replacement for any reason, using health claims data of a major German statutory health insurance provider for the years 2006 to 2019.

2 Methods

2.1 Data source and setting

To evaluate device runtime and to estimate costs, a retrospective health claims data analysis was performed. The analysis was based on health claims data from BARMER, a large nationwide statutory health insurance with 8.8 million insured [12]. In Germany, health insurance is mandatory, and the vast majority (approx. 90%) of the German population is insured in a statutory health insurance such as BARMER [13]. The BARMER database contains the complete longitudinal anonymized health claims data of all insured persons for the years 2005 to 2019 with information on e.g. costs, utilization, and socio-demographics. The age and gender distribution of BARMER insured can be generalized to the German population [14], [15].

2.2 Sample selection

To determine the runtime of CRT devices, all CRT implantations or device upgrades in the database were selected from the years 2006–2019. Implantation, change, and removal of a device were selected according to the Operation and Procedure Codes (OPS), an adaptation of the International Classification of Procedures in Medicine [16]. The first year (2005) was excluded from the analysis because OPS codes could not be distinguished between CRT-P and CRT-D devices.

All patients in the database who were coded with a CRT device implantation, device change, or device upgrade were selected ($N=19,899$). Patients who had been downgraded during the observational period were excluded ($n=64$), as well as patients who had an ambiguous OPS coding ($n=277$). Patients in whom neither de novo implantation nor device upgrade was coded first were excluded for analysis ($n=1,521$), as were patients who were not continuously insured in BARMER after CRT implantation ($n=134$). The final sample included 17,826 patients. More detailed information on the exclusion of patients is given in the flowchart (Figure 1).

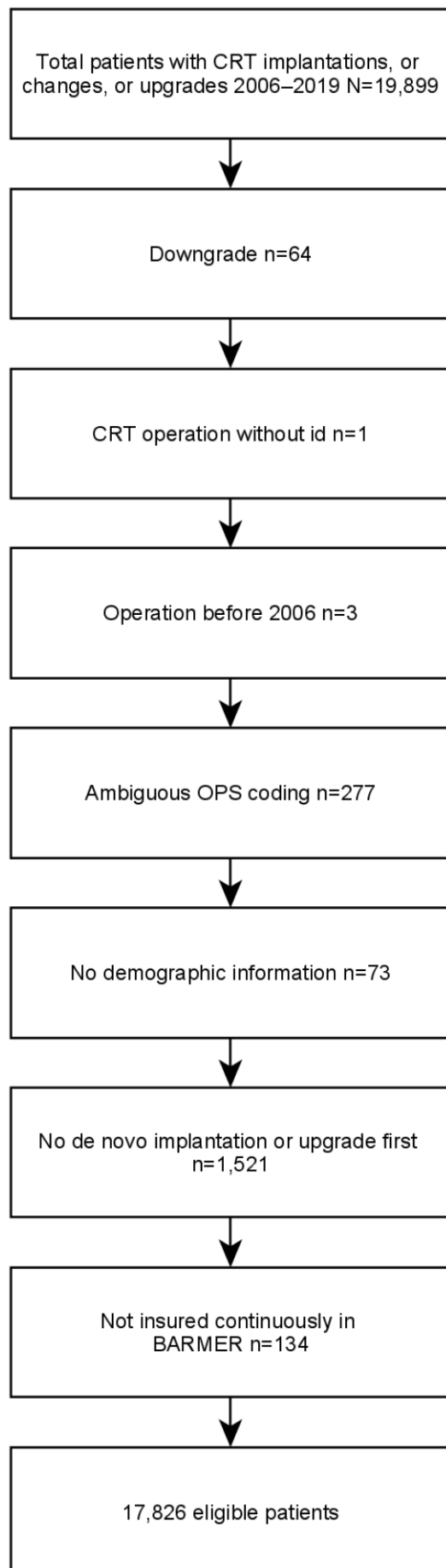


Figure 1: Flowchart

2.3 Outcomes

The main outcome was device runtime. The index date was defined as the date of device implantation or upgrade to a CRT device. Follow-up was defined as the time between the implantation and the date of generator change or removal for any reason or censoring. Reasons for censoring included death of the patient, a change in health insurer, or that the device was still in use at the end of the observation period, i.e. Dec. 31, 2019. Beside device runtime, considered outcomes were median costs in euros for implantation, generator change, and removal per device. To account for inflation in prices, only cost data for 2019 were used. In addition, we illustrate the median price development over time per device.

2.4 Statistical analysis

Median runtime per device type was calculated (two-sided 95% confidence interval). Time-to-event rates for device replacement were illustrated by Kaplan-Meier curves. Differences between CRT-D and CRT-P were analyzed using the long-rank test. A p -value of <0.05 was considered statistically significant. Statistical analysis was carried out in "R" [17]. In order to check if results were robust, we performed three sensitivity analyses.

3 Results

In total, 17,826 patients had a CRT implantation or upgrade in the years from 2006 to 2019. These patients caused 18,246 device implantations or upgrades, 4,043 generator changes, and 371 device removals. Of these 22,660 cases, 18,404 were CRT-D devices and 4,256 were CRT-P devices. Figure 2 illustrates the annual proportion of CRT devices types out of all CRT implantations per year. CRT-P cases were comparatively low, but have risen slightly in recent years. Per patient, the median follow-up time was 2.89 years (interquartile range 1.26–4.79 years). On average, CRT-P patients were 6.4 years older than CRT-D patients at their first CRT implantation, and more often female (Table 1).

A total of 4,725 complete runtimes were observed. Of these, 4,296 were CRT-D runtimes and 429 were CRT-P runtimes. The median device runtime was 6.04 years (95% confidence interval (CI) 6.00; 6.10) for CRT-D devices and 8.16 years (95% CI 7.93; 8.59) for CRT-P devices. The device survival is depicted in the Kaplan-Meier curves (Figure 3), indicating a difference in device runtime per type (log-rank test $p<0.0001$).

To validate the results of CRT runtimes, we conducted three sensitivity analyses. In the first analysis, only cases from 2010 or later were selected, which resulted in a median runtime of 6.29 years (95% CI 6.22; 6.39) for CRT-D and 8.00 years (95% CI 7.65; 8.44) for CRT-P. Second, observations with a runtime longer than 10 years were excluded, yielding a median runtime of 6.01 years (95% CI 5.95; 6.06) for CRT-D devices and 7.96 years

