Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2016-B-044 Empagliflozin

Stand: Februar 2022

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

Empagliflozin
Zur Behandlung der Herzinsuffizienz mit erhaltener Ejektionsfraktion

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“. Wirkstoffklassen: • ACE-Hemmer • AT1-Antagonisten • Betablocker • Diuretika • Digitalisglykoside • Sonstige
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	Es liegen keine Beschlüsse über die frühe Nutzenbewertung nach §35a in der Indikation Herzinsuffizienz mit erhaltener Ejektionsfraktion vor Weitere Beschlüsse des G-BA: 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)
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, FI)
Zu bewertendes Arzneimittel:	
Empagliflozin A10BX12 Jardiance®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Zur Behandlung von Erwachsenen bei chronischer Herzinsuffizienz mit **erhaltener** (HFpEF) oder reduzierter (HFrEF) Ejektionsfraktion zusätzlich zum Therapiestandard (Standard of Care) Bereits zugelassene Anwendungsgebiete: <u>Typ-2 Diabetes mellitus:</u> Jardiance wird zur Behandlung von Erwachsenen mit nicht ausreichend behandeltem Typ-2-Diabetes mellitus als Ergänzung zu Diät und Bewegung angewendet - als Monotherapie, wenn Metformin aufgrund einer Unverträglichkeit als ungeeignet erachtet wird - zusätzlich zu anderen Arzneimitteln zur Behandlung von Diabetes <u>Herzinsuffizienz</u> Jardiance wird zur Behandlung von Erwachsenen mit symptomatischer, chronischer Herzinsuffizienz mit reduzierter Ejektionsfraktion angewendet.
ACE-Hemmer	
Enalapril C09AA02 generisch	Behandlung der symptomatischen Herzinsuffizienz Prävention der symptomatischen Herzinsuffizienz bei Patienten mit asymptomatischer linksventrikulärer Dysfunktion (linksventrikuläre Ejektionsfraktion [LVEF] ≤35%) (FI Enalapril Abz® 2020/07)
Benazepril C09AA07 (Cibacen®)	Herzinsuffizienz - zusätzlich zu Diuretika und insbesondere bei schwerer Herzinsuffizienz auch zu Digitalis (FI Cibacen® 2019/11)
Quinapril C09AA06 (Accupro®)	Herzinsuffizienz – zusätzlich zu Diuretika und insbesondere bei schwerer Herzinsuffizienz auch zu Digitalis. (FI Accupro® 2021/05)
Fosinopril	Behandlung einer symptomatischen Herzinsuffizienz

II. Zugelassene Arzneimittel im Anwendungsgebiet	
09AA09, (Fisinorom®)	(FI Forsinorm 2019/05))
Ramipril C09AA05, (Delix®)	Behandlung einer symptomatischen Herzinsuffizienz (FI Delix® 2021/04)
Lisinopril C09AA03 (Lisinopril-ratiopharm®)	Behandlung einer symptomatischen Herzinsuffizienz (FI Lisinopril-Radiopharm® 2019/07)
Perindopril C09AA04 (Coversum®)	Behandlung einer symptomatischen Herzinsuffizienz (FI Conversum® 2021/10)
Cilazapril C09AA08 (Dynorm®)	Für die Behandlung von chronischer Herzinsuffizienz indiziert (FI Dynom® 2020/07)
AT1-Antagonisten (und andere Kombinationen)	
Candesartan C09CA06 (Candesartan AbZ®)	Behandlung erwachsener Patienten mit Herzinsuffizienz und eingeschränkter linksventrikulärer systolischer Funktion (linksventrikuläre Ejektionsfraktion <= 40 %), wenn ACE-Hemmer nicht vertragen werden, oder als Add-on-Therapie zu ACE-Hemmern bei Patienten, die trotz optimaler Therapie eine symptomatische Herzinsuffizienz aufweisen, wenn Mineralokortikoid-Rezeptor-Antagonisten nicht vertragen werden (siehe Abschnitte 4.2, 4.4, 4.5 und 5.1) (FI Candesartan AbZ® 2021/05))
Losartan C09CA01 (Losartan AbZ®)	Behandlung der chronischen Herzinsuffizienz bei erwachsenen Patienten, wenn die Behandlung mit einem „Angiotensin-Converting-Enzyme“ (ACE)-Hemmer wegen Unverträglichkeit, insbesondere Husten, oder Gegenanzeige als nicht geeignet erachtet wird. Patienten mit 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)
Valsartan C09CA03 (Valsartan	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 nicht angewendet werden können

II. Zugelassene Arzneimittel im Anwendungsgebiet

AbZ®)	(FI Valsartan Abz® 2021/05)
Betablocker	
Metoprolol C07AB02 (Beloc-Zok®)	Stabile chronische gering bis mäßig ausgeprägte Herzinsuffizienz mit eingeschränkter systolischer Ventrikelfunktion (Ejektionsfraktion <= 40 %) - zusätzlich zur üblichen Standardtherapie mit ACE-Hemmern und Diuretika und, falls erforderlich, Herzglykosiden (FI Beloc-Zok 2020/10)
Bisoprolol C07AB07 generisch	Behandlung der stabilen chronischen Herzinsuffizienz mit eingeschränkter linksventrikulärer Funktion, zusätzlich zu ACE-Hemmern und Diuretika sowie optional Herzglykosiden. (FI Bisopropol-Ratiopharm® 2021/03)
Carvedilol C07AG02 (Dilatrend®)	Chronische Herzinsuffizienz: wenn keine Kontraindikation vorliegt, ist Dilatrend bei allen Patienten mit stabiler, symptomatischer, chronischer Herzinsuffizienz aller Schweregrade, ischämischen oder nicht ischämischen Ursprungs in Kombination mit der Standardtherapie (wie ACE-Hemmern und Diuretika mit oder ohne Digitalis indiziert. Hinweis (zum Einsatz bei chronischer Herzinsuffizienz): Die Behandlung mit diesem Arzneimittel darf nur begonnen werden, wenn der Patient mit der konventionellen Basis-Herzinsuffizienz-Therapie stabil eingestellt ist, d.h. die Dosierung dieser bereits bestehenden Standardtherapie muss vor Therapiebeginn mit diesem Arzneimittel zumindest für vier Wochen stabil gewesen sein (FI Dilatrend® 2021/08)
Nebivolol C07AB12 generisch	Behandlung der stabilen leichten und mittelschweren chronischen Herzinsuffizienz zusätzlich zu einer Standardtherapie bei älteren Patienten >= 70 Jahren (FI Nebilet® 2018/10)
Diuretika (und Kombinationen)	
Hydrochlorothiazid C03AA03 generisch	Adjuvante symptomatische Therapie der chronischen Herzinsuffizienz zusätzlich zu ACE-Hemmern (FI HCT AAA® 2020/11)
Triamteren/ Hydrochlorothiazid C03EA01 generisch	Chronische Herzinsuffizienz (FI Triamteren comp.-ratiopharm® 2020/07=
Chlortalidon	Manifeste Herzinsuffizienz

II. Zugelassene Arzneimittel im Anwendungsgebiet

C03BA04 (Hygroton®)	(FI Hygroton® 2020/09)
Eplerenon C03DA04 generisch	Zusätzlich zu einer Standardtherapie, die Betablocker einschließt, zur Verringerung des Risikos der kardiovaskulären Mortalität und Morbidität bei stabilen Patienten mit linksventrikulärer Dysfunktion (LVEF <= 40 %) und klinischen Zeichen einer Herzinsuffizienz nach kürzlich aufgetretenem Myokardinfarkt (MI) (FI Eplerenon Abz® 2020/08)
Spironolacton C03DA01 generisch	Ödeme und/oder Aszites bei Erkrankungen, die mit einem sekundären Hyperaldosteronismus einhergehen (FI Spironolacton-ratiopharm® 2020/07)
Torasemid C03CA04 generisch	Behandlung und Vorbeugung des Wiederauftretens kardialer Ödeme und/oder Ergüsse aufgrund einer Herzinsuffizienz (FI Torasemid AAA-Pharma 2,5 mg / 5 mg / 10 mg Tabletten 2021/01)
Piretanid C03CA03 generisch	Zur Ausscheidung von Ödemen, bei Herzinsuffizienz zur Herzentlastung, bei Ödemen infolge Erkrankung der Nieren oder der Leber. (FI Arelix® 2020/01)
Digitalisglykoside	
Digitoxin C01AA04 generisch	Manifeste chronische Herzinsuffizienz (aufgrund systolischer Dysfunktion) (FI Digimerck 2020/09)
Digoxin C01AA05 Beta-Acetyldigoxin C01AA02 Metildigoxin C01AA08 (Lanitop®)	Manifeste chronische Herzinsuffizienz (aufgrund systolischer Dysfunktion) (FI 2015/09)
Sonstige	
Ivabradin	Ivabradin ist indiziert bei chronischer Herzinsuffizienz der NYHA-Klasse II bis IV mit systolischer Dysfunktion, bei Patienten im

C01EB17 (Procoralan®)	Sinusrhythmus mit einer Herzfrequenz ≥ 75 Schläge pro Minute (bpm), in Kombination mit Standardtherapie einschließlich Betablocker oder wenn Betablocker kontraindiziert sind oder eine Unverträglichkeit vorliegt (siehe Abschnitt 5.1) (FI Procoralan® 2021/09)

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2016-B-044 (Empagliflozin)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	12. Juni 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis 3
1 Indikation 5
2 Systematische Recherche....5
3 Ergebnisse....6
3.1 G-BA Beschlüsse 6
3.2 Cochrane Reviews 7
3.3 Systematische Reviews....15
3.4 Leitlinien....38
4 Detaillierte Darstellung der Recherchestrategie 62
Referenzen....64

