Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-066 Vericiguat

Stand: Mai 2020

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Vericiguat
Behandlung der Herzinsuffizienz bei einer Ejektionsfraktion unter 45 %

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	- Beschlüsse über die Nutzenbewertung nach § 35a SGB V: o Sacubitril/Valsartan vom 16. Juni 2016 (Patienten ohne Diabetes mellitus: Anhaltspunkt für einen beträchtlichen Zusatznutzen; Patienten mit Diabetes mellitus: Anhaltspunkt für einen geringen Zusatznutzen. Weitere Beschlüsse des G-BA im vorliegenden Anwendungsgebiet: - DMP Herzinsuffizienz (Beschluss vom 19.04.2018, In Kraft getreten am: 24.08.2018 - DMP Koronare Herzkrankheit (Beschluss vom 19.06.2008) - Erprobungs-Richtlinie Messung und Monitoring des pulmonalarteriellen Drucks bei Herzinsuffizienz im Stadium NYHA III (Beschluss vom 19.10.2017, In Kraft getreten am: 13.01.2018; letzte Änderung vom 21.02.2019, in Kraft getreten am04.05.2019) - Spezialisierte Diagnostik und Therapie der schweren Herzinsuffizienz (NYHA Stadium 3-4) gemäß 116b SGB V (Erkrankungen mit besonderen Krankheitsverläufen, ambulante Behandlungen im Krankenhaus)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Vericiguat	Geplantes Anwendungsgebiet laut Beratungsanforderung: Vericiguat ist indiziert zur Behandlung von Erwachsenen mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion unter 45% nach einem Ereignis einer sich verschlechternden Herzinsuffizienz.
ACE-Hemmer	
Benazepril C09AA07 (Cibacen®)	– Essenzielle Hypertonie. – Herzinsuffizienz – zusätzlich zu Diuretika und insbesondere bei schwerer Herzinsuffizienz auch zu Digitalis. (Siehe Abschnitte 4.3, 4.4, 4.5 und 5.1). (FI Cibacen® 2019-11)
Quinapril C09AA06 (Accupro®)	– Essenzielle Hypertonie. – Herzinsuffizienz – zusätzlich zu Diuretika und insbesondere bei schwerer Herzinsuffizienz auch zu Digitalis. (Siehe Abschnitte 4.3, 4.4, 4.5 und 5.1). (FI Accupro ® 2019-07)
Enalapril C09AA02 (Enalapril Abz®)	– Behandlung der Hypertonie – Behandlung der symptomatischen Herzinsuffizienz – Prävention der symptomatischen Herzinsuffizienz bei Patienten mit asymptomatischer linksventrikulärer Dysfunktion (linksventrikuläre Ejektionsfraktion [LVEF] ≤ 35 %) (FI Enalapril Abz ® 2019-07)
Fosinopril C09AA09 (Fosinorm®)	– Essenzielle Hypertonie. – Herzinsuffizienz – zusätzlich zu Diuretika und insbesondere bei schwerer Herzinsuffizienz auch zu Digitalis. (Siehe Abschnitte 4.3, 4.4, 4.5 und 5.1). (FI Fosinorm ® 2019-01)
Ramipril C09AA05 (Delix®)	– Behandlung der Hypertonie. – Behandlung der symptomatischen Herzinsuffizienz. (FI Ramipril Abz® 2019-05)
Lisinopril	– Behandlung einer Hypertonie.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
C09AA03 (Lisinopril Heumann®)	– Behandlung einer symptomatischen Herzinsuffizienz. (FI Lisinopril Heumann® 2019-04)
Perindopril C09AA04 (Coversum®)	– Behandlung der Hypertonie – Behandlung der symptomatischen Herzinsuffizienz (FI Coversum® 2019-02)
Cilazapril C09AA08 (Dynorm®)	– Behandlung von Hypertonie. – Behandlung von chronischer Herzinsuffizienz. (FI Dynom® 2019-03)
Captopril C09AA01 (Captopril AbZ®)	Hypertonie – Captopril AbZ ist zur Behandlung der Hypertonie angezeigt Herzinsuffizienz – Captopril AbZ ist indiziert zur Behandlung der chronischen Herzinsuffizienz mit Reduktion der systolischen ventrikulären Funktion, in Kombination mit Diuretika und, wenn erforderlich, mit Digitalis und Betablockern. (FI Captopril® 2019/07)
AT1-Antagonisten	
Valsartan C09CA03 (Valsartan Abz ®)	<u>Hypertonie</u> Behandlung der Hypertonie bei Kindern und Jugendlichen im Alter von 6 bis 18 Jahren <u>Herzinsuffizienz</u> Behandlung erwachsener Patienten mit symptomatischer Herzinsuffizienz, wenn ACE-Hemmer nicht vertragen werden oder bei Patienten mit Unverträglichkeit gegenüber Betablockern als Add-on-Therapie zu ACE-Hemmern, wenn Mineralokortikoid-Rezeptor-Antagonisten nichtangewendet werden können (siehe Abschnitte 4.2, 4.4, 4.5 und 5.1). (FI Valsartan Abz ® 2017-11)
Candesartan C09CA06 (CandesartanAbz)	– Behandlung der primären Hypertonie bei Erwachsenen – Behandlung erwachsener Patienten mit Herzinsuffizienz und eingeschränkter linksventrikulärer systolischer Funktion (linksventrikuläreEjektionsfraktion ≤ 40 %), wenn ACE-Hemmer nicht vertragen werden, oder als Add-on-Therapie zu ACE-Hemmern bei Patienten, die trotzoptimaler Therapie eine symptomatische Herzinsuffizienz aufweisen, wenn Mineralokortikoid-Rezeptor-Antagonisten nicht vertragenwerden (siehe Abschnitte 4.2, 4.4, 4.5 und 5.1 (FI Candesartancilexetil AbZ® 2018-02)
Losartan	– Behandlung der essenziellen Hypertonie bei Erwachsenen

II. Zugelassene Arzneimittel im Anwendungsgebiet	
C09DA01 (Losartan Abz®)	– Behandlung der chronischen Herzinsuffizienz bei erwachsenen Patienten, wenn die Behandlung mit einem „Angiotensin-Converting-Enzyme“ (ACE)-Hemmer wegen Unverträglichkeit, oder Gegenanzeige als nicht geeignet erachtet wird. Patienten mit insbesondere Husten, Herzinsuffizienz, die mit einem ACE-Hemmer stabil eingestellt sind, sollten nicht auf Losartan umgestellt werden. Die Patienten sollen eine erniedrigte linksventrikuläre Ejektionsfraktion ≤ 40 % aufweisen sowie unter bestehender Therapie der chronischen Herzinsuffizienz klinisch stabil sein. (FI Losartan Abz ® 2019-08)
Eprosartan C09CA02 (Eprosartan-ratiopharm®)	zur Behandlung des essentiellen Bluthochdrucks (FI Eprosartan-ratiopharm® 2018-03)
Irbesartan C09C A04 (Irbesartan Hennig®)	bei Erwachsenen zur Behandlung der essenziellen Hypertonie. (FI Irbesartan Hennig® 2019-02)
Olmesartan C09CA08 (Olmesartan Heumann®)	Behandlung der essentiellen Hypertonie bei Erwachsenen (FI Olmesartan Heumann® 2019-09)
Telmisartan C09DA07 (Telmisartan ratiopharm®)	Behandlung der essentiellen Hypertonie (FI Telmisartan ratiopharm® 2018-10)
Angiotensin-Rezeptor-Neprilysin-Inhibitor	
Sacubitril/Val-sartan C09DX04 (Entresto®)	Entresto wird bei erwachsenen Patienten zur Behandlung einer symptomatischen, chronischen Herzinsuffizienz mit reduzierter Ejektionsfraktion angewendet (siehe Ab-schnitt 5.1). (FI Entresto ® 2019-11)
Betablocker	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Carvedilol C07AG02 (Carvedilol-Teva®)	– Essentielle Hypertonie – Chronisch stabile Angina pectoris – Unterstützende Behandlung mittelschwerer bis schwerer stabiler chronischer Herzinsuffizienz (FI Carvedilol-Teva® 2013-12)
Nebivolol C07AB12 Generisch	– Behandlung der essentiellen Hypertonie – Behandlung der stabilen leichten und mittelschweren chronischen Herzinsuffizienz zusätzlich zur Standardtherapie bei älteren Patienten ≥ 70 Jahren (FI Nebivolol Heumann ® 2018-10)
Atenolol C07AB03 generisch	– chronische stabile Angina pectoris oder instabile Angina pectoris (falls gleichzeitig Tachykardie oder Hypertonie bestehen) – arterielle Hypertonie (FI Atenolol-CT ® 2019-11)
Bisoprolol C07AB07 generisch	– Behandlung der essenziellen Hypertonie – Behandlung der stabilen chronischen Angina pectoris – Behandlung der stabilen chronischen Herzinsuffizienz mit eingeschränkter systolischer linksventrikulärer Funktion, zu-sätzlich zu ACE-Hemmern und Diuretika sowie optional Herzglykosiden (weitere Informationen siehe 5.1). (FI Bisopropol Heumann ® 2013-06)
Metoprolol C07AB02 Generisch	– arterielle Hypertonie – koronare Herzkrankheit – hyperkinetisches Herzsyndrom (funktionelle Herzbeschwerden) – tachykarde Herzrhythmusstörungen – Akutbehandlung des Herzinfarkts und Reinfarktprophylaxe (FI Metoprolol Heumann® 2017-11)
Propranolol C07AA05 generisch	– arterielle Hypertonie – koronare Herzkrankheit – hyperkinetisches Herzsyndrom (funktionelle Herzbeschwerden) – tachykarde Herzrhythmusstörungen (FI Propra-Ratiopharm® 2014-02)
Sotalol C07AA07 generisch	– Lebensbedrohende symptomatische tachykarde ventrikuläre Herzrhythmusstörungen – Symptomatische und behandlungsbedürftige tachykarde supraventrikuläre Herzrhythmusstörungen, wie o Prophylaxe von chronischem Vorhofflimmern nach DC-Kardioversion

II. Zugelassene Arzneimittel im Anwendungsgebiet

	o Prophylaxe von paroxysmalem Vorhofflimmer (FI Sotalol-ratiopharm® 2014-09)
Digitalis	
Digoxin C01AA05. Lenoxin®	– Manifeste chronische Herzinsuffizienz (aufgrund systolischer Dysfunktion). – Tachyarrhythmia absoluta bei chroni-schem Vorhofflimmern/Vorhofflattern. (FI Lenoxin® 2019-09)
Digitoxin C01AA0 Generisch	– manifeste chronische Herzinsuffizienz (auf Grund systolischer Dysfunktion) – Tachyarrhythmia absoluta bei Vorhofflimmern/Vorhofflattern – paroxysmales Vorhofflimmern/Vorhofflatter (FI Digitoxin Teva® 2018-02)
Diuretika	
Hydrochlorothiazid C03AA03 generisch	Adjuvante symptomatische Therapie der chronischen Herzinsuffizienz zusätzlich zu ACE-Hemmern. Hinweis: Insbesondere bei schwerer Herzinsuffizienz sollte zusätzlich auch die Anwendung von Digitalis erwogen werden (FI HCT AbZ 2014-05)
Triamteren/ Hydrochlorothiazid C03EA01 Generisch	– Arterielle Hypertonie – Kardiale, hepatogene oder nephrogene Ödeme – Chronische Herzinsuffizienz (FI Triamteren comp.-ratiopharm® 2018-10)
Chlortalidon C03BA04 (Hygroton®)	– Behandlung von kardialen, hepatischen und nephrogenen Ödemen – Hypertonie – Manifeste Herzinsuffizienz (FI Hygroton® 2018-11)
Spironolacton C03DA01 generisch	Ödeme und/oder Aszites bei Erkrankungen, die mit einem sekundären Hyperaldosteronismus einhergehen (FI Spironolacton Heumann® 2016-06)
Torasemid C03CA04 generisch	Behandlung und Vorbeugung des Wiederauftretens kardialer Ödeme und/oder Ergüsse aufgrund einer Herzinsuffizienz (FI Torasemid Heumann 2016-04)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Piretanid C03CA03 Arelix®	Zur Ausscheidung von Ödemen, bei Herzinsuffizienz zur Herzentlastung (FI Arelix® 2018-11)
Xipamid C03BA10 generisch,	Kardiale, renale und hepatogene Ödeme (FI 2014-09)
Furosemid C03CA01 generisch	Ödeme infolge Erkrankungen des Herzens oder der Leber (FI 2016-05)
Spironolacton + Furosemid C03EB01	Ödeme und/oder Lungenstauung infolge Herzinsuffizienz (FI 2016-10)
Amilorid + Hydrochlorothiazid C03EA4	– Hypertonie – kardial bedingte Ödeme (FI Amilorid comp.-ratiopharm® 2018-10)
If-Kanal-Hemmer	
Ivabradin C01EB17 Ivabradin-AbZ®	– Ivabradin ist indiziert bei chronischer Herzinsuffizienz der NYHA-Klasse II bis IV mit systolischer Dysfunktion, bei Patienten im Sinusrhythmus miteiner Herzfrequenz ≥ 75 Schläge pro Minute (bpm), in Kombination mit Standardtherapie einschließlich Betablocker oder wenn Betablockerkontraindiziert sind oder eine Unverträglichkeit vorliegt (siehe Abschnitt 5.1 (FI Ivabradin-AbZ® 2017-10)
Calciumkanal-blocker	
Amlodipin C08CA01 generisch	– Hypertonie – Chronisch stabile Angina pectoris – Vasospastische (Prinzmetal-)Angina (FI Amlodipin [besilat] AbZ® 2019-09)
Verapamil C08DA01 generisch	– Symptomatische koronare Herzkrankheit: o chronisch stabile Angina pectoris (Belastungsangina) o instabile Angina pectoris (Crescendo-angina, Ruheangina)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	o vasospastische Angina pectoris (Prinzmetal-Angina, Variant-Angina) o Angina pectoris bei Zustand nach Myokardinfarkt bei Patienten ohne Herzinsuffizienz, wenn Betarezeptorenblocker nicht angezeigt sind. – Störungen der Herzschlagfolge bei: o paroxysmaler supraventrikulärer Tachykardie o Vorhofflimmern/Vorhofflattern mit schneller AV-Überleitung (außer bei WPW-Syndrom oder Lown-Ganong-Levine-Syndrom, siehe unter Abschnitt 4.3) – Hypertonie (FI Verapamil Hennig® 2019-01)
Diltiazem C08DB01 generisch	– Symptomatische koronare Herzkrankheit: o chronisch stabile Angina pectoris (Belas-tungs-Angina) o instabile Angina pectoris (Crescendo-Angina, Ruhe-Angina) o vasospastische Angina pectoris (Prinz-metal-Angina, Variant-Angina) – Hypertonie (FI Diltiazem-ratiopharm® 2015-08)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-066 (Vericiguat)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	21. April 2020

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Abkürzungsverzeichnis

ACE-Hemmer	Angiotensin-Conversions-Enzym-Hemmer
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
ARB	Angiotensinrezeptorblocker
ARNI	Angiotensin Rezeptor Neprilysin Inhibitor
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BB	Betablocker
CHF	Chronic Heart Failure
CPG	Committee for Practice Guidelines
CrI	Credible Intervals
ECRI	ECRI Guidelines Trust
eGFR	estimated by Gomerular Filtration Rate
G-BA	Gemeinsamer Bundesausschuss
GDG	Guideline Development Group
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HF	Heart Faillure
HFrEF	Heart Failure with reduced Ejection Fraction
HFmrEF	Heart Failure with imd-range Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
LVEF	Left Ventricular Ejection Fraction
MRA	Mineralkortikoid-Rezeptor-Antagonisten
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NVL	Nationale VersorgungsLeitlinie
NYHA	New York Heart Association
OR	Odds Ratio
RAAS	Renin-Angiotensin-Aldosteron-System
RR	Relatives Risiko
SCD	Sudden Cardiac Death
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization
WRF	Worsening Renal Function

1 Indikation

Anwendungsgebiet laut Beratungsanforderung:

Vericiguat ist indiziert zur Behandlung von Erwachsenen mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion unter 45% nach einem Ereignis einer sich verschlechternden Herzinsuffizienz.

Indikation für die Synopse:

Herzinsuffizienz bei Patienten mit reduzierter Ejektionsfraktion (HFrEF) (Ejektionsfraktion < 40%) und geringgradig eingeschränkter Ejektionsfraktion (HFmrEF) (Ejektionsfraktion von 40 bis < 45%).

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Herzinsuffizienz durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 27.03.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1962 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 17 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2016 [8].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. Juni 2016 - Sacubitril/Valsartan

Anwendungsgebiet

Entresto® wird bei erwachsenen Patienten zur Behandlung einer symptomatischen, chronischen Herzinsuffizienz mit reduzierter Ejektionsfraktion angewendet.

Zweckmäßige Vergleichstherapie

ACE-Hemmer, und sofern angezeigt, Betablocker unter Berücksichtigung des Zulassungsstatus

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber ACE-Hemmer (Enalapril) in Kombination mit einem Betablocker

Patienten ohne Diabetes mellitus:

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

Patienten mit Diabetes mellitus:

Anhaltspunkt für einen geringen Zusatznutzen.

G-BA, 2019 [6].

Richtlinie des Gemeinsamen Bundesausschusses zur Erprobung der Messung und des Monitorings des pulmonalarteriellen Drucks mittels implantierten Sensors zur Therapieoptimierung bei Herzinsuffizienz im Stadium NYHA III (MM-pul-art-Druck-Herzinsuff); zuletzt geändert am 21. Februar 2019

Anwendungsgebiet

Die Erprobung soll der Beantwortung der Frage dienen, ob bei Patientinnen und Patienten mit Herzinsuffizienz im Stadium NYHA III (Population) die Messung und das Monitoring des pulmonalarteriellen Drucks mittels implantierten Sensors (Intervention) gegenüber einem nicht-invasiven Monitoring (Vergleichsintervention) durch eine optimierte Therapie zu einer Verbesserung patientenrelevanter Zielgrößen führt (Endpunkte).

Zweckmäßige Vergleichstherapie

(1) Für die Intervention wird den Patientinnen und Patienten ein Sensor in der Pulmonalarterie platziert, mit dem ein telemedizinisches Monitoring des pulmonalarteriellen Drucks durchgeführt wird.

(2) Als Vergleichsintervention kommt ein Monitoring ohne pulmonalarterielle Druckmessung zum Einsatz, das allein die regelmäßige Selbstmessung von mindestens Körpergewicht und

Blutdruck sowie die Erfassung von Symptomen umfasst. [2] Den Patientinnen und Patienten, die die Vergleichsintervention erhalten, wird kein Pulmonalisdrucksensor implantiert.

G-BA, 2020 [7].

Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Absatz 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL); zuletzt geändert am 27. März 2020

Anlage 13: Anforderungen an strukturierte Behandlungsprogramme für Patientinnen und Patienten mit chronischer Herzinsuffizienz

1 Behandlung nach dem aktuellen Stand der medizinischen Wissenschaft unter Berücksichtigung von evidenzbasierten Leitlinien oder nach der jeweils besten, verfügbaren Evidenz sowie unter Berücksichtigung des jeweiligen Versorgungssektors (§ 137f Abs. 2 Satz 2 Nr. 1 SGB V)

1.2 Diagnostische Kriterien zur Abgrenzung der Zielgruppe

Zur Zielgruppe gehören Patientinnen und Patienten mit gesicherter Diagnose einer chronischen Herzinsuffizienz bei systolischer Dysfunktion, bei denen eine Einschränkung der linksventrikulären Auswurfleistung (Ejektionsfraktion, LVEF) ≤ 40 % festgestellt wurde. Die LVEF muss durch ein bildgebendes Verfahren bestimmt worden sein.

Auch asympotomatische Patientinnen und Patienten können am DMP teilnehmen, wenn eine Einschränkung der LVEF) ≤ 40 % bereits nachgewiesen wurde.

1.4 Therapeutische Maßnahmen

1.4.2 Medikamentöse Therapie der Herzinsuffizienz

1.4.2.1 Allgemeine Grundsätze der medikamentösen Therapie

Unter Berücksichtigung der Kontraindikationen sollen vorrangig Medikamente zur Behandlung der Herzinsuffizienz verwendet werden, deren positiver Effekt und deren Sicherheit im Hinblick auf die Erreichung der in Nummer 1.3 genannten Therapieziele in randomisierten, kontrollierten Studien (RCT) nachgewiesen wurden.

Um die nachgewiesene Morbiditäts- und Mortalitätsreduktion zu erreichen, soll eine vorsichtige Aufdosierung unter engmaschiger Kontrolle der subjektiven Verträglichkeit, der Vitalparameter und der laborchemischen Befunde erfolgen.

Die Titration soll in kleinen Schritten und mit der gebotenen Wartezeit zur Beobachtung der Wirkung erfolgen. Insbedondere bei bestehender Komorbidität sollten Blutdruck, Herzfrequenz, Herzrhythmus und der Elektrolythaushalt (Natrium und Kalium) sowie die Nierenfunktion kontrolliert werden.

1.4.2.2 Spezifische medikamentöse Therapieempfehlungen

Empfohlene medikamentöse Therapie für potentiell alle symptomatischen Patientinnen und Patienten mit systolischer Herzinsuffizienz:

Therapie mit Angiotensin-Conversions-Enzym-Hemmern (ACE-Hemmer):

Für alle Patientinnen und Patienten mit einer LVEF ≤ 40% wird, unabhängig vom Schweregrad der Herzinsuffizienz, eine Therapie mit einem ACE-Hemmer empfohlen. Eine Behandlung mit ACE-Hemmern verbessert die Prognose und Symptomatik der Erkrankung. Es sollen insbesondere ACE-Hemmer verwendet werden, für die eine Wirksamkeit in Bezug auf patientenrelevante Endpunkte bei Patientinnen und Patienten mit Herzinsuffizienz belegt ist.

Die jeweilige Zieldosis ist durch eine langsame Steigerung der Dosierung anzustreben. Wenn die optimale Zieldosis nicht erreicht wird, erfolgt die Behandlung in der maximal von der Patientin oder vom Patienten tolerierten Dosis.

Therapie mit Beta-Rezeptorenblockern (Betablocker):

Alle klinisch stabilen Patientinnen und Patienten sollten einen Betablocker erhalten. Es sollen nur Betablocker verwendet werden, für die eine Wirksamkeit in Bezug auf patientenrelevante Endpunkte bei Patientinnen und Patienten mit Herzinsuffizienz belegt ist (Bisoprolol, Carvedilol, Metoprolol succinate (CR/XL), Nebivolol für Patientinnen und Patienten > 70 Jahre).

Die jeweilige Zieldosis ist durch eine langsame Steigerung der Dosierung anzustreben. Wenn die optimale Zieldosis nicht erreicht wird, erfolgt die Behandlung in der maximal von der Patientin oder vom Patienten tolerierten Dosis.

Die Dosierung von ACE-Hemmern und von Betablockern ist bei symptomatischer Hypotonie entsprechend anzupassen, so dass die Behandlung von der Patientin oder vom Patienten toleriert wird. Dabei ist zu beachten, dass vor einer Dosisreduktion aufgrund einer symptomatischen Hypotonie zunächst die Dosierung der übrigen blutdrucksenkenden Begleitmedikation reduziert wird.

Therapie mit Mineralkortikoid-Rezeptor-Antagonisten (MRA):

Patientinnen und Patienten mit einer LVEF ≤ 30%, die trotz optimaler Therapie mit ACE-Hemmer und Betablocker und Diuretikum im Stadium NYHA II-IV sind, sollten additiv mit MRA in niedriger Dosierung behandelt werden. Vorraussetzungen bei Therapiebeginn sind eine ausreichende Nierenfunktion und der Ausschluss einer Hyperkaliämie. Es ist zu beachten, dass mit steigender Dosierung die Gefahr einer Hyperkaliämie zunimmt. Daher sind in diesem Fall in der Einstellungsphase in der Regel vierwöchentliche Kontrollen des Serum-Kaliums in den ersten drei Monaten erforderlivh, danach in regelmäßigen Abständen.

Empfohlene medikamentöse Therapie für ausgewählte Patientengruppen mit systolischer Herzinsuffizienz:

Therapie mit Angiotensin II-Rezeptor-Antagonisten (Angiotensinrezeptorblocker - ARB):

Bei Patientinnen und Patienten, die eine Behandlung mit ACE-Hemmern nicht tolerieren (z.B. aufgrund eines ACE-Hemmer bedingten Hustens), kann der Wechsel auf einen ARB zur Beschwerdebesserung oder zur Beschwerdefreiheit führen.

Die Kombination eines ACE-Hemmers mit einem ARB (duale Renin-Angiotensin-Aldosteron-System - RAAS-Blockade) wird aufgrund des ungünstigen Nutzen-Schaden-profils nicht empfohlen.

Therapie mit Ivabradin:

Bei Patientinnen und Patienten mit einer LVEF ≤ 35% und persistierenden Symptomen (NHYA II-IV), trotz einer Behandlung mit einer evidenzbasierten Betablockerdosierung (oder maximal

tolerierte Dosis oder Betablocker-Unvertrräglichkeit/-Kontraindikation), einem ACE-Inhibitor (oder ARB) und einem MRA (oder ARB), die einen stabilen Sinusrhtymus und eine Ruheherzfrequenz ≥ 75 Schläge/Minute aufweisen, sollte eine ergänzende Medikation mit Ivabradin erwogen werden. Liegt kein stabiler Sinusrhythmus vor, soll die Therapie mit Ivabradin beendet werden.

Therapie mit einem Angiotensin Rezeptor Neprilysin Inhibitor (ARNI):

Bei Patientinnen und Patienten, die unter einer optimalen Therapie mit einem ACE-Hemmer/ARB, einem Betablocker und einem MRA weiterhin symptomatisch sind, wird eine Umstellung des ACE-Hemmers/ARB auf ARNI (Sacubitril/Valsartan) empfohlen. Langzeitdaten mit Blick auf seltenere mögliche Nebenwirkungen mit dieser Therapie liegen bislang nicht vor.

Therapie mit Diuretika:

Alle Patientinnen und Patienten, die Stauungszeichen aufweisen, sollen mit Diuretika behandelt werden, da Diuretika die wichtigste Therapieoption zur Kontrolle des Volumenstatus darstellen. Der Nutzen ist belegt für Schleifendiuretika und Thiaziddiuretika. In Kombination mit der mortalitätssenkenden Therapie soll die zur Symptomkontrolle niedrigste erforderliche Dosis verwendet werden.

Therapie mit Herzglykosiden (Digitalis):

Alle Patientinnen und Patienten, die trotz Therapie mit einem Betablocker ein chronisches therapierefräkteres tachykardes Vorhofflimmern aufweisen, kann eine zusätzliche Therapie mit Digitalis erwogen werden. Für Patientinnen und Patienten mit Sinusrhythmus stellt Digitalis lediglich ein Reservemedikament dar und sollte bei diesen Patientinnen und Patienten nur gegeben werden, wenn sie trotz Ausschöpfung der vorgenannten medikamentösen Therapie weiterhin im Stadium NYHA III-IV sind.

Orale Antikoagulationstherapie:

Bei Vorhofflimmern besteht ein besonders hohes Risiko für thrombembolische Ereignisse, sodass hier in der Regel eine effektive orale Antikoagulation (bei Vitamin-K-Antagonisten INR 2-3) durchzuführen ist. In diesem Fall sollte eine ggf. bestehende Thrombozytenaggregationshemmung in der Regel beendet und auf die orale Antikoagulation umgestellt werden. Über eine in besonderen Situationen (z. B. Stent-Implantation) dennoch indizierte Kombinationstherapie ist in Kooperation mit der qualifizierten Fachärztin oder dem qualifizierten Facharzt bzw. der qualifizierten Einrichtung zu entscheiden. Die Herzinsuffizienz allein ist keine Indikation für eine orale Antikoagulation.

G-BA, 2011 [5].

Richtlinie des Gemeinsamen Bundesausschusses über die ambulante Behandlung im Krankenhaus nach § 116b SGB V: Anlage 3 Erkrankungen mit besonderen Krankheitsverläufen im Katalog gem. § 116b Abs. 3 SGB V; zuletzt geändert am 15. Dezember 2011

4. Spezialisierte Diagnostik und Therapie der schweren Herzinsuffizienz (NYHA Stadium 3 - 4)	
Konkretisierung der Erkrankung und des Behandlungsauftrages mittels Angabe von Diagnosen (mit ICD-Kodifizierung) mit diagnostischen und therapeutischen Prozeduren	Konkretisierung der Erkrankung: Patienten und Patientinnen mit schwerer Herzinsuffizienz der Stadien NYHA 3 (I50.13) oder NYHA 4 (I50.14) oder entsprechender Stadien einer Rechtsherz- oder Globalinsuffizienz (ICD I50.0-, I50.9) oder Patienten und Patientinnen, die innerhalb der letzten 12 Monate mindestens einmal vollstationär wegen einer Herzinsuffizienz der Stadien NYHA 3 oder NYHA 4 behandelt worden sind. Konkretisierung des Behandlungsauftrages: Spezialisierte Diagnostik und Therapie von Patientinnen und Patienten mit schwerer Herzinsuffizienz Zur spezialisierten Diagnostik und Therapie werden im Allgemeinen folgende Leistungen erbracht, sie sind Teil der vertragsärztlichen Versorgung, z. T. existieren Qualitätsvereinbarungen: • Anamnese • körperliche Untersuchung • Beratung • Laboruntersuchungen (z. B. BNP, Troponin T / I, Digitalis-spiegel, genetische Analysen bei fam. CMP) • bildgebende Untersuchungen z. B. -Röntgenuntersuchungen -CT-Untersuchungen -MRT • Sonographie, z. B. Duplexsonographie • Echokardiographie • Stressechokardiographie • transösophageale Echokardiographie EKG-Untersuchungen, inkl. 24 Std. EKG • 24 Std. Blutdruckmessung • Ergometrie, Spiroergometrie • Herzkatheter-Untersuchungen • Blutgasanalyse • Lungenfunktionsmessungen • Myokardszintigraphie, • medikamentöse Therapie • Diagnostik und Therapie von Herzrhythmusstörungen (einschließl. interventioneller Verfahren), soweit im EBM enthalten • Versorgung mit Herzschrittmachern • Funktionsanalysen von Herzschrittmachern, implantierten Kardiovertern und/oder implantierten Defibrillatoren • Hypertonieschulung / INR-Patientenschulung • Herzsportgruppen Bei progredientem Krankheitsverlauf oder Komplikationen sowie bei besonderen Fragestellungen können noch weitere Maßnahmen notwendig werden.
Sächliche und personelle Anforderungen	Hinsichtlich der fachlichen Befähigung, der Aufrechterhaltung der fachlichen Befähigung, den apparativen, organisatorischen, räumlichen Voraussetzungen einschließlich der Überprüfung der Hygienequalität gelten die
	Qualitätssicherungs-Vereinbarungen nach § 135 Abs. 2 SGB V entsprechend. Darüber hinaus gilt: Krankenhäuser verfügen über eine kardiologische Fachabteilung oder über eine Abteilung für Innere Medizin mit einem Schwerpunkt Kardiologie zur stationären Versorgung der Patientinnen und Patienten sowie eine Intensivstation. Die Betreuung von Patientinnen und Patienten mit schwerer Herzinsuffizienz erfolgt in einem interdisziplinären Team, das durch eine Fachärztin oder einen Facharzt für Innere Medizin und Schwerpunkt Kardiologie geleitet wird. In die interdisziplinäre Zusammenarbeit sollen folgende Fachabteilungen und/oder Fachärzte oder Fachärztinnen bzw. Disziplinen bei Bedarf einbezogen werden: • Labormedizin • Radiologie • Nephrologie • Nuklearmedizin • Kardiochirurgie • Transplantationsmedizin Diese Fachdisziplinen können auch durch vertraglich vereinbarte Kooperationen mit externen Leistungserbringern, mit niedergelassenen Vertragsärztinnen oder Vertragsärzten oder anderen nach § 108 SGB V zugelassenen Krankenhäusern eingebunden werden. Eine 24-Stunden-Notfallversorgung mindestens in Form einer Rufbereitschaft muss für die Fachdisziplin Kardiologie gewährleistet sein. Das Krankenhaus muss mindestens 500 dieser Patienten pro Jahr behandeln. Qualifikationsvoraussetzungen an das Behandlungsteam: Die Mitarbeiterinnen und Mitarbeiter des Behandlungsteams müssen über ausreichende Erfahrung in der Behandlung von Patientinnen und Patienten mit schwerer Herzinsuffizienz verfügen und sollen regelmäßig an spezifischen Fortbildungsveranstaltungen sowie interdisziplinären Fallkonferenzen teilnehmen. sowie Kompetenz in der Hypertonieschulung / INR -Patientenschulung erwerben. Verpflichtung zur Dokumentation und Auswertung: Das Krankenhaus führt eine Dokumentation durch, die eine ergebnisorientierte und qualitative Beurteilung der Behandlung ermöglicht. Leitlinienorientierte Behandlung: Die Behandlung soll sich an medizinisch wissenschaftlich anerkannten und möglichst qualitativ hochwertigen Leitlinien orientieren, die auf der jeweils besten verfügbaren Evidenz basieren.
Überweisungserfordernis	Bei Erstzuweisung besteht ein Überweisungserfordernis durch einen Vertragsarzt oder eine Vertragsärztin (im Ausnahmefall im stationären Bereich als Konsil oder hausinterne Überweisung).

3.2 Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews identifiziert werden.

3.3 Systematische Reviews

Al-Gobari M et al., 2018 [1].

Effectiveness of drug interventions to prevent sudden cardiac death in patients with heart failure and reduced ejection fraction: an overview of systematicreviews

Fragestellung

To summarise and synthesise the current evidence regarding the effectiveness of drug interventions to prevent sudden cardiac death (SCD) and all-cause mortality in patients with heart failure with reduced ejection fraction (HFrEF).

Methodik

Population:

- HF patients with an ejection fraction ≤45%

Intervention/Komparator:

- Beta-blockers (BBs) vs. placebo ‚usual care'
- Angiotensinconverting enzyme inhibitors (ACE-i) vs. Placebo
- Angiotensin receptor blockers (ARBs) vs. Placebo or ACE-i.
- Antialdosterones or mineralocorticoidreceptor antagonists vs. Placebo, ‚usual care'
- Sacubitril; valsartan/ACE-i
- Combined ARB/neprilysin inhibitors vs. placebo
- [Amiodarone, statins or fish oil supplementation vs. Placebo: nicht zugelassen für AWG]
- we categorised the evidence of the included interventions into three categories: (1) effective interventions; (2) ineffective interventions; and (3) uncertain evidence (conflicting or inconclusive evidence).

Endpunkte:

- sudden cardiac death (SCD) and/or all-cause mortality

Recherche/Suchzeitraum:

- MEDLINE, Embase, ISI Web of Science and Cochrane Library from inception to May 2017

Qualitätsbewertung der Studien:

- Assessing the Methodological Quality of Systematic Reviews (AMSTAR) & Grading of Recommendations, Assessment, Development and Evaluation (GRADE)

Ergebnisse

Anzahl eingeschlossener Studien:

- 41 trials

Charakteristika der Population:

- population of the included reviews consisted of HF patients with an ejection fraction ≤45% in most studies and a corresponding New York Heart Association classification ranging from I to IV.
- All reviews were systematic, except two reviews for antiarrhythmic drugs (AADs).
- At the time of their publication, 15 outof 41 reviews (37%) had corresponding authors based in the USA, 7 (17%) in Canada, 6 (15%) in China, 3 in Chile, 2 in France, 2 in the UK and the 6 remaining in other countries.

Qualität der Studien:

- AMSTAR scores for quality assessment of the included reviews widely ranged from 2 to 10 (out of 11).
- The quality of evidence for BBs and antialdosterone agents obtained a high quality on the GRADE scale, while ACE-i, amiodarone and statins obtained a moderate quality. However, combined ARB/neprilysin inhibitors had a moderate and high quality for SCD and all-cause mortality outcomes, respectively, whereas ARBs had a low quality of evidence (table 2).

Studienergebnisse:

- Beta-blockers, antialdosterones and combined ARB/neprilysin inhibitors appeared effective to prevent SCD and all-cause mortality (table 2).
- ACE-i significantly reduced all-cause mortality but not SCD events (table 2)..
- ARBs and statins were ineffective where antiarrhythmic drugs and omega-3 fatty acids had unclear evidence of effectiveness for prevention of SCD and allcause mortality (table 2).

Table 2 Summary of findings and GRADE evaluation for sudden cardiac death (SCD) and all-cause mortality prevention

Drug interventions for SCD and all-cause mortality prevention in heart failure patients

Outcome	Intervention/comparison	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (no. of studies)	Quality of the evidence (GRADE)	Comments
SCD							
	Beta-blockers/placebo	77 per 1000	54 per 1000 (49–60)	OR 0.69 (0.62 to 0.77)	24 779 (26 RCTs)	⊕⊕⊕⊕ High*	I^2=0% (p=0.57)
	Antialdosterone inhibitor/ placebo; 'usual care'	61 per 1000	49 per 1000 (41–60)	RR 0.81 (0.67 to 0.98)	8301 (5 RCTs)	⊕⊕⊕⊕ High*	I^2=8% (p=0.36)
	ARB; neprilysin inhibitor/ACE-i	74 per 1000	60 per 1000 (51–70)	RR 0.81 (0.69 to 0.95)	8399 (1 RCsT)	⊕⊕⊕⊖ Moderate†	
	ACE-i/placebo	59 per 1000	54 per 1000 (43–65)	OR 0.91 (0.73 to 1.11)	6988 (30 RCTs)	⊕⊕⊕⊖ Moderate‡	I^2=0% (p=0.94)
	ARB (or ARB+ACE i)/Placebo; ACE-i	See comment	See comment	Not estimable	13 884 (5 RCTs)	⊕⊕⊖⊖ Low‡§	I^2=78% (p=0.010). Overall, we did not pool the studies because of heterogeneity
	Statins/placebo; 'usual care'	108 per 1000	100 per 1000 (76–131) (99 per 1000 (72–131))	RR 0.92 (0.7 to 1.21) (OR 0.90 (0.64 to 1.24))	10 077 (8 RCTs)	⊕⊕⊕⊖ Moderate¶	I^2=42.6% (p=0.094)
	Amiodarone/placebo; 'usual care'	118 per 1000	93 per 1000 (79–110)	RR 0.79 (0.67 to 0.93)	5006 (11 RCTs)	⊕⊕⊖⊖ Low¶‡	
	Omega 3 fatty acids/placebo; 'usual care'	93 per 1000	88 per 1000 (77–102)	RR 0.94 (0.82 to 1.09)	6975 (1 RCT)	⊕⊕⊕⊖ Moderate†	
All-cause mortality							
	Beta-blockers/placebo	178 per 1000	127 per 1000 (113–141)	OR 0.67 (0.59 to 0.76)	24 779 (26 RCTs)	⊕⊕⊕⊕ High*	I^2=40 % (p = 0.02)
	Antialdosterone inhibitor / placebo; ' usual care'	200 per 1000	162 per 1000 (148–176)	RR 0.81 (0.74 to 0.88)	9019 (10 RCTs)	⊕⊕⊕⊕ High	I^2= 0% (p= 0.56)
	ARB; neprilysin inhibitor /ACE -i	183 per 1000	158 per 1000 (145–172)	RR 0.86 (0.79 to 0.94)	14 742 (3 RCTs)	⊕⊕⊕⊕ High	I^2= 0% (p = 0.42)
	ACE-i/placebo	219 per 1000	178 per 1000 (158–198)	OR 0.77 (0.67 to 0.88)	7105 (32 RCTs)	⊕⊕⊕⊖ Moderate	I^2=0% (p= 0.95)
	ARB (or ARB+ACE -i)/ placebo; ACE-i.	183 per 1000	177 per 1000 (161–197)	RR 0.97 (0.88 to 1.08)	19 510 (27 RCTs)	⊕⊕⊖⊖ Low‡**	I^2= 24% (p = 0.14)
	Statins/placebo; 'usual care'	273 per 1000	240 per 1000 (205–278) (233 per 1000 (199–273))	RR 0.88 (0.75 to 1.02) OR 0.81 (0.66 to 1)	11 024 (13 RCTs)	⊕⊕⊕⊖ Moderate¶	I^2= 37.7% (p =0.083)
	Amiodarone/placebo; 'usual care'	264 per 1000	237 per 1000 (211–266)	RR 0.90 (0.80 to 1.01)	5006 (11 RCTs)	⊕⊕⊖⊖ Low¶‡	
	Omega 3 fatty acids/ placebo; 'usual care'	291 per 1000	274 per 1000 (253–294)	RR 0.94 (0.87 to 1.01)	6975 (1 RCT)	⊕⊕⊕⊖ Moderate	

*Although graded high, this might be downgraded into moderate if we strictly consider the risk of bias of primary studies other than an overall estimation.
†Estimation comes from one single clinical trial. No data obtained from other relevant studies for this outcome.
‡The studies reported to generally have a moderate to high risk of bias due to allocation concealment and blinding reporting.
¶Likelihood of publication bias presence with an asymmetric funnel plot.
§Inconsistent results ranged from no effect to insignificant increase of events ($I^2 \approx$ 71%).
**Most studies have small sample and wide CIs including no effect with appreciable harm or benefit.
ACE-i, ACE inhibitors; ARBs, angiotensin receptor blockers; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; I^2, between-study variance due to heterogeneity; RR, risk ratio.

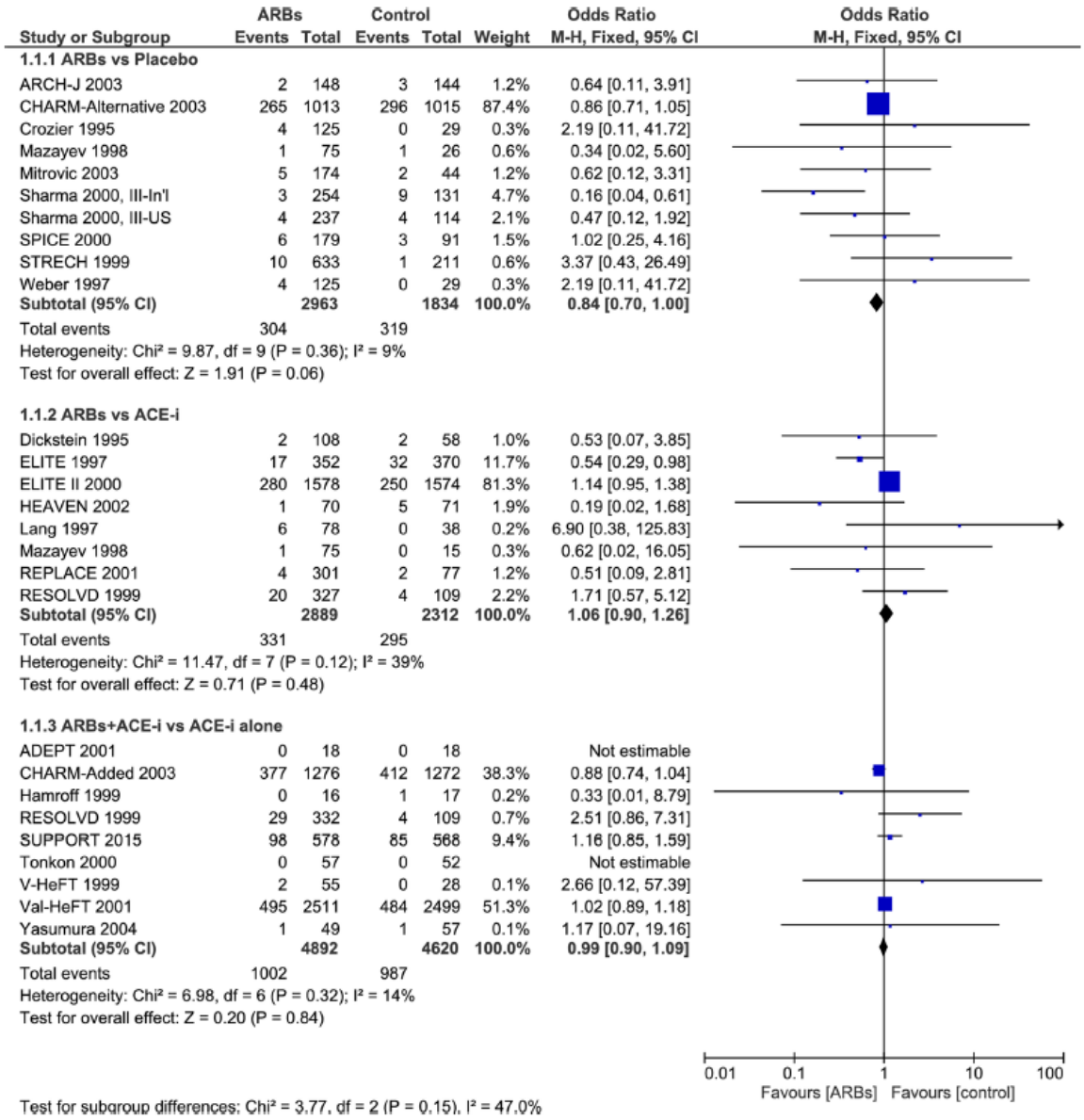


Figure 2 Efficacy of angiotensin receptor blockers (ARBs) compared with placebo, angiotensin-converting enzyme inhibitor (ACE-i) or combined in heart failure with reduced ejection fraction (HFrEF) for the prevention of all-cause mortality.