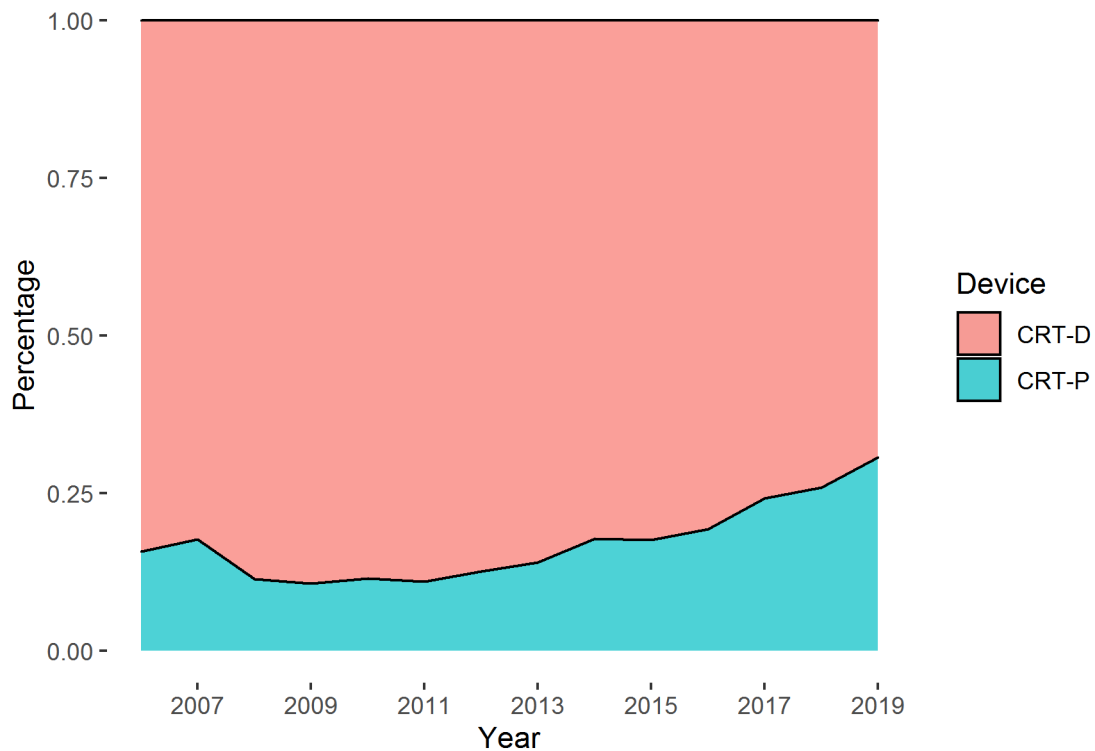


Figure 2: Proportion of CRT-D and CRT-P implantations per year out of all CRT implantations

Table 1: Patient characteristics, device runtime, and cost

Variable	CRT-D	CRT-P
Patients (first device implantation)	14,092	3,734
Device implantations (n)	14,401	3,845
Generator changes (n)	3,690	353
Device removals (n)	313	58
<i>Patient characteristics</i>		
Age (years), mean $\pm$ standard deviation	70.4 $\pm$ 9.82	76.8 $\pm$ 10.1*
Sex, female no (in %)	3,858 (27%)	1,447 (39%)*
<i>Device runtime; mean (95% CI)</i>		
Complete Sample	6.04 (6.00; 6.10)	8.16 (7.93; 8.59)
Sensitivity analysis device runtime: only implantations since 2010	6.29 (6.22; 6.39)	8.00 (7.65; 8.44)
Sensitivity analysis device runtime: only device runtime <10 years	6.01 (5.95; 6.06)	7.96 (7.72; 8.27)
Sensitivity analysis device runtime: only 1 case per individual	6.08 (6.02; 6.15)	8.27 (8.00; 8.66)
<i>Costs; median in EUR (IQR)</i>		
CRT implantation	14,270 (13,987–14,797)	9,349 (9,186–10,485)
CRT change	8,417 (7,502–8,916)	5,226 (4,982–5,969)
CRT removal	12,258 (8,884–17,284)	13,019 (10,858–20,980)

CRT-P = cardiac biventricular pacemaker; CRT-D = cardiac biventricular defibrillator; CI = confidence interval; IQR = interquartile range; *p-value for difference between the two groups <0.001

(95% CI 7.72; 8.27) for CRT-P devices. In the third sensitivity analysis, just one runtime observation per patient was considered, resulting in a median runtime of 6.08 years (95% CI 6.02; 6.15) for CRT-D devices and 8.27 years (95% CI 8.00; 8.66) for CRT-P devices.

The median cost of a CRT-D device implantation in 2019 was 14,270 EUR, 8,417 EUR for a generator change, and 12,258 EUR for a device removal. The median cost was 9,349 EUR for a CRT-P implantation, 5,226 EUR for a generator change, and 13,019 EUR for a device removal. Further information is given in Table 1.

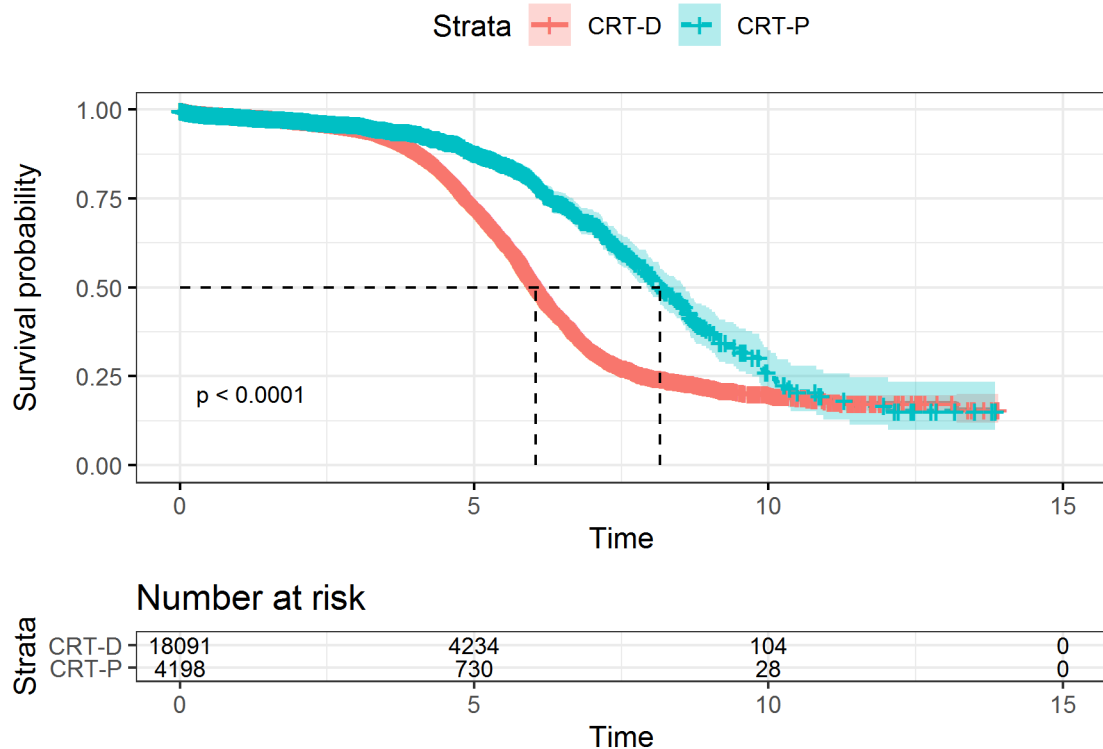


Figure 3: Kaplan-Meier curves for event-free survival of CRT devices (time to generator change/removal): CRT-D (blue), CRT-P (red)