Abkürzungsverzeichnis

6MWD	6 Min Walk Distance
ACC	American College of Cardiology
ACD	All-Cause Death
ACE-I	Angiotensin Converting Enzyme Inhibitors
AF	Atrial Fibrillation
AHA	American Heart Association
ARB	Angiotensin Receptor Blockers
ARNI	Angiotensin Receptor Neprilysin Inhibitors
ARR	Absolute Risikoreduktion
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BÄK	Bundesärztekammer
BB	Beta Blockers
BNP	B-type Natriuretic Peptide
BP	Blood Pressure
CAD	Coronary Artery Disease
CHF	Chronic Heart Failure
COR	Class of Recommendation
EF	Ejection Fraction
ESC	European Society of Cardiology
G-BA	Gemeinsamer Bundesausschuss
GDMT	Guideline-Directed Management and Therapy
GIN	Guidelines International Network
GoR	Grade of Recommendations
HF	Heart Failure
HFA	Heart Failure Association
HFmrEF	Heart Failure with mid range Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction

HFSA	Heart Failure Society of America
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KBV	Kassenärztliche Bundesvereinigung
KI	Konfidenzintervall
LAE	Left Atrial Enlargement
LoE	Level of Evidence
LVEF	Left Ventricular Ejaction Fraction
LVH	Left Ventricular Hypertrophy
MLHFQ	Minnesota Living With Heart Failure Questionnaire
MRA	Mineralocorticoid Receptor Antagonists
NICE	National Institute for Health and Care Excellence
NNT	Number Needed to Treat
NOAC	New Oral Anticoagulants
NVL	Nationale VersorgungsLeitlinie
NYHA	New York Heart Association
OCS	Observational Cohort Studies
OR	Odds Ratio
PS	Propensity Score
QoL	Quality of Life
RAAS	Renin-Angiotensin Aldosterone System
RAS	Renin-Angiotensin System
RCB	Angiotensin Receptor Blockers
RR	Relatives Risiko
SBP	Systolic Blood Pressure
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Anwendungsgebiet laut Beratungsanforderung:

Jardiance ist indiziert bei Erwachsenen zur Behandlung der chronischen Herzinsuffizienz mit erhaltener (HFpEF) oder reduzierter (HFrEF) Ejektionsfraktion zusätzlich zum Therapiestandard (Standard of Care).

Indikation für die Synopse:

Herzinsuffizienz bei Patientinnen und Patienten mit Herzinsuffizienz und erhaltener Ejektionsfraktion

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 16.05.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, CADTH, 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.

Die Recherche ergab 1807 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 17 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse

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. 2Den Patientinnen und Patienten, die die Vergleichsintervention erhalten, wird kein Pulmonalisdrucksensor implantiert.

3.2 Cochrane Reviews

Martin N et al., 2018 [9].

Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction

Fragestellung

To assess the effects of beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, and mineralocorticoid receptor antagonists in people with heart failure with preserved ejection fraction.

Methodik

Population:

- adult participants (aged≥18 years) with HFpEF defined by a left ventricular ejection fraction of greater than 40 percent (LVEF > 40%).

Intervention:

- BB, MRA, ACEI, or ARB, in addition to standard care

Komparator:

- Placebo or no treatment

Endpunkte:

- Cardiovascular mortality.
- Heart failure hospitalisation.
- Hyperkalaemia.
- All-cause mortality.
- Quality of life (measured using either the Minnesota Living With Heart Failure Questionnaire or Kansas City Cardiomyopathy Questionnaire).
- Withdrawal due to adverse event (hypotension, hyperkalaemia or renal impairment).

Recherche/Suchzeitraum:

- Bis Juli 2017

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 37 RCTs
- Beta-blockers
  - We included 10 studies (3087 participants) that investigated betablockers forHFpEF.
  - Of these, five studies compared beta-blockers versus placebo (ELANDD; Mittal 2017; Sahoo 2016; SENIORS; SWEDIC) and five versus usual care (Adamyan 2010; Aronow

1997; J-DHF; Shu 2005; Takeda 2004). Four studies investigated carvedilol: Adamyan 2010 (up to 50 mg daily), J-DHF (up to 10 mg twice daily), SWEDIC (up to 25 mg twice daily or 50 mg twice daily in people weighing over 85 kg), Takeda 2004 (up to 20 mg daily). Two studies used nebivolol: ELANDD (up to 10 mg daily) and SENIORS (up to 10 mg daily). One study used propranolol: Aronow 1997 (30mg, 3 times daily); and two studies investigated metoprolol succinate: Mittal 2017; Sahoo 2016 (up to 100 mg daily). Shu 2005 investigated bisoprolol (up to 10 mg daily).

- Mineralocorticoid receptor antagonists (MRA)
  - We included 12 studies that investigated MRAs for HFpEF.
  - Of these, eight compared MRA versus placebo (ALDO-DHF; AREA IN-CHF;Kurrelmeyer2014;Mottram2004; RAAM-PEF; STRUCTURE; TOPCAT; Upadhya 2017) and four versus usual care (Karapysh 2015; Mak 2009; Orea-Tejeda 2007; Wang 2010). Nine studies investigated spironolactone (ALDO-DHF; Kurrelmeyer 2014; Mottram 2004; STRUCTURE; Upadhya 2017 (25 mg/d); Karapysh 2015;Orea-Tejeda 2007 (25 mg/d uptitrated if tolerated to 50 mg/d); TOPCAT (15 mg/d, increased to a maximum of 45 mg/d);Wang 2010 (50 mg/d)). Two studies used eplerenone (Mak 2009; RAAM-PEF (25 mg/d to a maximum of 50 mg/d)). AREA IN-CHF investigated canrenone at a maximum dose of 50 mg/d.
- Angiotensin converting enzyme inhibitors (ACEI)
  - We included eight studies that investigated ACEIs for HFpEF.
  - Of these, three compared ACEI with placebo (Kitzman 2010; PEPCHF; Zi 2003), and five versus usual care (Aronow 1993; Aronow 1998;Hong Kong DHF; SNEGOVIK; Yuksek 2012).Two studies investigated enalapril (Aronow 1993, up to 20 mg daily; Kitzman 2010, up to 10 mg daily). Aronow 1998 investigated benazepril (up to 40 mg/d). Two studies investigated perindopril (PEP-CHF, up to 4 mg daily; Yuksek 2012, up to 10 mg). Hong Kong DHF investigated ramipril in one of two active arms (maximum of 10 mg daily). Two studies investigated quinapril (SNEGOVIK, dose not reported; Zi 2003, up to 40 mg daily).
- Angiotensin receptor blockers (ARB)
  - We included eight studies that investigated ARBs for HFpEF.
  - Of these, five compared ARB versus placebo (CAN-DHF; CHARM-Preserved; I-PRESERVE; Kasama 2005; Parthasarathy 2009) and three compared ARB versus usual care (CandHeart; Hong Kong DHF; SUPPORT). Four studies investigated candesartan (CAN-DHF; CandHeart; CHARM-Preserved (up to 32 mg daily), Kasama 2005 (8 mg to 12 mg daily)). Two studies investigated irbesartan (one of the two active treatment arms in Hong Kong DHF (up to 75 mg daily), I-PRESERVE (up to 300 mg)). Parthasarathy 2009 investigated valsartan (80 mg daily). SUPPORT investigated olmesartan (up to 40 mg daily).

<u>Charakteristika der Population:</u>

- Beta-blockers
  - Numbers of participants randomised ranged from 40 (Mittal 2017; Takeda 2004) to 643 (SENIORS). Four were multicentre studies.
  - Three studies did not report LVEF of the included participants at baseline (Adamyan 2010; Shu 2005; SWEDIC). Six studies reported LVEF at baseline with a mean ranging from 56%to 63% (Aronow 1997; ELANDD; J-DHF; Mittal 2017; Sahoo 2016; Takeda 2004).

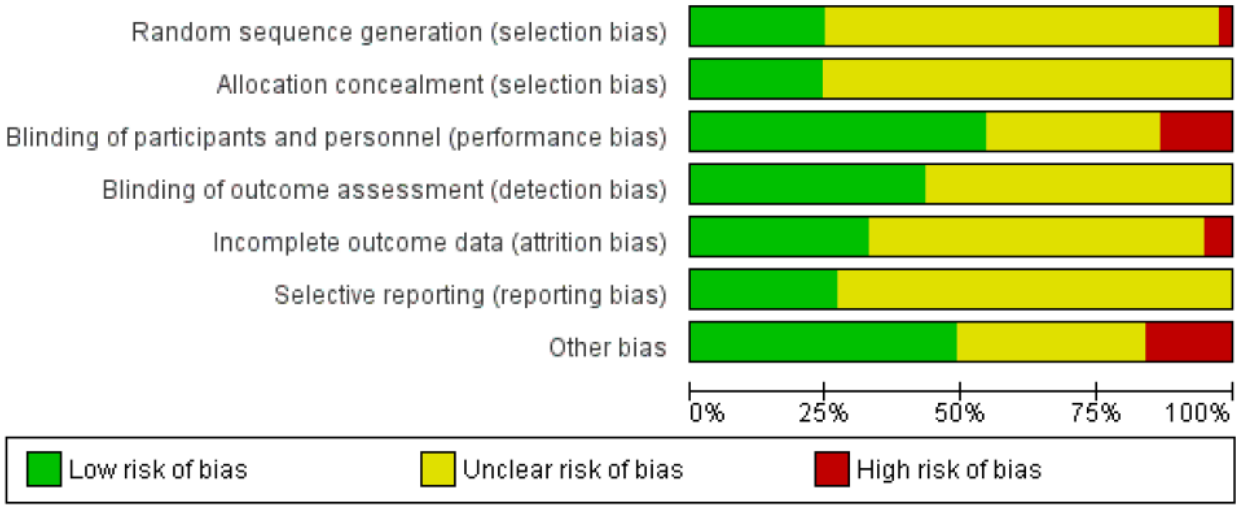
SENIORS included participants with a “clinical history of chronic HF with at least 1 of the following features: documented hospital admission within the previous 12 months with a discharge diagnosis of congestive HF or documented LVEF ≤ 35% within the previous 6 months”. The SENIORS study reported a subgroup of participants with LVEF > 40% and these outcome data were used in our analysis (643 participants).