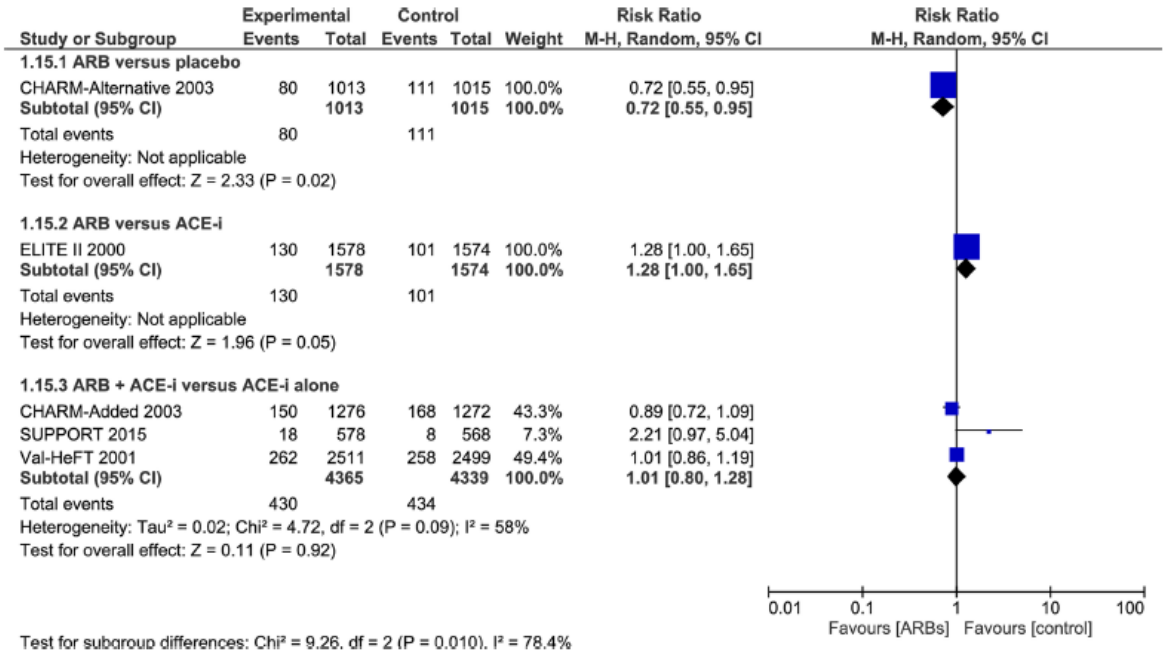


Figure 3 Efficacy of angiotensin receptor blockers (ARBs) compared with placebo, angiotensin-converting enzyme inhibitor (ACE-i) or combined in heart failure with reduced ejection fraction (HFrEF) for the prevention of sudden cardiac death (SCD).

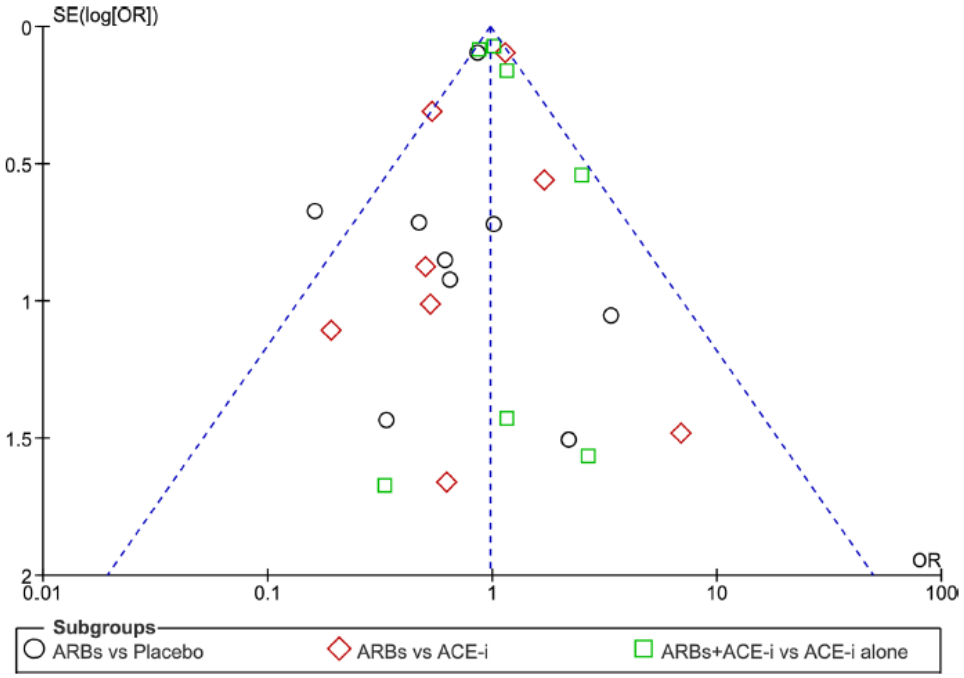


Figure 4 Funnel plot of SE (log OR) by OR to evaluate publication bias for the efficacy of angiotensin receptor blockers (ARBs) compared with control in heart failure and reduced ejection fraction (HFrEF) for the prevention of all-cause mortality.

Anmerkung/Fazit der Autoren

Our overview indicates that only three drug interventions (BBs, antialdosterones, combined ARB/neprilysin inhibitors) significantly reduce SCD and improve overall survival among individuals with HF and reduced ejection fraction. However, there is no evidence of effectiveness of ARBs to reduce neither all-cause mortality nor SCD (with a low quality of evidence), and ACE-

i do not significantly reduce SCD events. When the goal of drug therapy is to reduce SCD, especially in high-risk patients, our synthesis supports the use of the most effective regimen.

Kommentare zum Review

We did not assess the AMSTAR score for six studies, of which two [46 47] were narrative reviews, two [25 44] were individual participant or patient data meta-analyses and the other two [26 32] were overviews of reviews.

Hartmann C et al., 2018 [9].

The effect of ivabradine therapy on heart failure patients with reduced ejection fraction: a systematic review and meta-analysis

Fragestellung

To study the additional effect of therapy with ivabradine in terms of cardiovascular death, all-cause mortality, hospitalization due to HF, heart rate and functional status in studies reporting those effects in HFrEF populations.

Methodik

Population:

- Adult patients with chronic HFrEF and with the majority using beta-blockers

Intervention/Komparator:

- Ivabradine vs. carvedilol/bisoprolol/placebo

Endpunkte:

- cardiovascular death, all-cause mortality, hospitalization due to HF, heart rate and functional status outcomes before and after therapy

Recherche/Suchzeitraum:

- Embase, Medline, Pubmed, Cochrane Library, CINAHL, Web of Science, Scopus, SciELO and LILACS databases for studies published up to June 2016

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Seven trials (n= 17,747 participants)

Charakteristika der Population:

Table 1 Characteristics of included studies

Study, year	Reference number	Location	N	Male	Age (years)	Population	LVEF (%)	Ischemic HF	Baseline HR (beats/min)	Beta-blocker use	≥ 50% beta-blocker target dose	Beta-blocker target dose (%)	Intervention	Control	Duration (months)
Tsutsui et al. (2016)	[15]	Japan	103	85.7	59.0 (13.1)	Chronic HF, LVEF ≤ 35% and HR ≥ 75 beats/min	28.4 (5.1)	42.9	82.7 (7.4)	92.9	63.3	35	Ivabradine 7.5 mg BID	Placebo	1.5
Volterrani et al. (2011)	[14]	Italy	80	68	66.8 (9.5)	Chronic HF and NYHA II and III	27 (4.9)	81	76.7 (12.8)	100	100	Not reported	Ivabradine 5 mg BID	Carvedilol	3
Amosova et al. (2011)	[11]	Italy	29	89.7	59.0 (5.4)	Ischemic HF and LVEF < 45%	39.1 (5.5)	100	75.9 (2.97)	100	100	41.4	Ivabradine 7.5 mg BID	Bisoprolol	2
Mansour et al. (2011)	[12]	Egypt	53	60	49.0 (13)	Idiopathic dilated cardiomyopathy, LVEF < 40% and HR > 70 beats/min	30.2 (5.6)	0	84 (10)	100	19	Not reported	Ivabradine 7.5 mg BID	Carvedilol	3
Sarullo et al. (2010)	[13]	Italy	60	75	52.7 (5.3)	Chronic HF, LVEF ≤ 40% and HR > 70 beats/min	29.8 (6.0)	100	75 (3)	60	Not reported	Not reported	Ivabradine 7.5 mg BID	Placebo	3
Swedberg et al., 2010	[8]	37 countries	6505	76	60.4 (11.4)	Chronic HF, LVEF ≤ 35% and HR ≥ 70 beats/min	29 (5.1)	68	79.9 (9.6)	89	56	26	Ivabradine 7.5 mg BID	Placebo	22.9
Fox et al., 2008	[7]	33 countries	10,917	83	65 (8.4)	Stable coronary artery disease and LVEF < 40%	32.4 (5.5)	100	71.6 (9.9)	87	Not reported	Not reported	Ivabradine 7.5 mg BID	Placebo	19

Data are shown as n (%) or mean ± SD. *HF* heart failure, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *HR* heart rate, *BID* twice daily

Qualität der Studien:

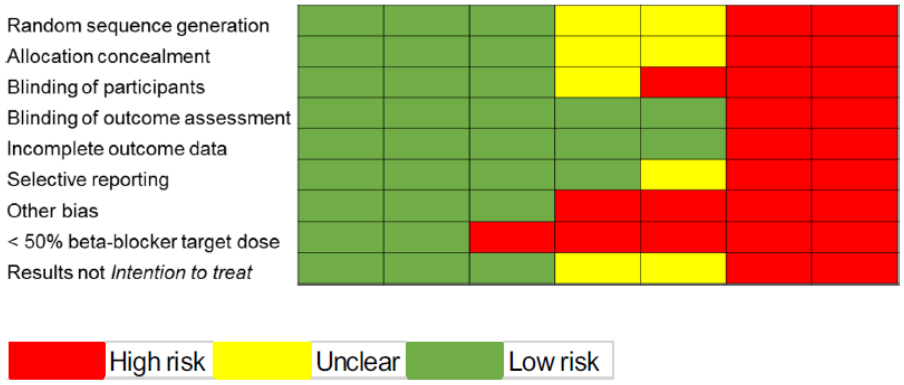
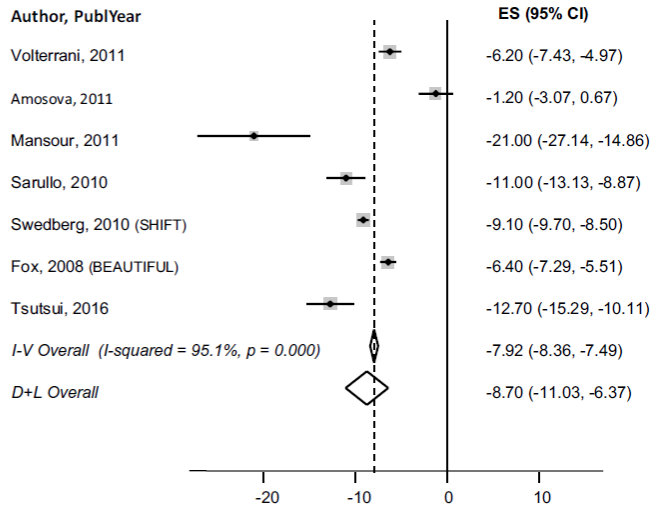


Fig. 2 Quality of included studies by the Cochrane risk of bias tool

Studienergebnisse:

- Pooled relative risks RR (95%) for HF:
  - all-cause mortality = 0.98 (0.90–1.06), (I^2= 57.8%, p = 0.124)
  - cardiovascular death for HF = 0.99 (0.91–1.08), (I^2= 65.8%, p = 0.087)
  - hospitalization for HF = 0.87 (0.68–1.12), (I^2 = 89.1%, p = 0.002)
- Heart rate analysis (CI 95%) showed a decrease of 8.7 (6.37–11.03) beats/ min with ivabradine compared to the control group (Fig. 4), with high heterogeneity between the studies (I^2 = 95.1%, p < 0.001).

Fig. 4 Effect of ivabradine on heart rate outcome



- The subgroup analysis by beta-blocker dose showed that, in studies reporting all of the studied population on recommended treatment (at least 50% of the beta-blocker target dose), heart rate (CI 95%) decreased by 4.70 (3.67–5.73). On the other hand, within groups or studies which reported < 100% of the studied population on recommended treatment or which did not report the dose, heart rate decreased by 8.60 (8.13–9.08). This indicates ivabradine had a significantly smaller effect on heart rate when the beta-blocker dose was optimum. Metaregression by beta-blocker target dose was prevented by the lack of sufficient beta-blocker usage information in the included studies.

- The pooled relative risk RR (95%) of cardiac disorders was 0.86 (0.67–1.11); of respiratory disorders, 0.80 (0.66–0.97); of neurological disorders, 0.84 (0.73–0.97); and of renal disorders, 1.24 (0.95–1.63)

Anmerkung/Fazit der Autoren

Ivabradine significantly reduces heart rate, and the heart rate effect size is smaller when beta-blocker dose was optimum. Therefore, the additional effect of ivabradine on heart rate appears to be inversely correlated with the dose of beta-blocker. The use of ivabradine shows no significant changes on hospitalization due to HF, cardiovascular death and all-cause mortality outcomes. Unreported beta-blocker doses and beta-blocker doses lower than recommended limit the conclusions on the additional effect of ivabradine. Further well-designed prospective studies are warranted to study the additional effects of ivabradine, especially on final outcomes.

Kommentare zum Review

The magnitude of the effect of ivabradine in HFrEF cannot be known with certainty since the beta-blocker dose was not achieved or not reported in all studies. Therefore, it remains unclear whether ivabradine has an isolated effect or if the effects reported in the included studies could be attributed to the beta-blocker target doses and their primary reduction in heart rate.

Tai C et al., 2017 [16].

Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular events in patients with heart failure: a meta-analysis of randomized controlled trials

Fragestellung

To assess the efficacy of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) on all-cause and cardiovascular (CV) mortality in patients with heart failure.

Methodik

Population:

- HF patients with reduced ejection fraction (HFrEF, left ventricular ejection fraction ≤45%)

Intervention/Komparator:

- ACEIs and ARBs treatment with placebo treatment, no treatment, or other anti-HF drugs treatment;

Endpunkte:

- All-cause mortality and CV mortality

Recherche/Suchzeitraum:

- PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for randomized clinical trials (RCTs) from November 1977 to June 2017

Qualitätsbewertung der Studien:

- Jadad score

Ergebnisse

Anzahl eingeschlossener Studien:

- 38 studies:
  - six trials (n = 8404) compared ARBs with placebo,
  - 32 trials (n = 39,254) compared ACEIs with various control therapies, (13 arms (n = 10,134) compared with placebo treatment; 10 arms (n = 8714) in which the comparator was active treatment
  - nine trials(n = 20,406) compared ACEIs with ARBs.

Charakteristika der Population:

Table 1 Study characteristics

Study, year	No of patients	Drugs		Baseline characteristics			Follow-up, w	Cause of heart failure					Risk factors			Jadad Score
		Treatment	Control	Men,%	Age, y	LVEF, %		MI, %	HTN,%	ICM, %	NICM, %	VHD, %	DM, %	HTN,%	AF,%	
ARBs vs Controls																
Havranek [43], 1999	218	Irbesartan	Placebo	82	60	≤0.40	12	–	–	67	–	–	–	–	–	2
STRETCH [45], 1999	844	Candesartan	Placebo	68	62	0.35–0.45	12	–	29	71	2	2	–	–	–	4
SPICE [44], 2000	270	Candesartan	Placebo	69	66	<0.35	12	–	4	71	16	11	48	34	24	5
ARCH-J [47], 2003	292	Candesartan	Placebo	78	64	≤0.45	24	25	7	–	57	8	–	–	–	4
Val-HeFT [46], 2001	5010	Valsartan	Placebo	80	63	≤0.40	100	–	7	57	31	–	26	–	12	5
CHARM-Alternative [13], 2003	2028	Candesartan	Placebo	68	67	≤0.40	135	–	6	68	–	–	27	50	25	5
ARBs vs ACEIs																
REPLACE [42], 2001	378	Telmisartan	Enalapril	89	64	≤0.40	12	–	–	–	–	–	–	–	–	4
HEAVEN [40], 2002	141	Valsartan	Enalapril	75	67	≤0.45	12	–	–	87	–	–	–	–	–	3
Dickstein [39], 1995	166	Losartan	Enalapril	78	64	<0.35	12	–	–	69	3	12	–	23	–	3
ELITE [14], 1997	722	Losartan	Captopril	67	73	≤0.40	48	–	–	68	–	–	25	57	23	4
ELITE II [10], 2000	3152	Losartan	Captopril	70	71	≤0.40	72	–	–	–	–	–	24	49	30	5
RESOLVD [12], 1999	768	Candesartan	Enalapril	84	63	<0.40	43	–	–	72	–	–	–	–	–	5
OPTIMAAL [9], 2002	5477	Losartan	Captopril	71	67	<0.35	130	100	0	0	0	0	17	36	10	5
VALIANT [11], 2003	14,703	Valsartan	Captopril	69	65	≤0.35–0.45	107	100	0	0	0	0	23	55	–	5
Lang [41], 1997	116	Losartan	Enalapril	78	58	≤0.45	12	–	4	47	44	3	–	–	–	3
ACEIs vs Controls																
AIRE [2], 1993	1986	Ramipril	Placebo	74	65	–	60	–	–	–	–	–	12	28	–	5
Balpitt [23], 1998	169	Captopril	Placebo	–	–	–	24	–	–	–	–	–	–	–	–	2
CASSIS [24], 1995	96	Enalapril	Placebo	83	58	<0.40	12	–	–	70	30	–	23	–	–	3
Chalmers [25], 1987	130	Lisinopril	Placebo	69	58	–	12	–	13	48	30	8	–	–	–	2
Colfer [26], 1992	172	Benazepril	Placebo	–	–	≤0.35	12	–	–	–	–	–	–	–	–	2
CONSENSUS [3], 1987	253	Enalapril	Placebo	70	71	–	27	–	–	73	15	26	23	25	58	3
FEST [27], 1995	308	Fosinopril	Placebo	74	63	≤0.35	12	–	–	–	–	–	–	–	–	4
FHFSG [28], 1995	241	Fosinopril	Placebo	80	62	≤0.35	24	–	–	–	–	–	–	–	–	3
Lechat [29], 1993	125	Perindopril	Placebo	–	–	–	12	–	–	–	–	–	–	–	–	3
Newman [30], 1988	105	Captopril	Placebo	–	–	–	12	–	–	–	–	–	–	–	–	2
SAVE [4], 1992	2231	Captopril	Placebo	82	59	≤0.40	144	100	–	–	–	–	21	43	–	5
SOLVD [5], 1991	2569	Enalapril	Placebo	80	61	≤0.35	166	–	–	–	–	–	26	42	10	5
TRACE [6], 1995	1749	Trandolapril	Placebo	72	68	≤0.35	96–200	100	–	–	–	–	14	23	–	5
Aguilar [31], 1999	345	Captopril	Digoxin	68	63	–	216	–	–	–	–	–	–	–	–	3

Table 1 Study characteristics *(Continued)*

Study, year	No of patients	Drugs		Baseline characteristics			Follow-up, w	Cause of heart failure					Risk factors			Jadad Score
		Treatment	Control	Men,%	Age, y	LVEF, %		MI, %	HTN,%	ICM, %	NICM, %	VHD, %	DM, %	HTN,%	AF,%	
CARMEN [32], 2008	381	Enalapril	Carvedilol	80	62	<0.40	72	–	–	–	–	–	14	32	17	4
CIBIS III [33], 2011	217	Enalapril	Bisoprolol	71	73	≤0.35	96	–	25	61	12	12	21	59	54	5
Cowley [34], 1994	209	Captopril	Flosequinan	–	–	–	48	–	–	–	–	–	–	–	–	3
Dohmen [35], 1997	266	Captopril	Ibopamine	84	62	<0.40	24	–	6	67	27	–	8	–	15	3
Hy-C [36], 1992	104	Captopril	Hydralazine	86	52	0.2(m)	32	–	–	59	34	4	–	–	17	3
IMPRESS [37], 2007	573	Lisinopril	Omapatrilat	89	64	–	>40	–	4	66	24	3	–	–	–	5
Northridge [38], 1999	45	Captopril	Candoxatril	87	63	<0.40	12	–	–	–	–	–	–	–	–	2
OVERTURE [7], 2002	5770	Enalapril	Omapatrilat	79	63	≤0.30	58	–	–	56	–	–	31	–	–	5
V-HeFT II [8], 1991	804	Enalapril	Nitrates	–	61	<0.45	96	–	–	–	–	–	20	48	14	3

Data was absent in the original article

No number, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *HTN* hypertension, *DM* diabetes mellitus, *AF* atrial fibrillation, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II Receptor Blockers, *ICM* ischemic cardiomyopathy, *NICM* non-ischemic cardiomyopathy, *VHD* valvular heart disease, *m* mean

Qualität der Studien:

- There were 32 studies of good quality (Jadad score ≥ 3) with low risk of bias and six studies of low quality (Jadad score < 3) with high risk of bias.

Studienergebnisse:

Effect of ACEIs and ARBs on all-cause mortality:

- Thirty-two studies reported the effect of ACEIs on all-cause mortality in a total of 39,254 HF patients with moderate heterogeneity in overall analysis (I^2 = 44%, p = 0.005). ACEIs were associated with a statistically significant 11% reduction in all-cause mortality (RR: 0.89, 95% CI: 0.83–0.96, p = 0.001, Fig. 2). Similar findings were observed when ACEIs were compared

with placebo treatment (p < 0.001). However, when ACEIs were compared with active treatment or ARBs, ACEIs did not significantly reduce all-cause mortality. There was no evidence of publication bias (p = 0.833).

- Moreover, 15 studies [9–14, 39–47] reported the effect of ARBs on all-cause mortality in a total of 28,814 HF patients with no significant heterogeneity in overall analysis (I^2 = 26%, p = 0.17). ARBs were not associated with a reduction in all-cause mortality (RR: 1.03, 95% CI: 0.98–1.08, p = 0.28, Fig. 3). There was no evidence of publication bias (p = 0.921).

Effect of ACEIs and ARBs on CV mortality:

- Seventeen studies reported the effectiveness of ACEIs for CV mortality in a total of 28,302 HF patients with moderate heterogeneity in overall analysis (I^2 = 51%, p = 0.009). ACEIs were associated with a statistically significant 14% reduction in CV mortality (RR: 0.86, 95% CI: 0.78–0.94, p = 0.001, Fig. 5). Similar findings were observed when ACEIs treatment was compared with placebo treatment (p < 0.001). However, when ACEIs were compared with active treatment or ARBs, ACEIs did not significantly reduce CV mortality. There was no evidence of publication bias (p = 0.967).
- Moreover, 11 studies reported the effectiveness of ARBs for CV mortality in a total of 27,991 HF patients with no significant heterogeneity in overall analysis (I^2 = 40%, p = 0.08). ARBs were associated with no reduction in CV mortality (RR: 1.01, 95% CI: 0.92–1.12, p = 0.78). Similar findings were observed when ARBs were compared with placebo or ACEIs (p ≤ 0.50). And there was no evidence of publication bias (p = 1.000).

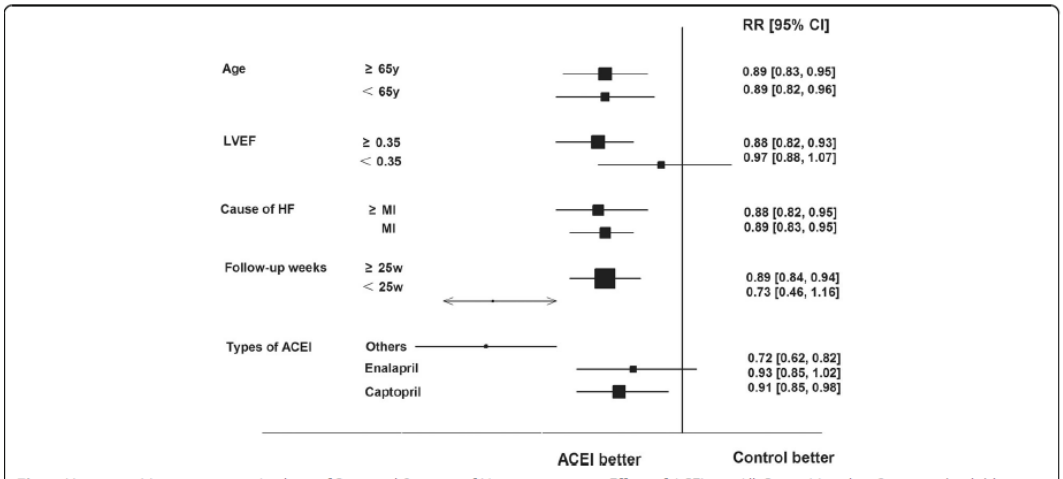


Fig. 6 Univariate Meta-regression Analysis of Potential Sources of Heterogeneity on Effect of ACEIs on All-Cause Mortality. Boxes and solid lines indicate RR and 95%CI, respectively for each study, and the diamonds and their width indicate the pooled RR and the 95% CI, respectively. Trials to the left of the vertical line showed a reduction in risk with the experimental intervention; those to the right showed an increase in risk with the experimental intervention. ACEI, angiotensin-converting enzyme inhibitor, MI, myocardial infraction, HF, heart failure, LVEF, left ventricular ejection fraction

Anmerkung/Fazit der Autoren

In 47,662 subjects, our meta-analysis shows that ACEIs, but not ARBs reduce all-cause mortality and cardiovascular deaths in HF patients. Thus, ACEIs should be considered as first-line therapy to limit excess mortality and morbidity in this population.

Kommentare zum Review

These trials used different ACEIs or ARBs at a different dosage. It is likely that different ACEIs and ARBs may have a total different effect on the cardiac mortality. Moreover, the present study is unable to address whether the efficacy may be varied in HF patients with different ethnic backgrounds.

Pei H et al., 2019 [11].

Ivabradine Improves Cardiac Function and Increases Exercise Capacity in Patients with Chronic Heart Failure A Systematic Review and Meta-Analysis

Fragestellung

To systematically review and conduct a meta-analysis of the ivabradine-induced improvement in cardiopulmonary function, exercise capacity, and primary composite endpoints in patients with chronic heart failure (CHF).

Methodik

Population:

- CHF patients whose ejection fraction was decreased or preserved

Intervention/Komparator:

- Ivabradine vs. standard anti-heart failure therapy, including angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), β-blockers, calcium antagonists and diuretics.

Endpunkte:

- Heart rate (HR), left ventricular ejection fraction (LVEF), peak early diastolic mitral flow velocity/late diastolic mitral flow velocity (E/A), peak early diastolic mitral flow velocity/peak early diastolic mitral annular velocity (E/Em), minute ventilation/carbon dioxide production (VE/VCO2), peak oxygen consumption (peak VO2), and NYHA class.
- The exercise capability evaluation index included the exercise duration with a submaximal load and the 6-minute walk distance.
- Severe adverse events, cardiac dysfunction, nervous system disorder, and visual disturbance during the treatment and follow-up period.

Recherche/Suchzeitraum:

- Electronic databases, including PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Clinical Trials and European Union Clinical Trials, were searched from inception until August 2017 for all clinical RCTs

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 22 studies, 12 with 6,526 systematically reviewed patients (qualitatitive analysis) and 10 studies with 18,036 patients, were subjected to metaanalysis.

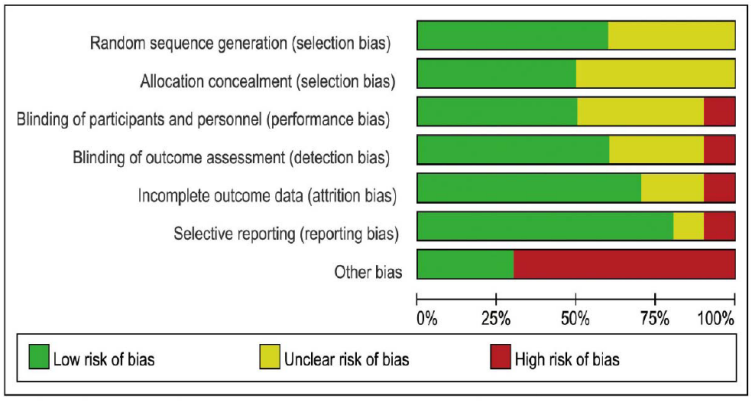
Charakteristika der Population:

Table II. Baseline Characteristics of the Ivabradine Group and the Standard Anti-Heart Failure Treatment Group

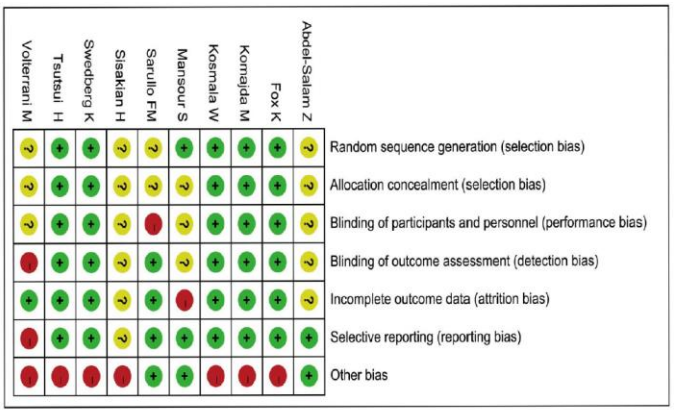
Study	Year	Number of partici-pants	Age (year)	BMI kg/m²	Males, *n*	HR, bpm	LVEF, %	SBP (mmHg)	DBP (mmHg)	NYHA class I/II/III/IV
Komajda M	2017	95	72.0 (66.0-78.0)	29.6 (26.4-35.6)	36	75 (72-78)	60 (54-66)	132 (123-142)	76 (69-84)	0/76/19/0
		84	73.0 (67.0-79.0)	28.8 (26.8-32.8)	27	74 (71-79)	61 (55-67)	133 (120-145)	80 (70-85)	0/69/15/0
Sisakian H	2016	27	58.2 ± 12.2	N/A	22	81.3 ± 7.9	30.6 ± 6.66	120.2 ± 15.59	76.2 ± 10.98	0/6/21/0
		27	61.4 ± 9.67	N/A	22	76.4 ± 4.95	30.3 ± 5.76	118.3 ± 12.33	74.3 ± 7.17	0/5/22/0
Tsutsui H	2016	42	60.0 ± 13.9	24.6 ± 4.6	37	83.4 ± 8.2	28.4 ± 4.9	119.5 ± 16.2	72.5 ± 12.1	0/39/3/0
		42	59.4 ± 12.7	24.3 ± 4.3	34	81.5 ± 7.4	28.5 ± 4.9	113.2 ± 16.9	70.3 ± 10.4	0/38/3/0
Abdel-Salam Z	2015	20	49.1 ± 15.7	N/A	10	85 ± 12	34 ± 4	101 ± 17	69 ± 12	0/6/12/2
		23	52.3 ± 13.5	N/A	13	84 ± 10	30 ± 8	91 ± 5	61 ± 4	0/5/14/4
Kosmala W	2013	30	66.5 ± 8.5	30.3 ± 4.0	7	72 ± 7	67 ± 7	130 ± 18	75 ± 8	N/A
		31	68.0 ± 8.7	29.1 ± 4.4	4	70 ± 6	69 ± 6	133 ± 17	76 ± 7	N/A
Volterrani M	2011	42	66.5 ± 9.2	26.4 ± 3.0	28	75.7 ± 12.5	28 ± 4.7	124.8 ± 12.9	71.9 ± 8.6	0/21/21/0
		38	66.7 ± 10.1	26.8 ± 3.2	26	76.7 ± 12.8	26 ± 5.0	125.4 ± 15.2	74.8 ± 9.1	0/22/16/0
Mansour S	2011	30	47 ± 13	N/A	18	96 ± 15	32.1 ± 6.1	97 ± 15	N/A	0/7/22/1
		23	52 ± 13	N/A	14	84 ± 10	29.0 ± 7.4	91 ± 5	N/A	0/3/14/6
Sarullo FM	2010	30	52.1 ± 6.1	N/A	23	75 ± 3	30.6 ± 6	109 ± 7	N/A	0/17/13/0
		30	52.9 ± 4.9	N/A	22	76.7 ± 12.8	29.9 ± 6	110 ± 9	N/A	0/18/12/0
Swedberg K	2010	3241	60.7 ± 11.2	28.0 ± 5.1	2462	79.9 ± 9.5	29.0 ± 5.1	122.0 ± 16.1	75.7 ± 9.6	0/1585/1605/50
		3264	60.1 ± 11.5	28.0 ± 5.0	2508	80.1 ± 9.8	29.0 ± 5.2	121.4 ± 15.9	75.6 ± 9.4	0/1584/1618/61
Fox K	2008	5479	65.3 ± 8.5	28.4 ± 4.4	4540	71.5 ± 9.8	32.4 ± 5.5	128.1 ± 15.7	77.4 ± 9.3	840/3346/1293/0
		5438	65.0 ± 8.4	28.5 ± 4.4	4507	71.6 ± 9.9	32.3 ± 5.5	127.9 ± 15.5	77.5 ± 9.2	840/3359/1239/0

BMI indicates body mass index; HR, heart rate; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association; and N/A, not applicable. Data are the median (IQR, interquartile range) or mean ± SD.

Qualität der Studien:



Supplemental Figure 1. Risk of bias graph.



Supplemental Figure 2. Risk of bias summary.

Studienergebnisse:

Cardiopulmonary function:

- treatment with added ivabradine reduced the heart rate (MD = −17.30, 95% confidence interval (CI): 19.52- −15.08, P < 0.00001),

LVEF:

- treatment with added ivabradine significantly increased the LVEF (MD = 3.90, 95% CI: 0.40-7.40, P < 0.0001) and led to a better New York Heart Association (NYHA) classification.

Lung function:

- Ivabradine significantly reduced the minute ventilation/carbon dioxide production (VE/VCO2) (MD = −2.68, 95% CI: −4.81- −0.55, P = 0.01) and improved the peak VO2 (MD = 2.80, 95% CI: 1.05-4.55, P = 0.002) and the exercise capacity, including the exercise duration with a submaximal load (MD = 7.82, 95% CI: −2.57-−18.21, P < 0.00001) and the 6-minute walk distance.

Cardiovascular composite endpoint events:

- the result showed that the RRs of all-cause mortality and cardiovascular mortality were not significantly different between the added ivabradine group and the standard antiheart failure therapy group (P = 0.59 and P = 0.79, respectively).
- The RR of cardiovascular death or worsening heart failure was significantly decreased (RR = 0.93, 95% CI: 0.87-−0.98, P = 0.01) in the patients treated with ivabradine.
- Additionally, the RRs of heart failure and hospitalization also decreased (RR = 0.91, 95% CI: 0.85-−0.97, P = 0.006; RR = 0.86, 95% CI: 0.79-−0.93, P = 0.0002).

Side effects and adverse events:

- Treatment with ivabradine did not change the RR of serious adverse events compared to the RR of the standard anti-heart failure therapy group (RR 0.97, 95% CI: 0.90-1.04, P = 0.40).
- adverse events such as cardiac dysfunction and nervous system disorders were also decreased (RR = 0.92, 95% CI: 0.83-1.01, P = 0.07), (RR = 0.81, 95% CI: 0.65-1.00, P = 0.06).
- Notably, the RR of visual symptoms in the ivabradine group was significantly higher than that of the standard anti-heart failure therapy group (RR = 3.82, 95% CI: 1.80-8.13, P = 0.0005).

Anmerkung/Fazit der Autoren

Unlike the results of a previous meta-analysis and systematic review, ivabradine did not reduce the risk of death and hospitalization for heart failure, and no difference was found in safety between ivabradine and placebo. Our current results are positive and optimistic. Presently, the evidence shows that adding ivabradine led to significant improvements in cardiopulmonary function, such as reduced heart rate, increased LVEF, reduced VE/VCO2, improved peak VO2, and increased exercise capacity in patients with CHF. Moreover, using ivabradine with the standard anti-heart failure treatment reduced the mortality and hospitalization and improved the quality of life. In addition, ivabradine significantly increased the RR of visual symptoms, thereby rendering ivabradine relatively safe in patients with CHF.

Kommentare zum Review

RCT von Komajda et al (2017) und Kosmala et al (2013) haben Patienten mit LVEF ≥ 45% eingeschlossen.

Beldhuis IE et al., 2017 [2].

Renin–Angiotensin System Inhibition, Worsening Renal Function, and Outcome in Heart Failure Patients With Reduced and Preserved Ejection Fraction A Meta-Analysis of Published Study Data

Fragestellung

To investigate the interaction between the phenotype of chronic heart faillure (HF), treatment with RAAS inhibitors, the occurence of WRF and association with clinical outcome in a meta-analysis of published studies.

Methodik

Population:

- HFpatients with reduced ejection fraction (HFREF) and HF patients with preserved ejection fraction and (HFPEF).

Intervention/Komparator:

- Angiotensin-converting enzyme inhibitors (ACEi): Enalapril, Captopril vs. placebo
- Angiotension II receptor blockers (ARB): Valsartan, Candesartan, Irbesartan vs. placebo
- Mineralcorticoid receptor antagonists (MRA): Spironalacton, Eplerenone vs. placebo

Endpunkte:

- worsening renal function (WRF) and mortality

Recherche/Suchzeitraum:

- MEDLINE was searched to identify eligible studies that were published from inception to December 1, 2015

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Eight RCTs (n= 28,961 patients were included in the individual studies (24,520 in HFREF and 4,441 in HFPEF)
- six investigated solely HFREF patients, one investigated only patients with HFPEF and 1 published information about both HFREF and HFPEF patients.

Charakteristika der Population:

Table 1. Baseline Characteristics of Included Studies for the Primary Analysis

Study	Year	Randomized Treatment	Total No. in Original Study	Follow-Up Time, d	LVEF (%)	Creatinine, mg/dL	eGFR, mL/min per 1.73 m²	Concomitant Therapy, %						Medical History, %				Baseline Vitals		
								ACEi	ARB	BBL	MRA	Loop Diuretic	Digoxin	AF	HT	DM	Ischemic	SBP, mm Hg	DBP, mm Hg	HR, bpm
HFREF																				
Angiotensin-converting enzyme inhibitors (ACEi)																				
SOLVD[18]	1991	Enalapril	6377	1230	27	1.20	65.6	50		18	6.1	32	33		38	19	75	119	74	76
SAVE[17]	1992	Captopril	2231	1278	31	1.19	70	50		35		35	26		43	22	100	113	70	78
Angiotensin II receptor blockers (ARB)																				
Val-HeFT[9]	2001	Valsartan	5010	1000	27		61.3	93	50	35	4.8	85			7	25	20	124	76	
CHARM-HFREF*[7]	2003	Candesartan	1569	1000	28	1.10	71.5	57	50	56	18	88	64	28	61	36	59	125	73	72
Mineralocorticoid receptor antagonists (MRA)																				
RALES[9]	1999	Spironolacton	1663	720	26	1.30	64	95	0	11	50	100	73				55	122	75	81
EPHESUS[10]	2003	Eplerenone	5792	480	33		70			76	50	59			61	32	100	118	71	
EMPHASIS-HF[11]	2010	Eplerenone	2737	630	26	1.15	71	78	19	87	50	85	27	31	66	31	50	124	75	72
HFPEF																				
Angiotensin II receptor blockers (ARB)																				
CHARM-HFPEF*[7]	2003	Candesartan	836	1000	57	1.00	73.5	24	50	57	10	83	33	31	76	39	41	134	75	70
I-Preserve[8]	2008	Irbesartan	3595	1380	60	1.00	73	26	50	59	15	83	14	29	89	28	24	137	79	72

*Total number of patients from renal substudy as the definition of HFREF/HFPEF was different in the main trial program. AF indicates atrial fibrillation; BBL, β-blocker; CHARM, Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HT, hypertension; I-Preserve, Irbesartan in Heart Failure With Preserved Ejection Fraction Study; LVEF, left ventricular ejection fraction; RALES, Randomized Aldactone Evaluation Study; SAVE, Survival and Ventricular Enlargement; SOLVD, Studies of Left Ventricular Dysfunction; SBP, systolic blood pressure; and Val-HeFT, Valsartan Heart Failure Trial.