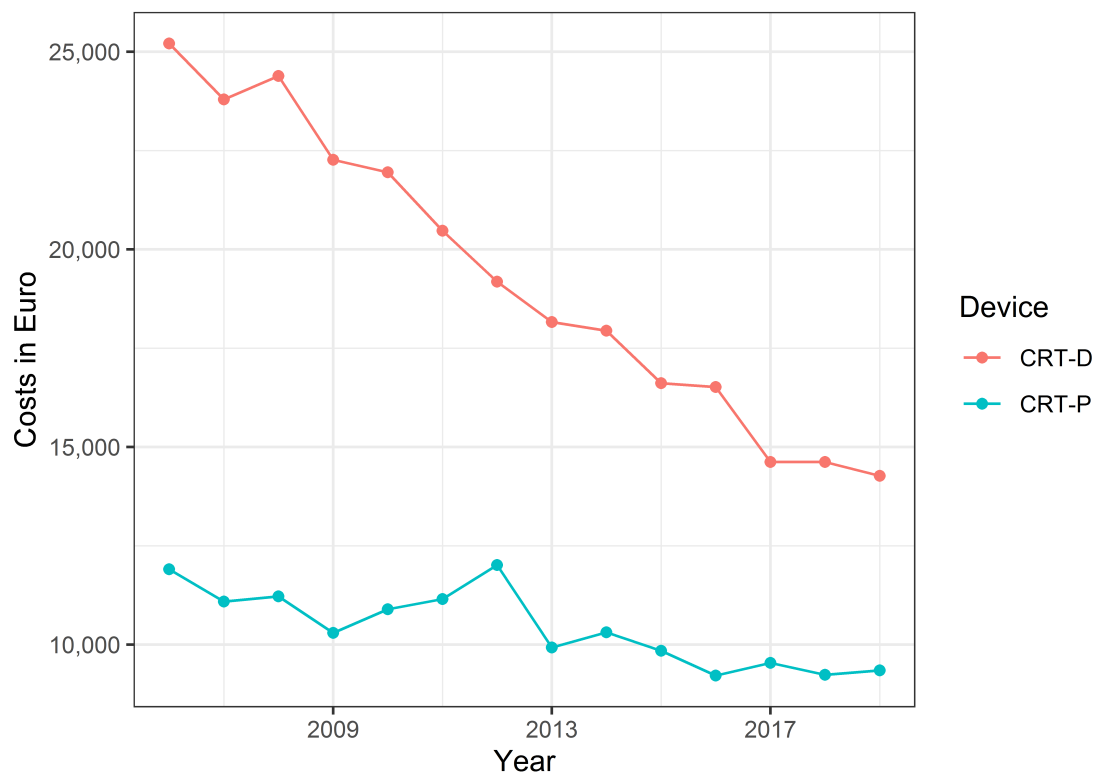


Figure 4: Development of the median implantation cost of the CRT devices

In Figure 4, the development of the median implantation cost of the CRT devices over time is depicted. Cost for CRT-P devices was stable over time, whereas cost for a CRT-D implantation decreased constantly.

4 Discussion

The analysis of CRT device runtime with routine data of a major German health insurance provider resulted in a median device runtime of 6.04 years for CRT-D and 8.16 years for CRT-P. CRT-D devices had a significantly

($p < 0.0001$) shorter runtime compared to CRT-P devices. The results are robust in three sensitivity analyses. CRT-D operations were associated with higher costs for implantation and generator change. Costs for device removal were slightly higher in CRT-P devices.

Overall, the result of the CRT-D runtime is similar to most other estimates from related studies. Landolina et al. [8] report a probability of survival free from battery depletion of 54% at 5 years for CRT-D. Zanon et al. [9] state a median device longevity of 4.9 (4.0–5.7) years for CRT-D. Time to battery depletion also differs by manufacturer and deviates significantly from published product performance reports [8], [18], [19]. In our analysis, we used survival data, and devices that were still operating at the end of the observation period had to be censored, which could potentially reduce the overall runtime.

The median longevity estimates reported in a final appraisal of a manufacturer's submission from the National Institute for Health and Care Excellence is the only source to our knowledge which reports the longevity of CRT-P devices. The median survival time of CRT devices is given as 10.4 years for CRT-P and 5.8 years for CRT-D. Estimates were calculated using Weibull curves. The runtime was calculated using data from the NHS Central Cardiac Audit Database for the years 2000 to 2011 [11]. The longevity result for CRT-D devices is comparable. However, the median runtime of CRT-P devices differs considerably from our results. The stated median longevity of CRT-P devices is 2.24 years higher than our results. Colquitt et al. [4] point out that clinicians have informed them that these runtimes may be overestimated.

Precise longevity estimates of CRT devices are important for health economic evaluations, as it is known that device runtime is a critical parameter in assessing cost-effectiveness [5]. Moreover, device cost is an important input parameter which is interconnected with device longevity. If the device lasts longer, the device must not be replaced as often, resulting in cost reduction [20]. The assumed device longevity in cost-effectiveness analysis differs approximately ± 2 years from the estimated result for CRT-P devices [4], [21], [22], [23], [24].

From the patient's perspective, a long runtime of the device is desirable because each admission to a hospital is associated with the risk of infection, and the operation with the risk of complications. Furthermore, CRT-D devices are more likely to cause problems compared to CRT-P devices [2], which could also be a reason for the shorter device runtime. A device runtime that matches the life expectancy of patients would save additional hospital admissions [25]. In addition, older age is positively correlated with complications in CRT devices [26].

Costs for CRT-D therapy are considerably higher than for CRT-P therapy. On average, the cost difference between a CRT-D implantation and a CRT-P implantation is 4,921 EUR, which is nearly half of the cost of a CRT-P device. Device cost is an important parameter in cost-effectiveness analysis, which is interconnected with the device runtime, and costs for device change are 3,191 EUR higher for CRT-D devices. It is known that

device runtime is a critical parameter in assessing cost-effectiveness [5]. If the device lasts longer, the device must not be replaced as often, resulting in cost reduction [20]. Device costs decreased over time, especially the implantation costs of CRT-D devices (Figure 4), which may be due to changes in the relative cost weights in the German diagnosis-related group codes. Holding all other parameters constant, the reduced cost difference has a positive effect on the incremental cost-benefit ratio of CRT-D devices compared to CRT-P devices. There is no randomized clinical trial with sufficient power for a direct comparison between CRT-P and CRT-D, and the additional defibrillator is still controversial. The still substantial cost differences between the two devices highlight the importance of cost-effectiveness analysis.

Due to the data's special characteristics, the analysis is limited in several ways. In the health claims data, the manufacturer of the device or the battery type could not be observed. For this reason, it was not possible to examine differences in the runtime of devices between manufacturers, which may vary significantly [9], [27]. Second, due to data unavailability, no influencing control variables like pacing mode could be included in the analysis. Third, a complete cost-effectiveness analysis would require survival data from CRT patients. However, for a comprehensive evaluation of the two CRT devices, this analysis provides robust estimates of device runtime, implantation costs, and change costs.

The usage of health claims data has major strengths. Real-world data with a long timeframe were used for the estimation of the device runtime and device complications. The analysis did not examine the battery longevity, but the entire device runtime including replacement due to device malfunctions, among other reasons, which is the more relevant parameter for patients, clinicians, and health insurance providers. For the medical practice it is important to know how long a complete CRT device runtime is and not only the battery longevity.

5 Conclusions

Using health claims data of 17,826 patients for researching CRT device runtime revealed a median device runtime of 6.04 years for CRT-D and 8.16 years for CRT-P. Results were robust in various sensitivity analyses. Besides a shorter device runtime, the costs are higher in CRT-D devices. For clinical practice, estimates of device runtime provide additional information for device selection in patients who have an indication for a CRT-D or CRT-P device. In addition, proper runtime data are crucial for a reliable evaluation of cost-effectiveness in this patient group. More information on device longevity of CRT-P devices, data on the respective manufacturer, battery technology used, and reason for replacement are needed. The study provides important findings that can be utilized by cost-effectiveness analyses.

Notes

Availability of data

The data that support the findings of this study are owned by BARMER (Wuppertal, Germany) and are not publicly available.

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Competing interests

The authors declare that they have no competing interests.

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Survival of patients undergoing cardiac resynchronization therapy with or without defibrillator: the RESET-CRT project

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Aims

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure. There is contradictory evidence whether defibrillator capability improves prognosis in patients receiving CRT. We compared the survival of patients undergoing *de novo* implantation of a CRT with defibrillator (CRT-D) option and CRT with pacemaker (CRT-P) in a large health claims database.