- Most participants were NYHA class II.
- Participants’ mean age ranged from 30 years to 81 years; six studies reported mean age less than 70 years (Adamyan 2010; ELANDD; Mittal 2017; Sahoo 2016; Shu 2005; SWEDIC) and four reported mean age above 70 years (Aronow 1997; J-DHF; SENIORS; Takeda 2004).

- Mineralocorticoid receptor antagonists (MRA)
  - Numbers of participants randomised ranged from 28 (Orea-Tejeda 2007) to 3445 (TOPCAT).
  - Two studies (Karapysh 2015; Mottram 2004) did not report participants’ LVEF at baseline. AREA IN-CHF had a mean LVEF at baseline of 39.9% (intervention) and 39.7% (control) for the overall included participants (N = 467). However, we obtained outcome data for the subgroup of participants with LVEF > 40% (N = 225). The LVEF in the remaining seven studies ranged from 62% to 72%.
  - Most participants in five studies were NYHA class II (52% to 88%; ALDO-DHF; Mak 2009; RAAM-PEF; STRUCTURE; TOPCAT).Most participants in two studies were NYHA class III (58% to 64%; Kurrelmeyer 2014; Upadhya 2017).
  - Participants’ mean age ranged from 54.5 years to 80 years; seven studies included participants whose mean age was less than 70 years (ALDO-DHF; AREA IN-CHF; Karapysh 2015; Mottram 2004; Orea-Tejeda 2007; STRUCTURE; TOPCAT). In four studies, participants’ mean age was over 70 years (Kurrelmeyer 2014; Mak 2009; RAAM-PEF; Upadhya 2017).
- Angiotensin converting enzyme inhibitors (ACEI)
  - Numbers of participants randomised ranged from 21 (Aronow 1993) to 850 (PEP-CHF).
  - The mean LVEF of the included participants at baseline was not reported by two studies (SNEGOVIK; Zi 2003). LVEF ranged from 61% to 69% in five studies (Aronow 1993; Aronow 1998; Hong Kong DHF; Kitzman 2010; PEP-CHF).
  - Most participants were classified inNYHA class II in four studies (Hong Kong DHF; Kitzman 2010; PEP-CHF; Zi 2003) and in NYHA class III in one study (Aronow 1993).Two studies did not report participants’ NYHA class at baseline (Aronow 1998; SNEGOVIK).
  - Participants’ mean age ranged from 70 years to 82 years with all studies equal to or over a mean age of 70 years.
- Angiotensin receptor blockers (ARB)
  - Numbers of participants randomised ranged from 22 (CANDHF) to 4128 (I-PRESERVE). The mean LVEF of the included participants at baseline was not reported by CAN-DHF and ranged from 49% to 72% in seven studies (CandHeart; CHARM-Preserved; Hong Kong DHF; I-PRESERVE; Kasama 2005; Parthasarathy 2009; SUPPORT).
  - Most participants were assessed as NYHA class II at baseline in five studies (CandHeart; CHARM-Preserved; Hong Kong DHF; Kasama 2005; SUPPORT);NYHA class III in I-PRESERVE; and was not reported by two studies (CAN-DHF; Parthasarathy 2009).

- Participants' mean age ranged from 61 years to 75 years. Mean age was below 70 years in six studies (CAN-DHF; CandHeart; CHARM-Preserved; Kasama 2005; Parthasarathy 2009; SUPPORT) and over 70 years in two studies (Hong Kong DHF; I-PRESERVE).

Qualität der Studien:



Studienergebnisse:

- Beta-blockers versus placebo or no treatment

Beta-blockers compared to placebo or no treatment for chronic heart failure with preserved ejection fraction

Patient or population: chronic heart failure with preserved ejection fraction
Setting: secondary care
Intervention: beta-blockers
Comparison: placebo/no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/no treatment	Risk with Beta-blockers				
Cardiovascular mortality (RR) follow-up: range 21 months to 3.2 years	Study population 173 per 1000	135 per 1000 (107 to 171)	RR 0.78 (0.62 to 0.99)	1046 (3 RCTs)	⊕⊕◯◯ LOW [12]	Three additional studies (ELANDD; SWEDIC; Takeda 2004) reported that no deaths occurred
Heart failure hospitalisation (RR) follow-up: range 6 months to 3.2 years	Study population 117 per 1000	86 per 1000 (55 to 133)	RR 0.73 (0.47 to 1.13)	449 (4 RCTs)	⊕◯◯◯ VERY LOW [134]	Follow-up unclear for SWEDIC. ELANDD reported that no hospitalisation due to heart failure occurred
Hyperkalaemia				245 (1 RCT)	⊕◯◯◯ VERY LOW [17]	J-DHF reported one participant in the intervention group (N = 120) experienced hyperkalaemia but did not report on this outcome for the control group. No further data were available from any of the other studies

All-cause mortality (RR) follow-up: range 21 months to 3.2 years	Study population		RR 0.82 (0.67 to 1.00)	1105 (4 RCTs)	⊕⊕◯◯ LOW [12]	Follow-up unclear for Adamyan 2010. ELANDD, SWEDIC and Takeda 2004 reported that no deaths occurred
	243 per 1000	199 per 1000 (163 to 243)				
Quality of life (Minnesota) Scale from: 0 to 105 follow-up: mean 6 months	Mean quality of life (Minnesota) was 24	MD 1 lower (9.05 lower to 7.05 higher)	-	93 (1 RCT)	⊕◯◯◯ VERY LOW [56]	Lower = better, 5 point difference considered to be clinically meaningful

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one level due to unclear selection bias in most studies.
[2] Downgraded by one level due to concerns about the smaller study being more precise than the larger study.
[3] Downgraded by one level due to large variation in size of effect.
[4] Downgraded by two levels due to few events and wide CI.
[5] Downgraded by two levels due to very small sample size.
[6] Suspected publication bias; this is a patient-relevant outcome that is not reported in most studies.
[7] Downgraded by two levels due to incomplete reporting.

- Mineralocorticoid receptor antagonists (MRA) versus placebo or no treatment

MRA compared to placebo or no treatment for chronic heart failure with preserved ejection fraction

Patient or population: chronic heart failure with preserved ejection fraction
Setting: secondary care
Intervention: MRA
Comparison: placebo/no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/no treatment	Risk with MRA				
Cardiovascular mortality (RR) follow-up: range 12 months to 3.3 years	Study population		RR 0.90 (0.74 to 1.11)	4070 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]	Two additional trials (RAAM-PEF, Kurrelmeyer 2014) reported that no deaths occurred
	88 per 1000	79 per 1000 (65 to 97)				
Heart failure hospitalisation (RR) follow-up: range 24 weeks to 3.3 years	Study population		RR 0.82 (0.69 to 0.98)	3714 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]	Three additional trials (ALDO-DHF, Kurrelmeyer 2014, Upadhya 2017) reported that no hospitalisation due to heart failure occurred
	136 per 1000	112 per 1000 (94 to 134)				
Hyperkalaemia follow-up: range 24 weeks to 3.3 years	Study population		RR 2.11 (1.77 to 2.52)	4291 (6 RCTs)	⊕⊕⊕⊕ HIGH	Two trials defined hyperkalaemia ≥ 5.5 mEg/L
	83 per 1000	175 per 1000 (146 to 208)				
All-cause mortality follow-up: range 9 months to 3.3 years	Study population		RR 0.91 (0.78 to 1.06)	4207 (5 RCTs)	⊕⊕⊕◯ MODERATE [1]	Two additional trials (RAAM-PEF, Kurrelmeyer 2014) reported that no deaths

						occurred
	133 per 1000	121 per 1000 (104 to 141)				
Quality of life (Minnesota) Scale from: 0 to 105 follow-up: range 9 months to 12 months	Mean quality of life (Minnesota) ranged from 20 to 25	MD 0.84 higher (2.30 lower to 3.98 higher)	-	511 (3 RCTs)	⊕⊕◯◯ LOW [2,3]	Lower = better, 5 points are considered a clinically significant difference We did not pre-specify which QoL scale was to be reported in the 'Summary of findings' table. To aid comparisons among 'Summary of findings' tables we chose to include the Minnesota Living with Heart Failure questionnaire and not the SMD across two scales

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one level due to imprecision.
[2] Downgraded by one level because one trial was open label.
[3] Downgraded by one level due to small sample size.

- Angiotensin converting enzyme inhibitors (ACEI) versus placebo or no treatment

ACEI compared to placebo or no treatment for chronic heart failure with preserved ejection fraction

Patient or population: chronic heart failure with preserved ejection fraction
Setting: secondary care
Intervention: ACEI
Comparison: placebo/no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/no treatment	Risk with ACEI				
Cardiovascular mortality (RR) follow-up: range mean 12 months to mean 26.2 months	Study population		RR 0.93 (0.61 to 1.42)	945 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	One additional trial (Kitzman 2010) reported that no deaths occurred
	86 per 1000	81 per 1000 (53 to 123)				
Heart failure hospitalisation (RR) follow-up: range 6 months to 26.2 months	Study population		RR 0.86 (0.64 to 1.15)	1019 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]	
	13 per 1000	11 per 1000 (8 to 15)				
Hyperkalaemia				74 (1 RCTs)	⊕◯◯◯ VERY LOW [1,3,4]	One trial (Zi 2003) reported 2 events in the intervention group (N = 36), 0 events in the control group (N = 38) (RR 5.27, 95% CI 0.26 to 106.16)
All-cause mortality (RR) follow-up: range mean 6 months to mean 26.2 months	Study population		RR 0.99 (0.71 to 1.38)	1079 (4 RCTs)	⊕⊕⊕◯ MODERATE [1]	One additional trial (Kitzman 2010) reported that no deaths occurred

	119 per 1000	119 per 1000 (84 to 166)				
Quality of life (Minnesota) Scale from: 0 to 105 follow-up: mean 12 months	Mean quality of life (Minnesota) ranged from 10.9 to 29	MD 0.09 lower (3.66 lower to 3.48 higher)	-	154 (2 RCTs)	⊕⊕◯◯ LOW [2,3]	Scale: 0 to 105, lower = better, 5 point difference considered clinically relevant One trial (SNEGOVIK) reported mean change from baseline of -19.8 for intervention and -10.7 for control

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one level due to wide CI.
[2] Downgraded by one level due to risk of bias (open label).
[3] Downgraded by one level due to low sample size.
[4] Downgraded by one level due to unclear selection bias.