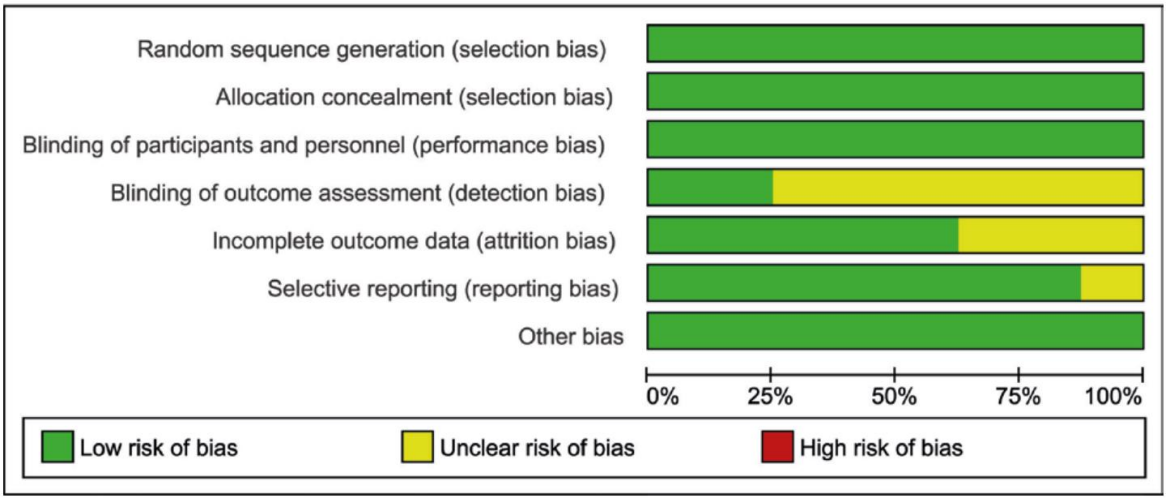
Supplementary Table 1. Definition of Worsening Renal Function in included studies

Study	Change in creatinine/eGFR	During Follow Period
SOLVD[1]	20% decrease in eGFR	2 weeks after randomization
SAVE[2]	≥ 0.3 mg/dL increase	2 weeks after randomization
RALES[3]	30% decrease in eGFR	12 weeks after randomization
Val-HeFT[4]	20% decrease in eGFR	4 weeks after randomization
CHARM[5]	≥ 0.3 mg/dL increase ánd ≥ 25% increase in serum creatinine	6 weeks after randomization
EPHESUS[6]	20% decrease in eGFR	2 weeks after randomization
I-PRESERVE[7]	≥ 0.3 mg/dL increase ánd ≥ 25% increase in serum creatinine	8 weeks after randomization
EMPHASIS-HF[8]	20% decrease in eGFR	5 months after randomization

Abbreviations: eGFR: estimated Glomerular Filtration Rate. CHARM: Candesartan in Heart Failure-Assessment of Reduction in Mortalityand Morbidity, EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure, EPHESUS: Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, I-PRESERVE: Irbesartan in Heart Failure with Preserved Ejection Fraction Study, RALES: Randomized Aldactone Evaluation Study, SAVE: Survival And Ventricular Enlargement Study, SOLVD:Studies Of Left Ventricular Dysfunction, Val-HeFT: Valsartan Heart Failure Trial

Qualität der Studien:

Figure: Risk of bias of included studies



Studienergebnisse:

Ergebnisse nur für HFREF dargestellt.

Table 2 shows the crude mortality rates stratified for treatment and WRF in each individual study.

Table 2. Incidence of Worsening Renal Function and Clinical Outcome in the Individual Studies

Study	Total No. (Renal Substudy)	Mortality						HF Hospitalization			
		Overall		RAASi		Placebo		RAASi		Placebo	
		WRF	No WRF	WRF	No WRF	WRF	No WRF	WRF	No WRF	WRF	No WRF
		Mortality, n (%)	Mortality, n (%)	Mortality, n (%)	Mortality, n (%)	Mortality, n (%)	Mortality, n (%)	HF Hospitalization, n (%)	HF Hospitalization, n (%)	HF Hospitalization, n (%)	HF Hospitalization, n (%)
HFREF											
SOLVD[18]	6377	186 (31)	1241 (22)	84 (26)	599 (21)	102 (36)	642 (22)	NA	NA	NA	NA
SAVE[17]	1813	59 (27)	308 (19)	26 (2 2)	137 (17)	33 (32)	171 (22)	16 (14)	98 (12)	22 (21)	130 (17)
Val-HeFT[8]	4928	104 (24)	627 (43)	71 (24)	404 (19)	33 (27)	436 (19)	NA	NA	NA	NA
CHARM-HFREF[7]	1569	49 (26)	31 (25)	31 (24)	152 (23)	18 (33)	189 (26)	47 (36)	151 (23)	27 (50)	204 (28)
RALES[9]	1663	98 (49)	627 (43)	56 (40)	256 (37)	42 (70)	371 (48)	31 (22)	117 (17)	21 (35)	204 (26)
EPHESUS[10]	5807	133 (15)	532 (11)	66 (13)	256 (11)	67 (16)	276 (11)	82 (17)	248 (10)	79 (19)	307 (12)
EMPHASIS-HF [11]	2763	48 (12)	224 (11)	24 (11)	98 (10)	24 (14)	126 (13)	23 (10)	116 (12)	35 (21)	172 (17)
HFPEF											
CHARM-HFPEF[7]	836	21 (22)	104 (14)	14 (23)	47 (13)	7 (20)	57 (15)	15(24)	66 (19)	9 (26)	87 (22)
I-Preserve[6]	3595	72 (31)	672 (20)	53 (35)	320 (19)	19 (25)	352 (21)	42 (27)	240 (14)	18 (24)	273 (16)

CHARM indicates Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HF heart failure; I-Preserve, Irbesartan in Heart Failure With Preserved Ejection Fraction Study; RAASi, renin–angiotensin aldosterone system inhibition; RALES, Randomized Aldactone Evaluation Study; SAVE, Survival and Ventricular Enlargement; SOLVD, Studies of Left Ventricular Dysfunction; Val-HeFT, Valsartan Heart Failure Trial; and WRF, worsening renal function.

- In the overall study population, WRF developed in 3268 patients (11%) and was more frequent with RAAS inhibition, compared with placebo (13 versus 9%).WRF was overall more frequent with HFREF (12%) compared with HFPEF (7%). However, the excess risk of WRF associated with RAASinhibitor was similar in HFREF (odds ratio, 1.68 [1.25–2.25] and HFPEF [odds ratio, 2.03 [1.60–2.57]; P=0.33).

RAAS Inhibitor–Induced WRF and Mortality in HFREF:

- In HFREF, in patients randomized to RAAS inhibitors, WRF was associated with worse outcomes, compared with patients who experienced no WRF (RR, 1.19 (1.08–1.31); Heterogenität: P=0.81, I^2=0%). However, the risk associated with WRF in patients allocated to placebo was larger (RR, 1.48 (1.35–1.62); P<0.001), and significantly different from patients randomized to RAAS inhibitors with WRF (P for interaction=0.005).

RAAS Inhibitor–Induced WRF and HF Hospitalization in HFREF:

- In HFREF, in patients randomized to RAAS inhibitors, WRF was associated with increased risk of HF hospitalization, compared with patients who experienced no WRF (RR, 1.33 (1.07–1.65); Heterogenität: P=0.07, I^2=53%). However, the risk did not significantly differ between RAAS and placebo-induced WRF (P for interaction=0.49).

RAAS Inhibitor–Induced, Investigator Reported, Renal Dysfunction in HFREF:

- In HFREF patients, RAAS inhibitor therapy resulted in higher renal dysfunction compared with placebo (RR, 1.59 (1.14–2.21); Heterogenität: P=0.04, I^2=46%).

RAAS Inhibitor–Induced Changes in eGFR in HFREF:

- For change in eGFR, we evaluated change during the entire study period, but for each study this time period differed. In HFREF patients, RAAS inhibitor therapy resulted in a greater decline in eGFR compared with placebo (mean treatment difference -3.47 mL/min per 1.73 m^2 [-4.26,-2.68]; Heterogenität: P=0.24, I^2=26%).

Anmerkung/Fazit der Autoren

RAAS inhibitors cause a significant decline in eGFR and lead to more renal adverse events with similar magnitude in both HFREF and HFPEF patients. Despite this fact, although RAAS inhibitor–induced WRF in HFREF is associated with slightly increased event rates, the prognostic benefit over placebo-induced WRF is maintained. However, in HFPEF, especially WRF that occurs with RAAS inhibition seem detrimental, cautioning the clinician to carefully evaluate these HFPEF patients with increases in creatinine during RAAS inhibitor treatment.

Kommentare zum Review

Another limitation of this meta-analysis is that we pooled different types of RAAS inhibitors: ACE inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor antagonists. Because their pharmacological working mechanisms differ, a difference in outcome could be expected as well. Finally, our analyses were carried out in a specific subset of patients, which included post myocardial left ventricular dysfunction, and specifically investigated WRF during initiation of (additional) RAAS-inhibition, not during long-term follow-up.

Burnett H et al., 2017 [4].

Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction A Network Meta-Analysis

Fragestellung

The objective of this study was to systematically identify RCTs evaluating recommended drug classes and combinations for HFrEF in terms of all-cause mortality and to perform a valid network meta-analysis (NMA) assessing the comparative efficacy of these therapies.

Methodik

Population:

- Patients with heart failure with reduced ejection fraction (HFrEF)

Intervention:

- Angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), β-blocker (BB), mineralocorticoid receptor antagonist (MRA) and angiotensin receptor–neprilysin inhibitor (ARNI), administered alone or in combination

Komparator:

- Placebo or any intervention of interest of a different class; comparisons within the same class were excluded (eg, ACEI versus ACEI).

Endpunkte:

- All cause mortality

Recherche/Suchzeitraum:

- Medline, EMBASE, and Cochrane CENTRAL were searched to identify studies published between January 1987 and April 28, 2015

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 57 RCTs

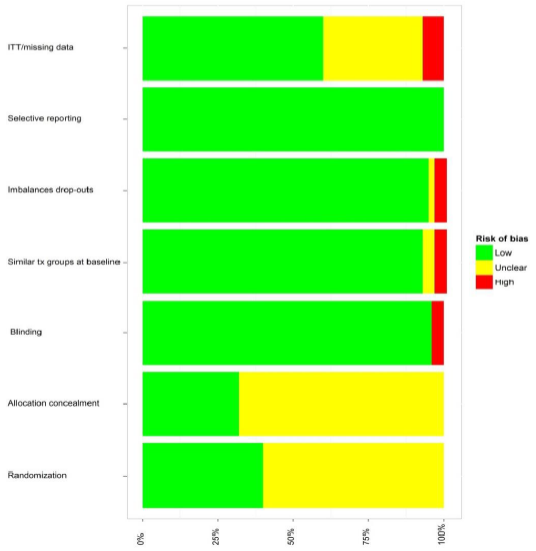
Charakteristika der Population:

- The majority were multicenter, double-blind, placebo-controlled trials, including between 28 and 8399 patients with a mean follow-up duration ranging from 8 weeks to 4 years.
- The treatment classes assessed included ACEI, BB, ARB, MRA, and ARNI.
- Patients were generally allowed concomitant therapies, such as diuretics, digoxin, and nitrates, as well as other permitted concomitant treatment classes.
- Enrolled patients were predominantly male (mean 76%, range 49%–90%) and between the ages of 52 and 73 years (mean 62 years; siehe Anhang).
- Most patients were classified as New York Heart Association class II–III (mean 86%), although 8 (14%) trials included a proportion of patients in class I and 36 (63%) trials included patients in class IV.
- Baseline left ventricular ejection fraction ranged between 15% and 40% (mean 27%)

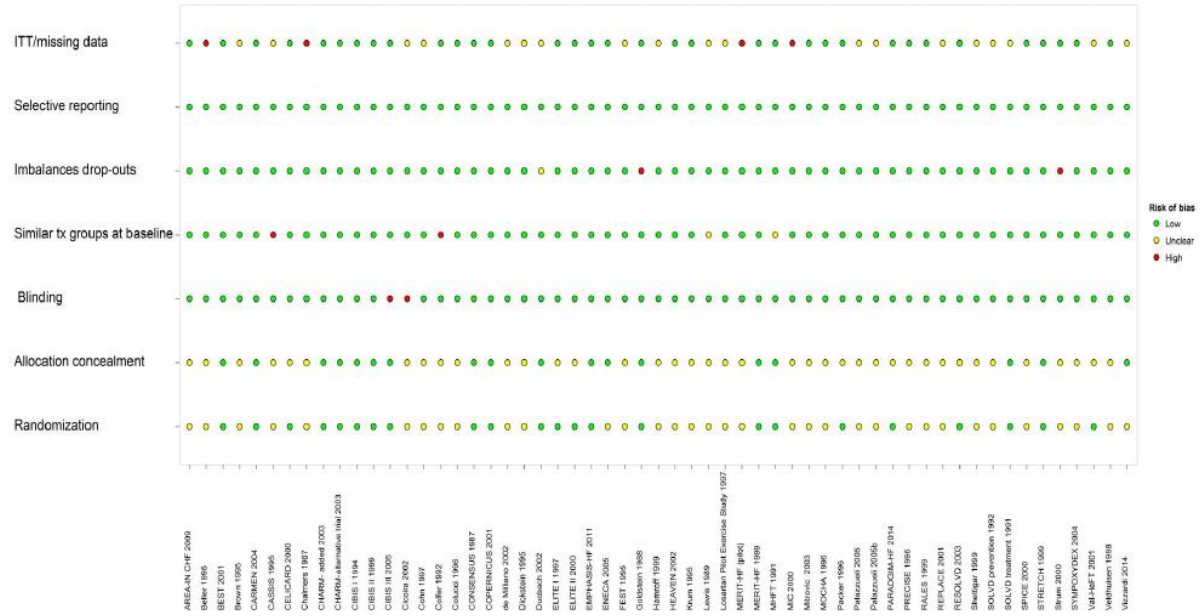
Qualität der Studien:

Supplementary Figure 1: Quality assessment results A) Summary by domain, B) Summary by RCT

A)



B)



Studienergebnisse:

Network of Evidence

In the network of connected RCTs (Figure 2), the thickness of the lines corresponds to the number of trials included per treatment comparison. The evidence was centralized around placebo and ACEI, with most RCTs informing the comparison of ACEI+BB versus ACEI. The treatment combination with ARNI was informed by a single RCT.

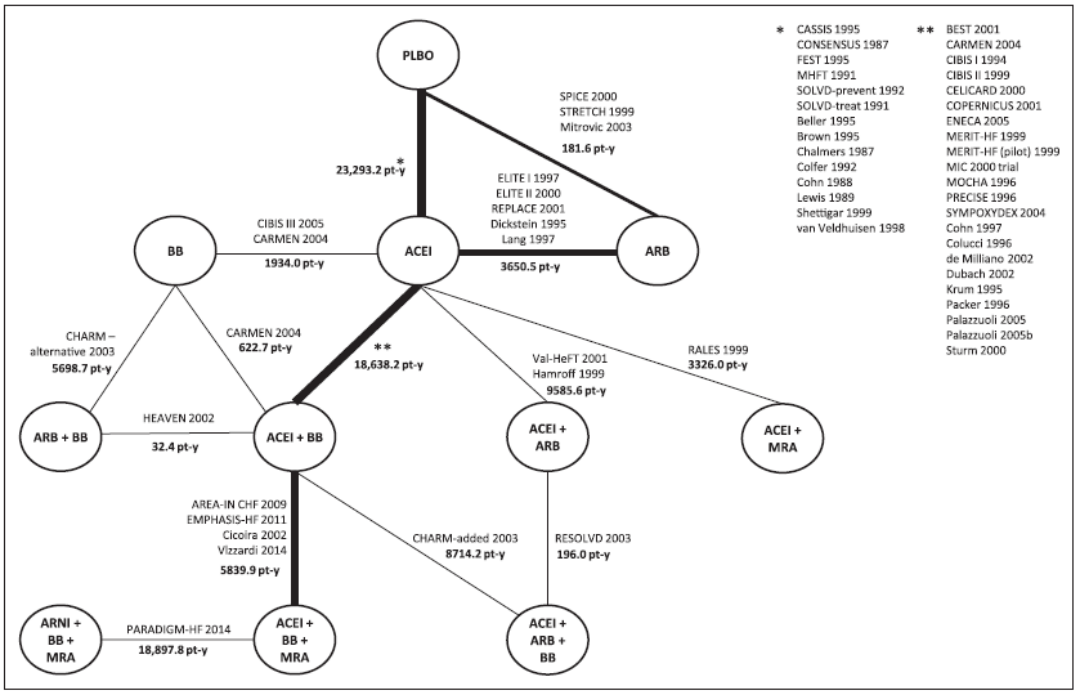


Figure 2. Network diagram of treatment classes and combinations reporting all-cause mortality. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; AREA-IN CHF, Anti-Remodelling Effect of Canrenone in Patients With Mild Chronic Heart Failure; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; BEST, Beta-Blocker Evaluation of Survival Trial; CARMEN, The Carvedilol and ACE-Inhibitor Remodelling Mild Heart Failure Evaluation Trial; CASSIS, Czech and Slovak Spirapril Intervention Study; CHARM-added, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity–Added; CHARM-alternative, Candesartan in Heart Failure–Assessment of Mortality and Morbidity Alternative; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; ELITE, Evaluation of Losartan in the Elderly Study; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; ENECA, Efficacy of Nebivolol in the Treatment of Elderly Patients With Chronic Heart Failure as Add-On Therapy to ACE Inhibitors or Angiotensin II Receptor Blockers, Diuretics, and/or Digitalis; FEST, Fosinopril Efficacy/Safety Trial; HEAVEN, Heart Failure Valsartan Exercise Capacity Evaluation; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MHFT, Munich Mild Heart Failure Trial; MIC, Metoprolol in Patients With Mild to Moderate Heart Failure: Effects on Ventricular Function and Cardiopulmonary Exercise Testing; MOCHA, Multicenter Oral Carvedilol Heart Failure Assessment; MRA, mineralocorticoid receptor antagonist; PARADIGM-HF, Prospective Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) With ACEI (Angiotensin–Converting–Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure; PLBO, placebo; PRECISE, Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise; RALES, Randomized Aldactone Evaluation Study; REPLACE, Replacement of Angiotensin Converting Enzyme Inhibition; RESOLVD, Randomized Evaluation of Strategies for Left Ventricular Dysfunction; SOLVD-prevent, Studies of Left Ventricular Dysfunction–Prevention Trial; SOLVD-treat, Studies of Left Ventricular Dysfunction–Treatment Trial; SPICE, Study of Patients Intolerant of Converting Enzyme Inhibitors; STRETCH, Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure; SYMPOXYDEX, Sympathetic and Oxydative Stress Kredex Study; and Val-HeFT, Valsartan Heart Failure Trial.[7,21–77]

- treatments were categorized to include the concomitant drug when the majority of patients in the study were receiving it at baseline. Specifically, if >50% of the trial patients received a concomitant drug of interest in the systematic review (eg, BB), the treatment was described as a combination therapy (the study drug class+the concomitant drug class(es), eg, ACEI+BB versus BB) in the analysis.

Supplementary Table 4: Proportion of patients taking concomitant ACEI and ARB in RCTs that allow concomitant use of ACEI or ARB

Criteria for ACEI or ARB	n studies	% of studies
ACEI or ARB allowed	9	100%
≥90% patients taking ACEI	3/9	33%
≥75% patients taking ACEI	6/9	67%
Only present pooled % (ACEI or ARB)	2/9	22%
Treatment classification unclear*	1/9	11%

* RESOLVD trial [51,52]

Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-II receptor antagonist

Network Meta-Analysis Results

- All identified RCTs were included in the NMA and provided comparative evidence on all-cause mortality in patients with HFrEF.
- Table 1 presents the results of the random effect NMA for all head-to-head comparisons and illustrates the HRs, the 95% CrIs, and the probability of a treatment being better than the comparator. We found significant between-study heterogeneity in the network of evidence (SD 0.18, 95% CrI 0.06–0.35; Table 1), which was expected given the differences observed in the included studies.

Table 1. Results of Random Effect Network Meta-Analysis for All-Cause Mortality Rates: Difference in Intervention Versus the Comparator, 95% Credible Intervals (CrI), and Probability That the Intervention Is Better Than the Comparator [*P*(better)]

	Comparator				
Intervention	PLBO	ACEI	ARB	BB	ACEI+BB
PLBO					
Estimate (95% CrI)	1 (1,1)	1.203 (0.989–1.512)	1.132 (0.793–1.65)	1.752 (1.067–3.041)	1.758 (1.382–2.424)
P(better)	NA	0.03	0.23	0.01	0.00
ACEI					
Estimate (95% CrI)	0.831 (0.661–1.011)	1 (1–1)	0.941 (0.679–1.292)	1.454 (0.92–2.38)	1.462 (1.255–1.783)
P(better)	0.97	NA	0.66	0.05	0.00
ARB					
Estimate (95% CrI)	0.883 (0.606–1.261)	1.063 (0.774–1.473)	1 (1–1)	1.548 (0.886–2.8)	1.552 (1.103–2.31)
P(better)	0.77	0.34	NA	0.06	0.01
BB					
Estimate (95% CrI)	0.571 (0.329–0.937)	0.688 (0.42–1.087)	0.646 (0.357–1.129)	1 (1–1)	1.008 (0.615–1.633)
P(better)	0.99	0.95	0.94	NA	0.49
ACEI+BB					
Estimate (95% CrI)	0.569 (0.413–0.724)	0.684 (0.561–0.797)	0.644 (0.433–0.906)	0.992 (0.612–1.626)	1 (1–1)
P(better)	1.0	1.0	0.99	0.51	NA
ACEI+ARB					
Estimate (95% CrI)	0.827 (0.505–1.243)	0.994 (0.658–1.448)	0.935 (0.548–1.514)	1.441 (0.789–2.672)	1.448 (0.964–2.232)
P(better)	0.84	0.52	0.62	0.11	0.03
ARB+BB					
Estimate (95% CrI)	0.472 (0.23–0.855)	0.567 (0.293–1.002)	0.534 (0.254–1.021)	0.828 (0.518–1.215)	0.831 (0.435–1.493)
P(better)	0.99	0.97	0.97	0.85	0.74
ACEI+MRA					
Estimate (95% CrI)	0.574 (0.348–0.908)	0.69 (0.448–1.058)	0.648 (0.378–1.103)	1.003 (0.54–1.935)	1.004 (0.653–1.649)
P(better)	0.99	0.96	0.95	0.50	0.49
ACEI+ARB+BB					
Estimate (95% CrI)	0.518 (0.308–0.795)	0.623 (0.397–0.926)	0.586 (0.334–0.97)	0.903 (0.486–1.68)	0.908 (0.614–1.358)
P(better)	1.0	0.99	0.98	0.64	0.72
ACEI+BB+MRA					
Estimate (95% CrI)	0.44 (0.264–0.661)	0.53 (0.342–0.762)	0.498 (0.286–0.804)	0.767 (0.417–1.397)	0.773 (0.535–1.091)
P(better)	1.0	1.0	1.0	0.81	0.94
ARNI+BB+MRA					
Estimate (95% CrI)	0.372 (0.189–0.647)	0.448 (0.24–0.758)	0.421 (0.206–0.774)	0.648 (0.308–1.329)	0.652 (0.371–1.11)
P(better)	1.0	1.0	0.99	0.89	0.95

Table 1. Continued

Intervention	Comparator					
	ACEI+ARB	ARB+BB	ACEI+MRA	ACEI+ARB+BB	ACEI+BB+MRA	ARNI+BB+MRA
PLBO						
Estimate (95% CrI)	1.21 (0.804–1.979)	2.121 (1.169–4.354)	1.744 (1.101–2.874)	1.929 (1.258–3.244)	2.272 (1.513–3.791)	2.689 (1.545–5.303)
P(better)	0.16	0.01	0.01	0.00	0.00	0.00
ACEI						
Estimate (95% CrI)	1.007 (0.691–1.521)	1.763 (0.998–3.415)	1.45 (0.945–2.232)	1.605 (1.08–2.518)	1.889 (1.312–2.925)	2.235 (1.319–4.166)
P(better)	0.48	0.03	0.04	0.01	0.00	0.00
ARB						
Estimate (95% CrI)	1.07 (0.66–1.824)	1.871 (0.98–3.945)	1.542 (0.907–2.645)	1.707 (1.031–2.997)	2.009 (1.243–3.501)	2.378 (1.291–4.847)
P(better)	0.38	0.03	0.05	0.02	0.00	0.01
BB						
Estimate (95% CrI)	0.694 (0.374–1.267)	1.207 (0.823–1.929)	0.997 (0.517–1.852)	1.107 (0.595–2.058)	1.304 (0.716–2.398)	1.543 (0.752–3.248)
P(better)	0.89	0.15	0.50	0.36	0.19	0.11
ACEI+BB						
Estimate (95% CrI)	0.691 (0.448–1.037)	1.203 (0.67–2.299)	0.996 (0.607–1.532)	1.102 (0.736–1.63)	1.294 (0.917–1.87)	1.533 (0.901–2.696)
P(better)	0.97	0.26	0.51	0.28	0.06	0.05
ACEI+ARB						
Estimate (95% CrI)	1 (1–1)	1.746 (0.883–3.743)	1.441 (0.787–2.537)	1.594 (0.944–2.734)	1.871 (1.111–3.326)	2.217 (1.148–4.567)
P(better)	NA	0.05	0.09	0.04	0.01	0.01
ARB+BB						
Estimate (95% CrI)	0.573 (0.267–1.132)	1 (1–1)	0.824 (0.368–1.655)	0.916 (0.427–1.838)	1.075 (0.517–2.146)	1.277 (0.551–2.847)
P(better)	0.95	NA	0.71	0.60	0.42	0.26
ACEI+MRA						
Estimate (95% CrI)	0.694 (0.394–1.27)	1.213 (0.604–2.715)	1 (1–1)	1.106 (0.621–2.083)	1.299 (0.755–2.439)	1.541 (0.784–3.311)
P(better)	0.91	0.29	NA	0.35	0.15	0.09
ACEI+ARB+BB						
Estimate (95% CrI)	0.627 (0.366–1.059)	1.092 (0.544–2.34)	0.904 (0.48–1.61)	1 (1–1)	1.174 (0.702–2.045)	1.392 (0.724–2.8)
P(better)	0.96	0.40	0.65	NA	0.25	0.13
ACEI+BB+MRA						
Estimate (95% CrI)	0.534 (0.301–0.9)	0.93 (0.466–1.935)	0.77 (0.41–1.325)	0.852 (0.489–1.425)	1 (1–1)	1.187 (0.784–1.799)
P(better)	0.99	0.58	0.85	0.75	NA	0.17
ARNI+BB+MRA						
Estimate (95% CrI)	0.451 (0.219–0.871)	0.783 (0.351–1.814)	0.649 (0.302–1.275)	0.718 (0.357–1.381)	0.843 (0.556–1.276)	1 (1–1)
P(better)	0.99	0.74	0.91	0.87	0.83	NA

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; MRA, mineralocorticoid receptor antagonist; and PLBO, placebo.

- Figure 5 illustrates the HRs for each treatment class versus placebo for all-cause mortality. The combination of ACEI+BB+MRA was associated with a 56% reduction in mortality versus placebo (HR 0.44, 95% CrI 0.26–0.66), while ARNI+BB+MRA was associated with the greatest reduction in all-cause mortality versus placebo (HR 0.37, 95% CrI 0.19–0.65).

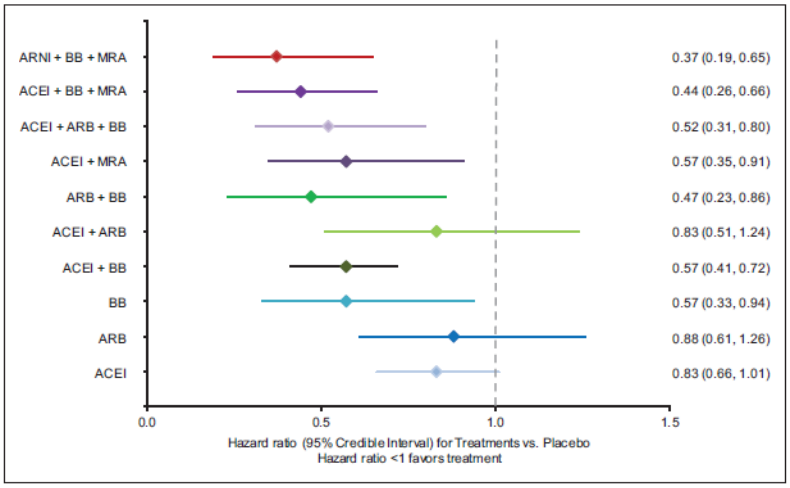


Figure 5. Results of random effect network meta-analysis for all-cause mortality: hazard ratios for intervention versus placebo for all-cause mortality and 95% credible intervals. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; and MRA, mineralocorticoid receptor antagonist.

- a sensitivity analysis ignored concomitant therapies and evaluated how ARNI monotherapy was compared with ACEI and ARB monotherapies. The random-effects model suggests that all active treatments are likely to be more efficacious than placebo, although with more uncertainty than the base case analysis.
- The sensitivity analysis showed that in comparison to placebo, ARNI was associated with a 29% reduction in mortality (HR 0.71, 95% CrI 0.39– 1.17); ACEI, a 16% reduction (HR 0.84, 95% CrI 0.65–1.01); and ARB, a 12% reduction (HR 0.88, 95% CrI 0.65–1.17).

Anmerkung/Fazit der Autoren

This report provides a comprehensive analysis of the comparative efficacy of the individual drug classes and combinations known to reduce mortality in patients with HFrEF. It was possible to pool and indirectly compare evidence from RCTs published over the last 34 years using NMA, providing insight into treatment comparisons in the absence of head-tohead trials. The threshold approach used to account for concomitant therapy provides a more accurate representation of the treatment comparisons evaluated in RCTs, often reflecting standard of care at the time. Our results show that the most efficacious combinations for reducing all-cause mortality are in line with the most recent guideline recommendations.

Kommentare zum Review

One limitation was the identification of concomitant therapy, which was based on data reported at baseline, which may have differed from treatments used during follow-up and certainly varied across the included trials.

Most notably, differences were identified in terms of study duration, which may imply differences in the study purpose or type of mortality analysis. The length of follow-up in each trial was accounted for in the analysis assuming a proportional hazards model, which allowed for an assessment of the broadest evidence base.

Sources of Funding: This work was supported by Novartis Pharma AG. The publication of this study was not contingent on the sponsor’s approval or censorship of the article.

3.4 Leitlinien

Bundesärztekammer (BÄK), 2019 [3].

Leitlinie Herausgegeben von BÄK, Kassenärztliche Bundesvereinigung (KBV) und Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)

Nationale VersorgungsLeitlinie Chronische Herzinsuffizienz, Langfassung, 3. Auflage, 2019, Version 1.

Zielsetzung /Fragestellung

Die NVL Chronische Herzinsuffizienz soll die sektorenübergreifende Versorgung von Patienten mit chronischer Herzinsuffizienz verbessern. Die Empfehlungen betreffen daher sowohl die Versorgung im gesamten ambulanten Bereich, als auch in Teilaspekten des stationären Bereichs (Behandlung der akuten Dekompensation, invasive Therapien). Außerdem definiert die NVL die Übergänge zwischen primärärztlicher und spezialfachärztlicher Versorgung sowie zwischen ambulanter und stationärer Versorgung

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: trifft zu. Diese Leitlinie wurde am 22. Oktober 2019 durch die Träger des NVL-Programms verabschiedet und ist bis zur nächsten Überarbeitung bzw. spätestens bis 22. Oktober 2024 gültig. Die Leitlinie wird regelmäßig überprüft und bei Bedarf kapitelweise überarbeitet.

Recherche/Suchzeitraum:

Für die 3. Auflage der NVL Chronische Herzinsuffizienz wurde abhängig von der jeweiligen Fragestellung systematisch und strukturiert nach Leitlinien, systematischen Übersichtsarbeiten und/oder Primärstudien recherchiert.

LoE/GoR

Die jeweilige Evidenzgrundlage wurde kritisch methodisch und klinisch bewertet. Die Graduierung der Empfehlungen folgte dem in Tabelle 1 dargestellten Grundprinzip. Zur besseren Unterscheidung zwischen Negativ- und Positivempfehlungen ergänzen Pfeilsymbole die Empfehlungen

Die Evidenzgraduierung („Level of Evidence“) der einzelnen Quellen folgte dem Schema des Oxford Centre for Evidence-Based Medicine (OCEBM, www.cebm.net). Die methodische Qualität systematischer Übersichtsarbeiten wurde mithilfe des AMSTAR-Tools bewertet [23]; die methodische Bewertung von Primärstudien erfolgte adaptiert nach den SIGN-Checklisten [24] sowie gegen Ende des Aktualisierungsprozesses nach den Empfeh-

lungen zur „Bewertung des Biasrisikos (Risiko systematischer Fehler) in klinischen Studien: ein Manual für die Leitlinienerstellung“ [25].

Tabelle 1: Einstufung von Leitlinien-Empfehlungen in Empfehlungsgrade (Grades of Recommendation) [5]

Empfehlungsgrad	Beschreibung	Formulierung	Symbol
A	Starke Positiv-Empfehlung	soll	⇑⇑
B	Abgeschwächte Positiv-Empfehlung	sollte	⇑
0	Offene Empfehlung	kann	⇔
B	Abgeschwächte Negativ-Empfehlung	sollte nicht	⇓
A	Starke Negativ-Empfehlung	soll nicht	⇓⇓

Die in der NVL verwendete Graduierung der Empfehlungen orientiert sich, wie im Methodenreport zum Programm für Nationale VersorgungsLeitlinien beschrieben [6], an GRADE (Grading of Recommendations, Assessment, Development and Evaluation) [8,9]. Die Vergabe der Empfehlungsgrade berücksichtigt dabei neben der zugrundeliegenden Evidenz z. B. ethische Verpflichtungen, klinische Relevanz der Effektivitätsmaße der Studien, Anwendbarkeit der Studienergebnisse auf die Patientenzielgruppe, Patientenpräferenzen und die Umsetzbarkeit im ärztlichen Alltag [1]. Infolgedessen kann es zu einem Auf- oder Abwerten des Empfehlungsgrades gegenüber der Evidenzklasse kommen. Die Gründe werden im Hintergrundtext bei der jeweiligen Empfehlung dargelegt. Auch Expertenmeinungen werden im formalisierten Konsensverfahren gemeinsam formuliert und abgestimmt.

Definition der Herzinsuffizienz mit reduzierter, geringgradig eingeschränkter und erhaltener linksventrikulärer Ejektionsfraktion

Tabelle 2: Definition der Herzinsuffizienz mit reduzierter, geringgradig eingeschränkter sowie erhaltener linksventrikulärer Ejektionsfraktion (nach [13])

Herzinsuffizienz mit reduzierter linksventrikulärer Ejektionsfraktion (HFrEF)	Herzinsuffizienz mit geringgradig eingeschränkter linksventrikulärer Ejektionsfraktion (HFmrEF)	Herzinsuffizienz mit erhaltener linksventrikulärer Ejektionsfraktion (HFpEF)
Symptome +/- Zeichen*	Symptome +/- Zeichen*	Symptome +/- Zeichen*
LVEF < 40%	LVEF 40-49%	LVEF ≥ 50%
	• erhöhte natriuretische Peptide (BNP > 35 pg/ml und/oder NT-proBNP > 125 pg/ml) • echokardiografisch objektivierte strukturelle oder funktionelle Störungen des linken Ventrikels	
* nicht zwingend bei frühen Stadien und bei Patienten unter Diuretika-Therapie		

Empfehlungen

6.2 Medikamentöse Therapie bei Herzinsuffizienz mit reduzierter links-ventrikulärer Ejektionsfraktion (HFrEF)

Im Mittelpunkt der medikamentösen Therapie der Herzinsuffizienz mit reduzierter linksventrikulärer Ejektionsfraktion (HFrEF) stehen Arzneimittel, die das Renin-Angiotensin-Aldosteron-System (RAAS) beeinflussen, sowie Betarezeptorenblocker und Diuretika. Für einige Wirkstoffe wurde dabei eine Verbesserung der Prognose nachgewiesen, während andere

lediglich symptomverbessernd wirken. Weitere Medikamente sind nur in spezifischen Situationen (siehe Kapitel 6.2.2 Empfohlene Medikamente für ausgewählte Patientengruppen sowie Kapitel 8 Komorbiditäten) oder bei Komplikationen (siehe Kapitel 9 Akute Dekompensation) indiziert.

Tabelle 18: Medikamentöse Stufentherapie nach NYHA-Klassen bei Herzinsuffizienz mit reduzierter LVEF

		NYHA I (asymptomatische LV-Dysfunktion)	NYHA II	NYHA III	NYHA IV (möglichst in enger Kooperation mit Kardiologen)
prognoseverbessernd	**ACE-Hemmer**	indiziert	indiziert	indiziert	indiziert
	Angiotensinrezeptor-blocker	bei ACE-Hemmer-Intoleranz	bei ACE-Hemmer-Intoleranz	bei ACE-Hemmer-Intoleranz	bei ACE-Hemmer-Intoleranz
	Betarezeptorenblocker	nach Myokardinfarkt oder bei Hypertonie	indiziert	indiziert	indiziert
	Mineralokortikoidrezep-torantagonisten		indiziert[1]	indiziert	indiziert
	Ivabradin[2]		bei Betarezeptoren-blocker-Intoleranz oder additiv bei Pati-enten mit Herz-frequenz ≥ 75/min	bei Betarezeptoren-blocker-Intoleranz oder additiv bei Pati-enten mit Herz-frequenz ≥ 75/min	bei Betarezeptoren-blocker-Intoleranz oder additiv bei Pati-enten mit Herz-frequenz ≥ 75/min
	Sacubitril/Valsartan		als ACE-Hemmer/ ARB-Ersatz bei per-sistierender Sympto-matik[3]	als ACE-Hemmer/ ARB-Ersatz bei per-sistierender Sympto-matik[3]	als ACE-Hemmer/ ARB-Ersatz bei per-sistierender Sympto-matik[3]
symptomverbessernd	**Diuretika**		bei Flüssigkeitsre-tention	indiziert	indiziert
	Digitalisglykoside			bei Sinusrhythmus als Reservemittel (mit niedrigem Zielserum-spiegel)	bei Sinusrhythmus als Reservemittel (mit niedrigem Zielserum-spiegel)
		bei nicht beherrschbarem tachyarrhythmischem Vorhofflimmern			

Diese Übersicht dient der grundsätzlichen Orientierung. Einschränkungen der Indikationen und Empfehlungen für Subgruppen sind in den Kapiteln zu den jeweiligen Medikamenten aufgeführt.

[1] bei persistierender Symptomatik unter leitliniengerechter Kombinationstherapie mit ACE-Hemmern/ARB und Betarezeptorenblockern

[2] nur bei stabilem Sinusrhythmus

[3] trotz leitliniengerechter Kombinationstherapie mit ACE-Hemmern/Angiotensinrezeptorblockern, Betarezeptorenblockern und Mineralokortikoidrezeptorantagonisten

6.2.1 Empfohlene Basismedikation

6.2.1.1 ACE-Hemmer

Empfehlungen/Statements	Empfehlungs-grad
6-5 Allen symptomatischen sowie asymptomatischen Patienten mit einer nachgewiesenen reduzierten Ejektionsfraktion und fehlenden Kontraindikationen sollen ACE-Hemmer empfohlen werden.	⇑⇑

Hintergrundinformationen:

Die Empfehlung beruht auf internationalen Leitlinien [13,17]. Nach Prüfung der dort zitierten Evidenz durch die Leitliniengruppe wurden Inhalt und Empfehlungsgrad übernommen.

In RCTs [153–156] und Metaanalysen [157,158] wurde nachgewiesen, dass ACE-Hemmer bei Patienten mit leichter, mäßiger und schwerer HFrEF (NYHA II-IV) die Gesamtsterblichkeit senken, die Progression der Pumpfunktionsstörung verzögern, die Hospitalisierungsrate senken sowie die Symptomatik und Belastungstoleranz verbessern. Bei herzinsuffizienten Patienten nach Myokardinfarkt senken ACE-Hemmer darüber hinaus die Re-Infarktrate [153–155].

Obwohl nur Captopril, Enalapril, Lisinopril und Ramipril in mortalitätsbezogenen Outcomestudien getestet wurden, geht man von einem Klasseneffekt bei ACE-Hemmern aus. Ob ein ACE-Hemmer anderen überlegen ist, lässt sich aus den vorliegenden Daten nicht ableiten. Der Nutzen von ACE-Hemmern hinsichtlich Mortalität und Morbidität steigt mit der Schwere der Herzinsuffizienz [159]. In Abhängigkeit vom Mortalitätsrisiko schwanken die Effektmaße in den ausgewerteten Studien deshalb erheblich:

• CONSENSUS 1987 [160]: NYHA IV, Follow-up 6 Monate, Enalapril vs. Placebo, Mortalität: ARR 15%, NNT 6 Monate = 7;

• SOLVD 1991 [161]: ~ 90% Patienten NYHA II oder III, Follow-up 3,5 Jahre, Enalapril vs. Placebo, Mortalität: ARR 4,5%, NNT 42 Monate = 22;

• SOLVD 1992 [162]: asymptomatische Patienten mit LVEF< 35-40%, NYHA I, Follow-up 40 Monate, Enalapril vs. Placebo, Progression der Erkrankung in NYHA II oder höher: ARR 9%, NNT 40 Monate = 11, NNT 1 Jahr = 37.

Für Patienten mit asymptomatischer HFrEF (NYHA I) ist die Evidenz inkonsistent: In einem RCT (n = 4 228) zeigte sich kein signifikanter Überlebensvorteil für asymptomatische Patienten (relative Risikoreduktion 8% (95% KI -8%; 21%), p = 0,30), jedoch reduzierten ACE-Hemmer die Hospitalisierungsrate und die Inzidenz einer symptomatischen Herzinsuffizienz [162].

Der Nutzen von ACE-Hemmern speziell für ältere Patienten mit Herzinsuffizienz kann aus der CONSENSUS-Studie abgeleitet werden, in der das durchschnittliche Alter der Patienten ca. 70 Jahre betrug (s. o.) [160]. Weitere Hinweise auf positive Effekte (Mortalität, Morbidität, kognitiver und funktionaler Status) liegen aus kleinen RCTs [163], retrospektiven Kohortenstudien [164,165] und Subgruppenanalysen [157] vor.

Es gibt Hinweise, dass ACE-Hemmer geschlechtsspezifisch wirken. So zeigte sich in einer Metaanalyse aus sieben großen ACE-Hemmer-Studien für Frauen mit symptomatischer Herzinsuffizienz (n = 1 079) ein geringerer mortalitätsbezogener Vorteil als bei Männern, während Frauen mit asymptomatischer Herzinsuffizienz (n = 1 294) gar nicht profitierten [158].

Bei der Auswahl des Medikaments ist der jeweilige Zulassungsstatus zu beachten, z. B. sind einige ACE-Hemmer nicht für NYHA I, nur in Kombination mit Diuretika und anderen Medikamenten und/oder nur nach Myokardinfarkt zugelassen (CAVE: Off-Label-Use, siehe Hinweis zum Off-Label-Use).

Referenzen:

13. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62(16):e147-e239. DOI: 10.1016/j.jacc.2013.05.019. http://www.ncbi.nlm.nih.gov/pubmed/23747642.
17. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62(16):e147-e239. DOI: 10.1016/j.jacc.2013.05.019. http://www.ncbi.nlm.nih.gov/pubmed/23747642.
153. Cleland JG, Erhardt L, Murray G, et al. Effect of ramipril on morbidity and mode of death among survivors of acute myocar-dial infarction with clinical evidence of heart failure. A report from the AIRE Study Investigators. Eur Heart J 1997; 18(1):41–51. http://www.ncbi.nlm.nih.gov/pubmed/9049514.
154. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995; 333(25):1670–6. http://www.ncbi.nlm.nih.gov/pubmed/7477219.
155. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dys-function after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992; 327(10):669–77. http://www.ncbi.nlm.nih.gov/pubmed/1386652.
157.Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 1995; 273(18):1450–6. http://www.ncbi.nlm.nih.gov/pubmed/7654275.