Methods and results

Using health claims data of a major German statutory health insurance, we analysed patients with *de novo* CRT implantation from 2014 to 2019 without indication for defibrillator implantation for secondary prevention of sudden cardiac death. We performed age-adjusted Cox proportional hazard regression and entropy balancing to calculate weights to control for baseline imbalances. The analysis comprised 847 CRT-P and 2722 CRT-D patients. Overall, 714 deaths were recorded during a median follow-up of 2.35 years. A higher cumulative incidence of all-cause death was observed in the initial unadjusted Kaplan–Meier time-to-event analysis [hazard ratio (HR): 1.63, 95% confidence interval (CI): 1.38–1.92]. After adjustment for age, HR was 1.13 (95% CI: 0.95–1.35) and after entropy balancing 0.99 (95% CI: 0.81–1.20). No survival differences were found in different age groups. The results were robust in sensitivity analyses.

Conclusion

In a large health claims database of CRT implantations performed in a contemporary setting, CRT-P treatment was not associated with inferior survival compared with CRT-D. Age differences accounted for the greatest part of the survival difference that was observed in the initial unadjusted analysis.

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Key question

Is the defibrillator capability needed in cardiac resynchronization therapy (CRT)?

Aim: Compare survival of patients receiving *de novo* CRT with and without defibrillator option between 2014 and 2019.

Health claims data, same inclusion and exclusion criteria as in RESET-CRT randomized trial.

Key finding

CRT-P patients 6.7 years older than CRT-D patients.

Comparable aetiology of heart failure.

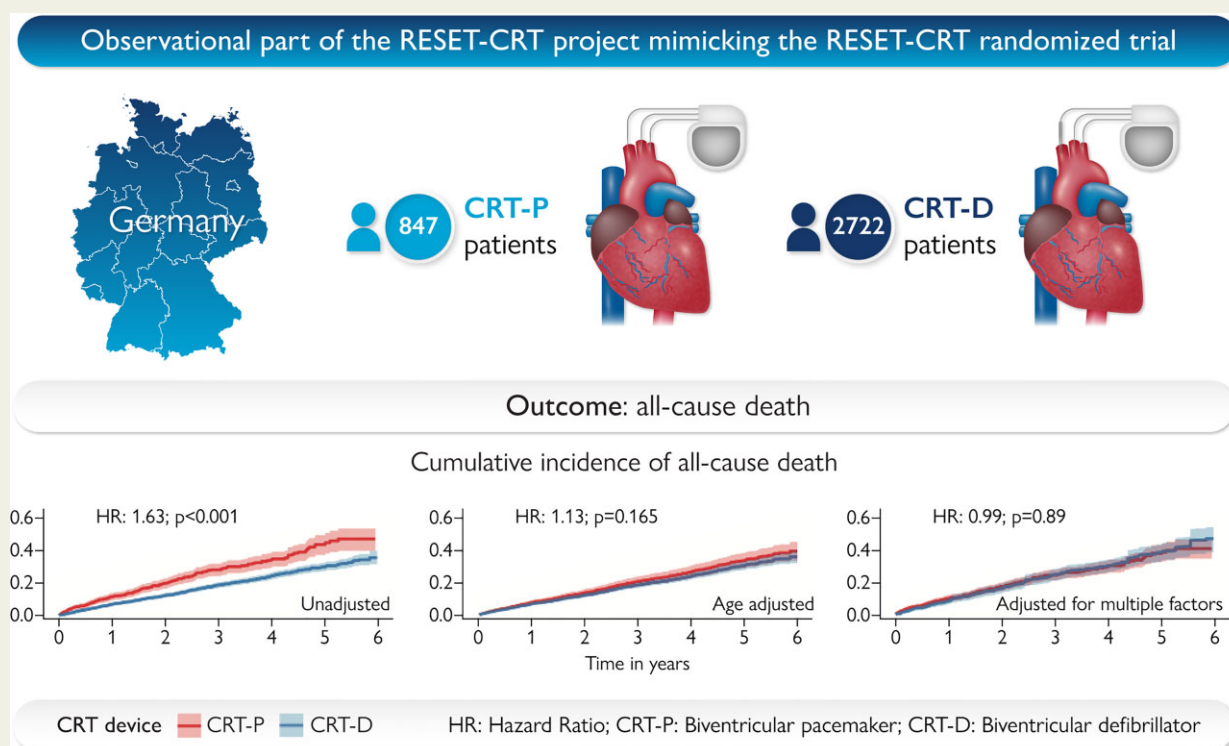
Median follow-up 2.35 years: 203 (24%) deaths in CRT-P and 511 (19%) deaths in CRT-D patients.

Age differences accounted for the greatest part of the survival difference.

Take-home message

No survival differences between CRT-D and CRT-P after adjustment for age and entropy balancing.

Results corroborate the hypothesis of the RESET-CRT randomized clinical trial.



Structured Graphical Abstract Comparison of patients undergoing *de novo* implantation of a cardiac resynchronisation therapy device with or without defibrillator option in a large health claims database.

Keywords

Cardiac resynchronization therapy • Health claims data • Survival • Mortality • Biventricular pacemaker

Introduction

Cardiac resynchronization therapy (CRT) is one of the main treatment pillars for heart failure patients with reduced left ventricular ejection fraction and conduction abnormalities with broad QRS complex.¹ Cardiac resynchronization therapy is delivered by biventricular pacemakers (CRT-P) or by biventricular pacemakers with additional defibrillator capability (CRT-D).

The need for the defibrillator capability in this setting is debated. Cardiac resynchronization therapy reduces *per se* the risk of sudden cardiac death.² In addition, modern pharmacologic heart

failure treatment further reduces that risk leading to a substantial overall decline of sudden cardiac death^{3–6} and a decrease of the expected benefit of the defibrillator.⁷

There is no randomized clinical trial (RCT) with a head-to-head comparison between CRT-P and CRT-D. The COMPANION study compared CRT-P and CRT-D devices with optimal medical therapy, but there was no direct comparison between CRT-D and CRT-P.⁸ In the DANISH trial in patients with non-ischaemic cardiomyopathy, no benefit for CRT-D over CRT-P devices could be shown in the large trial subgroup that received a CRT device.⁹ The evidence from observational studies is also ambiguous.^{10–14} As

a result, a recent European Society of Cardiology guidelines^{1,15} and a recent position statement¹⁶ recommend an individual decision-making for the choice of the type of CRT device in patients undergoing CRT implantation based on parameters that are considered to be associated with the risk for sudden cardiac death and the competing risk for dying from other causes.

The Re-evaluation of Optimal Re-synchronization Therapy in Patients with Chronic Heart Failure (RESET-CRT) project¹⁷ addresses this clinically important evidence gap. The project consists of a large ongoing RCT¹⁸ that compares CRT-P and CRT-D in a randomized fashion with total mortality as the primary end point. The hypothesis of the RESET-CRT project is that CRT-P is non-inferior to CRT-D. In addition to the randomized trial, we compared the survival of CRT-P and CRT-D patients in a large health claims database of a statutory health insurance in Germany from 2014 to 2019 reflecting contemporary medical practice.

Methods

For the analysis of the health claims data, we applied a retrospective, non-experimental, population-based weighted cohort study design.