- Angiotensin receptor blockers (ARB) versus placebo or no treatment

ARB compared to placebo or no treatment for chronic heart failure with preserved ejection fraction

Patient or population: chronic heart failure with preserved ejection fraction
Setting: secondary care
Intervention: ARB
Comparison: placebo/no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/no treatment	Risk with ARB				
Cardiovascular mortality (RR) follow-up: range mean 12 months to mean 49.5 months	Study population		RR 1.02 (0.90 to 1.14)	7254 (3 RCTs)	⊕⊕⊕⊕ HIGH	One additional trial (Parthasarathy 2009) reported that no deaths occurred
	131 per 1000	133 per 1000 (118 to 149)				
Heart failure hospitalisation (RR) follow-up: range mean 12 months to mean 49.5 months	Study population		RR 0.92 (0.83 to 1.02)	7254 (3 RCTs)	⊕⊕⊕⊕ HIGH	
	171 per 1,-000	157 per 1,-000 (142 to 174)				
Hyperkalaemia follow-up: range 36.6 months to 49.5 months	Study population		RR 1.88 (1.07 to 3.33)	7148 (2 RCTs)	⊕⊕⊕⊕ HIGH	
	3 per 1,000	5 per 1,000 (3 to 8)				
All-cause mortality (RR) follow up: range 1 years to 4.4 years	Study population		RR 1.01 (0.92 to 1.11)	7964 (4 RCTs)	⊕⊕⊕⊕ HIGH	One additional trial (Parthasarathy 2009) reported that no deaths occurred
	72 per 1000	73 per 1,-000 (66 to 80)				

Quality of life (Minnesota) scale from: 0 to 105 follow-up: range mean 13.8 weeks to mean 49.5 months	Mean quality of life (Minnesota) ranged from 10.9 to 31.6	MD 0.41 higher (0.86 lower to 1.67 higher)	-	3117 (3 RCTs)	⊕⊕⊕⊕ HIGH	Scale: 0 to 105, lower = better, 5 point difference considered clinically relevant

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Anmerkung/Fazit der Autoren

Our results were largely consistent with those from the most recent comprehensive review of evidence for beta-blockers and RAAS inhibitors in people with HFpEF (Zheng 2017 (*in der vorliegenden Evidenzsynopse eingeschlossen als [17]*)). However, important differences were noted. Our analysis included more studies for each comparison, but the additional studies were small and did not significantly alter the overall effect estimates. A further distinction is that we used a fixed-effect model rather than a random effects model for meta-analysis given the low heterogeneity among studies for all comparisons. We found a reduction in cardiovascular mortality for beta-blocker therapy but this was not robust to a sensitivity analysis that included only studies assessed at low risk of bias. In contrast to Zheng 2017, we did not find an effect of betablocker treatment on all-cause mortality that achieved statistical significance.

The available evidence for the effects of treatment with beta-blockers, MRA, ACEI, ARNI for HFpEF was limited. Beta-blockers may improve cardiovascular mortality however the quality of evidence was low. The evidence for MRA suggests that treatment reduces the risk of HF hospitalisation; there was little or no effect on cardiovascular and all-cause mortality however the quality of evidence was only moderate due to imprecision. Treatment with ACEI probably has little or no effect on the outcomes of cardiovascular and all-cause mortality and heart failure hospitalisation, however evidence was limited. There is high quality evidence that ARB treatment has no beneficial effect on these outcomes. For all comparisons, no effect on quality of life was observed however the quality of evidence was low. The mainstay of pharmacological therapy in HFpEF remains the treatment of comorbid conditions such as hypertension that are implicated in aetiology and as triggers for decompensation.

Kommentare zum Review

Nicht alle in den eingeschlossenen RCTs untersuchten Arzneimittel sind in Deutschland zugelassen:

- Betablocker: Metoprolol (2 Studien)
- MRA: Eplerenon, Canrenon (3 Studien)

3.3 Systematische Reviews

Zheng SL et al., 2018 [17].

Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis

Fragestellung

In this study, we aimed to systematically review the clinical trials of patients with HFpEF (defined as LV ejection fraction ≥40%), and identify treatment effects on mortality, heart failure hospitalisation, functional status and biomarker levels.

Methodik

Population:

- participants with heart failure and documented LV ejection fraction ≥40%

Intervention:

- drug therapy

Komparator:

- placebo, no treatment, diuretic treatment or standard medical treatment

Endpunkte:

- all-cause mortality,
- cardiovascular mortality,
- heart failure hospitalisation,
- exercise capacity (6 min walk distance (6MWD),
- exercise duration, VO2 max),
- quality of life as measured using the Minnesota Living With Heart Failure Questionnaire (MLHFQ)
- and biomarkers (B-type natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-proBNP))

Recherche/Suchzeitraum:

- Bis April 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 27 RCTs
  - 6 betablocker trials enrolling 1299 patients
  - 5 ACE inhibitor (1305 participants)

- 6 ARB (9704 participants)
- 5 MRA (4003 participants)
- 1 digoxin (988 participants)
- 2 calcium channel blocker (242 participants)
- 1 sildenafil (216 participants)
- 1 sitaxsentan (192 participants)
- 1 doxazosin (145 participants)

Charakteristika der Population:

- Seven studies used an LV ejection fraction threshold of 40%, and nine used LV ejection fraction thresholds of 45% and 50%

Author (Trial)	Arm	Year	Intervention	Control	Entry-EF cut-off	Follow-up (months)	Intervention (N)	Control (N)	Total (N)	Mean LVEF	Outcomes
Ahmed (DIG)[1]		2005	Digoxin	Placebo	45%	37	492	496	988	55	All-cause mortality, CV mortality, HFH
Aronow[2]		1997	Propranolol	No treatment	40%	12	79	79	158	57	All-cause mortality, CV mortality,
Bergstrom (SWEDIC)[3]		2004	Carvedilol	Placebo	45%	6	47	50	97	NR	HFH, biomarker
Cleland (PEP-CHF)[4]		2006	Perindopril	Placebo	40%	25.2	424	426	850	65	All-cause mortality, CV mortality, HFH, exercise time, biomarker
Conraads[5]		2012	Nebivolol	Placebo	45%	6	57	59	116	63	6MWD, VO_2, QOL, biomarker
Davis (ALLHAT)[6]	1	2008	Amlodipine	Chlorthalidone	50%	20.9	110	117	227	NR	All-cause mortality
Davis (ALLHAT)	2	2008	Lisinopril	Chlorthalidone		20.9	98		215	NR	
Davis (ALLHAT)	3	2008	Doxazosin	Chlorthalidone		18.6	79	66	145	NR	
Deswal (RAAM-PEF)[7]		2011	Eplenerone	Placebo	50%	6	22	22	44	62	HFH, 6MWD
Edelmann (ALDO-DHF)[8]		2013	Spironolactone	Placebo	50%	12	213	209	422	67	All-cause mortality, exercise time, 6MWD, VO_2, QOL, biomarker
Hung[9]		2003	Verapamil	Placebo	50%	3	15	15	15	70	Exercise time
Kasama[10]		2005	Candesartan	Placebo	40%	6	25	25	50	55	Biomarker
Kitzman[11]		2010	Enalapril	Placebo	50%	12	35	36	71	65	Exercise time, 6MWD, VO_2, QOL, biomarker
Kurrelmeyer[12]		2014	Spironolactone	Placebo	50%	6	24	24	48	63	6MWD, Biomarker
Little[13]		2006	Losartan	Hydrochlorothiazide	50%	6	19	21	40	67	Exercise time, VO_2,
Mak[14]		2009	Epleronone	Placebo	45%	12	24	20	44	63	QOL, biomarker

Massie (I-PRESERVE)[15]		2008	Irbesartan	Placebo	45%	49.5	2067	2061	4128	60	All-cause mortality, CV mortality, HFH, QOL, biomarker
Parthasarathy[16]		2009	Valsartan	Placebo	40%	3.5	70	82	152	71	Exercise time, 6MWD, VO_2, QOL, biomarker
Pitt (TOPCAT)[17]		2014	Spironolactone	Placebo	45%	49.5	1722	1723	3445	56	All-cause mortality, CV mortality, HFH
Rector (I-PRESERVE)[18]		2012	Irbesartan	Placebo	45%	56	1102	1103	2205	NR	QOL
Redfield (RELAX)[19]		2013	Sildenafil	Placebo	50%	6	113	103	216	60	All-cause mortality, 6MWD, VO_2, QOL, biomarker
Solomon (CHARM-Preserved)[20]		2004	Candesartan	Placebo	40%	36.6	1514	1509	3023	54	All-cause mortality
Takeda[21]		2004	Carvedilol	No treatment	45%	12	19	21	40	57	HFH, QOL, biomarker
Van Veldhuisen (SENIORS)[22]		2009	Nebivolol	Placebo	35%	21	320	323	643	NA	All-cause mortality, CV mortality
Yamamoto (J-DHF)[23]		2013	Carvedilol	Placebo	40%	38.4	120	125	245	63	All-cause mortality, CV mortality, HFH
Yip (HK-DHF)[24]	1	2008	Ramipril	Diuretics	45%	12	45	50	151	67	All-cause mortality, CV mortality, HFH, 6MWD, QOL, biomarker
Yip (HK-DHF)[24]	2	2008	Irbesartan			12	56			68	
Yusuf (CHARM-Preserved)[25]		2003	Candesartan	Placebo	40%	36.6	1514	1509	3023	54	CV mortality, HFH
Zi[26]		2003	Quinapril	Placebo	40%	6	36	38	74	59	All-cause mortality, HFH, 6MWD
Zile[27]		2014	Sitaxsentan		50%	6	128	64	192	61	HFH, exercise time, QOL
Mak[14]		2009	Epleronone	Placebo	45%	12	24	20	44	63	QOL, biomarker