158. Shekelle PG, Rich MW, Morton SC, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: A meta-analysis of major clinical trials. J Am Coll Cardiol 2003; 41(9):1529–38. http://www.ncbi.nlm.nih.gov/pubmed/12742294.
159. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dys-function: A systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet 2000; 355(9215):1575–81. http://www.ncbi.nlm.nih.gov/pubmed/10821360.
160.CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooper-ative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316(23):1429–35. http://www.ncbi.nlm.nih.gov/pubmed/2883575.
161. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and con-gestive heart failure. N Engl J Med 1991; 325(5):293–302. http://www.ncbi.nlm.nih.gov/pubmed/2057034.
162. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992; 327(10):685–91. http://www.ncbi.nlm.nih.gov/pubmed/1463530.
163. Hutcheon SD, Gillespie ND, Crombie IK, et al. Perindopril improves six minute walking distance in older patients with left ventricular systolic dysfunction: A randomised double blind placebo controlled trial. Heart 2002; 88(4):373–7. http://www.ncbi.nlm.nih.gov/pubmed/12231595.186. Jong P, Yusuf S, Rousseau MF, et al. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet 2003;361(9372):1843-8. http://www.ncbi.nlm.nih.gov/pubmed/12788569.
164.Gambassi G, Lapane KL, Sgadari A, et al. Effects of angiotensin-converting enzyme inhibitors and digoxin on health out-comes of very old patients with heart failure. SAGE Study Group. Systematic Assessment of Geriatric drug use via Epide-miology. Arch. Intern. Med 2000; 160(1):53–60. http://www.ncbi.nlm.nih.gov/pubmed/10632305.
165. Zuccala G, Onder G, Marzetti E, et al. Use of angiotensin-converting enzyme inhibitors and variations in cognitive perfor-mance among patients with heart failure. Eur Heart J 2005; 26(3):226–33. http://www.ncbi.nlm.nih.gov/pubmed/15618043.

Empfehlungen/Statements	Empfehlungs-grad
6-6 ACE-Hemmer sollten in zweiwöchentlichen Intervallen konsequent bis zur höchsten in Studien ermittelten Zieldosis oder, falls diese nicht erreicht werden kann, bis zur maximal tolerierten Dosis gesteigert werden.	⇑

Hintergrundinformationen:

Die Empfehlung stellt einen Expertenkonsens dar.

Nach der klinischen Erfahrung der Leitliniengruppe ist die Auftitration bis zur Zieldosis entscheidend, um eine möglichst effektive prognoseverbessernde Therapie zu gewährleisten; die Intervalle können dabei über den empfohlenen zweiwöchentlichen Abstand hinaus auch vergrößert werden. Kürzere Intervalle sind bei stationären oder engmaschiger überwachten ambulanten Patienten möglich.

Die Start- und Zieldosen sind den jeweiligen Fachinformationen zu entnehmen. Ob eine über die Zieldosen hinausgehende Dosierung zu stärkeren Effekten führt, ist nicht eindeutig [166–168].

Salzrestriktion und Diuretika erhöhen den blutdrucksenkenden Effekt von ACE-Hemmern. Bei einer Vorbehandlung der Patienten mit einem Diuretikum oder bei sonstigem Salz- und Volumenmangel wird eine besonders niedrige Startdosis empfohlen. Bei Niereninsuffizienz muss die Dosierung der ACE-Hemmer angepasst werden.

Bei Patienten mit Diabetes mellitus kann die Zugabe von ACE-Hemmern zu einer blutzuckersenkenden Medikation (insbesondere Sulfonylharnstoffe, Glinide, Insulin) zu verstärkter Blutzuckersenkung und Hypoglykämie führen.

Sicherheit

Bei etwa 5-10% der Patienten tritt ACE-Hemmer-Husten auf, bei Frauen und Patienten mit asiatischer Herkunft häufiger [169–171]. Da Husten auch andere Ursachen (Lungenödem, bronchiale/pulmonale Erkrankungen) haben kann, sollten diese abklärt werden (siehe Kapitel 8.5 Atemwegserkrankungen und Tabelle 27). Zur Anwendung von ACE-Hemmern bei Patienten mit Niereninsuffizienz siehe Kapitel 8.1 Nierenerkrankungen) In einer Ko-hortenstudie waren ACE-Hemmer im Vergleich zu Angiotensinrezeptorblockern (ARB) statistisch mit einem erhöhten Lungenkrebsrisiko assoziiert. [172] Da das Ausmaß insgesamt jedoch sehr gering und ein kausaler Zusammenhang durch die Daten nicht zu belegen ist, wird die Empfehlung zur ACE-Hemmer-Therapie bei chronischer Herzinsuffizienz aus Sicht der Autoren nicht infrage gestellt.

Referenzen:

166. The NETWORK Investigators. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. Eur Heart J 1998; 19(3):481–9. http://www.ncbi.nlm.nih.gov/pubmed/9568453.
167. Nanas JN, Alexopoulos G, Anastasiou-Nana MI, et al. Outcome of patients with congestive heart failure treated with stand-ard versus high doses of enalapril: A multicenter study. High Enalapril Dose Study Group. J Am Coll Cardiol 2000; 36(7):2090–5. http://www.ncbi.nlm.nih.gov/pubmed/11127445.
168. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation 1999; 100(23):2312–8. http://www.ncbi.nlm.nih.gov/pubmed/10587334.
169.Mackay FJ, Pearce GL, Mann RD. Cough and angiotensin II receptor antagonists: Cause or confounding? Br J Clin Phar-macol 1999; 47(1):111–4. http://www.ncbi.nlm.nih.gov/pubmed/10073748.

170. Kubota K, Kubota N, Pearce GL, et al. ACE-inhibitor-induced cough, an adverse drug reaction unrecognised for several years: Studies in prescription-event monitoring. Eur J Clin Pharmacol 1996; 49(6):431–7. http://www.ncbi.nlm.nih.gov/pubmed/8706766.
171. Strocchi E, Malini PL, Valtancoli G, et al. Cough during treatment with angiotensin-converting enzyme inhibitors. Analysis of predisposing factors. Drug Invest 1992; 4:69–72.
172. Hicks BM, Filion KB, Yin H, et al. Angiotensin converting enzyme inhibitors and risk of lung cancer: Population based co-hort study. BMJ (Clinical research ed.) 2018; 363:k4209. DOI: 10.1136/bmj.k4209. http://www.ncbi.nlm.nih.gov/pubmed/30355745.

6.2.1.2 Angiotensinrezeptorblocker (ARB)

Empfehlungen/Statements	Empfehlungs-grad
6-7 Patienten mit symptomatischer Herzinsuffizienz (NYHA II-IV) und reduzierter Ejektionsfraktion, die ACE-Hemmer nicht tolerieren, sollen Angiotensinrezeptorblocker empfohlen werden.	⇑⇑

Hintergrundinformationen:

Die Empfehlung beruht auf internationalen Leitlinien [13,17]. Nach Prüfung der dort zitierten Evidenz durch die Leitliniengruppe wurden Inhalt und Empfehlungsgrad übernommen.

Die Ergebnisse der Primärstudien zu Angiotensinrezeptorblockern (ARB, auch: AT1-Rezeptorblocker, Angioten-sin-II-Rezeptorantagonisten, „Sartane“) bei HFrEF sind inkonsistent:

• ARB vergleichbar effektiv bezüglich Gesamtmortalität: zwei RCTs zu Candesartan (RESOLVD) bzw. Losartan (ELITE II) im Vergleich zu ACE-Hemmern (Enalapril bzw. Captopril) bei symptomatischen Herzinsuffizienzpati-enten [173,174];

• ARB vergleichbar effektiv bezüglich Gesamtmortalität: zwei RCTs zu Losartan (OPTIMAAL) bzw. Valsartan (VALIANT) im Vergleich zu Captopril bei Postinfarktpatienten mit linksventrikulärer Dysfunktion und/oder Herz-insuffizienzzeichen [175,176];

• ARB effektiver bezüglich des kombinierten Endpunktes kardiovaskuläre Mortalität und herzinsuffizienzbedingte Hospitalisierung: RCT zu Candesartan (CHARM) bei ACE-Hemmer-intoleranten Patienten mit symptomatischer HFrEF im Vergleich zu Placebo [177] sowie Subgruppenanalysen der Val-HeFT-Studie [178].

Während eine Metaanalyse einen grenzwertig statistisch signifikanten Mortalitätsbenefit für ARB gegenüber Pla-cebo zeigen konnte (OR 0,83 (95% KI 0,69; 1,00)) [179], ergaben zwei weitere Metaanalysen keinen Benefit bezüglich Mortalität und Hospitalisierungen, verglichen mit Placebo oder ACE-Hemmern [180,181]. Aufgrund dieser Evidenzlage werden ARB von internationalen Leitlinien als Mittel der zweiten Wahl bei ACE-Hemmer-Unverträglichkeit empfohlen [13,17].

Referenzen:

13. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62(16):e147-e239. DOI: 10.1016/j.jacc.2013.05.019. http://www.ncbi.nlm.nih.gov/pubmed/23747642.
17. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62(16):e147-e239. DOI: 10.1016/j.jacc.2013.05.019. http://www.ncbi.nlm.nih.gov/pubmed/23747642.
173.McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: Randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. Circulation 1999; 100(10):1056–64. http://www.ncbi.nlm.nih.gov/pubmed/10477530.
174. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: Randomised trial - the Losartan Heart Failure Survival Study ELITE II. Lancet 2000; 355(9215):1582–7. http://www.ncbi.nlm.nih.gov/pubmed/10821361.
175. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myo-cardial infarction: The OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet 2002; 360(9335):752–60. http://www.ncbi.nlm.nih.gov/pubmed/12241832.
176. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N. Engl. J Med 2003; 349(20):1893–906. http://www.ncbi.nlm.nih.gov/pubmed/14610160.
177.Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: The CHARM-Alternative trial. Lancet 2003; 362(9386):772–6. http://www.ncbi.nlm.nih.gov/pubmed/13678870.
178. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001; 345(23):1667–75. http://www.ncbi.nlm.nih.gov/pubmed/11759645.

Empfehlungen/Statements	Empfehlungs-grad
6-8 Asymptomatischen Patienten (NYHA I), die ACE-Hemmer nicht tolerieren, können alternativ Angiotensinrezeptorblocker empfohlen werden.	⇔

Hintergrundinformationen:

Die Empfehlung stellt einen Expertenkonsens dar.

Die Gabe von Angiotensinrezeptorblockern bei asymptomatischen Herzinsuffizienzpatienten (NYHA I) wurde bis-her nicht in randomisierten kontrollierten Studien untersucht. In die Postinfarkt-Studien zu Valsartan und Losartan waren jedoch zum Teil auch Patienten ohne symptomatische Herzinsuffizienz (Killip-Klasse I) eingeschlossen. Es zeigten sich keine signifikanten Effektivitätsunterschiede zwischen ARB und ACE-Hemmern [175,176]. Zudem sprechen nach Ansicht der Autoren pathophysiologische und klinische Aspekte dafür, ihren Einsatz auch bei die-ser Patientengruppe zu erwägen.

Die additive Gabe von ARB zusätzlich zu ACE-Hemmern wird nicht mehr empfohlen [178,182,183].

Sicherheit

Typische Nebenwirkungen von Angiotensinrezeptorblockern resultieren aus der Beeinflussung des Renin-Angiotensin-Systems, z. B. Nierenfunktionseinschränkungen, Hyperkaliämie sowie Hypotension, insbesondere bei Vorbehandlung mit Diuretika. Vorsicht geboten ist bei einem Wechsel auf ARB nach ACE-Hemmer-induziertem Angioödem, da eine Kreuzreaktivität nicht ausgeschlossen ist. Zur Anwendung von ARB bei Patien-ten mit Niereninsuffizienz siehe Kapitel 8.1 Nierenerkrankungen.

6.2.1.3 Betarezeptorenblocker

Empfehlungen/Statements	Empfehlungs-grad
6-9 Allen klinisch stabilen* symptomatischen Patienten (NYHA II-IV) mit nachgewiesener Herzinsuffizienz mit reduzierter Ejektionsfraktion und Fehlen von Kontraindikationen sollen Betarezeptorenblocker (Bisoprolol, Carvedilol oder Metoprololsuccinat) empfohlen werden, Patienten über 70 Jahren alternativ auch Nebivolol. *1-2 Wochen konstantes Körpergewicht unter Diuretikatherapie, keine Zeichen einer Dekompensation	⇑⇑

Hintergrundinformationen:

Die Empfehlung beruht auf internationalen Leitlinien [13,17]. Nach Prüfung der dort zitierten Evidenz durch die Leitliniengruppe wurden Inhalt und Empfehlungsgrad übernommen.

Zum Nutzen von Betarezeptorenblockern bei chronischer Herzinsuffizienz liegen RCTs und Metaanalysen vor [158]. Für die Betarezeptorenblocker Bisoprolol, Carvedilol und Metoprololsuccinat konnte in diesen Studien die Senkung der Gesamtsterblichkeit für Patienten mit Herzinsuffizienz (NYHA II-IV), die bereits ACE-Hemmer und Diuretika erhielten, gezeigt werden. Außerdem wurden die kardiovaskuläre Sterblichkeit, die Häufigkeit des plötzlichen Herztods, die herzinsuffizienzbedingte Mortalität sowie die Anzahl von Hospitalisierungen reduziert [184–187]. Subgruppenanalysen der CIBIS II-Studie ergaben zudem keine unterschiedlichen Ergebnisse für ausgewertete Subgruppen (z. B. Alter, Geschlecht, NYHA-Stadium, EF) [188].

Zum Nutzen von Betarezeptorenblockern speziell bei älteren Patienten mit Herzinsuffizienz liegt ein RCT vor: Ne-bivolol wurde bei älteren Patienten > 70 Jahre mit einer herzinsuffizienzbedingten Krankenhauseinweisung oder einer EF < 35% eine Reduktion des kombinierten Endpunktes aus Sterblichkeit und Krankenhauseinweisung nachgewiesen; die Gesamtsterblichkeit war unter Nebivolol jedoch nicht signifikant reduziert [189]. Für Metoprololsuccinat liegen Hinweise aus Subgruppenanalysen eines RCT vor, dass dieser Betarezeptorenblocker auch bei älteren Patienten die Mortalität und Krankenhauseinweisungen reduzieren kann [185,190].

Einen Klasseneffekt gibt es bei Betarezeptorenblockern offenbar nicht, da bei anderen Betarezeptorenblockern keine Mortalitätsreduktion bzw. eine Erhöhung der Sterblichkeit beobachtet wurde [191,192]. Bei asymptomatischen Patienten (NYHA I) nach einem Herzinfarkt führte eine Therapie mit Carvedilol nicht zu einer signifikanten Reduktion des kombinierten Endpunkts aus Tod und Hospitalisierung. Es ergaben sich aber Hinweise auf eine Reduktion der Gesamtsterblichkeit (sekundärer Endpunkt; 12% vs. 15%, HR 0,77 (95% KI 0,60; 0,98); p = 0,03) [193].

Der Nutzen von Betarezeptorenblockern hinsichtlich Mortalität und Morbidität steigt mit der Schwere der Herzinsuffizienz. In Abhängigkeit von dem Mortalitätsrisiko schwanken die Effektmaße in den ausgewerteten Studien deshalb erheblich:

• Bisoprolol (CIBIS-II 1999) [184]: NYHA III-IV, LVEF durchschnittlich 27,5%, Follow-up 1,3 Jahre, Bisoprolol vs. Kontrollen, Basistherapie ACE-Hemmer + Diuretika + Digoxin bei 1/2 der Patienten: ARR = 5,5%, NNT 16 Monate = 18;

• Metoprololsuccinat (MERIT-HF 1999) [185]: NYHA II-IV, LVEF durchschnittlich 28%, Follow-up 12 Monate, Metoprolol vs. Kontrollen, Basistherapie ACE-Hemmer + Diuretika (+ Digoxin bei 2/3 der Pat.): ARR = 3,6%, NNT 12 Monate = 28;

• Carvedilol (COPERNICUS 2001) [187]: NYHA III und IV: schwere HI (≥ 2 Monate Ruhedyspnoe oder bei minimaler Belastung, LVEF < 25%), LVEF durchschnittlich 19,9%, Follow-up 10,4 Mon., Carvedilol vs. Kontrol-len, Basistherapie ACE-Hemmer oder ARB + Diuretika + Digoxin: ARR = 5,5%, NNT 10,4 Monate = 18; • Carvedilol (US Carvedilol HF 1996) [194]: NYHA II-III, LVEF durchschnittlich 23%, Follow-up 6,5 Monate, Carvedilol, Basistherapie ACE-Hemmer + Diuretika + Digoxin: ARR = 4,6%, NNT 6,5 Monate = 22; für den kombi-nierten Endpunkt Tod oder Hospitalisierung: ARR = 8,8%, NNT 6,5 Monate = 11;

• Nebivolol (SENIORS) [189]: HI Einweisung oder LVEF < 35%, NYHA I-IV (NYHA I ~ 3%, NYHA IV ~ 2%), EF durchschnittlich 36%, Follow-up durchschnittlich 21 Monate, Nebivolol vs. Placebo, Basistherapie ACE-Hemmer oder ARB + MRA + Diuretika + Digoxin: für den kombinierten Endpunkt Tod oder Hospitalisierung: ARR = 4,2%, NNT 21 Monate = 24 [195].

In einer Metanalyse von zehn RCTs profitierten Patienten mit Vorhofflimmern (Mortalität: HR 0,97 (95% KI 0,83; 1,14), p = 0,73) weniger von einer Therapie mit Betarezeptorenblockern als Patienten mit Sinusrhythmus (HR 0,73 (95% KI 0,67; 0,80); p < 0,001, p für Interaktion = 0,002) [196]. Auch wenn kein prognoseverbessernder Effekt zu erwarten ist, bleibt die Fortsetzung der Betarezeptorenblocker-Therapie zur Frequenzkontrolle nach An-sicht der Autoren bei Auftreten von Vorhofflimmern aus symptomatischer Sicht gerechtfertigt.

Bei der Auswahl des Medikaments ist der jeweilige Zulassungsstatus zu beachten (CAVE: Off-Label-Use, siehe Hinweis zum Off-Label-Use). Z. B. ist Nebivolol nicht für NYHA-Klasse IV zugelassen.

Ob die Behandlung zuerst mit ACE-Hemmern oder Betarezeptorenblocker oder mit beiden gleichzeitig begonnen wird, ist individuell zu entscheiden [197].

Referenzen:

184. CIBIS II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. Lancet 1999; 353(9146):9–13. http://www.ncbi.nlm.nih.gov/pubmed/10023943.
185. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: The Metoprolol CR/XL Randomized Intervention Trial in congestive heart fail-ure (MERIT-HF). MERIT-HF Study Group. JAMA 2000; 283(10):1295–302. http://www.ncbi.nlm.nih.gov/pubmed/10714728.
186. Krum H, Roecker EB, Mohacsi P, et al. Effects of initiating carvedilol in patients with severe chronic heart failure: Results from the COPERNICUS Study. JAMA 2003; 289(6):712–8. http://www.ncbi.nlm.nih.gov/pubmed/12585949.
187. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344(22):1651–8. http://www.ncbi.nlm.nih.gov/pubmed/11386263.
188. Erdmann E, Lechat P, Verkenne P, et al. Results from post-hoc analyses of the CIBIS II trial: Effect of bisoprolol in high-risk patient groups with chronic heart failure. Eur J Heart Fail 2001; 3(4):469–79. http://www.ncbi.nlm.nih.gov/pubmed/11511434.
189. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovas-cular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005; 26(3):215–25. http://www.ncbi.nlm.nih.gov/pubmed/15642700.
190.MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353(9169):2001–7. http://www.ncbi.nlm.nih.gov/pubmed/10376614.
196. Kotecha D, Holmes J, Krum H, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: An individ-ual-patient data meta-analysis. Lancet 2014; 384(9961):2235–43. http://www.ncbi.nlm.nih.gov/pubmed/25193873.
197.Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: Results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation 2005; 112(16):2426–35. http://www.ncbi.nlm.nih.gov/pubmed/16143696.

Empfehlungen/Statements	Empfehlungs-grad
6-11 Bei Patienten, deren Herzinsuffizienz sich akut verschlechtert (Übergang NYHA III-IV) sollten Betarezeptorenblocker möglichst beibehalten werden.	⇑

Hintergrundinformationen:

Die Empfehlung stellt einen Expertenkonsens dar. In einem kleinen RCT ([198], zitiert nach 1. Auflage dieser NVL) konnte eine Therapie mit Betarezeptorenblockern auch während einer Episode akuter Dekompensation fortgesetzt werden, ohne sich nachteilig auszuwirken; selektiv eingebrachte neuere Evidenz aus großen Kohortenstudien weist in dieselbe Richtung [199–201]. Nach Ansicht der Leitliniengruppe ist auch die Verschlechterung von Komorbiditäten kein zwingender Grund, Betarezeptorenblocker abzusetzen.

Sicherheit

Als typische Nebenwirkungen von Betarezeptorenblockern können Bradykardie, Hypotension sowie periphere Durchblutungsstörungen auftreten. Obwohl sie mit Bronchuskonstriktion assoziiert sein können, sind Betarezeptorenblocker auch bei herzinsuffizienten Patienten mit COPD indiziert. Auch Asthma bronchiale stellt keine absolute Kontraindikation für eine Therapie mit β1-selektiven Betarezeptorenblockern dar (siehe Kapitel 8.5 Atemwegserkrankungen).

Referenzen:
198. Jondeau G, Neuder Y, Eicher JC, et al. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Con-gestive heart failure hospitalizED for a decompensation episode. Eur Heart J 2009; 30(18):2186–92. DOI: 10.1093/eurheartj/ehp323. http://www.ncbi.nlm.nih.gov/pubmed/19717851.
199. Passos LC, Oliveira MG, Duraes AR, et al. Initiation or maintenance of beta-blocker therapy in patients hospitalized for acute heart failure. Int J Clin Pharm 2016; 38(4):802–7. DOI: 10.1007/s11096-016-0265-x. http://www.ncbi.nlm.nih.gov/pubmed/27138843.
200.Miro O, Muller C, Martin-Sanchez FJ, et al. BETAWIN-AHF study: Effect of beta-blocker withdrawal during acute decom-pensation in patients with chronic heart failure. Clin Res Cardiol 2016; 105(12):1021–9. DOI: 10.1007/s00392-016-1014-9. http://www.ncbi.nlm.nih.gov/pubmed/27379611.
201. Prins KW, Neill JM, Tyler JO, et al. Effects of Beta-Blocker Withdrawal in Acute Decompensated Heart Failure: A Systemat-ic Review and Meta-Analysis. JACC Heart Fail 2015; 3(8):647–53. DOI: 10.1016/j.jchf.2015.03.008. http://www.ncbi.nlm.nih.gov/pubmed/26251094.

6.2.1.4 Mineralokortikoidrezeptorantagonisten (MRA)

Empfehlungen/Statements	Empfehlungs-grad
6-12 Patienten mit Herzinsuffizienz und reduzierter Ejektionsfraktion, die trotz leitlinien-gerechter Therapie mit einem ACE-Hemmer und einem Betarezeptorenblocker symptomatisch sind, sollen zusätzlich Mineralokortikoidrezeptorantagonisten emp-fohlen werden.	⇑⇑

Hintergrundinformationen:

Die Empfehlung zu Mineralokortikoidrezeptorantagonisten (MRA, auch: Aldosteronantagonisten) beruht auf inter-nationalen Leitlinien [13,17]. Nach Prüfung der dort zitierten Evidenz durch die Leitliniengruppe wurden Inhalt und Empfehlungsgrad übernommen. Der Nutzen von MRA bei chronischer Herzinsuffizienz wurde in mehreren randomisierten Studien belegt:

• Spironolacton 12,5-50 mg/Tag (RALES) [202]: NYHA III/IV, LVEF ≤ 35%, n = 1 663; Follow-up 24 Monate; Ge-samtsterblichkeit signifikant reduziert (ARR 11%, NNT = 9); Rate der Krankenhauseinweisungen aufgrund der Herzinsuffizienz signifikant reduziert (ARR 29%, NNT = 4);

• Eplerenon 25-50 mg/Tag (EPHESUS) [203]: Patienten 3-14 Tage nach akutem Myokardinfarkt, LVEF ≤ 40%, mit Herzinsuffizienzsymptomen oder Diabetes mellitus, n = 6 632; Gesamtmortalität signifikant gesenkt (ARR 2,3%, NNT = 43); Komposit-Endpunkt Risiko kardiovaskuläre Sterblichkeit und Hospitalisierung aufgrund kar-diovaskulärer Ereignisse signifikant reduziert (ARR 3%, NNT = 34);

• Spironolacton [204]: NYHA I/II, LVEF ≤ 40%, Follow-up 6 Monate, n = 168; LVEF signifikant erhöht (p < 0,001), positive Effekte auf Remodeling und diastolische Funktion;

• Eplerenon (EMPHASIS-HF) [205]: NYHA II, EF ≤ 30% (≤ 35% bei QRS > 130ms), Hospitalisierung aus kardiovaskulären Gründen < 6 Monate oder erhöhte BNP-Werte, Follow-up 21 Monate, n = 2 737; Komposit-Endpunkt Risiko kardiovaskuläre Mortalität und herzinsuffizienzbedingte Hospitalisierung signifikant reduziert (ARR 7,7%, NNT = 13), Gesamtmortalität reduziert (ARR 3%, NNT = 33);

• Metaanalyse NYHA I//II, n = 3 929 [206]: Gesamtmortalität reduziert (RR 0,79 (95% KI 0,66; 0,95)), Rehospitalisierungen aus kardialen Gründen reduziert (RR 0,62 (95% KI 0,52; 0,74)).

Bezüglich des Nutzens von MRA speziell bei älteren Patienten weisen Subgruppenanalysen darauf hin, dass Patienten mit NYHA III/IV von Spironolacton (RALES [202]) sowie Patienten mit NYHA II von Eplerenon (EMPHA-SIS-HF [205]) profitieren können. Hingegen war der Effekt von Eplerenon nach akutem Myokardinfarkt bei Patien-ten ≥ 65 Jahren nicht signifikant (EPHESUS [203]), und für die Studie zu Spironolacton bei NYHA I/II wurden kei-ne gesonderten Auswertungen zum Alter identifiziert (Baseline-Alter im Spironolacton-Arm: 61 ± 13 Jahre) [204].

Bei der Auswahl des MRA ist der jeweilige Zulassungsstatus zu beachten (CAVE: Off-Label-Use, siehe Hinweis zum Off-Label-Use). So besitzt Eplerenon die Zulassung bei Patienten ohne Myokardinfarkt nur für NYHA-Klasse II, und Spironolacton ist nicht explizit für die Behandlung von Herzinsuffizienz zugelassen, sondern nur indirekt (bei Ödemen infolge eines sekundären Hyperaldosteronismus).

Referenzen:
202. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341(10):709–17. http://www.ncbi.nlm.nih.gov/pubmed/10471456.
203. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N. Engl. J Med 2003; 348(14):1309–21. http://www.ncbi.nlm.nih.gov/pubmed/12668699.
204. Vizzardi E, D'Aloia A, Giubbini R, et al. Effect of spironolactone on left ventricular ejection fraction and volumes in patients with class I or II heart failure. Am. J. Cardiol. 2010; 106(9):1292–6. DOI: 10.1016/j.amjcard.2010.06.052. http://www.ncbi.nlm.nih.gov/pubmed/21029826.
205. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011; 364(1):11–21. DOI: 10.1056/NEJMoa1009492. http://www.ncbi.nlm.nih.gov/pubmed/21073363.

Empfehlungen/Statements	Empfehlungs-grad
6-13 Auch Patienten mit Diabetes mellitus, eingeschränkter Nierenfunktion oder grenzwertiger Hyperkaliämie sollten Mineralokortikoidrezeptorantagonisten erhalten, wenn Nutzen und Schaden kritisch abgewogen werden.	⇑

Hintergrundinformationen:

Die Empfehlung stellt einen Expertenkonsens dar.

In den oben genannten Studien wurde eine Verbesserung der Prognose durch MRA bei Einschluss von Patienten mit initialen Serum-Kreatininwerten ≤ 2,5 mg/dl und Serum-Kaliumspiegeln ≤ 5,0 mmol/l gesehen. Vor dem Hintergrund einer potenziellen MRA-Unterversorgung von Patienten mit Diabetes mellitus und/oder eingeschränkter Nierenfunktion sieht die Leitliniengruppe keine Hinweise, dass diese Patienten nicht von MRA profitieren können und empfehlen deshalb die gründliche Prüfung der Indikation (siehe auch Kapitel 8.1 Nierenerkrankungen).

Sicherheit

Empfehlungen/Statements	Empfehlungs-grad
6-14 Das Monitoring von Patienten, die Mineralokortikoidrezeptorantagonisten erhalten, soll aufgrund des Hyperkaliämierisikos in der Einstellungsphase engmaschig, danach mindestens viermonatlich erfolgen.	⇑⇑

Hintergrundinformtionen:

Die Empfehlung stellt einen Expertenkonsens dar.

MRA-induzierte Hyperkaliämien wurden in den großen klinischen Studien bei 2-8% (NNH 23-100) [202,203,205], in Zeitreihenuntersuchungen jedoch bei bis zu 36% [152] der Patienten beobachtet und stellen somit unter Alltagsbedingungen eine erhebliche Einschränkung der Therapiesicherheit dar. Insbesondere bei älteren Patienten ist eine engmaschige Kontrolle der Kaliumspiegel erforderlich (siehe Kapitel 3.4 Verlaufskontrolle sowie 8.1 Nierenerkrankungen). Aus Sicht der Leitlinienautoren erfordern geringfügige Anstiege der Serumkaliumspiegel (bis ≤ 5,5 mmol/l) innerhalb der ersten Wochen der MRA-Therapie keine Intervention. Bei Kaliumspiegeln zwischen 5,5 und 5,9 mmol/l ist es ratsam, die Dosis zu halbieren und ab ≥ 6 mmol/l den MRA abzusetzen, ebenso bei Verschlechterung der Nierenfunktion, einer Episode von Diarrhoe oder Dehydration sowie bei Unterbrechung einer Diuretika-Therapie. Ab einem Serumkalium von < 5,0 mmol/l kann eine niedrigdosierte MRA-Therapie wiederaufgenommen werden (nach [205]).

Die unter Spironolacton [202] häufiger zu Therapieabbrüchen führende Gynäkomastie wurde unter Eplerenon nicht häufiger als in der Placebogruppe beobachtet [203,206].

Referenzen:

152. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N. Engl. J Med 2004; 351(6):543–51. http://www.ncbi.nlm.nih.gov/pubmed/15295047.
202. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341(10):709–17. http://www.ncbi.nlm.nih.gov/pubmed/10471456.
203. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N. Engl. J Med 2003; 348(14):1309–21. http://www.ncbi.nlm.nih.gov/pubmed/12668699.
204. Vizzardi E, D'Aloia A, Giubbini R, et al. Effect of spironolactone on left ventricular ejection fraction and volumes in patients with class I or II heart failure. Am. J. Cardiol. 2010; 106(9):1292–6. DOI: 10.1016/j.amjcard.2010.06.052. http://www.ncbi.nlm.nih.gov/pubmed/21029826.
205. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011; 364(1):11–21. DOI: 10.1056/NEJMoa1009492. http://www.ncbi.nlm.nih.gov/pubmed/21073363.
206. Hu LJ, Chen YQ, Deng SB, et al. Additional use of an aldosterone antagonist in patients with mild to moderate chronic heart failure: A systematic review and meta-analysis. Br J Clin Pharmacol 2013; 75(5):1202–12. DOI: 10.1111/bcp.12012. http://www.ncbi.nlm.nih.gov/pubmed/23088367.

6.2.1.5 Diuretika

Empfehlungen/Statements	Empfehlungs-grad
6-15 Patienten mit Herzinsuffizienz und reduzierter Ejektionsfraktion, die Zeichen einer Flüssigkeitsretention aufweisen, sollen Diuretika empfohlen werden.	⇑⇑

Hintergrundinformationen:

Die Empfehlung beruht auf internationalen Leitlinien [13,17]. Nach Prüfung der dort zitierten Evidenz durch die Leitliniengruppe wurden Inhalt und Empfehlungsgrad übernommen.

Diuretika stellen die wichtigste medikamentöse Therapieoption zur Kontrolle des Volumenhaushalts dar. Dennoch wird ihr Stellenwert häufig unterschätzt: zum einen, weil sie sich nicht in das gängige pathophysiologische Modell der Herzinsuffizienz einfügen, das die Hemmung des Renin-Angiotensin-Aldosteron-Systems sowie der sympathischen Stimulation als wesentliche therapeutische Elemente beinhaltet; zum anderen, weil für Diuretika keine Studien identifiziert werden können, die eine Reduktion der Mortalität nachweisen. Allerdings basiert ein Großteil der Studien, die eine Verbesserung der Langzeitprognose durch ACE-Hemmer, Betarezeptorenblocker, MRA und ARB zeigten, auf einer diuretischen Basismedikation. Unter dieser Prämisse und aufgrund ihrer symptomverbessernden Eigenschaften sind Diuretika zur symptomatischen Therapie der Herzinsuffizienz aus Sicht der Leitlinienautoren und in Übereinstimmung mit internationalen Leitlinien [13] unverzichtbar.

Die Dosierung der Schleifendiuretika orientiert sich an der Symptomatik und der Nierenfunktion. Zur Durchbrechung einer Diuretika-Resistenz wird international entweder die Aufdosierung der Schleifendiuretika oder eine Kombinationsbehandlung mit Thiazid- und Schleifendiuretikum (sequenzielle Nephronblockade) empfohlen [13,17,34]. Ein direkter Vergleich der beiden Strategien existiert nicht [37,43]. Da die Kombinationsbehandlung jedoch zu starken Kalium- und Magnesiumverlusten führen kann, ist die Indikation für eine dauerhafte Nephron-blockade streng zu prüfen. Die engmaschige Kontrolle der Elektrolytwerte im Verlauf ist wichtig.

Sicherheit

Kaliumsparende Diuretika (Amilorid, Triamteren) erhöhen das Hyperkaliämie-Risiko und sind bei gleichzeitiger Therapie mit ACE-Hemmern, ARB oder MRA nicht empfehlenswert und im Einzelfall nur unter engmaschigen Kontrollen der Kalium-Serumkonzentration einzusetzen. In Fall-Kontroll-Studien war Hydrochlorothiazid statistisch signifikant mit einem erhöhten Risiko für das Auftreten von nichtmelanozytärem Hautkrebs (NMSC) assoziiert; dabei stieg das Risiko mit höherer kumulativer Dosis [207–209]. Eine Therapieumstellung aller mit Hydrochlorothiazid behandelten Patienten (z. B. auf Chlortalidon) ist aus Sicht der Autoren jedoch nicht generell erforderlich, sondern lediglich individuell zu prüfen (z. B. bei Risikopatienten für Hautkrebs und jüngeren Patienten mit voraussichtlich langer Therapiedauer).

Für Informationen zu selbstständiger Gewichtskontrolle und individueller Dosisanpassung von Diuretika siehe Kapitel 5.6 Selbstmanagement.

Referenzen:

17. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62(16):e147-e239. DOI: 10.1016/j.jacc.2013.05.019. http://www.ncbi.nlm.nih.gov/pubmed/23747642.
34. Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can J Cardiol 2017; 33(11):1342–433. DOI: 10.1016/j.cjca.2017.08.022. http://www.ncbi.nlm.nih.gov/pubmed/29111106.
37. National Institute for Health and Care Excellence (NICE). Acute heart failure: diagnosing and managing acute heart failure in adults. 2014 (NICE Clinical Guideline; 187) [cited: 2018-11-09]. http://www.nice.org.uk/guidance/cg187/resources/acute-heart-failure-diagnosis-and-management-pdf-35109817738693.
43. National Institute for Health and Care Excellence (NICE). Surveillance programme Surveillance proposal consultation do-cument Acute heart failure NICE guideline CG187 – 2017 surveillance review. 2017 (NICE Clinical Guideline; 187) [cited: 2018-11-09].

6.2.2 Empfohlene Medikamente für ausgewählte Patientengruppen

6.2.2.1 Sacubitril/Valsartan

Empfehlungen/Statements	Empfehlungs-grad
6-16 Patienten, die trotz leitliniengerechter Therapie mit ACE-Hemmern, Betarezepto-renblockern und Mineralokortikoidrezeptorantagonisten symptomatisch sind, sollte ein Wechsel von ACE-Hemmern auf Sacubitril/Valsartan empfohlen werden, unter Berücksichtigung der Unsicherheiten bezüglich der Langzeitverträglichkeit und des Nebenwirkungsprofils.	⇑

Hintergrundinformationen:

In einer systematischen Recherche wurden zwei randomisierte kontrollierte Studien zu Sacubitril/Valsartan identifiziert, von denen aber nur eine Patienten mit HFrEF einschloss: In der Zulassungsstudie PARADIGM-HF wurde der Angiotensin-Rezeptor-Neprilysin-Inhibitor (ARNI) mit dem ACE-Hemmer Enalapril verglichen. Die Studie schloss über 8 000 Patienten mit LVEF < 40% (später geändert auf < 35%) und vorwiegend NYHA-Klasse II ein, die trotz mindestens vierwöchiger leitliniengerechter Vorbehandlung u. a. mit ACE-Hemmern oder ARB symptomatisch waren. Der primäre Komposit-Endpunkt – Tod durch kardiovaskuläre Ursachen oder herzinsuffizienzbedingte Hospitalisierung – wurde nach median 27 Monaten Nachbeobachtungszeit mit 21,8% unter Sacubitril/Valsartan gegenüber 26,5% unter Enalapril signifikant verbessert (HR 0,80 (95% KI 0,73; 0,87); p < 0,001, ARR 4,7%, NNT 22), zudem ergaben sich signifikante Vorteile bezüglich Gesamtmortalität (ARR 2,8%, NNT 36), kardiovaskulärer Mortalität und herzinsuffizienzbedingten Hospitalisierungen [210].

Allerdings wird die Studie aufgrund ihres Designs kritisiert: Zum einen wurde die Patientenpopulation über strenge Ausschlusskriterien (z. B. verringerte GFR, erhöhte Serumkaliumspiegel, Nicht-Toleranz von ACE-Hemmern oder ARB) stark vorselektiert. Zum anderen wurden während einer Run-in-Phase, bei der alle Teilnehmer nacheinander erst Enalapril und dann Sacubitril/Valsartan erhielten, Patienten mit relevanten Nebenwirkungen (12%) ausgeschlossen. Das Studiendesign führt daher zum einen zu einer möglichen Unterschätzung von Nebenwirkungen in beiden Armen und begünstigt zum anderen vermutlich bessere Ergebnisse als bei Patienten in der täglichen Praxis.

Die Patienten in PARADIGM-HF waren – wie häufig in klinischen Studien – im Vergleich zur herzinsuffizienten Gesamtpopulation verhältnismäßig jung. In einer Subanalyse ergaben sich aber keine Hinweise auf einen Ein-luss des Alters auf den Effekt von Sacubitril/Valsartan [211].

Der G-BA sah im Rahmen des Verfahrens zur Frühen Nutzenbewertung für Sacubitril/Valsartan „Anhaltspunkte für einen beträchtlichen Zusatznutzen“, allerdings nur bei Patienten ohne Diabetes mellitus. Die Einschränkung basiert auf einer Subgruppenanalyse in der Nutzenbewertung: Während Patienten ohne Diabetes mellitus signifikant bezüglich des Gesamtüberlebens profitierten (HR 0,77 (95% KI 0,68; 0,88); p < 0,001), ergab sich für Patienten mit Diabetes mellitus kein signifikanter Effekt (HR 0,97 (95% KI 0,83; 1,14); p = 0,727; p für Interaktion: 0,025). Bezüglich Lebensqualität und Hospitalisierungsrate ergaben sich jedoch positive Effekte, so dass in dieser Patientengruppe der Zusatznutzen als „gering“ eingeschätzt wird [212].

ARNI als Initialtherapie nach akuter Dekompensation von Patienten mit HFrEF (n = 881) führten im Vergleich zu Enalapril zu einer signifikant stärkeren Absenkung von NT-proBNP innerhalb der ersten 8 Wochen (-46,7% vs. -25,3%, p < 0,001). Klinische Outcomes wurden nur exploratorisch erhoben; aufgrund der mangelnden statistischen Power (geringe Eventanzahl) kann keine diesbezügliche Aussage abgeleitet werden. Die Leitliniengruppe schätzt die Evidenz daher als noch nicht überzeugend genug ein, um eine Empfehlung zur Initialtherapie auszusprechen. [213]

Sicherheit

Unter Enalapril kam es in der PARADIGM-HF-Studie häufiger zu Hyperkaliämien (Serumkaliumspiegel > 6,0 mmol/l), erhöhten Serumkreatininspiegeln (≥ 2,5 mg/dl) und Husten (jeweils p < 0,05, NNH 76, 83 bzw. 33) [210]. Das Hypotonierisiko war insgesamt signifikant erhöht unter Sacubitril/Valsartan (24,43% vs. 18,59%, RR 1,31 (95% KI 1,21; 1,43); p < 0,001, NNH 17) [214]. Milde und moderate Hypotonien kamen unter Sacubit-ril/Valsartan häufiger vor, wohingegen schwere Hypotonien eher unter Enalapril auftraten, jedoch jeweils ohne statistische Signifikanz [215]. Statistisch signifikante Nachteile von Sacubitril/Valsartan gegenüber Enalapril zeigten sich bezüglich der insgesamt aber seltenen (< 2%) Nebenwirkungen Orthostasesyndrom, orthostatischer Schwindel und Stürze [214].

Angioödeme traten in der Zulassungsstudie häufiger auf als unter Enalapril (RR adjudiziert 1,88, n.s.) [214]. Kontraindiziert ist Sacubitril/Valsartan bei Patienten mit anamnestisch bekanntem Angioödem im Zusammenhang mit einer früheren Therapie mit ACE-Hemmern oder ARB. Aufgrund des erhöhten Angioödem-Risikos darf eine Behandlung mit Sacubitril/Valsartan erst 36 Stunden nach Einnahme der letzten Dosis einer ACE-Hemmer-Therapie begonnen werden [216].

Zur Langzeitverträglichkeit von Sacubitril/Valsartan lassen sich auf Grundlage der vorliegenden Daten keine Aussagen treffen. So bestehen Bedenken zum Einfluss von Neprilysin-Inhibitoren auf den Abbau von Beta-Amyloid-Peptid in der Retina und im Gehirn, auch wenn eine kleine Studie eher für die zerebrale Sicherheit von Sacubit-ril/Valsartan spricht [217]. Die US-amerikanische Zulassungsbehörde FDA hat daher dem Hersteller auferlegt, die Wirkung von Sacubitril/Valsartan auf kognitive Funktionen bei Patienten mit HFpEF zu untersuchen [218].

Da bislang nur eine Studie zu Sacubitril/Valsartan bei HFrEF vorliegt und aufgrund der beschriebenen Unsicherheiten schränken die Autoren die Empfehlung von Sacubitril/Valsartan gegenüber dem Zulassungsstatus auf Patienten ein, die trotz leitliniengerechter Therapie mit ACE-Hemmern, Betarezeptorenblockern und MRA symptomatisch sind.

Aufgrund der Wirkungsweise von ARNI wird unter Therapie mit Sacubitril/Valsartan der Abbau von BNP gehemmt. Daher verlieren die BNP-Plasmaspiegel ihre diagnostische und prognostische Aussagekraft (nicht aber die Plasmaspiegel von NT-proBNP).