Setting

The survival analysis was based on health claims data of the second largest German health insurance, the BARMER, which operates nationwide and insures 10.7% of the German population, i.e. 8.9 million people.¹⁹ In Germany, health insurance is mandatory, either as private (~10% of the population) or as statutory health insurance such as the BARMER.²⁰ The BARMER database contains anonymized longitudinal information of all insured persons on the vital status, costs, utilization, and socio-demographics between 2005 and 2019. The database comprises generalizable information with a sex and age distribution which is comparable with the German population and has already been used for cardiovascular research.^{21,22} A diagnosis-related group system is used for reimbursement of inpatient treatment in Germany. Therefore, all codes of the International Classification of Diseases (ICD) and Operation and Procedure Classification (OPS) codes, an adaptation of the International Classification of Procedures in Medicine that are relevant for patient treatment are reported to the health insurance and are available in the database.

Study population

For the study population, we considered all patients in the BARMER database that underwent CRT implantation during 2014–19 ($n = 7082$). We operationalized the inclusion and exclusion criteria of the RESET-CRT randomized trial using ICD and OPS codes recorded in the BARMER database. The complete list of ICD and OPS codes that were used can be found in [Supplementary material online, Table S1](#).

In accordance with the inclusion and exclusion criteria of the RESET-CRT randomized trial, we excluded patients who were younger than 18 years ($n = 3$), without symptomatic heart failure ($n = 612$), with an indication for implantation of an implantable cardioverter defibrillator for secondary prevention of sudden cardiac death ($n = 1144$), an implanted cardiac pacemaker, defibrillator or CRT device ($n = 596$), unexplained syncope ($n = 477$), a hospitalization with unstable heart failure with New York Heart Association (NYHA) Class IV within 1 month prior CRT implantation ($n = 43$), or an acute coronary syndrome or cardiac revascularization therapy by coronary angioplasty or coronary artery bypass grafting 6 weeks prior to implantation ($n = 738$), cardiac valve surgery or percutaneous cardiac valvular

intervention such as transcatheter aortic valve replacement or transcatheter mitral valve repair within 3 month prior to CRT implantation ($n = 182$), severe chronic renal disease ($n = 125$) or on the waiting list for a heart transplant ($n = 2$). We further excluded patients who had not been consistently observed for 3 years prior to CRT implantation for risk adjustment ($n = 104$), patients without a minimum follow-up time of 3 months (or death during that period) ($n = 56$), as well as patients with no ($n = 321$) or ambiguous ($n = 141$) NYHA information prior to CRT implantation. After applying these inclusion and exclusion criteria, 3569 eligible CRT *de novo* implantations were included in the analysis. Of these, 847 were CRT-P implantations and 2722 were CRT-D implantations ([Figure 1](#)).

Outcome

The outcome was all-cause death occurring between CRT implantation and 31 December 2019. For each patient in the study cohort, it was established whether the patient had died, had left the BARMER (<1.05% of the study population) by the end of the observation period, or was still alive and BARMER paid for their health expenditures.

Covariates

Comorbidities were coded if they were recorded in the BARMER database. The complete list of ICD and OPS codes used for the identification of comorbidities can be found in [Supplementary material online](#). From the demographics, we included age and sex. From the clinical characteristics, we considered the number of hospitalizations within 1 year prior to CRT implantation (0, 1, 2, >2), NYHA Class (II, III, IV), and aetiology of heart failure (ischaemic/non-ischaemic). From the comorbidities, we included renal dysfunction (Stages III and IV), diabetes and atrial fibrillation. In addition, we added all comorbidities of the Elixhauser comorbidity groups that we had not already considered.²³

Statistical analyses

The statistical analysis was performed in three phases. First, we performed an analysis of the unadjusted cumulative incidence rates for all-cause death, illustrated by Kaplan–Meier time curves and a univariate Cox proportional hazard regression. Patients who were still alive at the end of the observational period (31 December 2019) were censored. For patients who left BARMER, the leaving date was used for censoring. The follow-up time was defined as the time between CRT device implantation (index date) and death or censoring. Patients who received a CRT-D device were the control group.

Second, we performed an analysis adjusted for age. The sample was divided into three groups: (i) younger than or equal to 65 years ($n = 898$), (ii) patients older than 65 and younger than or equal to 75 years ($n = 1207$), and (iii) patients older than 75 years ($n = 1464$). The cumulative incidence of death was illustrated by Kaplan–Meier time-to-event curves for each group and Cox proportional hazard regressions were performed. Additionally, we performed an age-adjusted Cox proportional hazard regression for the total sample. The age-adjusted cumulative incidence curves based on the Cox proportional hazard regression are illustrated, with age fixed at the sample mean.

Third, we performed an adjusted analysis using entropy balancing.²⁴ Entropy balancing is a reweighting method, which aims to produce exact covariate balance of CRT-P and CRT-D patients. Entropy balancing is considered a generalization of propensity score weighting and uses an optimization algorithm by assigning a scalar weight to each patient in the control group to balance means and variances between CRT-P patients and the reweighted CRT-D patients. The set of weights that deviates the least from the set of uniform weights is selected. In

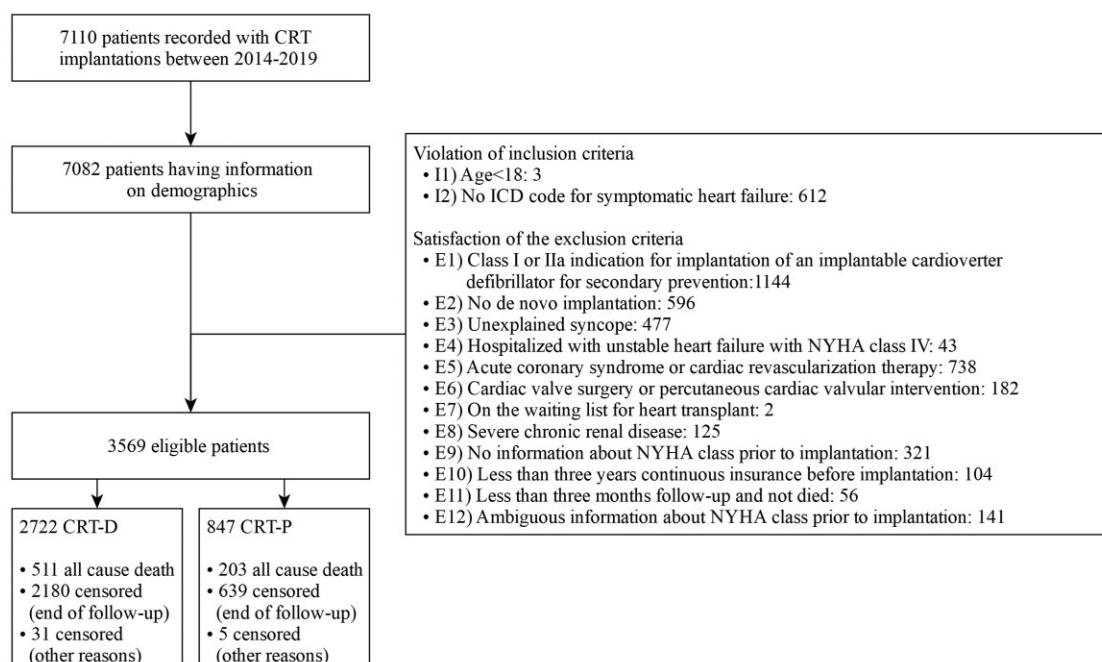


Figure 1 Flowchart. CRT-P, cardiac resynchronization therapy with pacemaker; CRT-D, cardiac resynchronization therapy with defibrillator.