Qualität der Studien:

- Five studies were identified as high risk of bias using the Cochrane risk of bias tool, and the remainder low risk

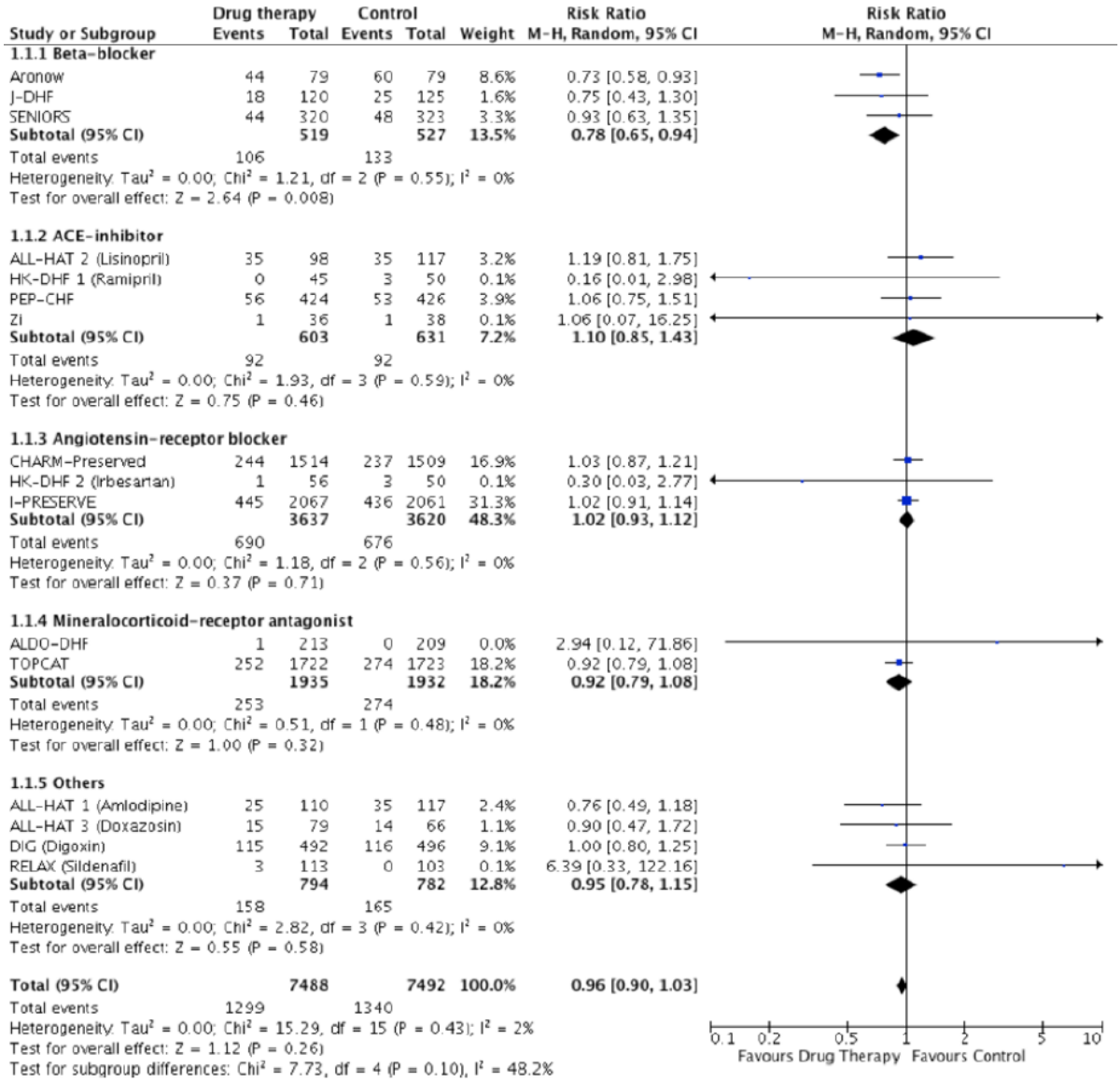
Studienergebnisse:

Table 1 Summary of effects for all-cause mortality, cardiovascular mortality and heart failure hospitalisation

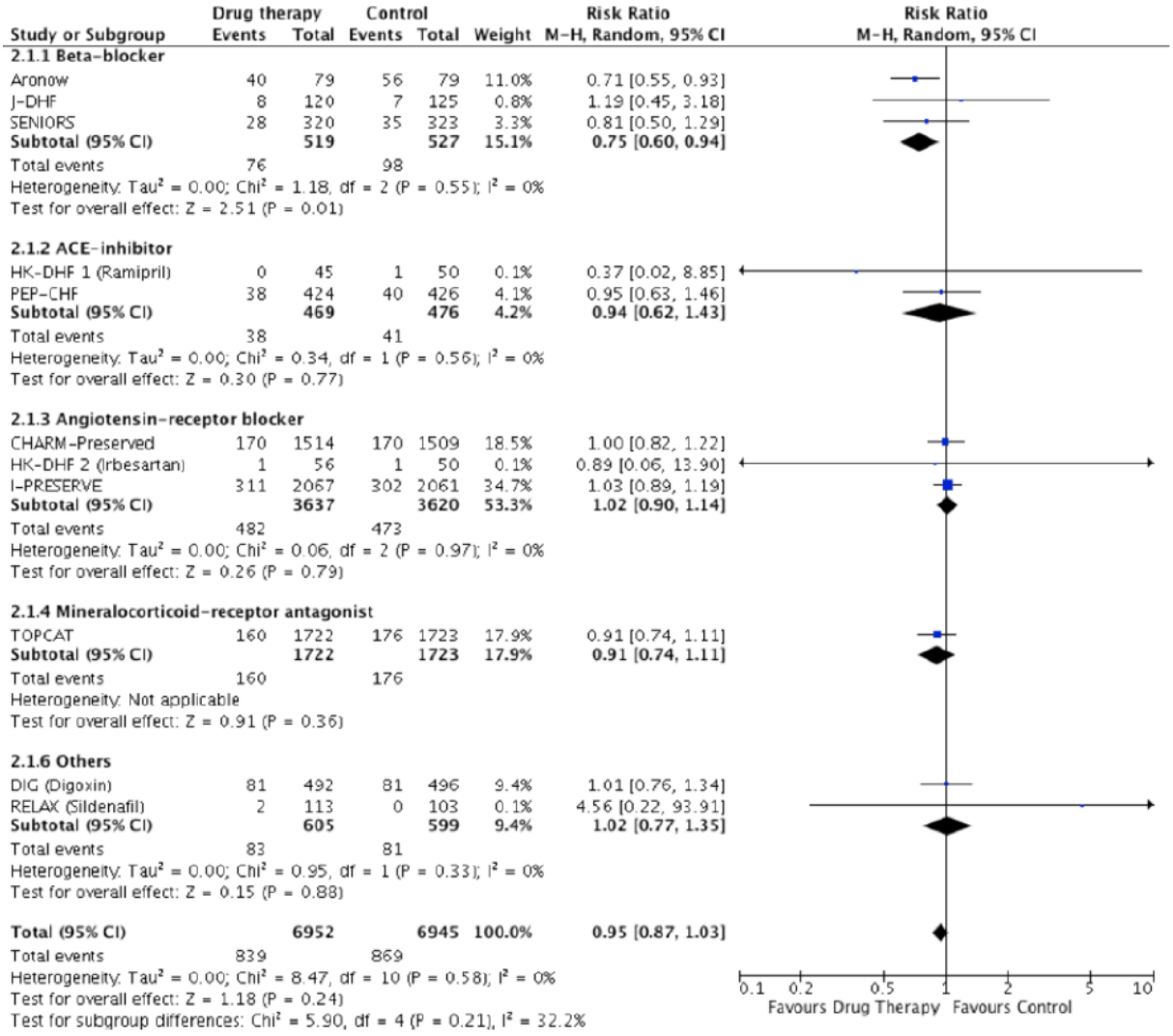
		Drug classes			Follow-up duration		Entry LV ejection fraction threshold		Mean LV ejection fraction	
Outcome	All trials	Beta-blockers	RAAS antagonists	Other	3–12 months	>12 months	40%–49%	≥50%	<60%	≥60%
All-cause mortality	0.96 (0.90 to 1.03)	0.78 (0.65 to 0.94) p=0.008	1.00 (0.93 to 1.08)	0.95 (0.78 to 1.15)	0.79 (0.66 to 0.95) p=0.01	0.99 (0.92 to 1.06)	0.96 (0.88 to 1.03)	0.99 (0.74 to 1.32)	0.93 (0.82 to 1.05)	1.01 (0.90 to 1.12)
Cardiovascular mortality	0.95 (0.87 to 1.03)	0.75 (0.60 to 0.94) p=0.01	0.99 (0.89 to 1.09)	1.01 (0.76 to 1.34)	0.71 (0.55 to 0.90) p=0.005	0.99 (0.90 to 1.08)	0.95 (0.87 to 1.03)	-	0.90 (0.78 to 1.05)	1.02 (0.89 to 1.17)
Heart failure hospitalisation	0.88 (0.81 to 0.95) p=0.002	0.67 (0.42 to 1.07)	0.90 (0.82 to 0.98) p=0.01	0.81 (0.64 to 1.04)	0.67 (0.48 to 0.94) p=0.02	0.90 (0.82 to 0.98) p=0.02	0.88 (0.82 to 0.96) p=0.002	0.51 (0.18 to 1.48)	0.85 (0.76 to 0.94) p=0.002	0.92 (0.82 to 1.04)

Data presented as risk ratios (for all-cause and cardiovascular mortality and hospitalisation outcomes) or mean difference (exercise capacity, 6MWD, VO_2 max and MLHFQ), with 95% CI and I^2 statistic. p values included for analyses that reached statistical significance at p=0.05. RAAS blockers include all trials using ACE inhibitors, angiotensin receptor blockers and mineralocorticoid (each class individually had no effect on all-cause mortality, cardiovascular mortality or heart failure hospitalisation). Only one trial that reported cardiovascular mortality had an entry LV ejection fraction ≥50%. Only one trial with LV ejection fraction threshold ≥50% reported cardiovascular mortality.
6MWD, 6 min walk distance; LV, left ventricular; MLHFQ, Minnesota Living With Heart Failure Questionnaire; RAAS, renin-angiotensin-aldosterone system.