Referenzen:
210.McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014; 371(11):993–1004. DOI: 10.1056/NEJMoa1409077. http://www.ncbi.nlm.nih.gov/pubmed/25176015.
211. Jhund PS, Fu M, Bayram E, et al. Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: Insights from PARADIGM-HF. Eur Heart J 2015; 36(38):2576–84. DOI: 10.1093/eurheartj/ehv330. http://www.ncbi.nlm.nih.gov/pubmed/26231885.
212. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). Sacubitril/Valsartan - Addendum zum Auftrag A15-60. Addendum. Auftrag A16-29. Version 1.0. 2016 (IQWiG-Berichte; 394) [cited: 2019-10-01]. http://www.g-ba.de/downloads/92-975-1411/Addendum%20zur%20Nutzenbewertung%20des%20IQWiG_Sacubitril_Valsartan.pdf.
213. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. N Engl J Med 2019; 380(6):539–48. DOI: 10.1056/NEJMoa1812851. http://www.ncbi.nlm.nih.gov/pubmed/30415601.
214. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). Sacubitril/Valsartan - Nutzenbewertung gemäß § 35a SGB V. Dossierbewertung. Auftrag: A15-60. Version: 1.0. 2016 (IQWiG-Berichte; 379) [cited: 2019-10-01]. http://www.iqwig.de/download/A15-60_Sacubitril-Valsartan_Nutzenbewertung-35a-SGB-V.pdf.
215.Gemeinsamer Bundesausschuss (G-BA). Dossier zur Nutzenbewertung gemäß § 35a SGB V. Sacubitril/Valsartan (Entres-to®) Modul 4 A. Erwachsene Patienten mit symptomatischer, chronischer Herzinsuffizienz mit reduzierter Ejektionsfraktion. 2015 [cited: 2019-10-01]. http://www.g-ba.de/downloads/92-975-1312/2015-12-21_Modul4A_Sacubitril-Valsartan.pdf.
216. Novartis Pharma, Rote Liste/Fachinfo-Service. Entresto® Filmtabletten. Fachinformation. 2016 [cited: 2017-02-22]. http://www.fachinfo.de.
217. Feldman AM, Haller JA, DeKosky ST. Valsartan/Sacubitril for Heart Failure: Reconciling Disparities Between Preclinical and Clinical Investigations. JAMA 2016; 315(1):25–6. DOI: 10.1001/jama.2015.17632. http://www.ncbi.nlm.nih.gov/pubmed/26641736.
218. Food and Drug Administration (FDA). Entresto Label and Approval History. 2015 [cited: 2019-10-01]. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207620Orig1s000ltr.pdf.

Patienten mit chronischer Nierenfunktionsstörung

Empfehlungen/Statements	Empfehlungs-grad
6-17 Patienten mit chronischer Herzinsuffizienz und chronischer Nierenerkrankung mit eGFR < 30 ml/min/1,73 m^2 sollte Sacubitril/Valsartan nicht empfohlen werden.	⇓

Hintergrundinformationen:

Patienten mit eGFR < 30 ml/min/1,73 m2 waren aus der Zulassungsstudie ausgeschlossen; dennoch ist Sacubitril/Valsartan formell auch für diese Patienten zugelassen. Die systemische Exposition von Sacubitrilat, dem aktiven Metaboliten von Sacubitril, ist bei Patienten mit leichter bis schwerer Niereninsuffizienz erhöht [216,219]. Wenn Patienten mit einer eGFR < 30 ml/min/1,73 m2 behandelt werden, soll dies laut Fachinformation „mit Vor-sicht“ erfolgen. Bei Patienten mit chronischem Nierenversagen wird von einer Anwendung abgeraten [216]. Sacubitril/Valsartan kann die Nierenfunktion (weiter) vermindern; laut Fachinformation soll bei klinisch bedeutsamer Abnahme eine schrittweise Dosisreduktion in Betracht gezogen werden [216].

Patienten mit leichter oder mittelschwerer Nierenfunktionsstörung hatten in der Zulassungsstudie ein erhöhtes Hypotonie-Risiko. [216]

Chronische Nierenerkrankungen führen zu einer Erhöhung der Plasmaspiegel natriuretischer Peptide, die durch die Akkumulation von Sacubitril/Valsartan bzw. Sacubitrilat weiter gesteigert wird. Die klinische Bedeutung dieses Umstandes ist unklar.

Es existieren bislang nur geringe klinische Erfahrungswerte für die Therapie mit Sacubitril/Valsartan bei Patienten mit schweren Nierenfunktionsstörungen. Die Leitliniengruppe plädiert daher mehrheitlich für eine schwache Nega-tiv-Empfehlung bei dieser Patientengruppe. In Ausnahmefällen, insbesondere bei einer eGFR nahe 30 ml/min/1,73 m2, ist eine vorsichtige Anwendung in Absprache mit dem behandelnden Nephrologen zu diskutieren (siehe auch Kapitel 8.1 Nierenerkrankungen).

Referenzen:
216. Novartis Pharma, Rote Liste/Fachinfo-Service. Entresto® Filmtabletten. Fachinformation. 2016 [cited: 2017-02-22]. http://www.fachinfo.de.
219. Food and Drug Administration (FDA). Entresto. Clinical Pharmacology Review. 2014 [cited: 2018-09-06]. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000ClinPharmR.pdf.

6.2.2.2 Ivabradin

Empfehlungen/Statements	Empfehlungs-grad
6-18 Symptomatischen Patienten sollte zusätzlich Ivabradin empfohlen werden, wenn sie folgende Voraussetzungen erfüllen: • LVEF ≤ 35%; • stabiler Sinusrhythmus; • Therapie mit ACE-Hemmern (bzw. Angiotensinrezeptorblockern) und Mineralokortikoidrezeptorantagonisten; • Ruheherzfrequenz ≥ 75/min trotz Zieldosis bzw. maximal tolerierter Betarezeptorenblocker-Dosis.	⇑
6-19 Symptomatischen Patienten mit Betarezeptorenblocker-Intoleranz oder -Kontraindikationen sollte Ivabradin empfohlen werden, wenn sie folgende Voraussetzungen erfüllen: • LVEF ≤ 35%; • stabiler Sinusrhythmus; • Therapie mit ACE-Hemmern (bzw. Angiotensinrezeptorblockern) und Mineralokortikoidrezeptorantagonisten; • Ruheherzfrequenz ≥ 75/min.	⇑
6-20 Unter Therapie mit Ivabradin soll der Herzrhythmus regelmäßig kontrolliert werden. Liegt kein stabiler Sinusrhythmus vor, soll die Therapie beendet werden.	⇑⇑

Hintergrundinformationen:

Eine systematische Recherche erbrachte drei Metaanalysen, zehn RCTs sowie 24 Subanalysen.

Die SHIFT-Studie untersuchte die Wirksamkeit des If-Kanal-Hemmers Ivabradin additiv zur Standardtherapie bei Patienten mit LVEF ≤ 35%, einer Ruheherzfrequenz ≥ 70/min und Sinusrhythmus, die innerhalb der letzten 12 Monate aufgrund der Herzinsuffizienz stationär behandelt werden mussten. Der primäre zusammengesetzte Endpunkt kardiovaskuläre Mortalität oder herzinsuffizienzbedingte Hospitalisierungen wurde mit 24% gegenüber 29% signifikant verringert (HR 0,82 (95% KI 0,75; 0,90); p < 0,0001, ARR 5%, NNT 20), nicht jedoch bei Patienten, die mindestens 50% der Zieldosis der Betarezeptorenblocker einnahmen [220]. Eine Post-hoc-Analyse bestätigte, dass der Effekt von Ivabradin mit zunehmender Dosis der Betarezeptorenblocker sinkt (bei ≤ 25% der Zieldosis: p = 0,007; bei 25-50% der Zieldosis: p = 0,029; > 50%: kein signifikanter Benefit) [221]. Bezüglich des Nutzens von Ivabradin bei Patienten ≥ 65 Jahren deutet eine Subgruppenanalyse auf einen nicht signifikanten Effekt hin (HR 0, 89 (95% KI 0,77; 1,02)) [220].

Eine weitere Post-hoc-Analyse [222] sowie eine Metaanalyse [223] zeigten weiterhin, dass nur Patienten mit einer Baseline-Herzfrequenz ≥ 75/min signifikant von Ivabradin profitierten. Die EMA-Zulassung für Ivabradin bei Herzinsuffizienz [224] basiert auf diesen Ergebnissen. Die Autoren der ESC-Leitlinie 2016 empfehlen Ivabradin abweichend davon für Patienten mit dem in der SHIFT-Studie vordefinierten Cut-off-Wert der Ruheherzfrequenz von 70/min [13].

Basierend auf der vorliegenden Evidenz befürworten die Autoren den Einsatz von Ivabradin erst nach der konsequenten Aufdosierung von Betarezeptorenblockern bis zur Zieldosis (siehe Kapitel 6.2.1.3 Betarezeptorenblocker) bzw. bei Betarezeptorenblocker-Intoleranz oder -Kontraindikationen. Da bislang nicht ausreichend nachgewiesen ist, ob auch Patienten mit permanentem oder intermittierendem Vorhofflimmern von einer Therapie mit Ivabradin profitieren [225–227], ist die Empfehlung auf Patienten mit stabilem Sinusrhythmus eingeschränkt.

Sicherheit

Die Ivabradin-Therapie ist mit einem signifikant häufigeren Auftreten symptomatischer Bradykardien, Sehstörungen (Phosphene, verschwommenes Sehen) und Vorhofflimmern verbunden [223,228]. Eine Metaanalyse von RCTs, die viele nicht publizierte Daten miteinschloss, errechnete ein um relativ 15% erhöhtes Risiko für das Auftreten von Vorhofflimmern (NNH 208 pro Behandlungsjahr) [229]. Eine regelmäßige klinische Überwachung der Patienten bezüglich des Auftretens von Vorhofflimmern und die regelmäßige Kontrolle der Herzfrequenz werden empfohlen [224,230]; zudem erscheint die vorzugsweise Erstverschreibung von Ivabradin durch Kardiologen sinnvoll [231].

Referenzen:

220. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. Lancet 2010; 376(9744):875–85. DOI: 10.1016/S0140-6736(10)61198-1. http://www.ncbi.nlm.nih.gov/pubmed/20801500.

221. Swedberg K, Komajda M, Bohm M, et al. Effects on outcomes of heart rate reduction by ivabradine in patients with conges-tive heart failure: Is there an influence of beta-blocker dose?: findings from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) study. J Am Coll Cardiol 2012; 59(22):1938–45. DOI: 10.1016/j.jacc.2012.01.020. http://www.ncbi.nlm.nih.gov/pubmed/22617188.
222. Bohm M, Borer J, Ford I, et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: Analysis from the SHIFT study. Clin Res Cardiol 2013; 102(1):11–22. DOI: 10.1007/s00392-012-0467-8. http://www.ncbi.nlm.nih.gov/pubmed/22575988.
223. Fox K, Komajda M, Ford I, et al. Effect of ivabradine in patients with left-ventricular systolic dysfunction: A pooled analysis of individual patient data from the BEAUTIFUL and SHIFT trials. Eur Heart J 2013; 34(29):2263–70. DOI: 10.1093/eurheartj/eht101. http://www.ncbi.nlm.nih.gov/pubmed/23536611.
224. Servier Deutschland GmbH, Rote Liste/Fachinfo-Service. Procoralan®. Fachinformation. 2015 [cited: 2016-07-17]. http://www.fachinfo.de.
225. Kosiuk J, Lindemann F, Hindricks G, et al. Need for further studies on ivabradine in patients with persistent atrial fibrillation. Int J Cardiol 2016; 223:915–6. DOI: 10.1016/j.ijcard.2016.08.329. http://www.ncbi.nlm.nih.gov/pubmed/27589039.
226. Cowie MR. Ivabradine and atrial fibrillation: What should we tell our patients? Heart 2014; 100(19):1487–8. DOI: 10.1136/heartjnl-2014-306287. http://www.ncbi.nlm.nih.gov/pubmed/24986893.
227. Kosiuk J, Oebel S, John S, et al. Ivabradine for rate control in atrial fibrillation. Int J Cardiol 2015; 179:27–8. DOI: 10.1016/j.ijcard.2014.10.062. http://www.ncbi.nlm.nih.gov/pubmed/25464400.
228. Cammarano C, Silva M, Comee M, et al. Meta-analysis of Ivabradine in Patients With Stable Coronary Artery Disease With and Without Left Ventricular Dysfunction. Clin Ther 2016; 38(2):387–95. DOI: 10.1016/j.clinthera.2015.12.018. http://www.ncbi.nlm.nih.gov/pubmed/26839043.
229.Martin RI, Pogoryelova O, Koref MS, et al. Atrial fibrillation associated with ivabradine treatment: Meta-analysis of random-ised controlled trials. Heart 2014; 100(19):1506–10. DOI: 10.1136/heartjnl-2014-305482. http://www.ncbi.nlm.nih.gov/pubmed/24951486.
230. Servier Deutschland GmbH. Information für medizinisches Fachpersonal. Procoralan (Ivabradin) - Neue Kontraindikation und Empfehlungen zur Risikominimierung von kardiovaskulären Ereignissen und schweren Bradykardien. 2014 [cited: 2016-07-17]. https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RHB/2014/rhb-procoralan.pdf?__blob=publicationFile&v=3.
231. Verordnungseinschränkungen für Ivabradin (PROCORALAN) in Frankreich. Arznei-Telegramm 2016; 48(6):54.

6.2.3 Weitere Medikamente

6.2.3.1 Digitalisglykoside

Empfehlungen/Statements	Empfehlungs-grad
6-21 Patienten im Sinusrhythmus, die trotz leitliniengerechter Therapie mit ACE-Hemmern (bzw. Angiotensinrezeptorblockern), Betarezeptorenblockern und Mineralokortikoidrezeptorantagonisten symptomatisch bleiben, können nach Zielplasmakonzentration dosierte Digitalisglykoside empfohlen werden.	⇔

Hintergrundinformationen:

Die Empfehlung beruht auf internationalen Leitlinien [13,17]. Nach Prüfung der dort zitierten Evidenz durch die Leitliniengruppe wurden Inhalt und Empfehlungsgrad übernommen.

Bei HFrEF und Sinusrhythmus sehen die Autoren Digoxin oder Digitoxin nur als zusätzliches Reservemittel, wenn die Patienten trotz optimaler Therapie im Stadium III-IV bleiben. Digoxin oder Digitoxin wirken nicht lebensverlän-gernd, können aber die Symptomatik und Lebensqualität verbessern sowie die Belastungstoleranz erhöhen und die Hospitalisierungsrate senken [232,233]. Bei Frauen sollte die Indikationsstellung für Digoxin oder Digitoxin besonders kritisch erfolgen, da die Evidenzlage zum Nutzen dieser Therapie unklar ist [234].

Die Kontrolle der Ruhefrequenz ist ein vorrangiges Therapieziel. Ist dies bei tachyarrhythmischem Vorhofflimmern mit Betarezeptorenblockern allein nicht möglich, können Digoxin oder Digitoxin bei Patienten mit Herzinsuffizienz (alle NYHA-Klassen) zur Kontrolle der Ruhefrequenz gegeben werden [232,235]. Zur Kontrolle der Frequenz unter Belastung ist dagegen die Therapie mit Betarezeptorenblockern besser geeignet [236], zitiert nach [237].

Obwohl sich sämtliche Studiendaten auf Digoxin beziehen, kommen nach Meinung der Leitlinienautoren auch die halbsynthetischen Digoxin-Derivate (Beta-Acetyldigoxin, Metildigoxin) und Digitoxin für die Therapie der Herzinsuffizienz in Betracht.

Referenzen:

232. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. N Engl J Med 1997; 336(8):525–33. http://www.ncbi.nlm.nih.gov/pubmed/9036306.
233. Hood WB, Dans AL, Guyatt GH, et al. Digitalis for treatment of heart failure in patients in sinus rhythm. Cochrane Database Syst Rev 2014(4):CD002901. DOI: 10.1002/14651858.CD002901.pub3. http://www.ncbi.nlm.nih.gov/pubmed/24771511.
234. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N. Engl. J Med 2002; 347(18):1403–11. http://www.ncbi.nlm.nih.gov/pubmed/12409542.

235. Ziff OJ, Lane DA, Samra M, et al. Safety and efficacy of digoxin: Systematic review and meta-analysis of observational and controlled trial data. BMJ 2015; 351:h4937. http://www.ncbi.nlm.nih.gov/pubmed/26374771.
236. Lewis RV, McMurray J, McDevitt DG. Effects of atenolol, verapamil, and xamoterol on heart rate and exercise tolerance in digitalised patients with chronic atrial fibrillation. J Cardiovasc Pharmacol 1989; 13(1):1–6. http://www.ncbi.nlm.nih.gov/pubmed/2468920.
237.McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012; 14(8):803–69. DOI: 10.1093/eurjhf/hfs105. http://www.ncbi.nlm.nih.gov/pubmed/22828712.

Empfehlungen/Statements	Empfehlungs-grad
6-22 Bei Patienten mit chronischer Herzinsuffizienz und chronischer Nierenerkrankung sollte die Erhaltungsdosis von Digoxin reduziert bzw. auf Digitoxin umgestellt werden.	⇑

Hintergrundinformationen:

Die Empfehlung stellt einen Expertenkonsens dar.

Digoxin wird ausschließlich renal eliminiert und hat nur eine geringe therapeutische Breite. Bei Patienten mit chronischer Niereninsuffizienz und generell bei älteren und weiblichen Patienten ist daher besondere Vorsicht geboten, um toxische Dosierungen zu vermeiden [234,238]. Die Leitliniengruppe empfiehlt Zielserumkonzentrati-onen im unteren therapeutischen Bereich [234,238,239] oder alternativ den Einsatz des bei Nierenfunktionsstö-rung hepatisch metabolisierten Digitoxins.

Referenzen:

234. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N. Engl. J Med 2002; 347(18):1403–11. http://www.ncbi.nlm.nih.gov/pubmed/12409542.
238. Ahmed A, Rich MW, Love TE, et al. Digoxin and reduction in mortality and hospitalization in heart failure: A comprehensive post hoc analysis of the DIG trial. Eur Heart J 2006; 27(2):178–86. http://www.ncbi.nlm.nih.gov/pubmed/16339157.
239. Bavendiek U, Aguirre DL, Koch A, et al. Assumption versus evidence: The case of digoxin in atrial fibrillation and heart fail-ure. Eur Heart J 2017(0):1–5. DOI: 10.1093/eurheartj/ehw577. http://www.ncbi.nlm.nih.gov/pubmed/28065909.

6.2.3.2 Orale Antikoagulanzien und Thrombozytenaggregationshemmer

Empfehlungen/Statements	Empfehlungs-grad
6-23 Patienten mit Herzinsuffizienz ohne weitere Indikation zur Blutgerinnungshemmung sollen keine Antikoagulanzien oder Thrombozytenaggregationshemmern erhalten.	⇓⇓

Hintergrundinformationen:

Die Empfehlung stellt einen Expertenkonsens dar.

Obwohl eine Herzinsuffizienz mit einem erhöhten Risiko für Thrombembolien assoziiert ist, stellt eine Herzinsuffizienz aus Sicht der Leitliniengruppe per se keine Indikation zur Gabe von Antikoagulanzien oder Thrombozytenaggregationshemmern dar:

• Eine orale Antikoagulation ist bei Herzinsuffizienzpatienten nur indiziert, wenn Erkrankungen wie Vorhofflim-mern, Zustand nach mechanischem Herzklappenersatz, intrakavitäre Thromben oder Zustand nach Lungenarterienembolie/tiefer Beinvenenthrombose vorliegen [240–242].

• Die Gabe von Thrombozytenaggregationshemmern ist bei Herzinsuffizienz nur indiziert, wenn andere Erkran-kungen wie KHK, pAVK oder zerebrovaskuläre Insuffizienz dies notwendig machen. Für die Therapie mit oralen Antikoagulanzien und Thrombozytenaggregationshemmern existieren spezifische Leitlinien [243,244].

Referenzen:

240. Homma S, Thompson JL, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med 2012; 366(20):1859–69. DOI: 10.1056/NEJMoa1202299. http://www.ncbi.nlm.nih.gov/pubmed/22551105.
241. Lip GY, Ponikowski P, Andreotti F, et al. Thrombo-embolism and antithrombotic therapy for heart failure in sinus rhythm. A joint consensus document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis. Eur J Heart Fail 2012; 14(7):681–95. DOI: 10.1093/eurjhf/hfs073. http://www.ncbi.nlm.nih.gov/pubmed/22611046.
242. Lip GY, Shantsila E. Anticoagulation versus placebo for heart failure in sinus rhythm. Cochrane Database Syst Rev 2014(3):CD003336. DOI: 10.1002/14651858.CD003336.pub3. http://www.ncbi.nlm.nih.gov/pubmed/24683002.

243. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), Encke A, Haas S, et al. S3-Leitlinie Prophylaxe der venösen Thromboembolie (VTE). 2015 [cited: 2016-06-30]. http://www.awmf.org/uploads/tx_szleitlinien/003-001l_S3_VTE-Prophylaxe_2015-12.pdf.
244. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Ther-apy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guide-lines. Chest 2012; 141(2 Suppl):e691S-e736S. DOI: 10.1378/chest.11-2300. http://www.ncbi.nlm.nih.gov/pubmed/22315276.

Empfehlungen für medikamentöse Therapie bei Herzinsuffizienz mit HFmrEF

Für Patienten mit einer geringgradig eingeschränkten linksventrikulären Ejektionsfraktion (LVEF 40-49%) („heart failure with mid-range ejection fraction, HFmrEF“) ist die Evidenzlage zur medikamentösen Therapie ähnlich unzureichend wie bei der HFpEF. Aus Sicht der Leitlinienautoren ist für diese Patienten, insbesondere wenn sie symptomatisch sind, eher die Therapie wie bei einer HFrEF geeignet.

National Guideline Centre and National Institute for Health and Care Excellence (NICE), 2018 [10].

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

Chronic Heart Failure in Adults: Diagnosis and Management.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: trifft zu.

Recherche/Suchzeitraum:

- 2009 – Dezember 2017

LoE

- The evidence for outcomes from the included RCTs and, where appropriate, non-randomised intervention studies, were evaluated and presented using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro138) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results.

GoR

Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Overall level of confidence for a review finding in GRADE-CERQual

Level	Description
High confidence	It is highly likely that the review finding is a reasonable representation of the phenomenon of interest.
Moderate confidence	It is likely that the review finding is a reasonable representation of the phenomenon of interest.
Low confidence	It is possible that the review finding is a reasonable representation of the phenomenon of interest.
Very low confidence	It is not clear whether the review finding is a reasonable representation of the phenomenon of interest.

Definitions

The Guideline Development Group (GDG) agreed on the following definitions:

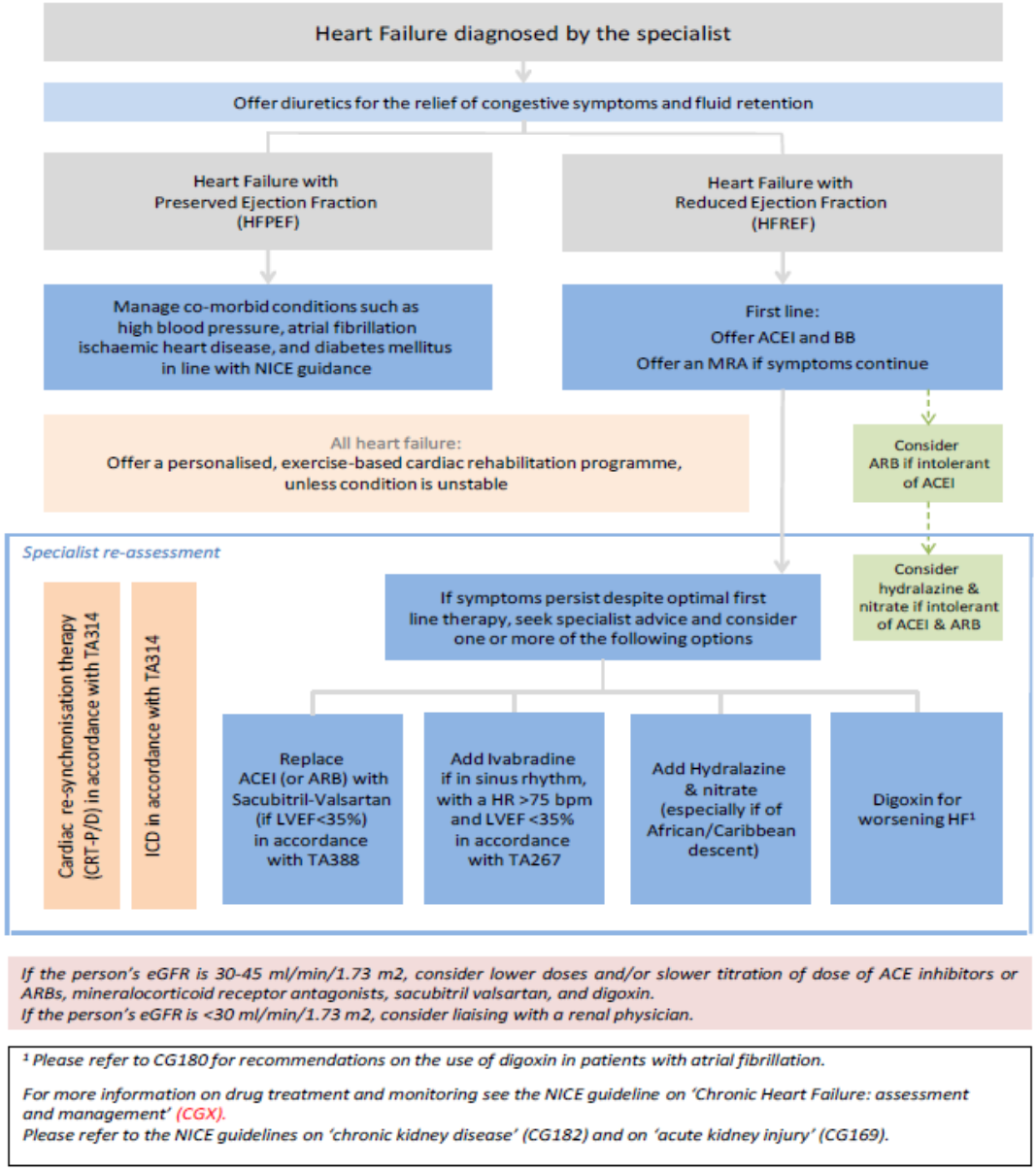
- Heart failure with reduced ejection fraction (HFREF)
  - This group of patients is characterised by heart failure with a left ventricular ejection fraction by echocardiography of less than 40%.
- Heart failure with preserved ejection fraction (HFPEF)
  - This group of patients with heart failure have a left ventricular ejection fraction greater than 50%,
  - no alternative cause for the syndrome,
  - the presence of a non-dilated left ventricle; evidence of structural remodelling (left ventricular hypertrophy or dilated left atrium); or diastolic dysfunction through imaging
  - and have abnormal biomarkers.

The GDG recognises that the two terms HFREF and HFPEF have several limitations. These include the variability of the left ventricular ejection fraction measured by different imaging modalities, and the lack of universal agreement on the threshold of ejection fraction at which these are defined or the exact definition of HFPEF. The GDG also recognised the proposal of another class as heart failure with mid-range ejection fraction (HFMREF). This proposal has not been fully clinically validated and remains the topic of further research [150, 354]

150. Hsu JJ, Ziaeian B, Fonarow GC. Heart Failure With Mid-Range (Borderline) Ejection Fraction: Clinical Implications and Future Directions. JACC Heart Fail. 2017; 5(11):763-771
354. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT et al. Significance of Ischemic Heart Disease in Patients With Heart Failure and Preserved, Midrange, and Reduced Ejection Fraction: A Nationwide Cohort Study. Circulation: Heart Failure. 2017; 10(6)

Empfehlungen

Therapeutic algorithm



6.2.7 All recommendations for the pharmacological treatment of heart failure

6.2.7.1 Diuretics

25. Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in people with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies. [2003]

26. People who have heart failure with preserved ejection fraction should usually be offered a low to medium dose of loop diuretics (for example, less than 80 mg furosemide per day). People

whose heart failure does not respond to this treatment will need further specialist advice. [2003, amended 2018]

6.2.7.2 Calcium-channel blockers

27. Avoid verapamil, diltiazem and short-acting dihydropyridine agents in people who have heart failure with reduced ejection fraction. [2003, amended 2018]

6.2.7.6 ACE inhibitors and beta-blockers

33. Offer an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker licensed for heart failure to people who have heart failure with reduced ejection fraction. Use clinical judgement when deciding which drug to start first. [2010]

34. Do not offer ACE inhibitor therapy if there is a clinical suspicion of haemodynamically significant valve disease until the valve disease has been assessed by a specialist. [2003]

35. Do not withhold treatment with a beta-blocker solely because of age or the presence of peripheral vascular disease, erectile dysfunction, diabetes, interstitial pulmonary disease or chronic obstructive pulmonary disease. [2010]

6.2.7.6.1 Starting and monitoring ACE inhibitors

36. Start ACE inhibitor therapy at a low dose and titrate upwards at short intervals (for example, every 2 weeks) until the target or maximum tolerated dose is reached. [2010]

37. Measure serum sodium and potassium and assess renal function before and 1 to 2 weeks after starting an ACE inhibitor, and after each dose increment.[2010,amended 2018]

38. Measure blood pressure before and after each dose increment of an ACE inhibitor. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension, in the NICE guideline on hypertension in adults. [2018]

39. Once the target or maximum tolerated dose of an ACE inhibitor is reached, monitor treatment monthly for 3 months and then at least every 6 months, and at any time the person becomes acutely unwell. [2010, amended 2018]

6.2.7.6.2 Starting and monitoring beta-blockers

40. Introduce beta-blockers in a ‘start low, go slow’ manner. Assess heart rate, and clinical status after each titration. Measure blood pressure before and after each dose increment of a beta-blocker. [2010, amended 2018]

41. Switch people whose condition is stable and who are already taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure with reduced ejection fraction, to a beta-blocker licensed for heart failure. [2010]

6.2.7.7 Alternative treatments if ACE inhibitors are not tolerated

6.2.7.7.1 Angiotensin II receptor antagonists (ARBs)

42. Consider an angiotensin II receptor blocker (ARB) licensed for heart failure as an alternative to an ACE inhibitor for people who have heart failure with reduced ejection fraction and intolerable side effects with ACE inhibitors. [2010]

43. Measure serum sodium and potassium and assess renal function before and after starting an ARB and after each dose increment.[2010, amended 2018]

44. Measure blood pressure after each dose increment of an ARB. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension, in the NICE guideline on hypertension in adults. [2018]

45. Once the target or maximum tolerated dose of an ARB is reached, monitor treatment monthly for 3 months and then at least every 6 months, and at any time the person becomes acutely unwell. [2010 amended 2018]

6.2.7.7.2 Hydralazine in combination with nitrate

46. If neither ACE inhibitors nor ARBs are tolerated, seek specialist advice and consider hydralazine in combination with nitrate for people who have heart failure with reduced ejection fraction. [2010]

6.2.7.8 Additional treatments if heart failure remains symptomatic or worsens

6.2.7.8.1 Mineralcorticoid receptor antagonists (MRAs)

47. Offer a mineralcorticoid receptor antagonist (MRA) in addition to an angiotensin-converting enzyme inhibitor (ACE) or ARB and beta-blocker, to people who have heart failure with reduced ejection fraction if they continue to have symptoms of heart failure. [2018]

48. Measure serum sodium and potassium and assess renal function before and after starting an MRA and after each dose increment. [2018]

49. Measure blood pressure before and after each dose increment of MRA. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension, in the NICE guideline on hypertension in adults. [2018]

50. Once the target, or maximum tolerated, dose of an MRA is reached, monitor treatment monthly for 3 months and then at least every 6 months, and at any time the person becomes acutely unwell. [2018]

6.2.7.8.2 Specialist treatment

Ivabradine

6.2.7.8.3 These recommendations are from Ivabradine for treating chronic heart failure (NICE technology appraisal guidance 267).

51. Ivabradine is recommended as an option for treating chronic heart failure for people:

- with New York Heart Association (NYHA) class II to IV stable chronic heart failure with systolic dysfunction and
- who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more and
- who are given ivabradine in combination with standard therapy including beta-blocker therapy, angiotensin-converting enzyme (ACE) inhibitor and aldosterone antagonists, or when beta-blocker therapy is contraindicated or not tolerated and
- with a left ventricular ejection fraction of 35% or less. [2012]

52. Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists. [2012]

53. Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be carried out by a heart failure

specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse. [2012]

Sacubitril valsartan

These recommendations are from Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (NICE technology appraisal guidance 388)a.

54. Sacubitril valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people

- With New York Heart Association (NYHA) class II to IV symptoms and
- With a left ventricular ejection fraction of 35% or less and
- Who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBS) [2016]

55. Treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be performed by the most appropriate team members as defined in NICE's guideline on chronic heart failure in adults: diagnosis and management. [2016]

56. This guidance is not intended to affect the position of patients whose treatment with sacubitril valsartan was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop. [2016]

Digoxin

For recommendations on digoxin for people with atrial fibrillation see the section on rate and rhythm control in the NICE guideline on atrial fibrillation

58. Digoxin is recommended for worsening or severe heart failure with reduced ejection fraction despite first line treatment for heart failureb. Seek specialist advice before initiating.[2010, amended 2018]

59. Routine monitoring of serum digoxin concentrations is not recommended. A digoxin concentration measured within 8–12 hours of the last dose may be useful to confirm a clinical impression of toxicity or non-adherence[2003]

60. the serum digoxin concentration should be interpreted in the clinical context as toxicity may occur even when the concentration is within the 'therapeutic range'. [2003]

Scottish Intercollegiate Guidelines Network (SIGN), 2016 [13].

Management of chronic heart failure

Zielsetzung/Fragestellung

The aim of this guideline is to improve the care of patients with heart failure (HF). This guideline provides recommendations, based on current evidence, for best practice in the management of patients with HF. In particular it focuses on the management of patients with stable HF rather than on in-hospital management of an episode of acute decompensation of HF (acute HF).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft teilweise zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: This guideline was first issued in 2016 and revalidated in 2019. Details can be found in the scoping report [14]. It will be considered again for review in 2023. The review history, and any updates to the guideline in the interim period, are noted in the review report.

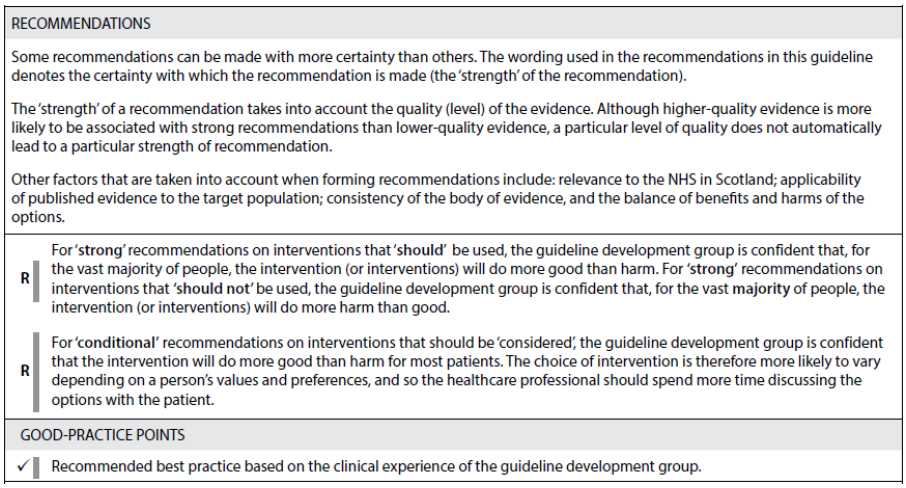
Recherche/Suchzeitraum:

- Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2006–2014. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse.

LoE

LEVELS OF EVIDENCE	
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GoR



RECOMMENDATIONS	
Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation). The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation. Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.	
R	For '**strong**' recommendations on interventions that '**should**' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For '**strong**' recommendations on interventions that '**should not**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.
R	For '**conditional**' recommendations on interventions that should be 'considered', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.
GOOD-PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group.

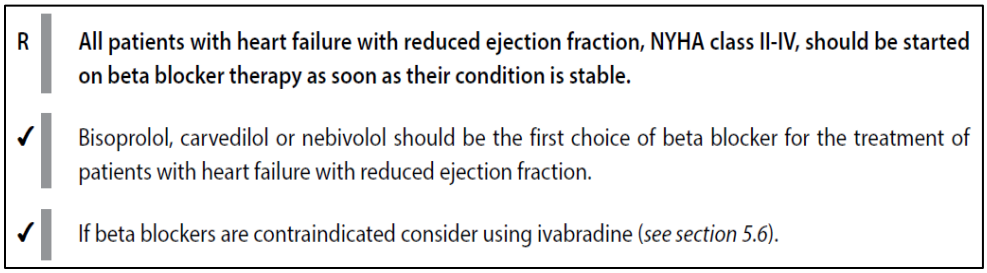
Definitions

- Heart failure can be defined on the basis of left ventricular ejection fraction (LVEF) as heart failure with reduced ejection fraction (HF-REF) or heart failure with preserved ejection fraction (HF-PEF). Heart failure with reduced ejection fraction (also referred to as HF with systolic dysfunction) is defined as the presence of signs and symptoms of HF with a left ventricular ejection fraction of <40% (although the cut-off level varies from ≤35% to ≤40% or ≤45%).
- This guideline will focus on the management of HF-REF. The term HF-REF will be used throughout in preference to other terms such as systolic dysfunction or reduced systolic function to refer to patients with heart failure and an ejection fraction of ≤40%, the upper limit for inclusion into the trials underpinning the guideline.

Empfehlungen

5. Pharmacological therapies

5.1 Beta Blockers



R	**All patients with heart failure with reduced ejection fraction, NYHA class II-IV, should be started on beta blocker therapy as soon as their condition is stable.**
✓	Bisoprolol, carvedilol or nebivolol should be the first choice of beta blocker for the treatment of patients with heart failure with reduced ejection fraction.
✓	If beta blockers are contraindicated consider using ivabradine (*see section 5.6*).

Hintergrundinformationen:

Many RCTs of beta blockers have been undertaken in patients with HF-REF. In the CIBIS II,[67] MERIT-HF,[68] and COPERNICUS[69] trials a consistent, approximately one third reduction in total mortality was seen with each of bisoprolol, extended release metoprolol succinate and carvedilol. In the SENIORS trial, nebivolol significantly reduced a composite outcome of death or cardiovascular hospitalisations in patients with heart failure aged 70 or older.[70]	1++ 1+
There is consistent evidence for positive benefits from beta blockers in patients with HF, NYHA II-IV, LVEF ≤35%, as risk of mortality from cardiovascular causes reduced by 29% (95% CI 14% to 42%); mortality due to pump failure reduced by 36% (95% CI 9% to 55%); and all-cause mortality reduced by 23% (95% CI 8% to 35%).[71] Benefits were seen with beta blockers with different pharmacological properties, whether β1 selective (bisoprolol, metoprolol, nebivolol) or non-selective (carvedilol).	
Two formulations of metoprolol were used in clinical trials of patients with HF. Only long-acting metoprolol succinate has been shown to perform better than placebo in reducing mortality (in the MERIT-HF trial).[68] Short-acting metoprolol tartrate, given twice daily, was compared to carvedilol in the COMET trial.[72] Carvedilol reduced mortality over five years by 17% compared with patients treated with metoprolol tartrate (33.8% *v* 39.5%), hazard ratio (HR) 0.83 (0.74 to 0.93), absolute risk reduction (ARR) 5.7%; p=0.0017.	1+
Extended-release metoprolol succinate is not available in the UK and no evidence was identified for the effectiveness of metoprolol tartrate, the preparation that is available in the UK.	
Beta blockers produce benefit in the medium to long term. In the short term they can produce decompensation with worsening of heart failure and hypotension. For that reason, they should be initiated at low dose and only gradually increased, with monitoring, up to their target doses shown to be effective in RCTs. Beta blockers are contraindicated in patients with asthma, second- or third- degree atrioventricular heart block or symptomatic hypotension and should be used with caution in those with low initial blood pressure (BP) (systolic BP <90 mm Hg). There is some evidence that cardioselective beta blockers can be used safely in patients with chronic obstructive pulmonary disease and HF.[73]	1+
A meta-analysis confirms that beta blockers also reduce mortality in patients with diabetes and HF(relative risk (RR) 0.84, 95% CI 0.73% to 0.96%; p=0.011).[74]	1++

Referenzen:

67. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. Lancet 1999;353(9146):9-13.
68. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart
failure: the Metoprolol CR/XL Randomised Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA Intern Med 2000;283(10):1295-302.
69. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344(22):1651-8.
70. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital
admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26(3):215-25.
71. Domanski MJ, Krause-Steinrauf H, Massie BM, Deedwania P, Follmann D, Kovar D, et al. A comparative analysis of the results from 4 trials of beta blocker therapy for heart failure: BEST, CIBIS-II,
MERIT-HF, and COPERNICUS. J Card Fail 2003;9(5):354-63.
72. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomized controlled trial. Lancet 2003;362(9377):7-13.
73. Salpeter SR, Ormiston TM, Salpeter EE , Poole PJ, Cates CJ. Cardioselective beta blockers for chronic obstructive pulmonary disease: a metaanalysis. Respir Med 2003;97(10):1094-101.
74. Haas SJ, Vos T, Gilbert RE, Krum H. Are beta blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of largescale clinical trials. Am Heart J 2003;146(5):848-53.

5.2 Angiotensin-converting enzyme inhibitors

R	**Patients with heart failure with reduced ejection fraction of all NYHA functional classes, should be given angiotensin-converting enzyme inhibitors.**

Hintergrundinformationen:

Angiotensin-converting enzyme (ACE) inhibitors were first shown to be effective in patients with HF in the 1980s. Since then, many RCTs have confirmed their benefit on mortality and morbidity, not only in HF itself,[52,53] but also in patients with left ventricular systolic dysfunction, HF or both after myocardial infarction (MI)[54-56] and in patients with asymptomatic left ventricular systolic dysfunction.[57] Meta-analysis of these and other major trials (n=7,105 patients) has shown that, in HF, treatment with an ACE inhibitor reduces RR of mortality by 23% (odds ratio (OR) 0.77, 95% CI 67 to 88; ARR 6.1%) and admission for HF is reduced by 35% (95% CI 26 to 43%, ARR 10.2%).[58] In a further meta-analysis in patients with reduced ejection fraction, heart failure or both after MI, and LVEF ≤40%, the relative risk of mortality was reduced by 26% (95% CI 17 to 34%, ARR 5.7%) and hospital admission by 27% (95% CI 15 to 37%, ARR 3.6%).[59] 1++

Important adverse effects are cough, hypotension, renal impairment and hyperkalaemia.[5,60] A key but rare adverse effect, which can be life threatening (due to laryngeal involvement), is angioedema. Any patient who experiences angioedema should have the ACE inhibitor withdrawn immediately and be prescribed an alternative agent. Renal impairment is likely to occur in those with unsuspected (bilateral) renovascular disease. ACE inhibitor-induced renal dysfunction is a possible indicator of renovascular disease and may warrant magnetic resonance imaging (MRI) renal scan.

A systematic review of six RCTs of concomitant ACE inhibitor and aspirin use did not show any significant reduction in efficacy of ACE-inhibitor therapy in patients also taking aspirin.[61] A randomised trial of aspirin versus warfarin in patients with HF-REF did not raise any concerns about a detrimental interaction between aspirin and ACE inhibitors.[62] This combination of drugs can be considered to be safe and effective in reducing cardiovascular disease events in patients with HF. 1++

Annex 2 provides practical guidance on the use of ACE inhibitors.