entropy balancing, no case is discarded.²⁵ The estimated weights can be used like survey sampling weights in the subsequent analyses. Standardized differences were used for the balancing diagnostics instead of *P*-values.²⁶ A standardized difference >0.1 indicates a meaningful difference.²⁷ The weights of entropy balancing were used to calculate a weighted Kaplan–Meier curve for the CRT-D patients and to perform a weighted univariate Cox proportional hazard regression.²⁸

Two sensitivity analyses were conducted. First, we performed a 1:1 propensity score matching (caliper = 0.05) without replacement, resulting in 727 CRT-P and 727 CRT-D patients and plotted Kaplan–Meier curves. Second, we included patients with ambiguous NYHA coding prior to CRT implantation (*n* = 141) and performed entropy balancing and weighted Kaplan–Meier curves again. Ambiguous NYHA class coding was defined as two different consecutive NYHA class codes at baseline. For the sensitivity analysis, the higher NYHA class was chosen. A *P*-value of <0.05 was considered statistically significant. Statistical analyses were carried out in 'R' (version 4.0.3).²⁹

Results

In total, the analysis included 3569 patients with CRT implantation from 2014 to 2019, of whom 847 were CRT-P patients and 2722 were CRT-D patients. Baseline characteristics are displayed in Table 1. Cardiac resynchronization therapy with pacemaker patients were on average 6.7 years older and more likely female (48 vs. 35%) than CRT-D patients. The aetiology of heart failure (ischaemic/non-ischaemic) was comparable between the two groups. Differences in NYHA classes and hospitalizations prior to CRT implantation were small. Cardiac resynchronization therapy with defibrillator patients were more likely to have diabetes, while Stages

III and IV renal dysfunction and atrial fibrillation were more common in CRT-P patients.

Median follow-up time was 2.35 years (interquartile range: 1.09–3.92 years). During follow-up, 203 (24%) deaths in CRT-P patients and 511 (19%) deaths in CRT-D patients were observed. In the unadjusted Kaplan–Meier time-to-event curves, CRT-P patients had a higher cumulative incidence of all-cause death than CRT-D patients (Figure 2 and Table 2) [hazard ratio (HR): 1.63, 95% confidence interval (CI): 1.38–1.92].

After adjustment for age, the HR for all-cause death in Cox regression was 1.13 (95% CI: 0.95–1.35), and the difference in survival was no longer significant (Figure 3 and Table 2). The HR was independent of age (*P* for interaction = 0.371). The cumulative incidence of death in the three age groups is depicted in Figure 4. No significant difference between CRT-D and CRT-P in the cumulative incidence of death was observed in any of the three age groups (for patients ≤ 65 years: HR: 1.45; 95% CI: 0.75–2.82; for patients >65 and ≤75 years: HR: 1.29; 95% CI: 0.92–1.81; for patients >75 years: HR: 1.19; 95% CI: 0.98–1.47). The HRs were similar in the three age groups (*P* for interaction = 0.598).

After the application of entropy balancing, the weighted average of the baseline characteristics of CRT-D patients was the same as that of CRT-P patients (see Supplementary material online, Table S2). Detailed information on the distribution of baseline characteristics of CRT-D patients according to the weight assigned to them is included in Supplementary material online, Table S3. Figure 5 shows the Kaplan–Meier curve for all-cause death for CRT-P patients and the weighted Kaplan–Meier curve for CRT-D patients. There was no difference in the cumulative incidence of all-cause death. The hazard ratio for all-cause death,

Table 1 Baseline characteristics of patients at cardiac resynchronization therapy implantation

Characteristic	CRT-P (n = 847)	CRT-D (n = 2722)	Standardized difference
Age (years), mean (SD)	76.7 (8.89)	69.9 (9.57)	0.75
Male sex, n (%)	440 (52)	1768 (65)	−0.25
Non-ischaemic heart failure aetiology, n (%)	225 (27)	678 (25)	0.04
CRT implantation year, n (%)			
2014	108 (13)	496 (18)	−0.16
2015	106 (13)	466 (17)	−0.14
2016	123 (15)	439 (16)	−0.05
2017	150 (18)	482 (18)	0
2018	178 (21)	445 (16)	0.12
2019	182 (21)	396 (15)	0.17
Number of hospitalizations one year prior to implantation, n (%)			
0	40 (5)	121 (4)	0.01
1	274 (32)	846 (31)	0.03
2	222 (26)	868 (32)	−0.13
>2	311 (37)	887 (33)	0.09
NYHA Class, n (%)			
II	131 (15)	420 (15)	0
III	548 (65)	1712 (63)	0.04
IV	168 (20)	590 (22)	−0.05
Heart failure specific comorbidities			
Diabetes, n (%)	272 (32)	982 (36)	−0.08
Renal dysfunction III, n (%)	300 (35)	749 (28)	0.17
Renal dysfunction IV, n (%)	58 (7)	112 (4)	0.11
Atrial fibrillation, n (%)	497 (59)	1105 (41)	0.37

CRT-P, cardiac resynchronization therapy with pacemaker; CRT-D, cardiac resynchronization therapy with defibrillator; NYHA, New York Heart Association; SD, standard deviation.

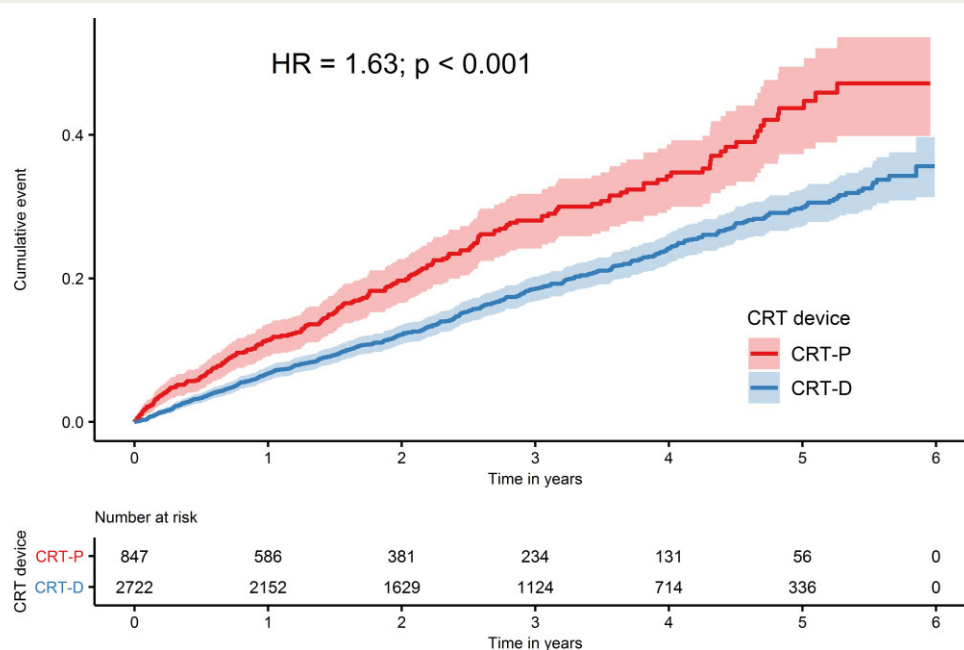
**Figure 2** Unadjusted Kaplan–Meier time-to-event curves for the cumulative incidence of all-cause death for cardiac resynchronization therapy with defibrillator and for cardiac resynchronization therapy with pacemaker.