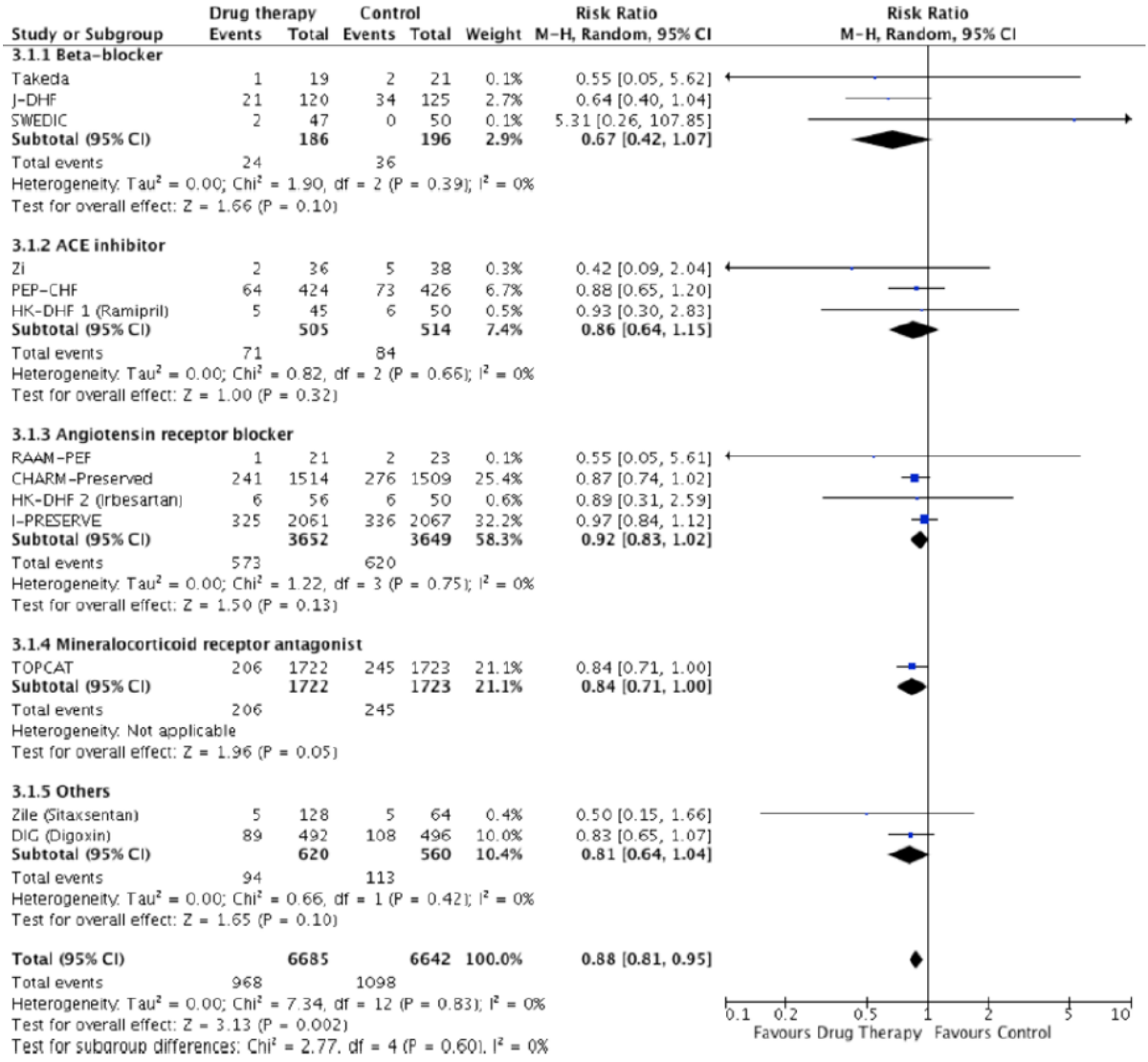
- All-cause mortality



- Cardiovascular mortality



- Heart failure hospitalisation



- Effect of therapy on exercise capacity
  - Ten studies (n=1870 patients) reported on 6MWD, eight studies (n=938) reported on exercise time after treatment and six studies (n=924) reported on VO2 max. There was no significant difference between groups for exercise time, VO2 max and 6MWD.
- Effect of therapy on quality of life
  - Nine trials reported the treatment effects on quality of life as measured by the MLHFQ, including a total of 3510 patients (beta-blocker: 116 patients, ACE inhibitor: 166, ARB: 2460, MRA: 444, other: 324). Overall estimate showed that treatment resulted in better quality of life scores (MD: −1.63, 95% CI: −2.94 to −0.31, p=0.001).

Anmerkung/Fazit der Autoren

The results of this meta-analysis show significant reductions in all-cause and cardiovascular mortality in RCTs using betablockers, while RAAS blockade (using ACE inhibitor, ARB and MRA individually) demonstrated no effect on mortality. Improvements in functional outcomes and

quality of life were not significantly or consistently demonstrated using pooled results. Heterogeneity within trials that reported biomarker outcomes was too high to allow comparison.

Notably, all three beta-blocker trials used an LV ejection fraction threshold of 40%, whereas trials using ACE inhibitor, ARB and MRA tended to use higher ejection fraction thresholds. The demonstrated reduction in mortality with beta-blockers may have been augmented by their effects on the HFmrEF population within these trials; a group that an emerging body of evidence suggests is more closely aligned with HFrEF.

Kommentare zum Review

Die Meta-Analyse zu Auswirkung von ARB auf Hospitalisierung beinhaltet eine Studie, in der Eplerenon eingesetzt wurde. Eplerenon hat in Deutschland keine Zulassung für die vorliegende Indikation.

Xiang Y et al., 2019 [13].

Efficacy and safety of spironolactone in the heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction: A meta-analysis of randomized clinical trials

Fragestellung

Recent studies have shown the efficacy for using spironolactone to treat heart failure with reduced ejection fraction (HFrEF), but the efficacy of spironolactone for heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) is unclear. This meta-analysis investigated the efficacy and safety of spironolactone in patients with HFmrEF and HFpEF.

Methodik

Population:

- patients with HFmrEF and HFpEF

Intervention:

- Spironolactone

Komparator:

- Placebo or standard conventional therapy

Endpunkte:

- Mortality
- Hospitalizations
- functional capacity using the New York Heart Association functional classifications (NYHA-FC)
- 6-minute walking distance (6-MWD) test

Recherche/Suchzeitraum:

- Bis Juni 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Eleven RCTs were included, involving a total of 4539 HFmrEF and HFpEF patients.

Charakteristika der Population:

Basic characteristics of clinical trials included in the meta-analysis.

Author, Year	Patient clinical characteristics	LVEF	Country	Number	Intervention: dose (mg/d)	Control group	Follow-up (months)	Mean age, y
Amil, 2015[33]	HFmrEF and HFpEF	≥45%	USA, Russia, and Georgia	935	Spironolactone 25 mg/d; n=121	Placebo; n=118	12-18	70.19
Bertram Pitt, 2014[11]	HFmrEF and HFpEF	≥45%	USA, Canada, Argentina, Brazil, Russia, Georgia	3445	Spironolactone 25 mg/d; n=1722	Placebo; n=1723	39.60	68.70
Karla 2014[28]	HFpEF	≥50%	USA	48	Spironolactone 25 mg/d; n=24	Placebo; n=24	6	71.35
Vatankulu, 2013[31]	HFmrEF and HFpEF with AMI	≥40%	Turkey	186	Spironolactone 12.5 or 25 mg/d; n=104	Placebo; n=56	6	56.40
Kosmala, 2013[27]	HFpEF with BMI >30 Kg/m^2	≥50%	Australia	113	Spironolactone 25 mg/d; n=58	Placebo; n=55	6	58
Edelmann, 2013[5]	HFpEF	≥50%	Germany and Australia	422	Spironolactone 25 mg/d; n=213	Placebo; n=209	12	67
Kosmala, 2011[24]	HFpEF with metabolic syndrome	≥50%	Australia	79	Spironolactone 25 mg/d; n=40	Placebo; n=39	6	59
Kayrak, 2010[26]	HFmrEF and HFpEF with AMI	≥40%	Australia	110	Spironolactone 25 mg/d; n=55	Standard conventional Therapy; n=55	6	56.25
Liu, 2006[32]	HFpEF with hypertension	≥50%	China	78	Spironolactone 25 mg/d; n=40	Standard conventional therapy; n=38	6	63.49
Roongsmtong, 2005[30]	HFmrEF and HFpEF	≥45%	USA	28	Spironolactone 25 mg/d; n=14	Placebo; n=14	4	71.55
Mottram, 2004[29]	HFpEF with hypertension	≥50%	Australia	30	Spironolactone 25 mg/d; n=15	Placebo; n=15	6	61.50

LVEF=left ventricular ejection fraction, HFmrEF=heart failure with mid-range ejection fraction, HFpEF=heart failure with preserved ejection fraction, BMI=body mass index, AMI=acute myocardial infarction.