Referenzen:

5. Joint Formulary Committee. Guidance on prescribing. In: British National Formulary (online) London: BMJ Group and Pharmaceutical Press. [cited 22 Jan 2016]. Available from url: https://www.medicinescomplete.com/mc/bnf/current/PHP97234-guidance-on-prescribing.htm
52. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316(23):1429-35.
53. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325(5):293-302.
54. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993;342(8875):821-8.
55. Køber L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995;333(25):1670-6.
56. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. N Engl J Med 1992;327(10):669-77.
57. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327(10):685-91.
58. Garg R, Yusuf S. Overview of randomised trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 1995;273(18):1450-6.
59. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, et al. Long-term ACE-inhibitor therapy in patients with heart failure or leftventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet 2000;355(9215):1575-81.
60. McMurray J, Cohen-Solal A, Dietz R, Eichhorn E, Erhardt L, Hobbs FD, et al. Practical recommendations for the use of ACE inhibitors, beta-blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. Eur J Heart Fail 2005;7(5):710-21.
61. Teo KK, Yusuf S, Pfeffer M, Torp-Pedersen C, Kober L, Hall A, et al. Effects of long-term treatment with angiotensin-convertingenzyme inhibitors in the presence or absence of aspirin: a systematic review. Lancet 2002;360(9339):1037-43.
62. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med 2012;366(20):1859-69.

5.3 Angiotensin Receptor Blockers

R	**Patients with heart failure with reduced ejection fraction, NYHA class II-IV, who are intolerant of angiotensin-converting enzyme inhibitors should be given an angiotensin receptor blocker.**
R	**An angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor should be considered in patients with heart failure with reduced ejection fraction NYHA class II-IV, who are unable to tolerate a mineralocorticoid receptor antagonist.**

Hintergrundinformationen:

Angiotensin II type 1 receptor blockers (ARBs) block the biological effect of angiotensin II. Unlike ACE inhibitors they do not produce cough as a side effect and should be used in patients who cannot tolerate an ACE inhibitor due to cough. In the CHARM-Alternative trial, 2,028 patients, NYHA class II-IV, LVEF ≤40%, intolerant to an ACE inhibitor were randomised to placebo or candesartan, there was a RR reduction of 23% (95% CI 11% to 33%, p=0.0004) in the primary composite outcome of cardiovascular death or hospitalisation for HF in patients receiving candesartan (ARR of seven fewer patients experiencing this outcome per 100 treated).[63]	1^{++}
Angiotensin receptor blockers can also be added to ACE-inhibitor therapy in patients with HF. In the ValHeFT trial, in which 93% of patients were already taking an ACE inhibitor and 35% using a beta blocker, adding the ARB valsartan had no effect on mortality, but it did significantly reduce HF hospitalisation and mortality combined (RR 0.87, 97.5% CI, 0.77 to 0.97, p=0.009).[64] The CHARM-Added trial showed a 15% RR reduction (95% CI 4% to 25%, p=0.01, ARR 4.4%; NNT=27) for cardiovascular death or hospitalisation for HF in patients receiving candesartan in addition to an ACE inhibitor.[65] The overall effect of ARBs on hospitalisations for heart failure was HR 0.81, 95% CI 0.74 to 0.89 in meta-analysis.[66]	1^{+} 1^{++}
The use of ARB in addition to an ACE inhibitor increased the risk of, and elevation in, serum creatinine (7.8% in the candesartan group versus 4.1% in the placebo group, p=0.0001) in the CHARM-Added trial. In the ValHeFT trial the use of valsartan increased serum creatinine by 7.8 micromol/l more than placebo (p<0.001). Valsartan increased serum potassium by 0.05 mmol/l compared to placebo (p<0.001) in ValHeFT. In CHARM-Added hyperkalaemia was more common in the candesartan group (3.4%) than the placebo group (0.7%), p<0.0001. Rates of hypotension were not increased by the addition of an ARB in ValHeFT or CHARM-Added.[66]	1^{++}

Referenzen:
63. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin converting- enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362(9386):772-6.
64. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomised trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345(23):1667-75.
65. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensinconverting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362(9386):767-71.
66. Heran BS, Musini VM, Bassett K, Taylor RS, Wright JM. Angiotensin receptor blockers for heart failure. Cochrane Database of Systematic Reviews 2012, Issue 4.

5.4 Mineralocorticoid Receptor Antagonists

R	**Patients with heart failure with reduced ejection fraction who have ongoing symptoms of heart failure, NYHA class II-IV, LVEF ≤35%, despite optimal treatment, should be given mineralocorticoid receptor anatgonists unless contraindicated by the presence of renal impairment** (chronic kidney disease stage ≥4–5) **and/or elevated serum potassium concentration** (K^+ >5.0 mmol/l)**.**
✓	Eplerenone can be substituted for spironolactone in patients who develop gynaecomastia.

Hintergrundinformationen:

Aldosterone produces many adverse extrarenal effects, for example on vascular function and myocardial fibrosis. The RALES trial demonstrated that adding the mineralocorticoid receptor anatgonist (MRA) spironolactone to an ACE inhibitor reduced all-cause mortality by 30% (RR 0.70, 95% CI 0.60% to 0.82%, p<0.001, ARR 11%; NNT=9) and cardiac mortality by 31% (RR 0.69, 95% CI 0.58% to 0.82%, p<0.001) in patients with HF-REF NHYA class II-IV, LVEF ≤35%.[75] The frequency of hospitalisation for worsening HF was 35% lower in the spironolactone group than in the placebo group (RR 0.65; 95 % CI 0.54 to 0.77, p<0.001).	1++
In the EMPHASIS-HF study, which included patients with less symptomatic but still severe HF (NYHA II and LVEF <30% or ≤35% with a QRS>130) on optimal therapy, who had either been hospitalised in the last six months for a cardiovascular event or had an elevated level of BNP or NT-proBNP, eplerenone reduced the risk of any-cause death by 24% (HR 0.76, 95% CI 0.62 to 0.93) and total hospitalisation by 23% (HR 0.77, 95% CI 0.67 to 0.88) compared to placebo.[76]	1++
The EPHESUS study, carried out in patients with LVEF ≤40% following MI and either diabetes or clinical signs of HF, on optimal therapy, found a 13% reduction (95% CI 5% to 21%, p=0.002, ARR 3.3%, NNT=30) in the rate of mortality from cardiovascular causes or hospitalisation due to cardiovascular events in patients taking eplerenone.[77]	1+
A systematic review comparing eplerenone to other MRAs reported the rate of gynecomastia to be lower in patients taking eplerenone (RR 0.74, 95% CI 0.43 to1.27) than other MRAs (RR 6.26, 95% CI 3.38 to 11.57).[78]	1+
The SMC reported that the use of eplerenone as adjunctive therapy to standard optimal therapy compared to standard optimal therapy alone in patients with NYHA class II HF and left ventricular systolic dysfunction (LVEF ≤30%) is cost effective. The base case cost-effectiveness ratio was a cost per quality-adjusted life year (QALY) of £3,140 based on a QALY gain of 1.21 and an incremental cost of £3,822.	

Referenzen:
75. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomised Aldactone Evaluation Study Investigators. N Engl J Med 1999;341(10):709-17.
76. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364(1):11-21.
77. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348(14):1309-21.
78. Chatterjee S, Moeller C, Shah N, Bolorunduro O, Lichstein E, Moskovits N, et al. Eplerenone is not superior to older and less expensive aldosterone antagonists. Am J Med 2012;125(8):817-25.

5.5 Angiotensin Receptor/Neprilysin Inhibitors

R	**Patients with heart failure with reduced ejection fraction who have ongoing symptoms of heart failure, NYHA class II-III, LVEF ≤40% despite optimal treatment should be given sacubitril/valsartan instead of their ACE inhibitor or ARB, unless contraindicated. It may be considered in patients with NYHA class IV symptoms.** **If the patient is already on an ACE inhibitor, the ACE inhibitor should be stopped for 36 hours before initiating sacubitril/valsartan to minimise the risk of angioedema.**
✓	Patients should be seen by a heart failure specialist with access to a multidisciplinary heart failure team before starting treatment with sacubitril/valsartan.

Scoping Report 2019 [14]:

1.4.22 Sacubitril valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people: with New York Heart Association (NYHA) class II to IV symptoms and with a left ventricular ejection fraction of 35% or less and who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or ARBs. [2016]	Section 5.5 SIGN recommends NYHA class 2-3 (and may be considered in class 4), LVEF 40% or less. May wish to consider changing wording

Hintergrundinformationen:

A large multicentre RCT (PARADIGM) has reported benefit from sacubitril/valsartan in comparison with enalapril. Patients (n=8,399) had HF-REF with NYHA class II, III or IV with an LVEF ≤40% (changed to ≤35% in a protocol amendment). Patients were required to have a plasma BNP level of at least 150 pg/ml (or NT-pro BNP >600 pg/ml), or, if they had been hospitalised for HF within the previous 12 months, a BNP of at least 100 pg/ml (or NT-pro BNP >400 pg/ml). Excluded patients included those with a history of angioedema, low blood pressure, renal dysfunction or an elevated serum potassium.[79]	
A run-in phase involved all patients receiving enalapril 10 mg twice daily for two weeks followed by sacubitril/valsartan for four to six weeks (target dose 200 mg twice daily). Patients with no unacceptable side effects were then randomised to either enalapril (10 mg twice daily) or sacubitril/valsartan (200 mg twice daily). To minimise the risk of angioedema caused by overlapping ACE inhibitor and neprilysin inhibition, patients stopped treatment 36 hours before initiating sacubitril/valsartan.	1++
The primary outcome was a composite of death from cardiovascular causes or a first hospitalisation for HF. The study was terminated early because of overwhelming benefit with a median follow up of 27 months. During the run-in phase, 12% of patients withdrew with a higher rate of withdrawal in the enalapril group.[79]	
The primary outcome occurred in 21.8% of sacubitril/valsartan patients versus 26.5% of enalapril patients (HR 0.80, 95% CI 0.73 to 0.87, p<0.001). Cardiovascular deaths were 13.3% versus 16.5% in sacubitril/valsartan versus enalapril (HR 0.80, CI 0.71 to 0.89, p<0·001). Hospitalisations for HF were 12.8% versus 15.6% for sacubitril/valsartan versus enalapril (HR 0.79, 95% CI 0.71 to 0.89, p <0·001). Total deaths were 17% for sacubitril/valsartan versus 19.8% for enalapril (HR 0.84, 95% CI 0.76 to 0.93, p<0·001). Over the trial duration, the NNT was 21 to prevent one death from cardiovascular causes or hospitalisation for HF and 32 to prevent one cardiovascular death.[79]	
A subsequent publication showed that the mortality benefit of sacubitril/valsartan compared to enalapril was the same irrespective of the mode of death; there was a similar reduction in both sudden cardiac deaths (20%) and in deaths due to worsening HF (21%).[80]	
The benefit of sacubitril/valsartan over enalapril was consistent over all age subgroups and over all categories of risk.[81,82] Only 60 patients in the study had HF-REF class IV, so efficacy in this group is less certain.[79]	
Reported adverse events of symptomatic hypotension was more common with sacubitril/valsartan than enalapril (14% *v* 9.2%) whereas cough, serum potassium >6.0mmol/L, and an elevated creatinine (>2.5 mg/dl) were more common with enalapril. Angioedema was non-significantly more common with sacubitril/valsartan (0.45% *v* 0.24%).[79]	1++
SMC has accepted sacubitricil/valsartan for use in NHSScotland in adult patients for treatment of HF-REF *(see*	

Referenzen:
79. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371(11):993-1004.
80. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Chen F, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. Eur Heart J 2015;36(30):1990-7.

5.6 Ivabradine

R	**Patients with a diagnosis of heart failure with reduced ejection fraction of NYHA class II-IV, LVEF ≤35%, who have had a previous hospital admission for heart failure in the preceding 12 months but have stabilised on standard therapy for at least four weeks should be given ivabradine. Patients must have a sinus rhythm heart rate ≥75 beats/minute despite maximum tolerated dose of beta blockers.**
✓	Specialist advice should be sought before initiating ivabradine.

Hintergrundinformationen:

Ivabradine is a new class of drug which targets the sinoatrial node and therefore only acts in patients in sinus rhythm. In a trial of 6,558 participants, when ivabradine was added to usual care for patients with HF-REF, NYHA class II-IV, LVEF ≤35%, heart rate ≥70 beats per minute and with a previous hospitalisation for HF in the previous 12 months, stabilised on treatment for at least four weeks, the primary end point of cardiovascular death or hospitalisations for HF was reduced (24% in the ivabradine group compared to 29% in the placebo group had an event over 22.9 months; NNT 24). Cardiovascular deaths and all cause mortality were not significantly reduced with ivabradine but there was a reduction in deaths due to HF (3% with ivabradine *v* 5% with placebo; HR 0.74, 95% CI 0.58 to 0.94).[83] 1++

Ivabradine had an increased risk of symptomatic and asymptomatic bradycardia compared with placebo (5% *v* 1% for symptomatic; 6% *v* 1% for asymptomatic), and an increased risk of phosphenes (3% *v* 1%).[83] 1++

An assessment by SMC found that ivabradine, in addition to standard care, was cost effective compared to standard care alone in patients whose resting heart rate remained ≥75 beats per minute despite optimal standard therapy *(see section 10.4)*. The estimated incremental cost-effectiveness ratio (ICER) was £6,002 per QALY based on an incremental cost of £1,875 and a QALY gain of 0.3. This result was supported by a further cost-utility analysis undertaken in the UK comparing ivabradine added to standard therapy with standard care which found an ICER of £8,498 for patients whose heart rate remained ≥75 bpm and £13,764 for those whose heart rate remained ≥70 bpm.[84] Probabilistic sensitivity analysis showed a 95% probability that ivabradine would be considered cost effective at a £20,000 per QALY threshold.[84]

Referenzen:
83. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. Lancet 2010;376(9744):875-85.
84. Griffiths A, Paracha N, Davies A, Branscombe N, Cowie MR, Sculpher M. The cost effectiveness of ivabradine in the treatment of chronic heart failure from the UK National Health Service perspective. Heart 2014;100(13):1031-6.

5.7 Diuretics/Loop Diuretics

R	**Patients with heart failure and clinical signs or symptoms of fluid overload or congestion should be considered for diuretic therapy.**

✓	The dose of diuretic should be individualised to reduce fluid retention without overtreating which may cause dehydration or renal dysfunction.

Hintergrundinformationen:

In the majority of patients with heart failure fluid retention occurs, causing ankle oedema, pulmonary oedema or both, contributing to the symptom of dyspnoea. Diuretic treatment relieves oedema and dyspnoea.

A meta-analysis of diuretic therapy found a 75% reduction in mortality (OR 0.25, 95% CI 0.07% to 0.84%, p=0.03, ARR 8.2%, NNT=12) and a 63% improvement in exercise capacity (OR 0.37, 95% CI 0.1% to 0.64%).[85] Although studies included in this meta-analysis were small and of poor quality they were reasonably consistent. The evidence supports the view that there is benefit in diuretic therapy for patients with dyspnoea or oedema. 1+

In most cases the agent of choice will be a loop diuretic although a thiazide might suffice where the fluid retention is very mild.

Care should be taken to select the dose of the loop diuretic on an individual basis, so that the dose chosen or reached should eliminate ankle or pulmonary oedema without dehydrating the patient and placing them at risk of renal dysfunction or hypotension.

The tendency of loop diuretics to cause hypokalaemia is offset by ACE inhibitors, ARBs and spironolactone. Serum potassium should be monitored to maintain its concentration in the range 4–5 mmol/l and adjustments in therapy should be made to prevent both hypokalaemia and hyperkalaemia.

Referenzen:
85. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. Int J Cardiol 2002;82(2):149-58.

5.8 Digoxin

R	**Digoxin should be considered as an add-on therapy for patients with heart failure in sinus rhythm who are still symptomatic after optimum therapy.**
✓	If excessive bradycardia occurs with concurrent beta blockade and digoxin therapy, digoxin should be stopped.

Scoping Report 2019 [14]:

1.4.26 Digoxin is recommended for worsening or severe heart failure with reduced ejection fraction despite first-line treatment for heart failure. Seek specialist advice before initiating.	Section 5.8 May wish to include 'seek specialist advice before initiating'.

Hintergrundinformationen:

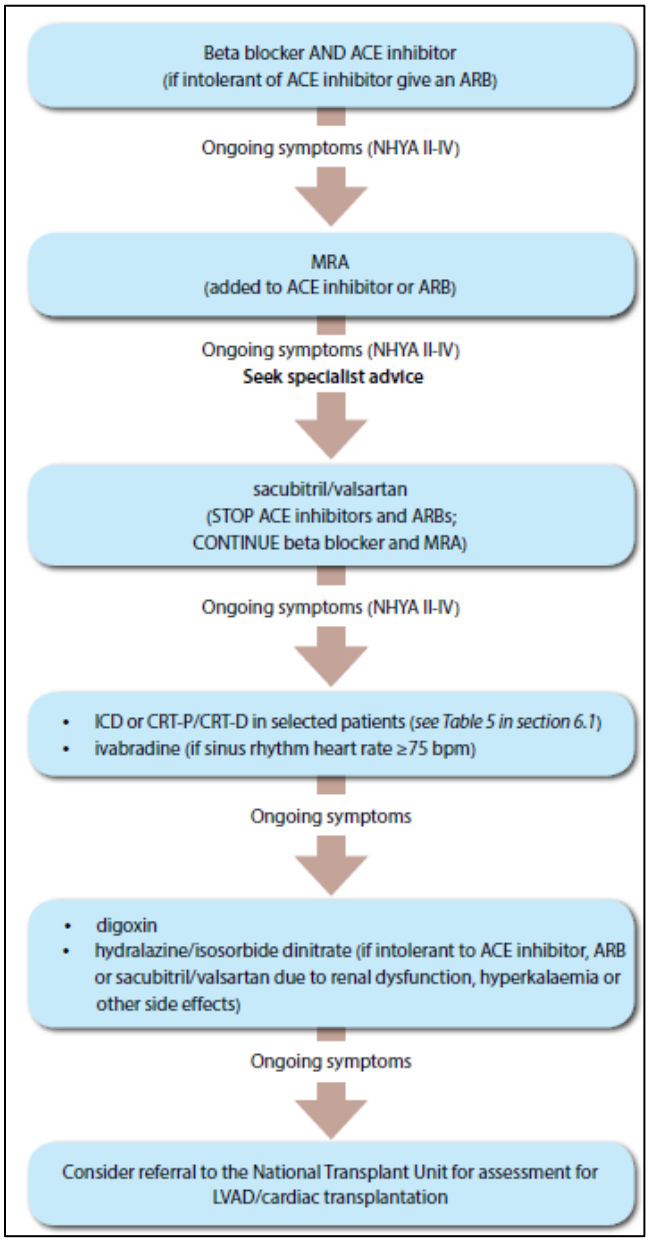
A Cochrane review found a 64% improvement in symptoms (OR 0.31, 95% CI 0.21% to 0.43%, ARR 11.5%, NNT=9) and a 23% reduction in hospitalisation (OR 0.68, 95% CI 0.61% to 0.75%, ARR 5.7%, NNT=18) for patients receiving digoxin (digitalis). Digoxin did not improve survival.[86] This review is dominated by one large trial (the DIG study) which was carried out before the introduction of beta blockers and spironolactone for the treatment of patients with HF, which may have influenced the conclusions.[87] Evidence of benefit must be weighed against the possibility of an increase in sudden deaths associated with digoxin. The risk of digoxin toxicity is increased by hypokalaemia.	1^{++}
In patients with HF and atrial fibrillation a beta blocker is preferred for control of the ventricular rate, although digoxin may be used initially while the beta blocker is being introduced. If excessive bradycardia occurs with both drugs, digoxin should be stopped (*see the SIGN guideline on cardiac arrhythmias in coronary heart disease)*.[88]	
In patients with HF and sinus rhythm, digoxin may reduce symptoms and hospital admission for worsening HF although it has not been tested in addition to optimum therapy and is usually only reserved for patients with severe HF who have not responded to other treatments.[86] In two smaller and shorter studies of digoxin withdrawal in patients with stable HF, the PROVED and RADIANCE trials, withdrawal of digoxin was associated with a decline in exercise capacity, deterioration in left ventricular systolic function, and significantly increased risk of hospitalisation for worsening HF.[89,90]	1^{++} 1^{+}

Referenzen:
86. Hood WJ, Dans A, Guyatt G, Jaeschke R, McMurray J. Digitalis for treatment of congestive heart failure in patients in sinus rhythm. Cochrane Database of Systematic Reviews 2004, Issue 1.
87. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336(8):525-33.
88. Scottish Intercollegiate Guidelines Network (SIGN). Cardiac arrhythmias in coronary heart disease. Edinburgh: SIGN; 2007. (SIGN publication number 94). [cited 21 Jan 2016]. Available from url: http://www.sign.ac.uk/guidelines/fulltext/94/index.html
89. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomised study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure:
results of the PROVED trial. PROVED Investigative Group. J Am Coll Cardiol 1993;22(4):955-62.
90. Packer M, Gheorghiade M, Young JB, Costantini PJ, Adams KF, Cody RJ, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-convertingenzyme inhibitors.
RADIANCE Study. N Engl J Med 1993;329(1):1-7.

Summary of the use of major drug classes for treatment of heart failure

Unless contraindicated, all patients with HF-REF should be started on an ACE inhibitor and a beta blocker (and a diuretic, in most cases). For those who remain symptomatic, the addition of an MRA may be considered. No patient should receive three drugs which block the renin-angiotensin-aldosterone system as hyperkalaemia and renal dysfunction will be common. Figure 2 provides a flowchart for sequence of therapy.	
✓	The safety and efficacy of combining an ACE inhibitor, an ARB and MRA is uncertain and the use of these three drugs together is not recommended.

Figure 2: Algorithm for pharmacotherapy and device therapy in patients with HF-REF, NYHA class II-IV



Yancy CW et al., 2017 [18].

American College of Cardiology, American Heart Association, Heart Failure Society of America. Developed in Collaboration with the American Academy of Family Physicians, American College of Chest Physicians, and International Society for Heart and Lung Transplantation

ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Siehe auch: Yancy CW et al., 2013 [17]. ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.

Zielsetzung /Fragestellung

The scope of the focused update includes revision to the sections on biomarkers; new therapies indicated for stage C HF with reduced ejection fraction (HFrEF); updates on HF with preserved ejection fraction (HFpEF); new data on important comorbidities, including sleep apnea, anemia, and hypertension; and new insights into the prevention of HF.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- To identify key data that influence guideline recommendations, the Task Force and members of the 2013 HF guideline writing committee reviewed clinical trials that were presented at the annual scientific meetings of the ACC, AHA, and European Society of Cardiology and other scientific meetings and that were published in peer-reviewed format from April 2013 through November 2016.
- Externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

LoE/GoR

Table 1. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated August 2015)

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
CLASS I (STRONG) — Benefit >>> Risk Suggested phrases for writing recommendations: ▪ Is recommended ▪ Is indicated/useful/effective/beneficial ▪ Should be performed/administered/other ▪ Comparative-Effectiveness Phrases†: ○ Treatment/strategy A is recommended/indicated in preference to treatment B ○ Treatment A should be chosen over treatment B	**LEVEL A** ▪ High-quality evidence‡ from more than 1 RCT ▪ Meta-analyses of high-quality RCTs ▪ One or more RCTs corroborated by high-quality registry studies
CLASS IIa (MODERATE) — Benefit >> Risk Suggested phrases for writing recommendations: ▪ Is reasonable ▪ Can be useful/effective/beneficial ▪ Comparative-Effectiveness Phrases†: ○ Treatment/strategy A is probably recommended/indicated in preference to treatment B ○ It is reasonable to choose treatment A over treatment B	**LEVEL B-R** (Randomized) ▪ Moderate-quality evidence‡ from 1 or more RCTs ▪ Meta-analyses of moderate-quality RCTs
CLASS IIb (WEAK) — Benefit ≥ Risk Suggested phrases for writing recommendations: ▪ May/might be reasonable ▪ May/might be considered ▪ Usefulness/effectiveness is unknown/unclear/uncertain or not well established	**LEVEL B-NR** (Nonrandomized) ▪ Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies ▪ Meta-analyses of such studies
CLASS III: No Benefit (MODERATE) — Benefit = Risk *(Generally, LOE A or B use only)* Suggested phrases for writing recommendations: ▪ Is not recommended ▪ Is not indicated/useful/effective/beneficial ▪ Should not be performed/administered/other	**LEVEL C-LD** (Limited Data) ▪ Randomized or nonrandomized observational or registry studies with limitations of design or execution ▪ Meta-analyses of such studies ▪ Physiological or mechanistic studies in human subjects
CLASS III: Harm (STRONG) — Risk > Benefit Suggested phrases for writing recommendations: ▪ Potentially harmful ▪ Causes harm ▪ Associated with excess morbidity/mortality ▪ Should not be performed/administered/other	**LEVEL C-EO** (Expert Opinion) Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Sonstige methodische Hinweise

- Keine Angabe zu systematischer Suche.
- Auswahl der Evidenz online verfügbar, Bewertung der Evidenz nicht dargelegt.
- Konsensusprozess nicht dargelegt.

Definitions of HFrEF and HFpEF (aus Yancy CW et al 2013 [17])

Classification	EF (%)	Description
I. Heart failure with reduced ejection fraction (HF*r*EF)	≤40	Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HF*r*EF, and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart failure with preserved ejection fraction (HF*p*EF)	≥50	Also referred to as diastolic HF. Several different criteria have been used to further define HF*p*EF. The diagnosis of HF*p*EF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HF*p*EF, borderline	41 to 49	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HF*p*EF.
b. HF*p*EF, improved	>40	It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

EF indicates ejection fraction; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; and HF*r*EF, heart failure with reduced ejection fraction.

7.3.2 Pharmacological Treatment for Stage C HF With Reduced Ejection Fraction: Recommendation

7.3.2.10 Renin-Angiotensin System Inhibition With Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker or ARNI: Recommendations

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI

COR	LOE	Recommendations	Comment/Rationale
I	**ACE-I: A ARB: A ARNI: B-R**	**The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors *(Level of Evidence: A)* (128–133), OR ARBs *(Level of Evidence: A)* (134–137), OR ARNI *(Level of Evidence: B-R)* (138) in conjunction with evidence-based beta blockers (9,139,140), and aldosterone antagonists in selected patients (141,142), is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality.**	**NEW:** New clinical trial data prompted clarification and important updates.
See Online Data Supplements 1, 2, 18-20.		Angiotensin-converting enzyme (ACE) inhibitors reduce morbidity and mortality in heart failure with reduced ejection fraction (HF*r*EF). Randomized controlled trials (RCTs) clearly establish the benefits of ACE inhibition in patients with mild, moderate, or severe symptoms of HF and in patients with or without coronary artery disease (128–133). ACE inhibitors can produce angioedema and should be given with caution to patients with low systemic blood pressures, renal insufficiency, or elevated serum potassium. ACE inhibitors also inhibit kininase and increase levels of bradykinin, which can induce cough but also may contribute to their beneficial effect through vasodilation. Angiotensin receptor blockers (ARBs) were developed with the rationale that angiotensin II production continues in the presence of ACE inhibition, driven through alternative enzyme pathways. ARBs do not inhibit kininase and are associated with a much lower incidence of cough and angioedema than ACE inhibitors; but like ACE inhibitors, ARBs should be given with caution to patients with low systemic blood pressure, renal insufficiency, or elevated serum potassium. Long-term therapy with ARBs produces hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system and have been shown in RCTs (134–137) to reduce morbidity and mortality, especially in ACE inhibitor–intolerant patients. In ARNI, an ARB is combined with an inhibitor of neprilysin, an enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides. In an RCT that compared the first approved ARNI, valsartan/sacubitril, with enalapril in symptomatic patients with HF*r*EF tolerating an adequate dose of either ACE inhibitor or ARB, the ARNI reduced the composite endpoint of cardiovascular death or HF hospitalization significantly, by 20% (138). The benefit was seen to a similar extent for both death and HF hospitalization and was consistent across subgroups. The use of ARNI is associated with the risk of hypotension and renal insufficiency and may lead to angioedema, as well.	

(*continued on next page*)

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI (*Continued*)

COR	LOE	Recommendations	Comment/Rationale
I	ACE-I: A	**The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality (128–133,143).**	2013 recommendation repeated for clarity in this section.
See Online Data Supplement 18.		ACE inhibitors have been shown in large RCTs to reduce morbidity and mortality in patients with HFrEF with mild, moderate, or severe symptoms of HF, with or without coronary artery disease (128–133). Data suggest that there are no differences among available ACE inhibitors in their effects on symptoms or survival (143). ACE inhibitors should be started at low doses and titrated upward to doses shown to reduce the risk of cardiovascular events in clinical trials. ACE inhibitors can produce angioedema and should be given with caution to patients with low systemic blood pressures, renal insufficiency, or elevated serum potassium (>5.0 mEq/L.). Angioedema occurs in <1% of patients who take an ACE inhibitor, but it occurs more frequently in blacks and women (144). Patients should not be given ACE inhibitors if they are pregnant or plan to become pregnant. ACE inhibitors also inhibit kininase and increase levels of bradykinin, which can induce cough in up to 20% of patients but also may contribute to beneficial vasodilation. If maximal doses are not tolerated, intermediate doses should be tried; abrupt withdrawal of ACE inhibition can lead to clinical deterioration and should be avoided. Although the use of an ARNI in lieu of an ACE inhibitor for HFrEF has been found to be superior, *for those patients for whom ARNI is not appropriate, continued use of an ACE inhibitor for all classes of HFrEF remains strongly advised.*	
I	ARB: A	**The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE inhibitors because of cough or angioedema (134–137,145,146).**	2013 recommendation repeated for clarity in this section.
See Online Data Supplements 2 and 19.		ARBs have been shown to reduce mortality and HF hospitalizations in patients with HFrEF in large RCTs (134–137). Long-term therapy with ARBs in patients with HFrEF produces hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system (145,146). Unlike ACE inhibitors, ARBs do not inhibit kininase and are associated with a much lower incidence of cough and angioedema, although kininase inhibition by ACE inhibitors may produce beneficial vasodilatory effects. Patients intolerant to ACE inhibitors because of cough or angioedema should be started on ARBs; patients already tolerating ARBs for other indications may be continued on ARBs if they subsequently develop HF. ARBs should be started at low doses and titrated upward, with an attempt to use doses shown to reduce the risk of cardiovascular events in clinical trials. ARBs should be given with caution to patients with low systemic blood pressure, renal insufficiency, or elevated serum potassium (>5.0 mEq/L.). Although ARBs are alternatives for patients with ACE inhibitor–induced angioedema, caution is advised because some patients have also developed angioedema with ARBs. Head-to-head comparisons of an ARB versus ARNI for HF do not exist. *For those patients for whom an ACE inhibitor or ARNI is inappropriate, use of an ARB remains advised.*	
I	ARNI: B-R	**In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (138).**	**NEW:** New clinical trial data necessitated this recommendation.
See Online Data Supplements 1 and 18.		Benefits of ACE inhibitors with regard to decreasing HF progression, hospitalizations, and mortality rate have been shown consistently for patients across the clinical spectrum, from asymptomatic to severely symptomatic HF. Similar benefits have been shown for ARBs in populations with mild-to-moderate HF who are unable to tolerate ACE inhibitors. In patients with mild-to-moderate HF (characterized by either 1) mildly elevated natriuretic peptide levels, BNP [B-type natriuretic peptide] >150 pg/mL. or NT-proBNP [N-terminal pro-B-type natriuretic peptide] ≥600 pg/mL.; or 2) BNP ≥100 pg/mL. or NT-proBNP ≥400 pg/mL. with a prior hospitalization in the preceding 12 months) who were able to tolerate both a target dose of enalapril (10 mg twice daily) and then subsequently an ARNI (valsartan/sacubitril; 200 mg twice daily, with the ARB component equivalent to valsartan 160 mg), hospitalizations and mortality were significantly decreased with the valsartan/sacubitril compound compared with enalapril. The target dose of the ACE inhibitor was consistent with that known to improve outcomes in previous landmark clinical trials (129). This ARNI has been approved for patients with symptomatic HFrEF and is intended to be substituted for ACE inhibitors or ARBs. HF effects and potential off-target effects may be complex with inhibition of the neprilysin enzyme, which has multiple biological targets. Use of an ARNI is associated with hypotension and a low-frequency incidence of angioedema. To facilitate initiation and titration, the approved ARNI is available in 3 doses that include a dose that was not tested in the HF trial; the target dose used in the trial was 97/103 mg twice daily (147). Clinical experience will provide further information about the optimal titration and tolerability of ARNI, particularly with regard to blood pressure, adjustment of concomitant HF medications, and the rare complication of angioedema (14).	
III: Harm	B-R	**ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (148,149).**	**NEW:** Available evidence demonstrates a potential signal of harm for a concomitant use of ACE inhibitors and ARNI.
See Online Data Supplement 3.		Oral neprilysin inhibitors, used in combination with ACE inhibitors can lead to angioedema and concomitant use is contraindicated and should be avoided. A medication that represented both a neprilysin inhibitor and an ACE inhibitor, omapatrilat, was studied in both hypertension and HF, but its development was terminated because of an unacceptable incidence of angioedema (148,149) and associated significant morbidity. This adverse effect was thought to occur because both ACE and neprilysin break down bradykinin, which directly or indirectly can cause angioedema (149,150). An ARNI should not be administered within 36 hours of switching from or to an ACE inhibitor.	
III: Harm	C-EO	**ARNI should not be administered to patients with a history of angioedema.**	**NEW:** New clinical trial data.
N/A		Omapatrilat, a neprilysin inhibitor (as well as an ACE inhibitor and aminopeptidase P inhibitor), was associated with a higher frequency of angioedema than that seen with enalapril in an RCT of patients with HFrEF (148). In a very large RCT of hypertensive patients, omapatrilat was associated with a 3-fold increased risk of angioedema as compared with enalapril (149). Blacks and smokers were particularly at risk. The high incidence of angioedema ultimately led to cessation of the clinical development of omapatrilat (151,152). In light of these observations, angioedema was an exclusion criterion in the first large trial assessing ARNI therapy in patients with hypertension (153) and then in the large trial that demonstrated clinical benefit of ARNI therapy in HFrEF (138). ARNI therapy should not be administered in patients with a history of angioedema because of the concern that it will increase the risk of a recurrence of angioedema.	

7.3.2.11 *Ivabradine: Recommendation*

Recommendation for Ivabradine

COR	LOE	Recommendation	Comment/Rationale
IIa	B-R	**Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF*r*EF (LVEF ≤35%) who are receiving GDEM*, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (154–157).**	**NEW:** New clinical trial data.
See Online Data Supplement 4.		Ivabradine is a new therapeutic agent that selectively inhibits the I_f current in the sinoatrial node, providing heart rate reduction. One RCT demonstrated the efficacy of ivabradine in reducing the composite endpoint of cardiovascular death or HF hospitalization (155). The benefit of ivabradine was driven by a reduction in HF hospitalization. The study included patients with HF*r*EF (NYHA class II-IV, albeit with only a modest representation of NYHA class IV HF) and left ventricular ejection fraction (LVEF) ≤35%, in sinus rhythm with a resting heart rate of ≥70 beats per minute. Patients enrolled included a small number with paroxysmal atrial fibrillation (<40% of the time) but otherwise in sinus rhythm and a small number experiencing ventricular pacing but with a predominant sinus rhythm. Those with a myocardial infarction within the preceding 2 months were excluded. Patients enrolled had been hospitalized for HF in the preceding 12 months and were on stable GDEM* for 4 weeks before initiation of ivabradine therapy. The target of ivabradine is heart rate slowing (the presumed benefit of action), but only 25% of patients studied were on optimal doses of beta-blocker therapy (9,139,140,155). Given the well-proven mortality benefits of beta-blocker therapy, it is important to initiate and up titrate these agents to target doses, as tolerated, before assessing the resting heart rate for consideration of ivabradine initiation (155).	

*In other parts of the document, the term "GDMT" has been used to denote guideline-directed management and therapy. In this recommendation, however, the term "GDEM" has been used to denote this same concept in order to reflect the original wording of the recommendation that initially appeared in the "2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure" (10).

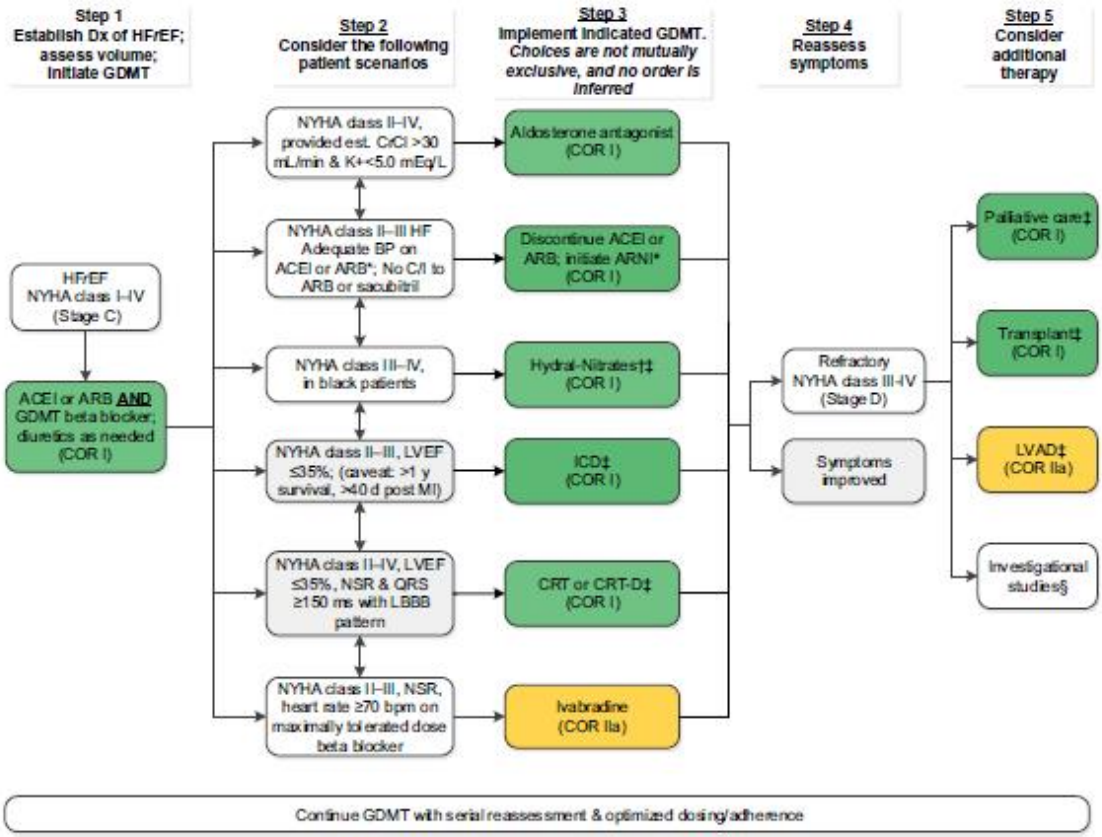


Figure 2. Treatment of HF*r*EF Stage C and D
Colors correspond to COR in Table 1. For all medical therapies, dosing should be optimized and serial assessment exercised.
*See text for important treatment directions.
†Hydral-Nitrates green box: The combination of ISDN/HYD with ARNI has not been robustly tested. BP response should be carefully monitored.
‡See 2013 HF guideline (9).
§Participation in investigational studies is also appropriate for stage C, NYHA class II and III HF.
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor-blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; bpm, beats per minute; C/I, contraindication; COR, Class of Recommendation; CrCl, creatinine clearance; CRT-D, cardiac resynchronization therapy–device; Dx, diagnosis; GDMT, guideline-directed management and therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ISDN/HYD, isosorbide dinitrate hydral-nitrates; K+, potassium; LBBB, left bundle-branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSR, normal sinus rhythm; and NYHA, New York Heart Association.

Referenzen:
128. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med 1987;316:1429–35.
129. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 1991;325:293–302.
130. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation 1999;100:2312–8.
131. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. The SAVE Investigators. N Engl J Med 1992;327:669–77.
132. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet 1993;342:821–8.
133. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995;333:1670–6.
134. Cohn JN, Tognoni G, Investigators VHFT. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667–75.
135. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893–906.
136. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet 2009;374:1840–8.
137. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759–66.
138. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.
139. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERITHF). Lancet 1999;353:2001–7.
140. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002;106:2194–9.
141. Eschalier R, McMurray JJV, Swedberg K, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). J Am Coll Cardiol 2013;62:1585–93.
142. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709–17.
143. Garg R, Yusuf S. Overview of randomized trials of angiotensinconverting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 1995;273:1450–6.
144. Woodard-Grice AV, Lucisano AC, Byrd JB, et al. Sex-dependent and race-dependent association of XPNPEP2 C-2399A polymorphism with angiotensin-converting enzyme inhibitor-associated angioedema. Pharmacogenet Genomics 2010;20:532–6.
145. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547– 59.
146. Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 2008;372:1174–83.
147. Entresto [package insert]. Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015.
148. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation 2002;106:920–6.
149. Kostis JB, Packer M, Black HR, et al. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. Am J Hypertens 2004;17:103–11.
154. Bohm M, Robertson M, Ford I, et al. Influence of cardiovascular and noncardiovascular co-morbidities on outcomes and treatment effect of heart rate reduction with ivabradine in stable heart failure (from the SHIFT Trial). Am J Cardiol 2015;116:1890–7.
155. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875–85.
156. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med 2014;371:1091–9.
157. Fox K, Ford I, Steg PG, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:807–16.

Ponikowski P et al., 2016 [12].

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: erhebliche finanzielle Abhängigkeiten. Diese wurden in Stollberger et al. [15] untersucht und kritisiert: *„Of the 21 authors only 2 (10%) indicated no COI in the years 2014–2015. Among the authors, the chairperson of the task force had the second most COIs (33) and the co-chairperson the fourth most COIs (21). Among the 87 reviewers only 18 (21%) were without COIs."*
- Systematische Suche, Auswahl und Bewertung der Evidenz: Selected experts in the field undertook a comprehensive review of the published evidence for management (including diagnosis, treatment, prevention and rehabilitation) of a given condition according to ESC Committee for Practice Guidelines (CPG) policy.
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft teilweise zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: unklar.

Recherche/Suchzeitraum:

- Keine Angabe

LoE

Level of evidence A	**Data derived from multiple randomized clinical trials or meta-analyses.**
Level of evidence B	**Data derived from a single randomized clinical trial or large non-randomized studies.**
Level of evidence C	**Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.**

GoR

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Sonstige methodische Hinweise

- Keine Angabe zu systematischer Recherche, Auswahl und Bewertung der Evidenz.
- Konsensusprozess wurde durchgeführt, es liegen aber keine Angaben zu Vorgehen und Formalisierung vor.
- Kein externes Begutachtungsverfahren beschrieben.
- Keine Angaben zur Überprüfung der Aktualität und Gültigkeitsdauer der LL.

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund von Therapieempfehlungen für Patienten mit HFmrEF, wird die LL jedoch ergänzend dargestellt.

Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.
[b]BNP>35 pg/ml and/or NT-proBNP>125 pg/mL.