Table 2 Cox proportional hazard regressions: hazard ratio for all-cause death in cardiac resynchronization therapy with pacemaker vs. cardiac resynchronization therapy with defibrillator

Analysis	Hazard ratio (95% CI)	P-value
Unadjusted	1.63 (1.38–1.92)	<0.001
Age-adjusted ^{a,b}	1.13 (0.95–1.35)	0.165
Age and comorbidity adjusted ^c	0.99 (0.81–1.20)	0.89
<i>Sensitivity analysis</i>		
Age and comorbidity adjusted + ambiguous NYHA patients ^c	1.04 (0.86–1.27)	0.67
<i>PSM approach</i>		
Age and comorbidity adjusted ^d	1.16 (0.93–1.44)	0.195

CI, confidence interval; CRT-P; cardiac resynchronization therapy with pacemaker; CRT-D; cardiac resynchronization therapy with defibrillator; NYHA; New York Heart Association; PSM, propensity score matching.

^aBivariate Cox regression.

^bHazard ratio for increasing age (per year) 1.06 (95% CI: 1.05–1.07), $P < 0.001$.

^cUnivariate Cox regression using weights from entropy balancing.

^dUnivariate Cox regression using the propensity score matched sample.

calculated using weighted univariate Cox proportional hazard regression, was 0.99 (95% CI: 0.81–1.20) (Table 2 and Figure 5).

In the sensitivity analyses, the results were virtually identical to the results of entropy balancing. First, propensity score matching as a different method to adjust for the baseline imbalances was applied. In the propensity score-matched population, no significant difference in mortality could be found either (HR: 1.16; 95% CI: 0.93–1.44) (see Supplementary material online, Figure S1B and Table 2). The distributions of the propensity scores can be found in the statistical Supplementary material online, Figure S2.

Second, when repeating the entropy balancing analysis with the additional patients with ambiguous NYHA class prior to CRT implantation, the HR was 1.04 (95% CI: 0.86–1.27) (see Supplementary material online, Figure S1A and Table 2).

Discussion

This analysis of a large German health claims database of 3569 *de novo* CRT implantations provides real-world data on the survival of CRT patients. In the unadjusted analysis, treatment with CRT-P was associated with a higher incidence of all-cause death. Our inference is based on the results of the final balancing analysis, which showed no difference in survival between CRT-P and CRT-D treated patients. The difference in survival in the unadjusted analysis could primarily be explained by the difference in age between CRT-P and CRT-D recipients. After full adjustment for age and comorbidities, (cumulative) mortality was virtually identical for CRT-P and CRT-D treated patients. The results were robust in sensitivity analyses (Structured Graphical Abstract).

The choice between CRT-P and CRT-D is a frequent clinical dilemma. Despite the large number of CRT implantations, there is no RCT with a head-to-head comparison of CRT-P and CRT-D survival. In a *post hoc* analysis of the randomized COMPANION study, no differences in survival were found in the overall population.³⁰ The analysis of the CRT subgroup of the DANISH trial indicated no survival difference either. Observational studies have provided contradictory results. The unadjusted analysis of an individual patient data network meta-analysis³¹ and the evaluation of large samples of administrative data of the National Health Service Digital and National Health Service Hospital Episode Statistics reported a survival benefit of CRT-D devices compared with CRT-P devices.^{10,11} In contrast and very similar to our results, a large multinational analysis of patients who survived the first 5 years after implantation reported identical late survival of CRT-P and

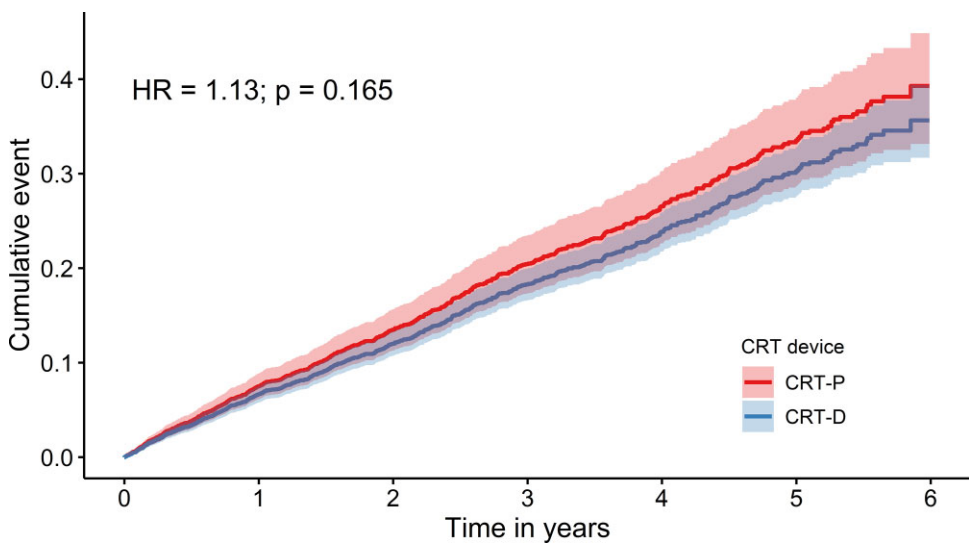


Figure 3 Age-adjusted cumulative incidence of all-cause death based on the Cox proportional hazard model (fixed at a mean age) for cardiac resynchronization therapy with defibrillator and for cardiac resynchronization therapy with pacemaker.

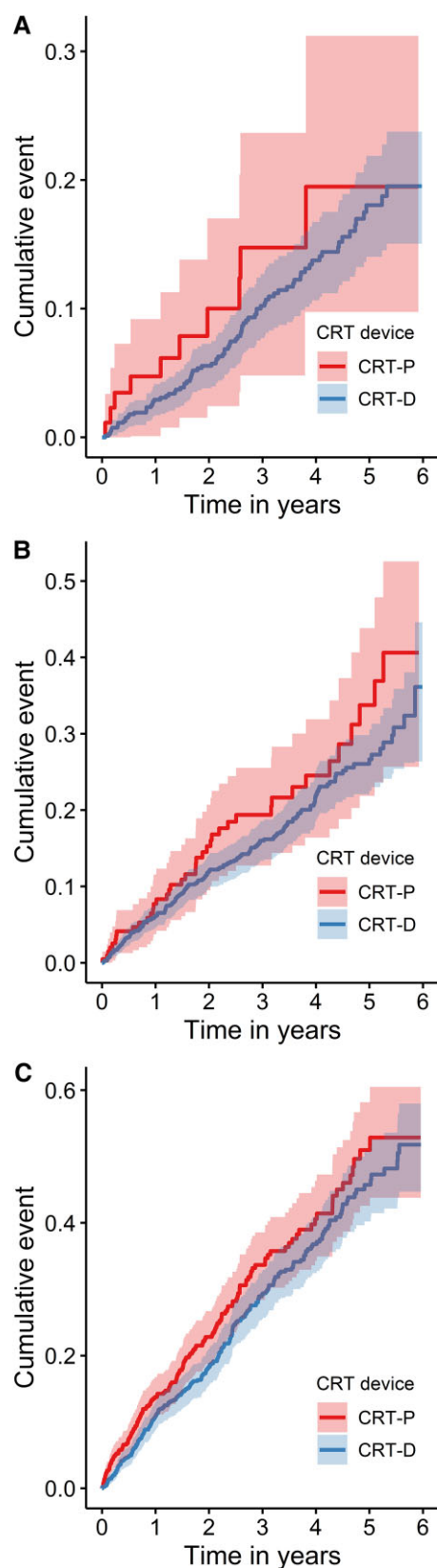


Figure 4 Unadjusted Kaplan-Meier time-to-event curves for the cumulative incidence of all-cause death for cardiac
Continued

Figure 4 Continued

resynchronization therapy with defibrillator and for cardiac resynchronization therapy with pacemaker: (A) patients ≤ 65 years; (B) patients between >65 years and ≤ 75 years; (C) patients >75 years. A χ^2 test comparing a regression model with only the device and age groups as an ordinal variable and a regression with an additional interaction between age groups and device was not statistically significant ($P = 0.598$). A χ^2 test comparing a regression model with only the device and age groups as categorical variables for the middle and oldest age group and a regression model with additional interaction between the device and the age groups was not statistically significant ($P = 0.843$).