Qualität der Studien:

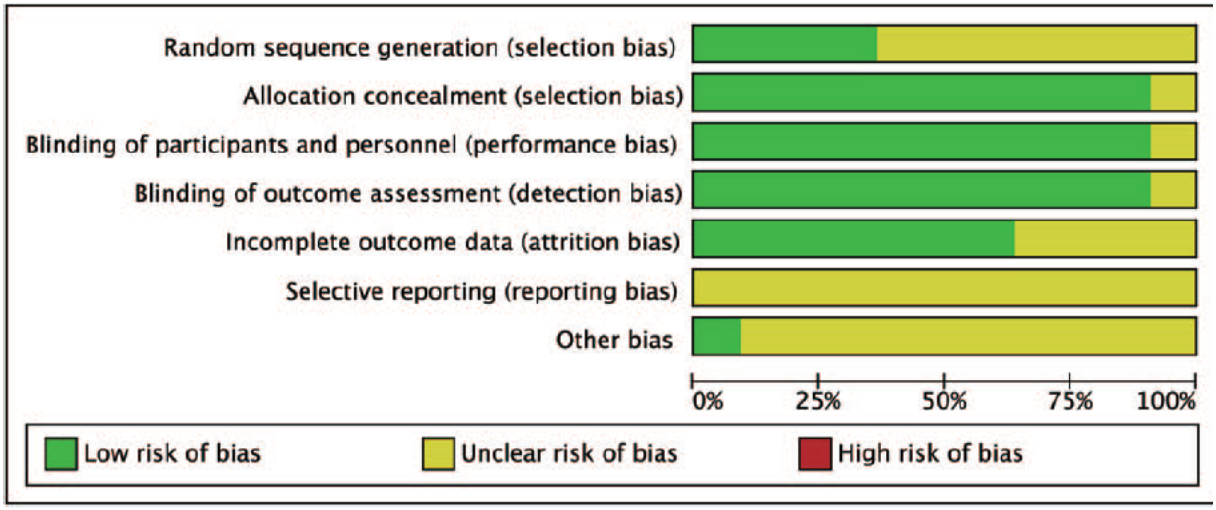


Figure 1. Quality assessment of each included study.

Studienergebnisse:

- Mortality
  - The mortality was defined with death from cardiovascular causes, reported in 3 studies with overall 3715 patients. There was no significant differences in mortality between spironolactone and control group in HFmrEF and HFpEF (RR, 0.72; 95% confidence interval [CI], 0.31–1.69; P=.45). The fixed effects model was used (P=.24, I2=29%).
- Hospitalisation
  - Overall hospitalizations were reported in 2 studies including 3845 patients. The results showed that spironolactone decreased the readmission of patients with HFmrEF and HFpEF (OR, 0.84; 95% CI, 0.73–0.95; P=.006).

- Functional capacity and serum indicator
  - An evaluation of the NYHA-FC involving 527 patients from three studies showed that spironolactone improved the NYHA-FC of patients with HFmrEF and HFpEF (OR, 0.35; 95% CI, 0.19–0.66; P=.001).
- 6-MWD
  - The 6-MWD was reported in three studies with 497 HFpEF subjects. Spironolactone treatment of HFpEF patients showed significant improvement in 6-MWD (SMD, 0.45 m; 95% CI, 0.27–0.64; P<.001)

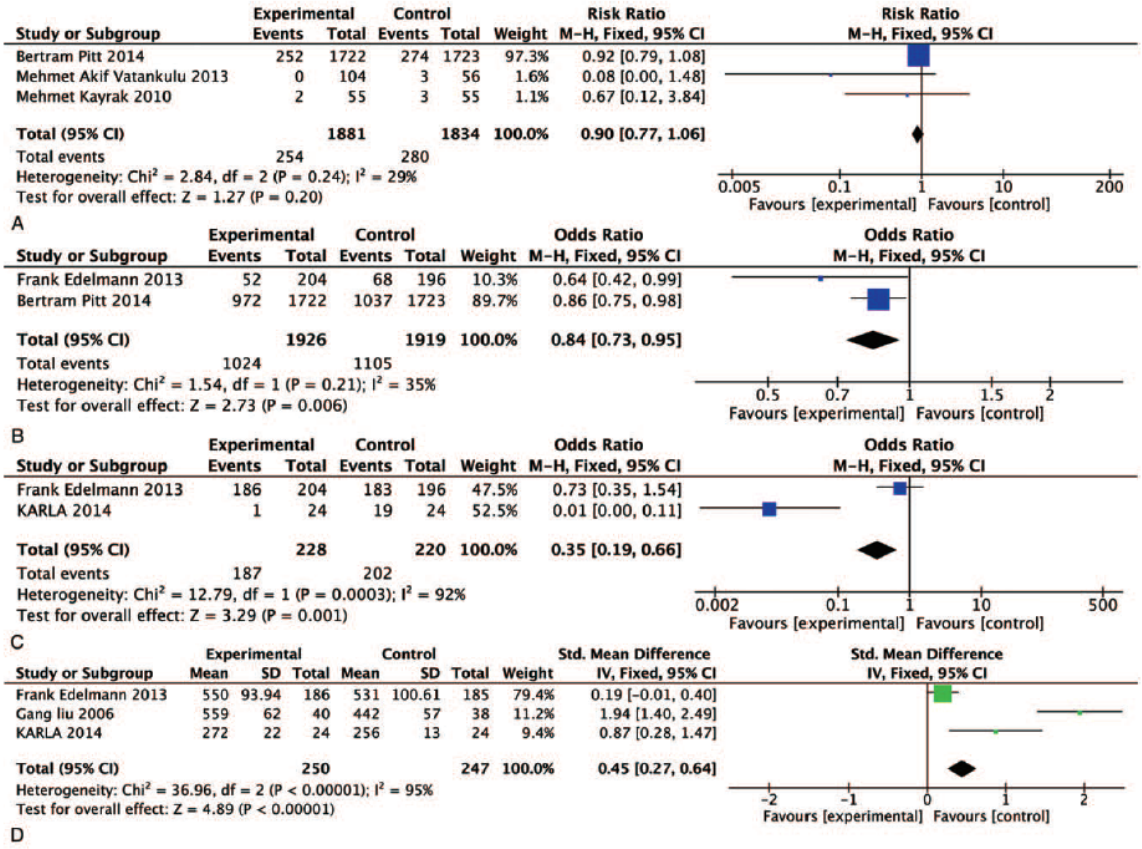


Figure 2. Forest plot of hospitalizations and functional capacity outcomes. (A) Mortality. (B) Hospitalizations. (C) New York Heart Association functional classifications (NYHA-FC). (D) Six-minute walking distance (6-MWD). All were assessed using fixed effects analyses. Squares indicated the risk ratio, odds ratio, or standard weighted mean difference; the horizontal lines indicated the 95% confidence intervals for each included trial. The statistical weight of a trial in the meta-analysis was proportional to the size of each square; diamonds indicated pooled risk ratios and 95% confidence intervals, with the center indicating the point estimate and the left and the right ends indicated the 95% confidence interval.

- Safety
  - In these studies, spironolactone increased serum potassium levels (MD, 0.25mmol/L; 95% CI, 0.18–0.33; P<.001). Subgroup analyses showed spironolactone increase the risk of hyperkalemia (OR, 2.56; 95% CI, 1.54–4.27; P<.001) and gynecomastia (OR, 7.82; 95% CI, 3.82–16.01; P<.001) both in HFmrEF and HFpEF patients, with no subgroup differences observed (hyperkalemia, P=.67, I2=0%; gynecomastia, P=.78, I2=0%).

Anmerkung/Fazit der Autoren

The present meta-analysis including eleven RCTs with 4539 patients to evaluate the efficacy and safety of spironolactone in patients with HFmrEF and HFpEF, which is different with previous meta-analysis about the MRAs treatment including spironolactone, eplerenone, or

finerenone together. It avoided the heterogeneity from different MRAs. The main findings of this study were that spironolactone significantly reduced hospitalizations and myocardial fibrosis through decreasing serum PICP, improved NYHA-FC and BNP levels in HFmrEF and HFpEF. Besides, spironolactone could also decrease the levels of PIIINP and increase 6-MWD compared with control group in HFpEF.

However, no benefit was observed for mortality and diastolic function, neither HFmrEF nor HFpEF. The results of previous clinical studies about the efficacy of spironolactone on HFmrEF and HFpEF remain controversial. The Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial in 2014 indicated that spironolactone could improve left ventricular diastolic function but not affect hospitalizations or exercise capacity. But the improvement of diastolic function was not significant in the study of Vatankulu in 2013, and TOPCAT trial in 2014, which only showed the improvement in the hospitalization due to heart failure. The present meta-analysis showed that spironolactone significantly reduced the primary clinical outcome hospitalizations, while the improvement of left ventricular diastolic function was not significant.

The risks of hyperkalemia and gynecomastia were significantly increased. The serum potassium monitoring should be concerned.

Fukuta H et al., 2017 [4].

The effect of beta-blockers on mortality in heart failure with preserved ejection fraction: A meta-analysis of observational cohort and randomized controlled studies.

- Zu Beta-Blockern siehe auch folgenden systematischen Review mit vergleichbaren Ergebnissen:
  - Bavishi C, et al., 2015. Beta-blockers in heart failure with preserved ejection fraction: a meta-analysis [1].

Fragestellung

Although several observational cohort studies (OCSs) with propensity score (PS) analysis examined the effect of betablockers on mortality in HFpEF, a pooled analysis of OCSs with PS analysis was not performed in earlier meta-analyses. Accordingly, we aimed to conduct an updated meta-analysis of RCTs and OCSs with PS analysis and those without PS analysis on the effect of beta-blockers on mortality in HFpEF.