Empfehlungen

7. Pharmacological treatment of heart failure with reduced ejection fraction

7.2 Treatments recommended in all symptomatic patients with heart failure with reduced ejection fraction

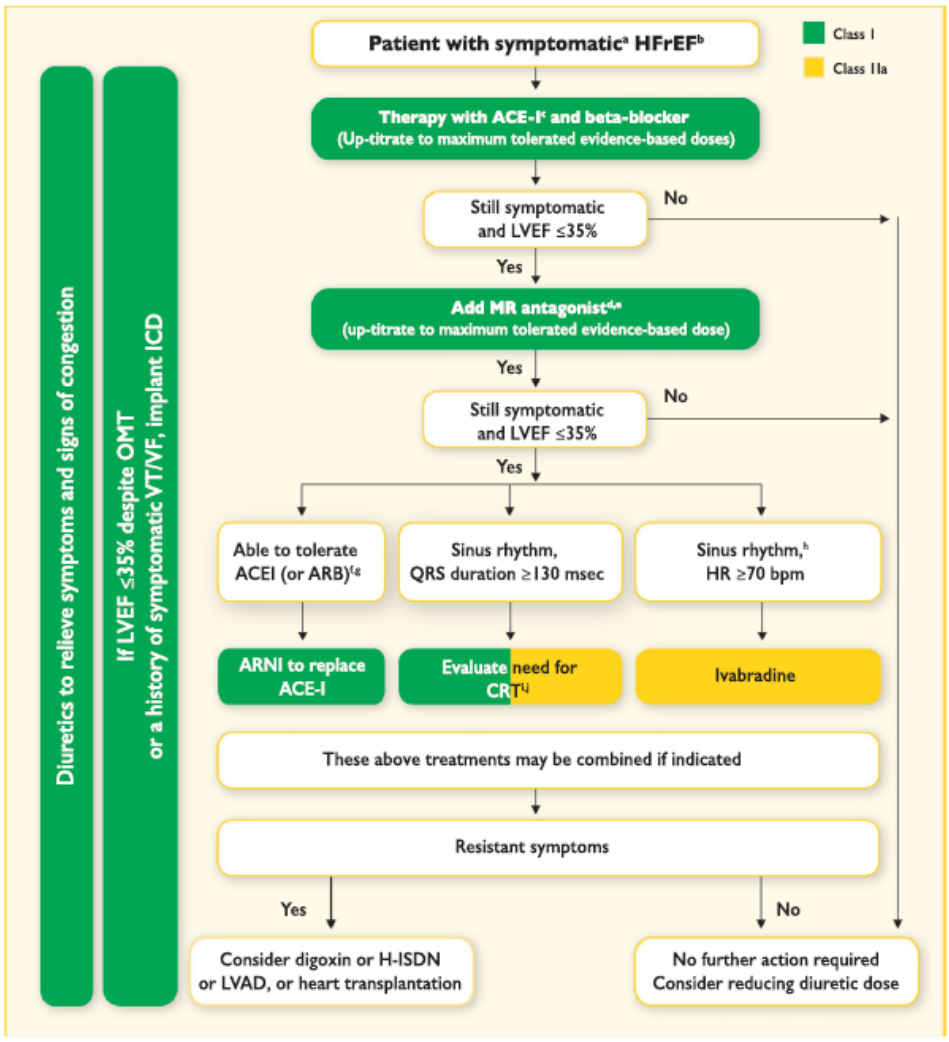


Figure 7.1 Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction. Green indicates a class I recommendation; yellow indicates a class IIa recommendation. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BNP = B-type natriuretic peptide; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; H-ISDN = hydralazine and isosorbide dinitrate; HR = heart rate; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR = mineralocorticoid receptor; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; OMT = optimal medical therapy; VF = ventricular fibrillation; VT = ventricular tachycardia. [a]Symptomatic = NYHA Class II-IV. [b]HFrEF = LVEF <40%. [c]If ACE inhibitor not tolerated/contra-indicated, use ARB. [d]If MR antagonist not tolerated/contra-indicated, use ARB. [e]With a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP > 250 pg/ml or NTproBNP > 500 pg/ml in men and 750 pg/ml in women). [f]With an elevated plasma natriuretic peptide level (BNP ≥ 150 pg/mL or plasma NT-proBNP ≥ 600 pg/mL, or if HF hospitalization within recent 12 months plasma BNP ≥ 100 pg/mL or plasma NT-proBNP ≥ 400 pg/mL). [g]In doses equivalent to enalapril 10 mg b.i.d. [h]With a hospital admission for HF within the previous year. [i]CRT is recommended if QRS ≥ 130 msec and LBBB (in sinus rhythm). [j]CRT should/may be considered if QRS ≥ 130 msec with non-LBBB (in a sinus rhythm) or for patients in AF provided a strategy to ensure bi-ventricular capture in place (individualized decision). For further details, see Sections 7 and 8 and corresponding web pages.

Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
An ACE-I[d] is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A	2, 163–165
A beta-blocker is recommended, in addition an ACE-I[d], for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A	167–173
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I[d] and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A	174, 175

ACEI = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Or ARB if ACEI is not tolerated/contraindicated

Hintergrundinformationen:

7.2.1 Angiotensin-converting enzyme inhibitors

ACEIs have been shown to reduce mortality and morbidity in patients with HFrEF [2,5,163 – 165] and are recommended unless contraindicated or not tolerated in all symptomatic patients. ACEIs should be up-titrated to the maximum tolerated dose in order to achieve adequate inhibition of the renin–angiotensin–aldosterone system (RAAS). There is evidence that in clinical practice the majority of patients receive suboptimal doses of ACEI. [166] ACEIs are also recommended in patients with asymptomatic LV systolic dysfunction to reduce the risk of HF development, HF hospitalization and death.

7.2.2 Beta-blockers

Beta-blockers reduce mortality and morbidity in symptomatic atients with HFrEF, despite treatment with an ACEI and, in most cases, a diuretic, [167,168,170,172,173] but have not been tested in congested or decompensated patients. There is consensus that beta-blockers and ACEIs are complementary, and can be started together as soon as the diagnosis of HFrEF is made.

There is no evidence favouring the initiation of treatment with a beta-blocker before an ACEI has been started. [176] Betablockers should be initiated in clinically stable patients at a low dose and gradually up-titrated to the maximum tolerated dose. In patients admitted due to acute HF (AHF) beta-blockers should be cautiously initiated in hospital, once the patient is stabilized.

An individual patient data meta-analysis of all the major betablocker trials in HFrEF has shown no benefit on hospital admissions and mortality in the subgroup of patients with HFrEF who are in AF. [177] However, since this is a retrospective subgroup analysis, and because beta-blockers did not increase the risk, the guideline committee decided not to make a separate recommendation according to heart rhythm. Beta-blockers should be considered for rate control in patients with HFrEF and AF, especially in those with high heart rate (see Section 10.1 for details).

Beta-blockers are recommended in patients with a history of myocardial infarction and asymptomatic LV systolic dysfunction to reduce the risk of death (see Section 6).

7.2.3 Mineralocorticoid/aldosterone receptor antagonists

MRAs (spironolactone and eplerenone) block receptors that bind aldosterone and, with different degrees of affinity, other steroid hormone (e.g. corticosteroids, androgens) receptors. Spironolactone or eplerenone are recommended in all symptomatic patients (despite treatment with an ACEI and a beta-blocker) with HFrEF and LVEF ≤35%, to reduce mortality and HF hospitalization. [174,175]

Caution should be exercised when MRAs are used in patients with impaired renal function and in those with serum potassium levels 5.0 mmol/L. Regular checks of serum potassium levels and renal function should be performed according to clinical status.

Referenzen:
2. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429–1435.
5. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–691.163. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995; 273:1450–1456.
164. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF, Ryde´n L, Thygesen K, Uretsky BF, ATLAS Study Group. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation 1999;100:2312–2318.
165. SOLVD Investigattors. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325: 293–302.
166. Maggioni AP, Anker SD, Dahlstro¨m U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozdz J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12 440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2013;15:1173–1184.
167. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, ElAllaf D, Vı´tovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Ja´nosi A, Thorgeirsson G, Dunselman PH, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P. MERIT-HF Study Group. Effects of controlled-release metoprolol on total mortality, hospitalizations, and wellbeing in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure (MERIT-HF). JAMA 2000;283:1295–1302.
168. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–1658.
170. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353:2001–2007.
172. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9–13.
173. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Bo¨hm M, Anker SD, Thompson SG, Poole-Wilson PA, SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26:215–225.
174. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709–717.
175. Zannad F, McMurray JJV, Krum H, Van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11–21.
177. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JGF, Lip GYH, Coats AJS, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD. Efficacy of b blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet 2014; 384:2235–2243.

7.3 Other treatments recommended in selected symptomatic patients with heart failure with reduced ejection fraction

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

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

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; bpm = beats per minute; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; PUFA = polyunsaturated fatty acid. OMT = optimal medical therapy (for HFrEF this mostly comprises an ACEI or sacubitril/valsartan, a beta-blocker and an MRA).
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Patient should have elevated natriuretic peptides (plasma BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL, or if HF hospitalization within the last 12 months, plasma BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL) and able to tolerate enalapril 10 mg b.i.d.
[e]Applies only to preparation studied in cited trial.

Hintergrundinformationen:

7.3.1 Diuretics

Diuretics are recommended to reduce the signs and symptoms of congestion in patients with HFrEF, but their effects onmortality and morbidity have not been studied in RCTs. A Cochrane meta-analysis has shown that in patients with chronic HF, loop and thiazide diuretics appear to reduce the risk of death and worsening HF compared with placebo, and compared with an active control, diuretics appear to improve exercise capacity. [178,179] Loop diuretics produce a more intense and shorter diuresis than thiazides, although they act synergistically and the combination may be used to treat resistant oedema. However, adverse effects are more likely and these combinations should only be used with care. The aim of diuretic therapy is to achieve and maintain euvolaemia with the lowest achievable dose. The dose of the diuretic must be adjusted according to the individual needs over time. In selected asymptomatic euvolaemic/hypovolaemic patients, the use of a diuretic drug might be (temporarily) discontinued. Patients can be trained to self-adjust their diuretic dose based on monitoring of symptoms/signs of congestion and daily weight measurements.

7.3.2 Angiotensin receptor neprilysin inhibitor

A new therapeutic class of agents acting on the RAAS and the neutral endopeptidase system has been developed [angiotensin receptor neprilysin inhibitor (ARNI)]. The first in class is LCZ696, which is a molecule that combines the moieties of valsartan and sacubitril (neprilysin inhibitor) in a single substance. By inhibiting neprilysin, the degradation of NPs, bradykinin and other peptides is slowed. High circulating A-type natriuretic peptide (ANP) and BNP exertphysiologic effects through binding to NP receptors and the augmented generation of cGMP, thereby enhancing diuresis, natriuresis and myocardial relaxation and anti-remodelling. ANP and BNP also inhibit renin and aldosterone secretion. Selective AT1-receptor blockade reduces vasoconstriction, sodium and water retention and myocardial hypertrophy.[187,188]

A recent trial investigated the long-term effects of sacubitril/valsartan compared with an ACEI (enalapril) on morbidity and mortality in patients with ambulatory, symptomatic HFrEF with LVEF ≤40% (this was changed to ≤35% during the study), elevated plasma NP levels (BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL or, if they had been hospitalized for HF within the previous 12 months, BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL), and an estimated GFR (eGFR) ≥30 mL/min/1.73 m2 of body surface area, who were able to tolerate separate treatments periods with enalapril (10 mg b.i.d.) and sacubitril/valsartan (97/103 mg b.i.d.) during a run-in period. [162] In this population, sacubitril/valsartan (97/ 103 mg b.i.d.) was superior to ACEI (enalapril 10mg b.i.d.) in reducing hospitalizations for worsening HF, cardiovascular mortality and overall mortality.162 Sacubitril/valsartan is therefore recommended in patients with HFrEF who fit this profile,

Despite the superiority of sacubitril/valsartan over enalapril in the PARADIGM-HF trial, some relevant safety issues remain when initiating therapy with this drug in clinical practice. Symptomatic hypotension was more often present in the sacubitril/ valsartan group (in those ≥75 years of age, it affected 18% in the sacubitril/valsartan group vs. 12% in the enalapril group), although there was no increase in the rate of discontinuation. [162] The risk of angioedema in the trial was reduced by recruiting only those who tolerated therapy with enalapril 10 mg b.i.d. and an sacubitril/valsartan during an active run-in phase of 5–9 weeks (it resulted in a 0.4% rate of angioedema in sacubitril/valsartan group vs. 0.2% in an enalapril group). Also, the number of African American patients, who are at a higher risk of angioedema, was relatively small in this study. To minimize the risk of angioedema caused by overlapping ACE and neprilysin inhibition, the ACEI should be withheld for at least 36 h before initiating sacubitril/valsartan. Combined treatment with an ACEI (or ARB) and sacubitril/valsartan is contraindicated. There are additional concerns about its effects on the degradation of beta-amyloid peptide in the brain, which could theoretically accelerate amyloid deposition. [189 – 191] However, a recent small 14-day study with healthy subjects showed elevation of the beta-amyloid protein in the soluble rather than the aggregable form, which if confirmed over longer time periods in patients with HFrEF may indicate the cerebral safety of sacubitril/valsartan. [192] Long-term safety needs to be addressed.

7.3.3 If-channel inhibitor

Ivabradine slows the heart rate through inhibition of the If channel in the sinus node and therefore should only be used for patients in sinus rhythm. Ivabradine reduced the combined endpoint of mortality or hospitalization for HF in patients with symptomatic HFrEF or LVEF ≤35%, in sinus rhythm and with a heart rate ≥70 beats per minute (bpm) who had been hospitalized for HF within the previous 12 months, receiving treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose), an ACEI (or ARB) and an MRA. [180] The European Medicines Agency (EMA) approved ivabradine for use in Europe in patients with HFrEF with LVEF ≤35% and in sinus rhythm with a resting heart rate ≥75 bpm, because in this group ivabradine conferred a survival benefit [193] based on a retrospective subgroup analysis requested by the EMA.

7.3.4 Angiotensin II type I receptor blockers

ARBs are recommended only as an alternative in patients intolerant of an ACEI.182 Candesartan has been shown to reduce cardiovascular mortality.[182] Valsartan showed an effect on hospitalization for HF (but not on all-cause hospitalizations) in patients with HFrEF receiving background ACEIs. [194] The combination of ACEI/ARB for HFrEF was reviewed by the EMA, which suggested that benefits are thought to outweigh risks only in a select group of patients with HFrEF in whom other treatments are unsuitable. Therefore, ARBs are indicated for the treatment of HFrEF only in patients who cannot tolerate an ACEI because of serious side effects. The combination of ACEI/ARB should be restricted to symptomatic HFrEF patients receiving a beta-blocker who are unable to tolerate an MRA, and must be used under strict supervision.

7.3.5 Combination of hydralazine and isosorbide dinitrate

There is no clear evidence to suggest the use of this fixed-dose combination therapy in all patients with HFrEF. Evidence on the clinical utility of this combination is scanty and comes from one relatively small RCT conducted exclusively in men and before ACEIs or beta-blockers were used to treat HF. [184] A subsequent RCT conducted in self-identified black patients (defined as being of African descent) showed that addition of the combination of hydralazine and isosorbide dinitrate to conventional therapy (ACEI, beta-blocker and MRA) reduced mortality and HF hospitalizations in patients with HFrEF and NYHA Classes III–IV. [183] The results of this study are difficult to translate to patients of other racial or ethnic origins. Additionally, a combination of hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither ACEI nor ARB (or they are contraindicated) to reduce mortality. However, this recommendation is based on the results of the Veterans Administration Cooperative Study, which recruited symptomatic HFrEF patients who received only digoxin and diuretics. [184]

Referenzen:

178. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. Cochrane Database Syst Rev 2012;2:CD003838.
179. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomized controlled trials. Int J Cardiol 2002;82:149–158.
180. Swedberg K, Komajda M, Bo¨hm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875–885.
184. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, Goldman S, Cobb FR, Shah PM, Saunders R, Fletcher RD, Loeb HS, Hughes VC, Baker B. Effect of vasodilator therapy on mortality in chronic congestive heart failure. N Engl J Med 1986; 314:1547–1552.

187. King JB, Bress AP, Reese AD, Munger MA. Neprilysin inhibition in heart failure with reduced ejection fraction: a clinical review. Pharmacother J Hum Pharmacol Drug Ther 2015;35:823–837.
188. Mangiafico S, Costello-Boerrigter LC, Andersen IA, Cataliotti A, Burnett JC. Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. Eur Heart J 2013;34:886–893.
189. Vodovar N, Paquet C, Mebazaa A, Launay J-M, Hugon J, Cohen-Solal A. Neprilysin, cardiovascular, and Alzheimer's diseases: the therapeutic split? Eur Heart J 2015;36:902–905.
190. Yasojima K, McGeer EG, McGeer PL. Relationship between beta amyloid peptide generating molecules and neprilysin in Alzheimer disease and normal brain. Brain Res 2001;919:115–121.
191. Vepsalainen S, Helisalmi S, Mannermaa A, Pirttila T, Soininen H, Hiltunen M, Vepsa¨la¨inen S, Helisalmi S, Mannermaa A, Pirttila¨ T, Soininen H, Hiltunen M. Combined risk effects of IDE and NEP gene variants on Alzheimer disease. J Neurol
Neurosurg Psychiatry 2009;80:1268–1270.
192. Langenickel TH, Tsubouchi C, Ayalasomayajula S, Pal P, Valentin M-A, Hinder M, Jhee S, Gevorkyan H, Rajman I. The effect of LCZ696 on amyloid-b concentrations in cerebrospinal fluid in healthy subjects. Br J Clin Pharmacol 2015 Dec 12. doi:10.1111/bcp.12861 [Epub ahead of print]
193. Bo¨hm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J, Reil J-C, Swedberg K, Tavazzi L. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the
SHIFT study. Clin Res Cardiol 2013;102:11–22.
194. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667–1675.

7.4 Other treatments with less certain benefits in symptomatic patients with heart failure with reduced ejection fraction

This section describes treatments that have shown benefits in terms of symptomatic improvement, reduction in HF hospitalizations or both, and are useful additional treatments in patients with HFrEF.

7.4.1 Digoxin and other digitalis glycosides

Digoxin may be considered in patients in sinus rhythm with symptomatic HFrEF to reduce the risk of hospitalization (both all-cause and HF hospitalizations), [185] although its effect on top of betablockers has never been tested. The effects of digoxin in patients with HFrEF and AF have not been studied in RCTs, and recent studies have suggested potentially higher risk of events (mortality and HF hospitalization) in patients with AF receiving digoxin. [195,196] However, this remains controversial, as another recent meta-analysis concluded on the basis of non-RCTs that digoxin has no deleterious effect on mortality in patients with AF and concomitant HF, most of whom had HFrEF.[197]

In patients with symptomatic HF and AF, digoxin may be useful to slow a rapid ventricular rate, but it is only recommended for the treatment of patients with HFrEF and AF with rapid ventricular rate when other therapeutic options cannot be pursued. [196,198 – 201] Of note, the optimal ventricular rate for patients with HF and AF has not been well established, but the prevailing evidence suggests that strict rate control might be deleterious. A resting ventricular rate in the range of 70– 90 bpm is recommended based on current opinion, although one trial suggested that a resting ventricular rate of up to 110 bpm might still be acceptable.[202] This should be tested and refined by further research.

Digitalis should always be prescribed under specialist supervision. Given its distribution and clearance, caution should be exerted in females, in the elderly and in patients with reduced renal function. In the latter patients, digitoxin should bepreferred.

Referenzen:

185. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525–533. ESC Guidelines 2199 Downloaded from https://academic.oup.com/eurheartj/article-abstract/37/27/2129/1748921 by Charité - Med. Bibliothek user on 31 May 2019
195. Ouyang A-J, Lv Y-N, Zhong H-L,Wen J-H,Wei X-H, Peng H-W, Zhou J, Liu L-L. Meta-analysis of digoxin use and risk of mortality in patients with atrial fibrillation. Am J Cardiol 2015;115:901–906.
196. Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. Eur Heart J 2015;36:1831–1838.
197. Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GYH, Steeds RP, Townend J, Kotecha D. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. BMJ 2015; 351:h4451.
198. Van Gelder IC, Groenveld HF, Crijns HJGM, Tuininga YS, Tijssen JGP, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkie R, Bosker HA, Van Veldhuisen DJ, Van den Berg MP, RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010;362:1363–1373.
199. Bavishi C, Khan AR, Ather S. Digoxin in patients with atrial fibrillation and heart failure: a meta-analysis. Int J Cardiol 2015;188:99–101.
200. Freeman JV, Reynolds K, Fang M, Udaltsova N, Steimle A, Pomernacki NK, Borowsky LH, Harrison TN, Singer DE, Go AS. Digoxin and risk of death in adults with atrial fibrillation: the ATRIA-CVRN Study. Circ Arrhythmia Electrophysiol 2015; 8:49–58.
201. Washam JB, Stevens SR, Lokhnygina Y, Halperin JL, Breithardt G, Singer DE, Mahaffey KW, Hankey GJ, Berkowitz SD, Nessel CC, Fox KAA, Califf RM, Piccini JP, Patel MR. Digoxin use in patients with atrial fibrillation and adverse cardiovascular outcomes: a retrospective analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). Lancet 2015;385:2363–2370.

202. Mulder BA, Van Veldhuisen DJ, Crijns HJGM, Tijssen JGP, Hillege HL, Alings M, Rienstra M, Groenveld HF, Van den Berg MP, Van Gelder IC, RACE II investigators. Lenient vs. strict rate control in patients with atrial fibrillation and heart failure: a post-hoc analysis of the RACE II study. Eur J Heart Fail 2013;15:1311–1318.

9. Treatment of heart failure with preserved ejection fraction

Patients with **HFmrEF** have generally been included in trials of HFpEF. Accordingly, the guidance in this section applies to patients with both HFmrEF and HFpEF. As new data and analyses become available, it might be possible to make recommendations for each phenotype separately.

In clinical practice and clinical trials, compared with HFrEF patients, only slightly fewer patients with HFpEF and HFmrEF currently appear to receive diuretics, beta-blockers, MRAs and ACEIs or ARBs. [166,300–302] This may reflect treatment of cardiovascular co-morbidities, such as hypertension, CAD and AF, or extrapolation of results from trials conducted for these conditions showing a reduction in new-onset HF, [127] or failure to distinguish between guideline recommendations for HFrEF and HFmrEF/HFpEF or a belief that existing clinical trials provide some evidence of benefit with these agents. The pathophysiology underlying HFpEF and HFmrEF is heterogeneous, and they are associated with different phenotypes including diverse concomitant cardiovascular diseases (e.g. AF, arterial hypertension, CAD, pulmonary hypertension) and non-cardiovascular diseases [diabetes, chronic kidney disease (CKD), anaemia, iron deficiency, COPD and obesity]. [303,304] Compared with HFrEF patients, hospitalizations and deaths in patients with HFmrEF/HFpEF are more likely to be non-cardiovascular. [305,306] Therefore patients should be screened for cardiovascular and non-cardiovascular comorbidities, which if present should be managed with interventions that have been shown to improve symptoms, well-being or outcome related to that co-morbidity and not to exacerbate HF.

No treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with HFpEF or HFmrEF. However, since these patients are often elderly and highly symptomatic, and often have a poor quality of life, [307] an important aim of therapy may be to alleviate symptoms and improve well-being. [308]

Recommendations for treatment of patients with heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C	
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B	178, 179

HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Hintergrundinformationen:

9.1 Effect of treatment on symptoms in heart failure with preserved ejection fraction

Diuretics will usually improve congestion, if present, thereby improving symptoms and signs of HF. The evidence that diuretics improve symptoms is similar across the spectrum of LVEF. [178,179] Evidence that beta-blockers and MRAs improve symptoms in these patients is lacking. There is inconsistent evidence for an improvement in symptoms in those treated with ARBs (only for candesartan was there an improvement in NYHA class) [309,310] and ACEIs. [311]

9.2 Effect of treatment on hospitalization for heart failure in heart failure with preserved ejection fraction

For patients in sinus rhythm, there is some evidence that nebivolol, [173,312,313] digoxin, [314] spironolactone [301] and candesartan [310] might reduce HF hospitalizations. For patients in AF, beta-blockers do not appear to be effective and digoxin has not been studied. The evidence in support of either ARBs [315] or ACEIs [311] is inconclusive.

9.3 Effect of treatment on mortality in heart failure with preserved ejection fraction

Trials of ACEIs, ARBs, beta-blockers and MRAs have all failed to reduce mortality in patients with HFpEF or HFmrEF. However, in older patients with HFrEF, HFpEF or HFmrEF, nebivolol reduced the combined endpoint of death or cardiovascular hospitalization,173,312 with no significant interaction between treatment effect and baseline LVEF. [313]

9.4 Other considerations

Patients in AF should receive an anticoagulant to reduce the risk of thromboembolic events (for details, see the ESC guidelines of AF [316]. Antiplatelet agents are ineffective for this purpose. Renal dysfunction, which is common in this population, may contraindicate or increase the risk of haemorrhage with NOACs.

The optimal ventricular rate in patients with HFmrEF/HFpEF and AF is uncertain, and aggressive rate control might be deleterious. Whether digoxin, beta-blockers or rate-limiting CCBs, or a combination of these, should be preferred is unknown. Verapamil or diltiazem should not be combined with a beta-blocker. There are insufficient data to recommend ablation strategies (either pulmonary venous or AV node) for HFpEF and HFmrEF. Circumstantial evidence suggests that treating hypertension, often predominantly systolic, is important in HFmrEF/HFpEF. [127,317]

Diuretics, ACEIs, ARBs and MRAs all appear appropriate agents, but beta-blockers may be less effective in reducing SBP. A recent study suggests that patients with hypertension and HFpEF or HFmrEF should not receive an ARB (olmesartan) if they are receiving ACEIs and beta-blockers. [318]

The first-line oral hypoglycaemic drug for patients with HFpEF and HFmrEF should be metformin [319] Recently, a trial of empagliflozin showed a reduction in blood pressure and body weight, probably by inducing glycosuria and osmotic diuresis. Its use was associated with a reduction in hospitalization for HF and in cardiovascular mortality.[130] However, aggressive management of dysglycaemia may be harmful. [153,320]

Myocardial ischaemia may contribute to symptoms, morbidity and mortality and should be considered when assessing patients. However, there is only anecdotal evidence that revascularization improves symptoms or outcome. Patients with angina should follow the same management route as patients with HFrEF. [112] Patients with HFpEF and HFmrEF have impaired exercise tolerance, commonly accompanied by an augmented blood pressure response to exercise and chronotropic incompetence. Combined endurance/resistance training appears safe for patients with HFpEF and HFmrEF and improves exercise capacity (as reflected by an increase in peak oxygen consumption), physical functioning score and diastolic function. [307,321]

Referenzen:

112. Windecker S, Kolh P, Alfonso F, Collet J-P, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–2619.
127. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887–1898.
153. Udell JA, Cavender MA, Bhatt DL, Chatterjee S, Farkouh ME, Scirica BM. Glucoselowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials. Lancet Diabetes Endocrinol 2015;3:356–366.
166. Maggioni AP, Anker SD, Dahlstro¨m U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozdz J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12 440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2013;15:1173–1184.
173. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26:215–225.
178. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. Cochrane Database Syst Rev 2012;2:CD003838.
179. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomized controlled trials. Int J Cardiol 2002;82:149–158.
300. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012; 380:1387–1395.
301. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–1392.
302. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Felker GM, Goldsmith SR, Bart BA, McNulty SE, Ibarra

JC, Lin G, Oh JK, Patel MR, Kim RJ, Tracy RP, Velazquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E, RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2013; 309:1268–1277.
303. Senni M, Paulus WJ, Gavazzi A, Fraser AG, Diez J, Solomon SD, Smiseth OA, Guazzi M, Lam CSP, Maggioni AP, Tschope C, Metra M, Hummel SL, Edelmann F, Ambrosio G, Stewart Coats AJ, Filippatos GS, Gheorghiade M, Anker SD, Levy D, Pfeffer MA, Stough WG, Pieske BM. New strategies for heart failure with preserved ejection fraction: the importance of targeted therapies for heart failure phenotypes. Eur Heart J 2014;35:2797–2815.
304. Ferrari R, Bo¨hm M, Cleland JGF, Paulus WJS, Pieske B, Rapezzi C, Tavazzi L. Heart failure with preserved ejection fraction: uncertainties and dilemmas. Eur J Heart Fail 2015;17:665–671.
307. Fukuta H, Goto T, Wakami K, Ohte N. Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. Eur J Prev Cardiol 2016; 23:78–85.
308. Lewis EF, Lamas GA, O'Meara E, Granger CB, Dunlap ME, McKelvie RS, Probstfield JL, Young JB, Michelson EL, Halling K, Carlsson J, Olofsson B, McMurray JJV, Yusuf S, Swedberg K, Pfeffer MA. Characterization of health-related quality of life in heart failure patients with preserved versus low ejection fraction in CHARM. Eur J Heart Fail 2007;9:83–91.
309. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359: 2456–2467.
310. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ V, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–781.
311. Cleland JGF, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338–2345.
312. Mulder BA, van Veldhuisen DJ, Crijns HJGM, Bo¨hm M, Cohen-Solal A, Babalis D, Roughton M, Flather MD, Coats AJS, Van Gelder IC. Effect of nebivolol on outcome in elderly patients with heart failure and atrial fibrillation: insights from SENIORS. Eur J Heart Fail 2012;14:1171–1178.
313. van Veldhuisen DJ, Cohen-Solal A, Bo¨hm M, Anker SD, Babalis D, Roughton M, Coats AJS, Poole-Wilson PA, Flather MD. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction.
J Am Coll Cardiol 2009;53:2150–2158.
314. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF, Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial.
Circulation 2006;114:397–403.
315. McMurray JJ V, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362:767–771.
316. Kirchof P, Benussi S et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016. doi: 10.1093/ eurheartj/ehw210. Forthcoming.
317. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;34:2159–2219.
318. Sakata Y, Shiba N, Takahashi J, Miyata S, Nochioka K, Miura M, et al. Clinical impacts of additive use of olmesartan in hypertensive patients with chronic heart failure: the supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial. Eur Heart J 2015;36:915–923.
319. Ryde´n L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2013;34:3035–3087.
320. Gilbert RE, Krum H. Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy. Lancet 2015;385:2107–2117.
321. Edelmann F, Gelbrich G, Dungen H-D, Fro¨hling S, Wachter R, Stahrenberg R, Binder L, To¨pper A, Lashki DJ, Schwarz S, Herrmann-Lingen C, Loffler M, Hasenfuss G, Halle M, Pieske B. Exercise training improves exercise capacity

Web Table 9.1 **Phase II and III clinical trials performed in patients with heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction**

Trial	Intervention	Major inclusion criteria	Mean follow-up	Primary endpoints
PEP-CHF[320]	Perindopril vs placebo.	LV wall motion index ≥1.4 (corresponding to LVEF ≥40%), symptomatic HF treated with diuretic, diastolic dysfunction in echocardiography, age ≥70 y.	2.1 y	No difference in combined all-cause mortality or cardiovascular hospitalization (36% vs 37%, P =0.35).
I-PRESERVE [318]	Irbesartan vs placebo.	LVEF ≥45%, NYHA III–IV with corroborative evidence, or NYHA II with HF hospitalization in recent 6 months, age ≥60 y.	4.1 y	No difference in combined all-cause mortality or HF hospitalization (24% vs 25%, P =0.54).
CHARM-Preserved[319]	Candesartan vs placebo.	LVEF >40%, NYHA II–IV, history of cardiac hospitalization.	3.0 y	Trend towards a reduction in combined cardiovascular mortality or HF hospitalization by 11% (22% vs 24%, unadjusted P =0.12, adjusted P =0.051).
Aldo-DHF[330]	Spironolactone vs placebo.	LVEF ≥50%, NYHA II–III, peak VO_2 ≤25 mL/min/kg, diastolic dysfunction on echocardiography or atrial fibrillation, age ≥50 y.	1.0 y	Reduction in E/e' by – 1.5 (P < 0.001) No change in peak VO_2 (P =0.81).
TOPCAT[310]	Spironolactone vs placebo.	LVEF ≥45%, ≥1 HF sign, ≥1 HF symptom, HF hospitalization within recent 12 months, or BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL, age ≥50 y.	3.3 y	No difference in combined cardiovascular death, aborted cardiac arrest, or HF hospitalization (19% vs 20%, P =0.14).
SENIORS[173]	Nebivolol vs placebo.	HF confirmed as HF hospitalization in recent 12 months and/or LVEF ≤35% in recent 6 months, age ≥70 y, 36% with LVEF >35%.	1.8 y	Reduction in combined all-cause mortality or cardiovascular hospitalization by 14% (31% vs 35%, P =0.04).
DIG-PEF[323]	Digoxin vs placebo.	HF with LVEF >45%, sinus rhythm.	3.1 y	No difference in combined HF mortality or HF hospitalization (21% vs 24%, P =0.14)
PARAMOUNT[309]	Sacubitril/ valsartan vs valsartan.	HF with LVEF ≥45%, NYHA II-III, NT-proBNP >400 pg/mL.	12 w	Reduction in NT-proBNP: ratio of change sacubitril/ valsartan 0.77, 95% CI 0.64–0.92 (P =0.005).
RELAX[311]	Sildenafil vs placebo.	HF with LVEF ≥45%, NYHA II-IV, peak VO_2 <60% of reference values, NT-proBNP >400 pg/mL or high LV filling pressures.	24 w	No change in peak VO_2 (P =0.90).

Aldo-DHF = Aldosterone Receptor Blockade in Diastolic Heart Failure; BNP = B-type natriuretic peptide; CHARM-Preserved = Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality; DIG-PEF = ancillary Digitalis Investigation Group trial; HF = heart failure; I-PRESERVE = Irbesartan in Heart Failure with Preserved Ejection Fraction Study; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; PARAMOUNT = LCZ696 Compared to Valsartan in Patients With Chronic Heart Failure and Preserved Left-ventricular Ejection Fraction; Peak VO_2 = peak oxygen uptake; PEP-CHF = Perindopril in Elderly People with Chronic Heart Failure; RELAX = Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure; SENIORS = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisations in Seniors with Heart Failure; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; w = week; y = year.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 3 of 12, March 2020) am 26.03.2020

#	Suchfrage
1	MeSH descriptor: [Heart Failure] explode all trees
2	((cardiac OR heart OR myocardial) NEAR/3 (failure* OR decompensat*)):ti
3	(HFrEF):ti,ab,kw OR (HFmrEF):ti,ab,kw
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from Mar 2015 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 26.03.2020

#	Suchfrage
1	"heart failure/therapy"[MeSH Major Topic]
2	((cardiac[ti] OR heart[ti] OR myocardial[ti]) AND (failure*[ti] OR decompensat*[ti]))
3	HFrEF[tiab] OR HFmrEF[tiab]
4	((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
5	(#2 OR #3) AND #4
6	#1 OR #5
7	(#6) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND

	(search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
8	(#7) AND ("2015/03/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT "The Cochrane database of systematic reviews"[Journal]
10	(#9) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 26.03.2020

#	**Suchfrage**
1	heart failure[MeSH Major Topic]
2	((cardiac[ti] OR heart[ti] OR myocardial[ti]) AND (failure*[ti] OR decompensat*[ti]))
3	HFrEF[tiab] OR HFmrEF[tiab]
4	(#1 OR #2 OR #3)
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(#5) AND ("2015/03/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Referenzen

1. **Al-Gobari M, Al-Aqeel S, Gueyffier F, Burnand B.** Effectiveness of drug interventions to prevent sudden cardiac death in patients with heart failure and reduced ejection fraction: an overview of systematic reviews. BMJ Open 2018;8(7):e021108.

2. **Beldhuis IE, Streng KW, Ter Maaten JM, Voors AA, van der Meer P, Rossignol P, et al.** Renin-Angiotensin system inhibition, worsening renal function, and outcome in heart failure patients with reduced and preserved ejection fraction: a meta-analysis of published study data. Circ Heart Fail 2017;10(2).

3. **Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF).** Nationale VersorgungsLeitlinie Chronische Herzinsuffizienz, Langfassung, 3. Auflage [online]. AWMF-Registernummer nvl-006. Berlin (GER): Ärztliches Zentrum für Qualität in der Medizin; 2019. [Zugriff: 27.03.2020]. URL: https://www.leitlinien.de/mdb/downloads/nvl/herzinsuffizienz/herzinsuffizienz-3aufl-vers1-lang.pdf.

4. **Burnett H, Earley A, Voors AA, Senni M, McMurray JJ, Deschaseaux C, et al.** Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: a network meta-analysis. Circ Heart Fail 2017;10(1).

5. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie des Gemeinsamen Bundesausschusses über die ambulante Behandlung im Krankenhaus nach § 116b SGB V: Anlage 3 Erkrankungen mit besonderen Krankheitsverläufen im Katalog gem. § 116b Abs. 3 SGB V; zuletzt geändert am 15. Dezember 2011 [online]. Berlin (GER): G-BA; 2011. [Zugriff: 27.03.2020]. URL: https://www.g-ba.de/downloads/62-492-576/ABK-RL_2011-12-15_WZ-Seite-38_39_43-45_63_rot.pdf.

6. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie des Gemeinsamen Bundesausschusses zur Erprobung der Messung und des Monitorings des pulmonalarteriellen Drucks mittels implantierten Sensors zur Therapieoptimierung bei Herzinsuffizienz im Stadium NYHA III (MM-pul-art-Druck-Herzinsuff); zuletzt geändert am 21. Februar 2019 [online]. Berlin (GER): G-BA; 2019. [Zugriff: 27.03.2020]. URL: https://www.g-ba.de/downloads/62-492-1812/Erp-RL_MM-pul-art-Druck-Herzinsuff_2019-02-21_iK-2019-05-04.pdf.

7. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Absatz 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL); zuletzt geändert am 27. März 2020 [online]. Berlin (GER): G-BA; 2020. [Zugriff: 27.03.2020]. URL: https://www.g-ba.de/downloads/62-492-1788/DMP-A-RL_2019-01-17_iK-2019-04-01.pdf.

8. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. Juni 2016 - Sacubitril/Valsartan [online]. Berlin (GER): GBA; 2016. [Zugriff: 07.04.2020]. URL: https://www.g-ba.de/downloads/91-1385-213/2016-06-16_Geltende-Fassung_Sacubutril_Valsartan_D-207.pdf.

9. **Hartmann C, Bosch NL, de Aragao Miguita L, Tierie E, Zytinski L, Baena CP.** The effect of ivabradine therapy on heart failure patients with reduced ejection fraction: a systematic review and meta-analysis. Int J Clin Pharm 2018;40(6):1443-1453.

10. **National Guideline Centre, National Institute for Health and Care Excellence (NICE).** Chronic heart failure in adults: Diagnosis and management [online]. London (GBR): NICE; 2018. [Zugriff: 27.03.2020]. (NICE Guideline; Band 106). URL: https://www.nice.org.uk/guidance/ng106/evidence/full-guideline-pdf-6538850029.

11. **Pei H, Miao W, Xie WZ, Wang W, Zhao D, Su GH, et al.** Ivabradine improves cardiac function and increases exercise capacity in patients with chronic heart failure. Int Heart J 2019;60(4):899-909.

12. **Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al.** 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Rev Esp Cardiol (Engl Ed) 2016;69(12):1167.

13. **Scottish Intercollegiate Guidelines Network (SIGN).** Management of chronic heart failure: A national clinical guideline [online]. Edinburgh (GBR): SIGN; 2016. [Zugriff: 27.03.2020]. (SIGN Publication; Band 147). URL: https://www.sign.ac.uk/assets/sign147.pdf.

14. **Scottish Intercollegiate Guidelines Network (SIGN).** Management of chronic heart failure: SIGN 147 (2014) [online]. SIGN Publication: 3-year scoping report. Edinburgh (GBR): SIGN; 2019. [Zugriff: 27.03.2020]. URL: https://www.sign.ac.uk/assets/sign147_scoping_report.pdf.

15. **Stollberger C, Schneider B.** Concerns about the ESC heart failure guidelines. Int J Cardiol 2017;228:707-708.

16. **Tai C, Gan T, Zou L, Sun Y, Zhang Y, Chen W, et al.** Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular events in patients with heart failure: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord 2017;17(1):257.

17. **Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr., Drazner MH, et al.** 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62(16):e147-239.

18. **Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, et al.** 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Card Fail 2017;23(8):628-651.

Anhang

Al Gobari M et al, 2018 [1].