CRT-D patients.¹² In line with our results, the survival benefit of CRT-D could not be confirmed in another study in older patients¹³ and in a Medicare analysis of non-ischaemic patients.¹⁴

Cardiac resynchronization therapy may significantly affect the risk for sudden cardiac death. In the CARE-HF trial, CRT was associated with a significantly decreased risk for sudden death.² The decrease of life-threatening arrhythmias is more pronounced in patients with lower left ventricular ejection fraction and non-responders experience more ventricular arrhythmias than CRT responders.^{32,33} Interestingly, in a recent systematic review on sudden cardiac death risk in CRT patients, the absolute decrease in sudden cardiac death risk was more pronounced in CRT-P than CRT-D patients³⁴ and the CeRTiTuDe study reported that 95% of the excess mortality in CRT-P recipients was not associated with sudden cardiac death.³⁵ Thus, this evidence indicates that CRT exerts *per se* an antiarrhythmic effect and may render the addition of defibrillation capability unnecessary.

Our analysis differs from previous studies in that it was restricted to the time period from 2014 to 2019 to reflect contemporary clinical practice, thus taking into account current technological and medical treatment standards. Indeed, the risk of sudden cardiac death in heart failure patients has decreased over time,³ most probably due to advances in pharmacological and non-pharmacological treatment.³⁶ The distribution of baseline characteristics between CRT-P and CRT-D patients in our study was similar with the distribution in previous CRT studies as the ESC CRT Survey II.³⁷

In Germany, the vast majority of patients undergoing CRT implantation receive a CRT-D device. In 2019, approximately 61% of all CRT implantations were CRT-D implantations.³⁸ The underlying rationale is the desired protection from sudden cardiac death. However, this comes with additional costs and risks as CRT-D devices have a higher risk of device-related problems such as infections,³⁹ a shorter device longevity and cause significantly higher costs for the healthcare system. Additionally, the quality of life of CRT-D patients could be impaired due to inappropriate shocks.⁴⁰ Our results further indicate a considerable bias in the device selection in clinical practice in favour of CRT-D in younger and of CRT-P in older patients.

Our study has several limitations. First, we used a retrospective cohort design for our analysis, and the limitations associated with this design and health claims data should be considered when interpreting the results. The conclusions of the entropy balancing weighted analysis are based on the assumption that all relevant baseline characteristics were included and that there are no other,

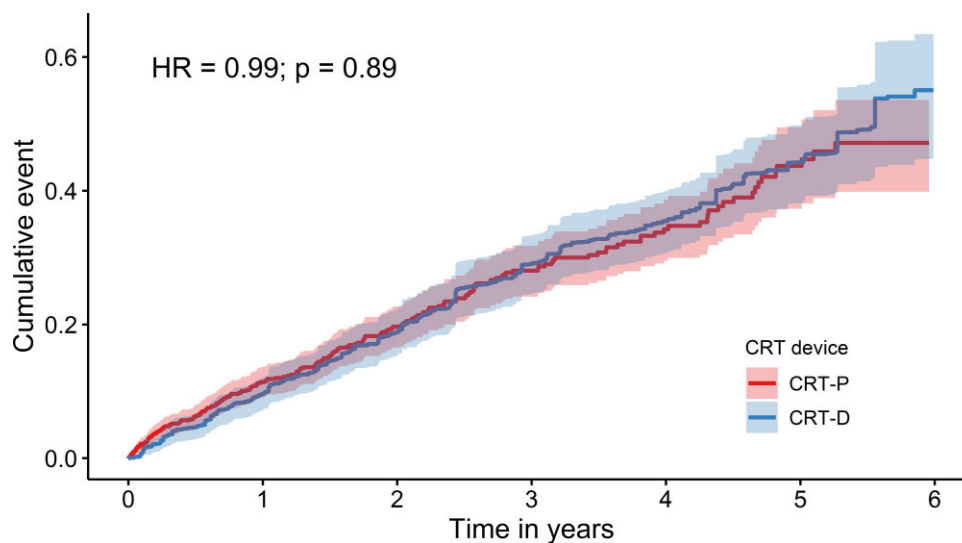


Figure 5 Weighted Kaplan–Meier time-to-event curves for the cumulative incidence of all-cause death for cardiac resynchronization therapy with defibrillator and for cardiac resynchronization therapy with pacemaker.

unobserved confounders. Second, we could not consider further potentially relevant parameters such as QRS duration, or left ventricular function because these are not included in claims data. Third, a possible incorrect coding, for example of ICD codes, cannot be excluded. Fourth, a sensitivity analysis restricting the end point to arrhythmic or cardiovascular death would have been informative for our study and would have provided additional insight into the mechanisms by which the choice of the device type may affect the outcome. Unfortunately, the BARMER database as a claims database does not contain information on the cause and mode of death. The absence of this sensitivity analysis does not invalidate our conclusions with regard to all-cause death, which is the conventional primary end point in almost all randomized arrhythmia trials. Fifth, the results of the analysis can only be applied to patients with similar characteristics as those in the group analysed in our study. In particular, our study specifically excluded patients who received a device for secondary prevention of sudden cardiac death because in this patient population, the implantation of a device with defibrillation capability appears to be mandatory. Sixth, the size of the study groups was determined by the availability in the BARMER health claims database and not by a formal sample size calculation. Nevertheless, the power of the study can be retrospectively established on the basis of the numbers of fatalities in the final entropy balancing adjusted analysis, with adjustments for age and comorbidities. This weighed analysis is statistically the equivalent of an observational cohort study with 406 ($=2 \times 203$) fatalities. The power calculation for the RESET-CRT trial required 361 fatalities to achieve 80% for testing non-inferiority of CRT-P (vs. CRT-D) with a non-inferiority limit of 1.34 for the HR. Therefore, this observational study, with the equivalent of 406 fatalities in the final analysis, matches 80% power of the randomized RESET-CRT trial. Furthermore, we note that the upper boundary of the 95% CI for the HR in the final (entropy balancing) adjusted analysis (1.20) easily meets the non-inferiority criterion of 1.34 of the RESET-CRT trial.

Our analysis also has major strengths. It comprises a relatively long time frame with a large number of patients in a real-world setting and reflecting contemporary therapy. As an innovative element, in our analysis, we attempted to mimic an RCT by applying entropy balancing rendering the type of CRT independent of the measured covariates.

Conclusions

Using health claims data of 3569 patients in a period reflecting contemporary clinical practice (2014–19), the HR for all-cause death for CRT-P and CRT-D recipients was close to 1 after adjusting for age and further potential confounders. The survival difference in favour of the CRT-D patients that was observed in the unadjusted analysis was primarily due to the younger age of the CRT-D patients. Thus, the results of this observational study corroborate the hypothesis of the RESET-CRT randomized clinical trial that CRT-P is non-inferior to CRT-D with regard to survival.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: none declared.

Data availability statement

The data that support the findings of this study are owned by the BARMER (Wuppertal, Germany) and are not publicly available.

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