Abbildung 1: Summary of characteristics of included studies of HF

Table 1 Summary of characteristics of included studies of HF (ordered by intervention)

Author (year), country	Review type	Intervention/comparator	Population type; ejection fraction (%); NYHA	Study design n; participants n	Mean follow-up/ range (months)	Authors' findings summary	AMSTAR score
Al-Gobari *et al* (2013), France[16]*	Systematic review and meta-analysis.	Beta-blockers/placebo; 'usual care'.	HF; <45% except one study <62%; I–IV.	RCTs n=30; n=24 779.	Mean: 11.51.	Beta-blockers significantly reduced SCD, cardiovascular death and all-cause mortality.	6
Chatterjee *et al* (2013), USA[15]	Systematic review and meta-analysis.	Beta-blockers/placebo; beta-blocker; 'usual care'.	HF; <45%; II–IV.	RCTs n=21; n=23 122.	Median: 12.	The study confirmed mortality benefits of BBs compared with placebo or usual care in HF with reduced ejection fraction.	8
Brophy *et al* (2001), Canada[17]	Meta-analysis.	Beta-blockers/placebo; 'usual care'.	CHF; <45%; I–IV.	RCTs n=22; n=10 135.	Range: 3–23.	This study reported a reduction in mortality and morbidity in CHF.	4
Lee *et al* (2001), USA[18]	Systematic review and meta-analysis.	Beta-blockers/placebo.	HF; <30%; II–III.	RCTs n=6; n=9335.	Range : 12–23.	The authors recommended use of beta-blockers in HF with reduced ejection fraction and NYHA II–III.	4
Bonet *et al* (2000), USA[19]	Meta-analysis.	Beta-blockers/placebo; 'usual care'.	HF; <45%; NA.	RCTs n=21; n=5849.	Median: 6.	Beta-blockers reduce total mortality by reducing pump failure and SCD events. Vasodilating beta-blockers have perhaps greater effects on overall mortality than non-vasodilating agents.	4
Heidenreich *et al* (1997), USA[20]	Meta-analysis.	Beta-blockers/placebo; 'usual care'.	HF; <30%; I–IV	RCTs n=17; n=3039.	Range: 3–24.	Beta-blockers significantly reduced all-cause mortality but showed a trend towards better reduction in non-SCD compared with SCD.	5
Le *et al* (2016), France[21]*	Systematic review and meta-analysis.	Anti-aldosterone/placebo; 'usual care'.	HF, post-MI; <40%–>50%; I–IV.	RCTs n=25; n=19 333.	Range: 3–39.6.	In HF, antialdosterones or mineralocorticoid receptor blockers reduced SCD (subgroup analysis: 5 RCTs), all-cause mortality (subgroup analysis: 10 RCTs) and cardiovascular, all-cause and cardiovascular hospitalisation. Adverse effects (hyperkalaemia, degradation of renal function and gynaecomastia) were, however, significantly higher in the treated group compared with placebo.	7
Bapoje *et al* (2013), USA[54]	Systematic review and meta-analysis.	Antialdosterone/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=8; n=11 875.	Range: 3–24.	Mineralocorticoid receptor antagonists (or aldosterone antagonists) reduced the risk of SCD in patients with left ventricular dysfunction.	8
Wei *et al* (2010), China[22]	Meta-analysis.	Antialdosterone/placebo; 'usual care'.	HF; <45%; NA.	RCTs n=6 (two are not double blind); n=00 000.	Range: 2–24.	Two [67 68] of the six included studies showed a significant reduction of SCD in the group of spironolactone versus placebo and the group of eplerenone versus placebo cited respectively.	5
Solomon *et al* (2016), USA[23]*	Meta-analysis.	Sacubitril; valsartan/ACE-i.	HF; <30%; II–IV.	RCTs n=3; n=14 742.	Range: 6–27.	The authors concluded that combined neprilysin/RAS inhibition reduced all-cause mortality in HFrEF.	7
Flather *et al* (2000), Canada[25]	Systematic review.	ACE-i/placebo.	CHF; post-MI <45%; NA.	RCTs n=5; n=12 763.	Range: 15–42.	This meta-analysis showed a lower risk of death in ACE-i treated group compared with placebo.	NA
Garg *et al* (1995), Canada[24]*	Systematic review and meta-analysis.	ACE-i/placebo.	CHF; <45%; I–IV.	RCTs n=32; n=7105.	Range: 3–42.	Overall, this study reported a significant reduction of total mortality (attributed mainly to less progressive HF deaths) and hospitalisation for worsening HF.	2

Table 1 Continued

Author (year), country	Review type	Intervention/comparator	Population type; ejection fraction (%); NYHA	Study design n; participants n	Mean follow-up/ range (months)	Authors' findings summary	AMSTAR score
Rain and Rada (2015), Chile[26]	Systematic review.	ARB/ACE-i.	HF; <45%–<35%; II–IV.	RCTS=8; n=5201.	NA	The authors concluded that ARBs are probably as effective in mortality reduction as ACE-i with probably less withdrawal rate due to adverse effects.	NA
Heran *et al* (2012), Canada[27]*	Systematic review and meta-analysis (Cochrane).	ARB (or ARB+ACEi)/ placebo; ACE-i.	HF; ≤40% ; II–IV.	RCTS n=24; n=25 051.	Range: 1–49.5.	Compared with placebo or in addition to ACE-i, ARBs did not reduce all-cause mortality.	10
Shibata *et al* (2008), Canada[28]	Systematic review and meta-analysis	ARB/placebo; ACE-i.	HF; <40%; I–IV.	RCTs n=7; n=27 495.	Range: 11–41.	Compared with ACE-i or used in combination, ARBs provided no beneficial effects on mortality. A 17% reduction in hospitalisations was observed.	4
Lee *et al* (2004), USA[29]	Meta-analysis.	ARB/placebo; ACE-i.	CHF, AMI; ≤45%; II–IV.	RCTs n=24; n=38 080.	Range: 1–41.	Compared with ACE-i, ARBs do not differ in efficacy for reducing all-cause mortality in CHF and AMI patients.	7
Dimopoulos *et al* (2004), UK[30]	Meta-analysis.	ARB/placebo; ACE-i.	CHF; <40%; II–IV.	RCTs n=4; n=7666.	Mean: 31.	ARBs can be used to prevent events in ACE-i-treated HF patients who are not suitable for beta-blockers.	3
Jong *et al* (2002), Canada[31]	Systematic review and meta-analysis.	ARB (or ARB+ACEi)/ placebo ; ACE-i.	HF; ≤35%–≤45%; II–IV.	RCTs n=17; n=12 469.	Range: 1–23.	The authors could not conclude any superiority of ARBs versus controls, stating this might be due to the use of ACE-i as a comparator or background treatment in the majority of included trials.	8
Rain and Rada (2017), Chile[32]	Systematic review.	Statins/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=25; n=NR.	NA	The authors summarised that statins do not decrease mortality in chronic HF and might lead to a small reduction in hospital admissions for HF.	NA
Al-Gobari *et al* (2017), Switzerland[6]*	Systematic review and meta-analysis.	Statins/placebo; 'usual care'.	HF, ischaemic/non-ischaemic; NA; I–IV NA.	RCTs n=24; n=11 463.	Range: 1–46.8.	Statins do not significantly reduced SCD and all-cause mortality. They may or may not reduce hospitalisations due to worsening HF.	7
Bonsu *et al* (2015), Malaysia[33]	Meta-analysis.	Statins/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=13; n=10 966.	Range: 3–46.8.	Lipophilic statins showed significant decrease in all-cause mortality, cardiovascular mortality and hospitalisation for worsening HF.	8
Wang *et al* (2014), China[34]	Meta-analysis.	Statins/placebo; 'usual care'.	HF; NA; NA.	RCTs n=6 (9: observational studies); n=10 016.	Range: 12–46.8.	The authors concluded that statins reduce SCD and all-cause mortality in HF.	5
Liu *et al* (2014). China[35]	Meta-analysis.	Statins/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=13; n=1532.	Range: 3–35.5.	The authors reported significant decrease in all-cause mortality but recommended cautious interpretation and further research.	7
Rahimi *et al* (2012), UK[40]	Meta-analysis.	Statins/placebo; 'usual care'.	HF, MI, primary prevention, diabetes, ACS, CHD; NA; NA.	RCTs n=37; n=155 020.		Statins have a modest effect on SCD but no substantial protective effect on ventricular arrhythmic events.	6
Zhang *et al* (2011), China[36]	Meta-analysis.	Statins/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=13; n=10 447.	Range: 2–46.8.	This meta-analysis concluded of no difference between treatment groups but benefits may occur in some specific populations and with a specific statin.	7

Table 1 Continued

Author (year), country	Review type	Intervention/comparator	Population type; ejection fraction (%); NYHA	Study design n; participants n	Mean follow-up/ range (months)	Authors' findings summary	AMSTAR score
Xu *et al* (2010), China[37]	Meta-analysis.	Statins/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=7; n=540.	Range: 3–31.	The authors suggested that atorvastatin treatment is effective and reduce all-cause mortality and hospitalisation for worsening HF.	6
Lipinski (2009), USA[38]	Meta-analysis.	Statins/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=10; n=10 192.	Range: 3–47.	The authors stated that statins are safe and improve LVEF and decrease hospitalisation for worsening HF.	7
Levantesi *et al* (2007), Italy[39]	Meta-analysis.	Statins/placebo; 'usual care'.	Secondary prevention; NA; NA.	RCTs n=10; n=22 275.	Range: 6–73.2.	Statins were associated with a significant risk reduction for SCD (in secondary prevention settings).	3
Claro *et al* (2015), Chile[41]*	Systematic review and meta-analysis (Cochrane).	Amiodarone/placebo; 'usual care'.	Subanalysis: HF; NA; NA.	RCTs n=11; n=5006.	NA	In HF subpopulation, amiodarone showed a statistically significant reduction for SCD but not for all-cause mortality. Authors judged the quality of the evidence for the whole population (primary prevention) as low to moderate and for secondary prevention population as very low.	10
Santangeli *et al* (2012), USA[42]	Systematic review.	Amiodarone/placebo.	Cardiovascular disease; NA; NA.	NA	NA	Amiodarone has less favourable net clinical benefits for prophylaxis of SCD because of adverse effects.	5
Piccini *et al* (2009), USA[43]	Meta-analysis.	Amiodarone/placebo; 'usual care'.	HF, AMI; <45%; II–IV.	RCTs n=15; n=8522.	Range: 2–12.	In HF subpopulation, amiodarone showed a statistically significant reduction for SCD but not all-cause mortality.	7
ATMA Investigators (1997)[44]	Meta-analysis.	Amiodarone/placebo; 'usual care'.	Post-MI and CHF; 31%; NA.	NA	Range: 4.8–25.8.	Amiodarone reduced arrhythmic/sudden death in high-risk patients with recent MI or CHF. All-cause mortality decreased by 13%.	NA
Sim *et al* (1997), USA[45]	Meta-analysis	Amiodarone/placebo; 'usual care'.	Subgroup: HF;<45%; NA.	RCTs n=5; n=4125.	Range: 6–45.6.	Amiodarone reduced all-cause mortality in high SCD risk groups.	5
Das *et al* (2010), USA[46]	Narrative review.	Antiarrhythmics/placebo; 'usual care'.	Subgroup: HF; NA; NA.	NA	NA	Class I antiarrhythmic drugs (AADs) increased all-cause mortality and SCD in post-MI patients. Amiodarone (class III AADs) decreased or have neutral effect on SCD. Caution is warranted to outweigh risks of proarrhythmia and other adverse effects.	NA
Hilleman *et al* (2001), USA[47]	Narrative review.	Antiarrhythmics/placebo; 'usual care'.	HF; <45%; NA.	RCTs n=6; n=10 440.	Range: 6.5–45.	Beta-blockers (bisoprolol, carvedilol and metoprolol) reduced total mortality and SCD in HF. Class I antiarryhthmics increased mortality and SCD in a post hoc analysis of SPAF-I study. Amiodarone had mixed results, and dofetilide did not reduce mortality or SCD.	NA
Rizos *et al* (2012), Greece[48]	systematic review and meta-analysis.	Omega 3 Fatty acids/ placebo; 'usual care'.	Cardiovascular diseases; NA; NA.	RCTs n=20; n=68 680.	NA	Omega-3 polyunsaturated fatty acids supplementation were not associated with a lower risk of all-cause mortality or SCD.	8
Kotwal *et al* (2012), Australia[49]	Systematic review and meta-analysis.	Omega 3 Fatty acids/ placebo; 'usual care'.	Cardiovascular diseases, HF admissions; NA; NA.	RCTs n=20; n=62 851.	Range: 6–72.	The authors concluded that there is no clear effect on total mortality and sudden death outcomes.	7

Table 1 Continued

Author (year), country	Review type	Intervention/comparator	Population type; ejection fraction (%); NYHA	Study design n; participants n	Mean follow-up/ range (months)	Authors' findings summary	AMSTAR score
Kwak *et al* (2012), Korea[50]	Meta-analysis.	Omega 3 fatty acids/ placebo; 'usual care'.	Secondary prevention of cardiovascular disease; NA; NA.	RCTs n=14; n=20 485.	NA	This meta-analysis concluded of insufficient evidence.	8
Chen *et al* (2011), China[51]	Meta-analysis.	Omega 3 fatty acids/ placebo; 'usual care'.	Cardiovascular disease; NA; NA.	RCTs n=10; n=33 429.	NA	Omega-3 fatty acids did not appear to reduce SCD under guideline-adjusted treatment for CVD secondary prevention.	7
Marik *et al* (2009), USA[52]	Systematic review.	Omega t3 dietary supplements/placebo; olive oil; corn oil, sunflower oil; 'usual care'.	Cardiovascular disease; NA; NA.	RCTs n=11; n=39 044.	Range: 12–55.2.	Dietary supplementation with omega-3 fatty acids reduced SCD and all-cause mortality.	4
Wang *et al* (2006), USA[53]	Systematic review.	n-3 Fatty acids/placebo/ olive oil; corn oil, sunflower oil; 'usual care'.	Primary and secondary prevention; NA; NA.	RCTs n=12; n=32 981.	Range: 12–48.	The authors concluded of a significant reduction in all-cause mortality and SCD with n-3 fatty acids from fish or fish oil supplements but not α-linolenic acid.	6

ACE-i, angiotensin-converting enzyme ACE inhibitors; ACS, acute coronary syndrome; AMI, acute myocardial infarction; AMSTAR, assessing the methodological quality of systematic reviews ; ARBs, angiotensin receptor blockers ; BBs, beta-blockers; HF, heart failure; CHD, coronary heart disease; CHF, Chronic heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; NYHA, New York Heart Association classification ; RAS, renin-angiotensin system; RCTs, randomized clinical trials; SCD, sudden cardiac death; SPAF-I, stroke prevention atrial fibrillation study

Pei H et al, 2019 [11].

Abbildung 2: Basic characteristics oft he Study

Table I. Basic Characteristics of the Study

Study	Year	Patients	Agents used	Ivabradine Dose	Follow-up duration
Komajda M	2017	CHF patients in NYHA classes II and III, in sinus rhythm, with HR ≥ 70 bpm, NT-proBNP ≥ 220 pg/mL (BNP ≥ 80 pg/mL) and LVEF ≥ 45%.	ACEI and/or ARBs: 88.4%, Beta-blockers: 74.7%, MRAs: 31.6%, Diuretic (excluding MRAs): 58.9%, CCB: 37.9%	7.5-10 mg b.i.d.	8-month
			ACEI and/or ARBs: 85.7%, Beta-blockers: 73.8%, MRAs: 26.2%, Diuretic (excluding MRAs): 70.2%, CCB: 35.7%	0	
Sisakian H	2016	Patients in NYHA classes II and III with moderate to severe CHF and pseudonormal/restrictive type of diastolic dysfunction with LVEF ≤ 40% and resting HR ≥ 70 beats per minute (bpm) in sinus rhythm	MRAs: 96.3%, ACEI and/or ARBs: 85.2%, Beta-blockers: 81.5%, Diuretic: 77.8%, Digitalis: 25.9%	2.5-7.5 mg b.i.d.	3-month
			MRAs: 92.6%, ACEI and/or ARBs: 85.2%, Beta-blockers: 77.8%, Diuretic: 70.4%, Digitalis: 22.2%	0	
Tsutsui H	2016	Japanese patients resting HR ≥ 75 bpm in sinus rhythm, CHF of NYHA class II or higher, LVEF ≤ 35%, and under optimal, stable treatment according to the Japanese Guideline for Treatment of Chronic Heart Failure (JCS 2010).	Beta-blockers: 92.9%, ACEI and/or ARBs: 70.2%, Diuretic: 84.5%, MRAs: 54.8%, Digitalis: 9.5%	2.5-5 mg b.i.d.	2-month
			Beta-blockers: 92.9%, ACEI and/or ARBs: 71.4%, Diuretic: 76.2%, MRAs: 54.4%, Digitalis: 0%	0	
Abdel-Salam Z	2015	Patients with dilated cardiomyopathy of no apparent cause, LVEF < 40%, NYHA class ≥ II, sinus HR ≥ 70 bpm, and symptomatic for at least 4 weeks.	Beta-blockers: 100%, ACEI: 100%, MRAs: 100%,	2.5-7.5 mg b.i.d.	3-month
			Beta-blockers: 100%, ACEI: 100%, MRAs: 100%,	0	
Kosmala W	2013	CHF patients with diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF), exercise capacity < 80%, E/e > 13 after exercise, and NYHA class II or III.	ACEI and/or ARBs: 97%, Beta-blockers: 57%, Diuretic: 76%, CCB: 37%, Hypoglycemic: 40%	5 mg b.i.d.	7-day
			ACEI and/or ARBs: 97%, Beta-blockers: 52%, Diuretic: 67%, CCB: 39%, Hypoglycemic: 29%	0	
Volterrani M	2011	HF at least 12 months prior to selection, NYHA functional class II to III, and clinically stable for 3 weeks. Patients were either not receiving β-blockers or were receiving beta-blockers but in combination with a suboptimal dose of ACEI.	ACEI: 93%, Diuretic (excluding MRAs): 83%, Beta-blockers: 55%, MRAs: 45%, Cardiac glycosides: 36%, ARBs: 7%	5 mg b.i.d.	3-month
			ACEI: 100%, Diuretic (excluding MRAs): 84%, Beta-blockers: 58%, MRAs: 37%, Cardiac glycosides: 32%, ARBs: 3%	0	
Mansour S	2011	CHF patients with NYHA class III or IV and LVEF < 40%, HR > 70 bpm in sinus rhythm at rest, as measured on a 12-lead ECG performed after at least a 5-minute rest.	ACEI (% of target): 66.1 ± 23.7%, Carvedilol (mg/day): 18.0 ± 13.6	5-7.5 mg b.i.d.	3-month
			ACEI (% of target): 74.0 ± 25.5%, Carvedilol (mg/day): 12.8 ± 10.0	0	
Sarullo FM	2010	Patients with documented clinical signs and symptoms of heart failure, LVEF ≤ 40%, NYHA classes II to III, and sinus rhythm with a resting HR > 70 bpm were eligible to participate.	Diuretic: 100%, ACEI: 83.3%, Beta-blockers: 56.6%, Nitrates: 46.6%, Amiodarone: 23.3%	5 mg b.i.d.	3-month
			Diuretic: 96.6%, ACEI: 86.6%, Beta-blockers: 63.3%, Nitrates: 50.0%, Amiodarone: 20.0%	0	

Table I. Basic Characteristics of the Study (continued)

Study	Year	Patients	Agents used	Ivabradine Dose	Follow-up duration
Swedberg K	2010	CHF patients with resting HR > 70 bpm in sinus rhythm, as measured on 12-lead ECG after at least a 5-minute rest, with stable symptomatic CHF of 4 or more weeks' duration, a previous admission to a hospital for worsening heart failure within the previous 12 months, and LVEF < 35%.	Beta-blockers: 89%, Diuretic (excluding MRAs): 84%, ACEI: 79%, Antialdosterone: 61%, Cardiac glycosides: 22%, ARBs: 14%	2.5-7.5 mg b.i.d.	32-month
			Beta-blockers: 90%, Diuretic (excluding MRAs): 83%, ACEI: 78%, Antialdosterone: 59%, Cardiac glycosides: 22%, ARBs: 14%	0	
Fox K	2008	Patients with CAD, LVEF < 40% and an end-diastolic short-axis internal dimension of greater than 56 mm by ECG, resting HR > 60 bpm in sinus rhythm, heart failure for at least 3 months and appropriate conventional cardiovascular medication for at least 1 month.	ACEI and/or ARBs: 89%, Beta-blockers: 83%, Diuretic (excluding MRAs): 63%, Antialdosterone: 29%,	5-7.5 mg b.i.d.	24-month
			ACEI and/or ARBs: 90%, Beta-blockers: 84%, Diuretic (excluding MRAs): 63%, Antialdosterone: 30%,	0	

CHF indicates chronic heart failure; NYHA, New York Heart Association; b.i.d., twice a day; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; ECG, electrocardiogram; E/e, peak early diastolic mitral flow velocity/peak early diastolic mitral annular velocity; ACEI, angiotensin converting enzyme inhibitors, ARB, angiotensin receptor blocker; MRAs, mineralocorticoid receptor antagonists; CCB, calcium channel blocker; and CAD, coronary artery disease.

Burnett H et al., 2017 [4].

Abbildung 3: Study design and baseline patient characteristics of included RCTs

Trial/ Author year	Study design	# centers/ location	Study duration	N	Interventions	LVEF inclusion criteria	mean LVEF (%)	% male	mean age	NYHA class 1 (%)	NYHA class 2 (%)	NYHA class 3 (%)	NYHA class 4 (%)	duration of HF (months)	Ischaemic HF (%)	Prior MI (%)
CASSIS 1995[1]	DB, MC, PC	18/ Czech and Slovak Rep	104 weeks	152 48 48	Spirapril Enalapril Placebo	≤40%	28%	83%	58	0%	25%	56%	19%	NR	70%	46%
CONSENSUS 1987[2]	DB, MC, PC	35/ Finland, Norway, Sweden	52 weeks	126 127	Enalapril Placebo	Reduced	NR	71%	70	0%	0%	0%	100%	NR	NR	48%
FEST 1995[3]	DB, MC, PC	42/ EU (8 countries)	12 weeks	155 153	Fosinopril Placebo	≤35%	26%	75%	63	0%	65%	36%	0%	NR	71%	NR
MHFT 1991[4]	DB, SC, PC	1/ Germany	2.7 years (median)	83 87	Captopril Placebo	≤35%	35%	78%	62	26%	50%	24%	0%	NR	58%	69%
SOLVD-prevent 1992[5]	DB, MC, PC	23/ US, Canada, Belgium	37.4 months (mean)	2111 2117	Enalapril Placebo	≤35%	28%	89%	59	0%	67%	33%	0%	NR	83%	80%
SOLVD-treat 1991[6]	DB, MC, PC	23/ US, Canada, Belgium	48 months	1285 1284	Enalapril Placebo	≤35%	25%	80%	61	11%	57%	30%	2%	NR	71%	66%
Beller 1995[7]	DB, MC, PC	12/ US	12 weeks	130 63	Lisinopril Placebo	<45%	28%	75%	60	0%	35%	56%	9%	36	NR	0%
Brown 1995[8]	DB, MC, PC	41/ US	24 weeks	116 125	Fosinopril Placebo	≤35%	25%	80%	62	0%	37%	54%	9%	NR	NR	NR
Chalmers 1987[9]	DB, MC, PC	13/ 10 countries	12 weeks	87 43	Lisinopril Placebo	<45%	NR	69%	58	0%	22%	65%	13%	45	NR	NR
Colfer 1992[10]	DB, MC, PC	22/ US	12 weeks	114 58	Benazepril Placebo	≤35%	25%	83%	62	0%	54%	45%	1%	48	56%	NR
Goldstein 1988[11]	DB, SC, PC	NR/ NA	26 weeks	104 100	Captopril Placebo	≤40%	25%	82%	56	4%	85%	11%	1%	35	63%	NR

Lewis 1989[12]	DB, MC, PC	13/ AUS, EU, SA, NA, Africa (10 countries)	12 weeks	87 43	Lisinopril Placebo	NR	38%	NR	NR	0%	22%	64%	14%	48	NR	NR
Shettigar 1999[13]	DB, MC, PC	28/ US	12 weeks	102 104	Fosinopril Placebo	≤35%	24%	75%	62	0%	39%	52%	31%	NR	43%	34%
Veldhuisen 1999[14]	DB, MC, PC	25/ Ntherlnds, Germany, Belgium	12 weeks	182 62	Imidapril Placebo	<45%	34%	77%	61	0%	77%	23%	0%	35	63%	NR
SPICE 2000[15]	DB, MC, PC	270/ NA, EU	12 weeks	179 91	Candesartan Placebo	≤35%	27%	69%	66	0%	54%	41%	6%	NR	71%	62%
STRETCH 1999[16]	DB, MC, PC	86/ Germany, Czech Rep, Slovenia	12 weeks	633 211	Candesartan Placebo	30-45%	39%	69%	62	0%	81%	19%	0%	39	NR	NR
Mitrovic 2003[17]	DB, MC, PC	EU	12 weeks	174 44	Candesartan Placebo	≤40%	28%	85%	54	0%	61%	39%	0%	40	NR	NR
ELITE I 1997[18]	DB, MC	125/ US, SA, EU	48 weeks	352 370	Losartan Captopril	≤40%	30%	67%	73	0%	65%	34%	2%	NR	68%	50%
ELITE II 2000[19]	DB, MC	289/ NA, SA, EU	700 days	1578 1574	Losartan Captopril	≤40%	31%	70%	71	0%	52%	43%	5%	NR	79%	58%
REPLACE 2001[20]	DB, MC	NR/ EU, Israel	12 weeks	301 77	Telmisartan Enalapril	<40%	26%	89%	64	0%	64%	36%	0%	NR	NR	69%
Dickstein 1995[21]	DB, MC	19/ Denmark, Finland, Norway, Sweden	8 weeks	108 58	Losartan Enalapril	≤35%	23%	78%	64	0%	0%	84%	16%	46	69%	63%
Lang 1997[22]	DB, MC	16 / NA	12 weeks	78 38	Losartan Enalapril	≤45%	25%	78%	58	0%	47%	51%	2%	53	47%	NR
CIBIS III 2008[23]	OL, MC	128/ EU and AUS and Tunisia	30 months	505 505	Bisoprolol Enalapril	≤35%	29%	68%	72	0%	49%	51%	0%	19	NR	49%
CARMEN 2004[24]	DB, MC, PC	65/ EU	18 months	191 190 191	Carvedilol + Placebo Enalapril + Placebo Carvedilol + Enalapril	<40%	30%	81%	62	8%	65%	27%	0%	NR	67%	52%
CHARM-alternative 2003[25]	DB, MC, PC	618/ NA, EU	3.5 years	1013 1015	Candesartan Placebo	≤40%	30%	68%	67	0%	48%	49%	4%	NR	68%	61%
HEAVEN 2002[26]	DB, MC, PC	NR/ Sweden	12 weeks	70 71	Valsartan Enalapril	≤45%	NR	53%	67	0%	70%	30%	0%	47	43%	NR
RALES 1999[27]	DB, MC, PC	195/ 15 countries	24 months (mean)	822 841	Spironolactone Placebo	≤35%	25%	73%	65	0%	0%	70%	29%	NR	54%	NR
Val-HeFT 2001[28]	DB, MC, PC	302/ US, EU, Africa	23 months (mean)	2511 2499	Valsartan Placebo	<40%	27%	80%	63	0%	62%	36%	2%	NR	NR	NR
Hamroff 1999[29]	DB, MC	4/ NR	6 months	16 17	Losartan Placebo	Reduced	26%	49%	61	NR	NR	NR	NR	NR	30%	NR
BEST 2008[30]	DB, MC, PC	90/ US and Canada	3 years	1354 1354	Bucindolol Placebo	≤35%	23%	78%	60	0%	0%	92%	8%	37	42%	NR
CIBIS I 1994[31]	DB, MC, PC	NR/ EU	2 years	320 321	Bisoprolol Placebo	< 40%	17%	83%	60	0%	0%	95%	5%	38	54%	47%
CIBIS II 1999[32]	DB, MC, PC	47/ Western and Eastern EU	1.3 years (mean)	1327 1320	Bisoprolol Placebo	≤35%	28%	81%	61	0%	0%	83%	17%	43	50%	NR
CELICARD 2000[33]	DB, MC, PC	NR/ France, Poland	1 year	62 62	Celiprolol Placebo	<40%	26%	90%	57	0%	57%	43%	1%	NR	NR	40%
COPERNICUS 2001[34]	DB, MC, PC	334/ NA, EU, AUS	28.7 months	1156 1133	Carvedilol Placebo	<25%	20%	79%	63	0%	NR	NR	NR	NR	67%	NR
ENECA 2005[35]	DB, MC, PC	70/ NR	48 weeks	134 126	Nebivolol Placebo	≤35%	26%	73%	72	0%	49%	47%	5%	NR	NR	58%

MERIT-HF 1999[36]	DB, MC, PC	14/ US, EU	18 months	1990 2001	Metroproplol Placebo	≤40%	28%	78%	64	0%	41%	55%	4%	NR	66%	49%
MERIT-HF (pilot) 1999[37]	DB, MC, PC	NR	6 months	42 19	Metroproplol Placebo	≤40%	27%	75%	NR	0%	56%	41%	3%	NR	NR	NR
MIC 2000[38]	DB, MC, PC	NR/ Germany, Sweden	6 months	26 26	Metroproplol Placebo	<40%	28%	71%	54	0%	58%	42%	0%	NR	NR	NR
MOCHA 1996[39]	DB, MC, PC	NR/ US	6 months	261 84	Carvedilol Placebo	≤ 35%	23%	76%	60	0%	53%	60%	2%	57	52%	NR
PRECISE 1996[40]	DB, MC, PC	31/ US	6 months	133 145	Carvedilol Placebo	≤35%	22%	73%	60	0%	40%	56%	4%	NR	52%	NR
SYMPOXYDEX 2004[41]	DB, MC, PC	NR/ France	6 months	28 22	Carvedilol Placebo	≤40%	26%	84%	59	0%	78%	22%	0%	NR	40%	NR
Cohn 1997[42]	DB, MC, PC	42 / US	6 months	70 35	Carvedilol Placebo	< 35%	22%	58%	60	0%	1%	86%	13%	49	45%	NR
Colucci 1996[43]	DB, MC, PC	NR/ US	12 months	232 134	Carvedilol Placebo	≤ 35%	23%	85%	54	0%	85%	14%	0%	48	41%	NR
de Milliano 2002[44]	DB, MC, PC	Netherlands	8 months	43 11	Metroproplol Placebo	<35%	25%	67%	65	0%	54%	46%	0%	NR	56%	NR
Dubach 2002[45]	DB, PC	NR	1 year	13 15	Bisoprolol Placebo	<40%	26%	NR	58	0%	NR	NR	0%	NR	57%	NR
Krum 1995[46]	DB, PC	NR/ US	14 weeks	33 16	Carvedilol Placebo	≤ 35%	16%	78%	55	0%	27%	63%	10%	NR	10%	NR
Packer 1996[47]	DB, MC, PC	NR/ US	6/12 months	696 398	Carvedilol Placebo	≤ 35%	23%	77%	58	0%	53%	44%	3%	NR	NR	NR
Palazzuoli 2005[48]	DB, PC	Italy	12 months	33 25	Carvedilol Placebo	<40%	32%	66%	71	0%	0%	57%	43%	NR	69%	NR
Palazzuoli 2005[49]	DB, PC	Italy	12 months	32 27	Carvedilol Placebo	<40%	32%	64%	71	0%	0%	58%	42%	NR	69%	NR
Sturm 2000[50]	DB, SC, PC	1/ Austria	2 years	51 49	Atenolol + Enalapril Placebo + Enalapril (Candesartan, Enalapril, or Candesartan + Enalapril) + Metroprolol (Candesartan, Enalapril, or Candesartan + Enalapril) + Placebo	≤25%	17%	88%	52	0%	78%	20%	2%	NR	28%	NR
RESOLVD 2000[51, 52]	DB, MC, PC	60/ NA, Italy	43 weeks	214 212		<40%	28%	82%	61	7%	69%	23%	1%	NR	69%	64%
CHARM-added 2003[53]	DB, MC, PC	618/ NA, EU	3.5 years	1276 1272	Candesartan Placebo	≤40%	28%	79%	64	0%	24%	73%	0%	NR	62%	56%
AREA-IN CHF 2009[54]	DB, MC, PC	46/ Italy	12 months	231 236	Canrenone Placebo	≤45%	40%	84%	63	0%	100%	0%	0%	NR	52%	NR
EMPHASIS-HF 2011[55]	DB, MC, PC	278/ US, EU, AUS	3 years	1364 1373	Eplerenone Placebo	≤30%	26%	78%	69	0%	100%	0%	0%	58	69%	50%
Cicoira 2002[56]	OL	Italy	12 months	54 52	Spironolactone Placebo	≤45%	33%	87%	62	NR	NR	NR	NR	NR	64%	NR
Vizzardi 2014[57]	SB, SC, PC	1/Italy	44 months (mean)	65 65	Spironolactone Placebo	<40%	36%	NR	63	18%	82%	0%	0%	NR	NR	NR
PARADIGM-HF 2014[58]	DB, MC	1043/ 46 countries	27 months (median)	4187 4212	Valsartan/ sacubitril Enalapril	≤40%	29%	78%	64	5%	70%	24%	1%	NR	60%	43%

Abbreviations: AUS = Australia; d = day(s); DB = double-blind; EU = Europe; heart failure = heart failure; MC = multicentre; mos = months; MI = myocardial infarction; NA = North America; NYHA = New York heart association; LVEF = left ventricular ejection fraction; mo = month(s); NR = not reported; OL = open label; PC = placebo controlled; SB = single blind; SC = single centre; US = United States; yrs= years; wk = week(s); yr = year(s)

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2020_B-066

Kontaktdaten

Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 21.04.2020

Indikation gemäß Beratungsantrag

Ist indiziert zur Behandlung von Erwachsenen mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion unter 45% nach einem Ereignis einer sich verschlechternden Herzinsuffizienz.

Was ist der Behandlungsstandard in der Behandlung von Erwachsenen mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion unter 45 % nach einem Ereignis einer sich verschlechternden Herzinsuffizienz?

In den 2016 aktualisierten und in Deutschland als Standard akzeptierten „Guidelines for the diagnosis and treatment of acute and chronic heart failure“ der Europäischen Gesellschaft für Kardiologie (ESC) wird eine Einteilung der Herzinsuffizienz vorgenommen in

- Heart Failure with reduced Ejection Fraction < 40 % (HFrEF)
- Heart Failure with mid-range Ejection Fraction 40 % bis 49 % (HFmrEF) und
- Heart Failure with preserved Ejection Fraction ≥ 50 % (HFpEF)

Insofern ist die Fragestellung („Was ist der Behandlungsstandard in der Behandlung von Erwachsenen mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion unter 45 % nach einem Ereignis einer sich verschlechternden Herzinsuffizienz?“) schwer nachvollziehbar, da der Grenzwert willkürlich erscheint.

Die Herzinsuffizienz ist ein klinisches Syndrom, das durch verschiedene kardiale Erkrankungen hervorgerufen wird. Prinzipiell sollte bei einer sich verschlechternden Herzinsuffizienz die zugrunde liegende Pathophysiologie erneut evaluiert werden, da hiervon die Therapie abhängt.

Vermutlich standen die Erwachsenen mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion unter 45 % vor dem Ereignis einer sich verschlechternden Herzinsuffizienz unter einer Therapie mit einem ACE-Hemmer und einem Betablocker? Wenn ja, besteht die Standardtherapie in

- **Optimierung der Dosis von ACE-Hemmer und Betablocker**, wenn weiter Symptome
- Gabe eines **Mineralokortikoid-Rezeptor-Antagonisten** bei EF ≤ 35 %
- **Diuretika** bei Zeichen der Kongestion
- wenn weiter Symptome trotz optimierter medikamentöser Therapie, EF ≤ 35 % und ACE-Hemmer gut toleriert wurden: Gabe von **Sacubitril/Valsartan** in aufsteigender Dosierung anstelle eines ACE-Hemmers

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der „Behandlung von Erwachsenen mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion unter 45 % nach einem Ereignis einer sich verschlechternden Herzinsuffizienz“, die regelhaft

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berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

- **Unverträglichkeit von ACE-Hemmern:** stattdessen Gabe eines **Angiotensin Rezeptor Blockers**
- **Sinustachykardie in Ruhe** ≥ 70/min (EMA: ≥ 75/min) trotz maximal tolerierter Betablockerdosis, ACE-Hemmer und Mineralokortikoid-Rezeptor-Antagonist und bei EF ≤ 35 %: Gabe von **Ivabradin**
- **Diabetes mellitus:** Einstellung des Diabetes vorzugsweise mit **SGLT2 Inhibitoren und GLP1-Rezeptor Antagonisten**, ggf. Metformin
- **Eisenmangel:** intravenöse Eisensubstitution
- **Vorhofflimmern mit schneller Überleitung:** Betablocker, ggf. Amiodaron, Digoxin, ggf. elektrische Kardioversion
- **Linksschenkelblock, QRS-Dauer ≥ 150 (≥ 130) msec** und EF ≤ 35 %: Implantation eines **CRT-Systems**
- **Ventrikuläre Arrhythmien mit hämodynamischer Instabilität**: Implantation eines **ICD zur Sekundärprävention**
- **EF ≤ 35 % und ischämische Herzerkrankung oder dilatative CMP**: Implantation eines **ICD zur Primärprävention**
- **Aortenklappenstenose:** bei signifikanter Stenose TAVI
- **Funktionelle Mitralklappeninsuffizienz:** bei EF ≤ 30 % und hochgradiger sekundärer Mitralklappeninsuffizienz interventionelle Therapie

Ist eine Aufteilung der Patientenpopulation in „Erwachsene mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion von 40 bis < 45 % (Patienten mit HFmrEF)“ und „Erwachsene mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion von < 40 % (Patienten mit HFrEF)“ angezeigt?

Der Begriff **„Heart Failure with mid-range Ejection Fraction“ (HFmrEF)** wurde von der Europäischen Gesellschaft für Kardiologie (ESC) in die 2016 aktualisierten Guidelines for the diagnosis and treatment of acute and chronic heart failure neu aufgenommen. Er ist definiert als eine Herzinsuffizienz mit einer **linksventrikulären Ejektionsfraktion zwischen 40 % und 49 %.** Von dieser Definition abweichend eine Patientenpopulation mit einer linksventrikulären Ejektionsfraktion von 40 % bis < 45 % abzugrenzen ergibt klinisch keinen Sinn, zumal die meist echokardiographisch bestimmte Ejektionsfraktion eine deutliche Intra- und Interobserver-Variabilität aufweist und sich die Ejektionsfraktion außerdem unter der Herzinsuffizienztherapie ändern kann.

Die Therapie der Herzinsuffizienz richtet sich nicht nach der Ejektionsfraktion, sondern nach der Symptomatik (NYHA-Stadium) und den klinischen Befunden. Neben der systolischen linksventrikulären Funktion, gemessen als Ejektionsfraktion, sind für das klinische Syndrom Herzinsuffizienz weitere Parameter wie diastolische linksventrikuläre Funktion, Dyssynchronie, Herzklappenfehler, Arrhythmien und die Ätiologie der kardialen Grunderkrankung sowie Begleiterkrankungen verantwortlich.

Die Herzinsuffizienz-Leitlinien der American Heart Association und des American College of Cardiology von 2013 und 2017 nehmen keine Einteilung in „Heart Failure with mid-range Ejection Fraction (HFmrEF)“

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vor.

Literatur (1-4)

1. Branca L, Sbolli M, Metra M, Fudim M: Heart failure with mid-range ejection fraction: pro and cons of the new classification of Heart Failure by European Society of Cardiology guidelines. ESC Heart Fail 2020; 7: 381-399.

2. Cosentino F, Grant PJ, Aboyans V et al.: 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2020; 41: 255-323.

3. Yancy CW, Jessup M, Bozkurt B et al.: 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017; 136: e137-e161.

4. Ponikowski P, Voors AA, Anker SD et al.: 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-2200.

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2020_B-066

Für die Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM)

Erstellt unter Beteiligung der DGK und mit Zustimmung der DGIM.

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Ist indiziert zur Behandlung von Erwachsenen mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion unter 45% nach einem Ereignis einer sich verschlechternden Herzinsuffizienz.

Vorbemerkung: die Formulierung ist unpräzise:

1. …nach einem Ereignis: dies impliziert, dass ein Ereignis stattgefunden hat, nun aber wieder Stabilität eingetreten ist.
2. …einer sich verschlechternden Herzinsuffizienz: welche Art der Verschlechterung ist hier gemeint? Die technisch gemessene (z.B. Abnahme der EF) oder die klinische Verschlechterung?

Die Formulierung muss also in beiden Aspekten präzisiert werden.

Frage 1: Was ist der Behandlungsstandard in der Behandlung von Erwachsenen mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion unter 45 % nach einem Ereignis einer sich verschlechternden Herzinsuffizienz?

Antwort: Es existiert kein „Behandlungsstandard“, vielmehr wird in dem individuellen Fall auf der Basis *klinischer* Symptomatik entschieden, ob der Patientin/dem Patienten über die Behandlung der Grunderkrankungen hinaus weitere herzinsuffizienzspezifische medikamentöse Therapiemaßnahmen angeboten werden, als ob ihre/seine EF <40% betragen würde.

Begründung: Eine EF <45% erfüllt bei Symptomen / klinischen Zeichen die Bedingungen der kürzlich eingeführten Kategorie „Herzinsuffizienz mit geringgradig eingeschränkter linksventrikulärer Ejektionsfraktion (HFmrEF)“ mit EF >40% bis 49%.(1) Für diese hinsichtlich ihrer Prävalenz abnehmende Patientengruppe mit HFmrEF (von 15% auf 13%, (1, 2)) existiert keine hinreichende Evidenz hinsichtlich wirksamer Therapiemaßnahmen. Daher wurden in der NVL ‚Chronische Herzinsuffizienz‘ keine konsentierten Empfehlungen für Patienten mit HFmrEF verabschiedet. Als alleiniger Hinweis findet sich im Hintergrundtext die folgende Formulierung: „Aus Sicht der Leitlinienautoren ist für diese Patienten, insbesondere wenn sie symptomatisch sind, eher[sic!] die Therapie wie bei einer HFrEF geeignet.“(1)

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Vom Charakter ist dies also einem individuellen Behandlungsversuch, nicht jedoch einer klaren Behandlungsempfehlung gleichzusetzen. Zudem verweist die NVL ‚Chronische Herzinsuffizienz' (2019) auf die „mögliche durch das [bildgebende] Messverfahren bedingte Über- oder Unterschätzung der LVEF, patienten- und untersucherabhängige inter- und intraindividuelle sowie zeitliche intraindividuelle Varianzen".(1) Dieser Verweis findet sich im Übrigen in den Tragenden Gründen zum DMP ‚Herzinsuffizienz' unter Nummer 1.2 ‚Diagnostische Kriterien zur Abgrenzung der Zielgruppe zum DMP': „Der Einschluss einer LVEF ≤ 40% gegenüber der Vorgängerversion als Modul erfolgte wegen der bekannten Problematik der Rundung von Werten bei gegebener Messunschärfe."(3)

Frage 2: Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der „Behandlung von Erwachsenen mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion unter 45% nach einem Ereignis einer sich verschlechternden Herzinsuffizienz", die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Antwort: Es wird regelhaft die *klinische* Symptomatik, d.h. das NYHA-Stadium berücksichtigt. Die Therapieoptionen für Patienten mit HFmrEF bestehen in erster Linie in der Therapie der Grunderkrankung. Unter Berücksichtigung individueller Risiken (z.B. bestehende Ko- und Multimorbidität) können den betroffenen Patient*innen darüber hinaus im Sinne eines individuellen Therapieversuchs (bei fehlender Evidenz) dieselben Therapieoptionen angeboten werden, wie bei Vorliegen einer EF < 40%.

Begründung: vgl. Begründung unter Frage 1.

Frage 3: Ist eine Aufteilung der Patientenpopulation in „Erwachsene mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion von 40 bis < 45 % (Patienten mit HFmrEF)" und „Erwachsene mit symptomatischer chronischer Herzinsuffizienz und einer Ejektionsfraktion von < 40 % (Patienten mit HFrEF)" angezeigt?

Antwort: Die Unterteilung in Patienten mit HFmrEF und HFrEF unter Beibehaltung des cut-offs von >40% vs. <40% ist angezeigt.

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Begründung: Wie in der Begründung zu Frage 1 dargestellt, existiert keine hinreichende Evidenz für wirksame Therapien bei Patienten mit HFmrEF (Nationale VersorgungsLeitlinie (NVL) ‚Chronische Herzinsuffizienz', 2019). Viele der randomisierten kontrollierten Studien mit Patienten mit HFrEF wendeten Einschlusskriterien mit cut-offs von EF < 35% an. Die auf deren Ergebnissen beruhenden Empfehlungen der NVL Chronische Herzinsuffizienz wurden daher bereits für einen cut-off von <40% adaptiert, um Messungenauigkeiten der bildgebenden Verfahren zu berücksichtigen. Eine Gleichbehandlung von Patienten mit HFmrEF und Patienten mit HFrEF würde daher einer unzulässigen Indikationsausweitung gleichkommen, da der Nutzenbeleg nur für Patienten mit HFrEF erbracht wurde, für Patienten mit HFmrEF jedoch (noch) aussteht, wohingegen für beide Gruppen aber derselbe potentielle Schaden (z.B. unerwünschte Arzneimittelwirkungen) angenommen werden muss. Würde man die Patientenpopulation nicht in die genannten Gruppen aufteilen, würde man Patienten mit HFmrEF in gleicher Weise behandeln wie Patienten mit HFrEF und damit bei unbekanntem Nutzen einem potentiellen Schaden aussetzen, würde man den ersten ethischen Behandlungsgrundsatz nil nocere verletzen.

Ergänzung DGK: Anders zu werten sind allerdings Patienten, bei denen sich unter einer leitliniengerechten Herzinsuffizienztherapie die linksventrikuläre Ejektionsfraktion von < 40% auf > 40% verbessert hat. Hier existieren belastbare Hinweise, dass eine Reduktion bzw. ein Pausieren der medikamentösen Herzinsuffizienztherapie nachteilig ist und insofern eine Fortführung der evidenzbasierten HFrEF-Therapie geboten ist.

Zitierte Literatur

References

1. Bundesärztekammer (BÄK) KBK, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Chronische Herzinsuffizienz. Langfassung. 3. Auflage, 2019. Version 1. AWMF-Register-Nr.: nvl-006.2019 [last access: 26.03.2020]. Available from: www.herzinsuffizienz.versorgungsleitlinien.de.
2. Vasan RS, Xanthakis V, Lyass A, Andersson C, Tsao C, Cheng S, et al. Epidemiology of Left Ventricular Systolic Dysfunction and Heart Failure in the Framingham Study: An Echocardiographic Study Over 3 Decades. JACC Cardiovasc Imaging. 2018;11(1):1-11.
3. Bundesausschuss G. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über die 11. Änderung der DMP-Anforderungen - Richtlinie: Änderung der Anlagen 2 und 5, Ergänzung der Anlage 13 (DMP Herzinsuffizienz) und Anlage 14 (Herzinsuffizienz Dokumentation) vom 19. April 2018 [last access: 26.03.2020]. Available from: https://www.g-ba.de/beschluesse/3299/.