Methodik

Population:

- HF patients with EF ≥0.40

Intervention:

- beta-blocker(s)

Komparator:

- standardmedical care or placebo

Endpunkte:

- all-cause mortality

- HF hospitalization

Recherche/Suchzeitraum:

- Bis März 2016

Qualitätsbewertung der Studien:

- For RCTs, the trial qualitywas assessed using Jadad score. For OCSs, the quality of the individual studies was graded as good, fair, or poor, based on the published criteria.

Ergebnisse

Anzahl eingeschlossener Studien:

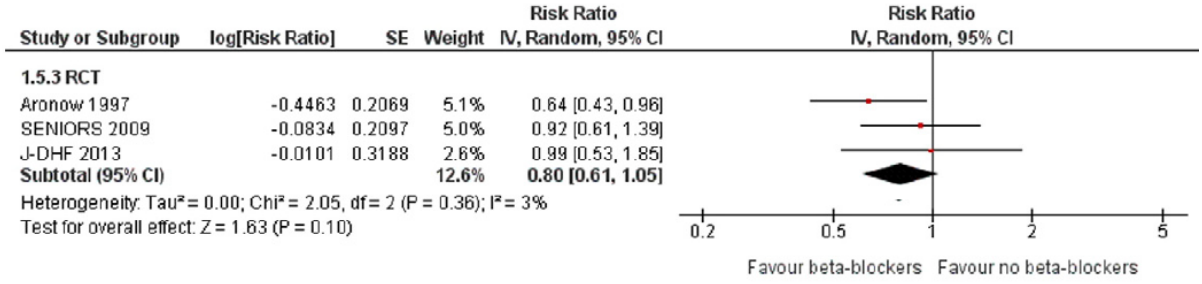
- A total of 5 OCSs with PS analysis (12,315 patients), 6 OCSs without PS analysis (15,275 patients), and 3 RCTs (1046 patients) were included in the present meta-analysis.
- Im Folgenden werden nur die Ergebnisse der RCT dargestellt.

Charakteristika der Population und Qualität der Studien:

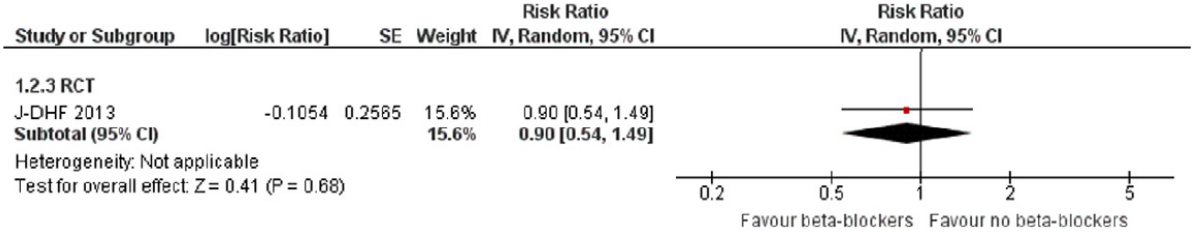
Study	Design	Country	Entry EF	Follow-up	End points	Type of BB	Study quality	PS analysis	Used method for PS analysis	Overall population Treatment/control (number)
Aronow et al. [33]	RCT	USA	≥0.40	2.7 years	ACD	Propranolol	Good	...	...	79/79
SENIORS [21]	RCT	Italy	>0.40	1.75 years	ACD ACD or HF admission	Nebivolol	Good	...	...	320/323
J-DHF [22]	RCT	Japan	>0.40	3.2 years	ACD ACD or HF admission HF admission	Carvedilol	Good	...	...	120/125

Studienergebnisse:

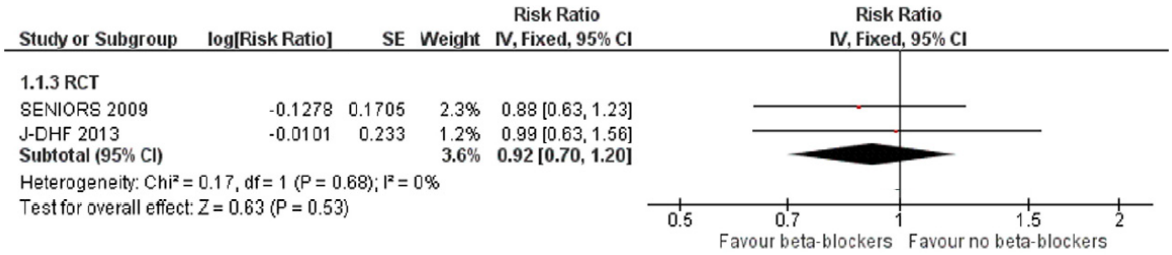
- Mortality



- Heart failure hospitalization



- composite endpoint of mortality or heart failure hospitalization



Anmerkung/Fazit der Autoren

Although two recent RCTs on the prognostic effect of beta-blockers in HFpEF patients failed to show the mortality and morbidity benefit, the definite conclusion cannot be drawn. Specifically, in the SENIORS trial including >2000 HF patients regardless of EF, nebivolol showed a benefit on the primary endpoint of death from all-causes or cardiovascular hospitalization. Nevertheless, there was no clear benefit in the subgroup analysis of the patients who had preserved (>.40) EF. However, it is important to recognize that the SENIORS trial was not specifically designed to assess the effect of nevibolol in HFpEF. In the J-DHF trial including 245 patients with HF and preserved (>.40) EF, carvedilol did not show a clear benefit on the primary endpoint of the composite endpoint of cardiovascular death and HF hospitalization. However, the number of study patients was lower than planned and thus the trial was underpowered. In the present study, the pooled analysis of RCTs showed that use of beta-blockers reduced the risk of mortality by 20%. Although the magnitude of risk reduction of mortality in the RCTs was similar to that seen in the OCSs with PS analysis, the treatment effect was not statistically significant due to limited power.

Kawano H et al., 2019 [7].

Effects of blood pressure lowering in patients with heart failure with preserved ejection fraction: a systematic review and meta-analysis.

Fragestellung

Hypertension is a major contributor to the development of HFpEF, whereas, obesity, coronary artery disease, diabetes mellitus, atrial fibrillation, and hyperlipidemia are also highly prevalent in HFpEF according to population-based studies and registries. The current guidelines for managing hypertension recommend strict blood pressure (BP) control in patients with HFpEF. However, in patients with HFpEF, there was no convincing evidence per se for the efficacy and safety of BP lowering. In this study, we aimed to systematically review clinical trials that evaluated the effects of drug therapy lowering BP among patients with HFpEF.

Methodik

Population:

- patients with HFpEF, which was defined as HF with LVEF ≥ 40%

Intervention:

- BP lowering (e.g., renin-angiotensin system inhibitors, diuretics, and β-blockers)

Komparator:

- placebo or control treatment

Endpunkte:

- all-cause mortality
- cardiovascular mortality
- heart failure hospitalization
- renal dysfunction
- hypotension

Recherche/Suchzeitraum:

- from January 1996 to 24 July 2017

Qualitätsbewertung der Studien:

- The Cochrane Collaboration's tool was used for assessing the risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- Ten RCTs (13,091 patients)

Qualität der Studien:

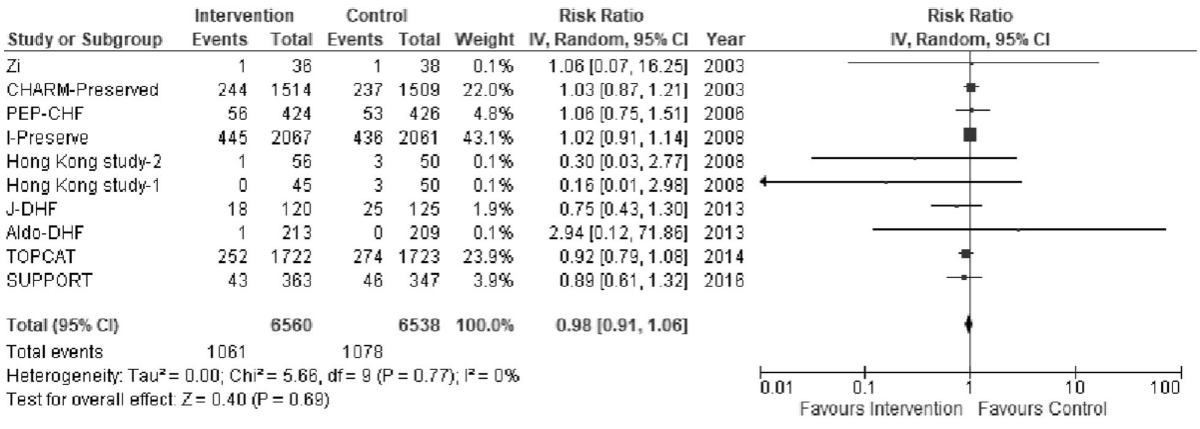
Individual research		Risk of bias					
		Selection bias		Performance bias	Detection bias	Attrition bias	
Study	Design	Randomization	Concealment	Blinding	Blinding	ITT	Incomplete outcome data
Zi	RCT	Low	High	High	High	Low	Low
CHARM-Preserved	RCT	Low	Low	Low	Low	Low	Low
PEP-CHF	RCT	Low	Low	Low	Low	Low	Low
I-PRESERVE	RCT	Low	Low	Low	Low	Low	Low
HK-HDF1	RCT	Low	Low	Moderate/unclear	Low	Low	Low
HK-DHF2	RCT	Low	Low	Moderate/unclear	Low	Low	Low
J-DHF	RCT	Low	Low	Moderate/unclear	Low	Low	Low
Aldo-DHF	RCT	Low	Low	Low	Low	Low	Low
TOPCAT	RCT	Low	Low	Low	Low	Low	Low
SUPPORT	RCT	Low	Low	Low	Low	Low	Low

Charakteristika der Population:

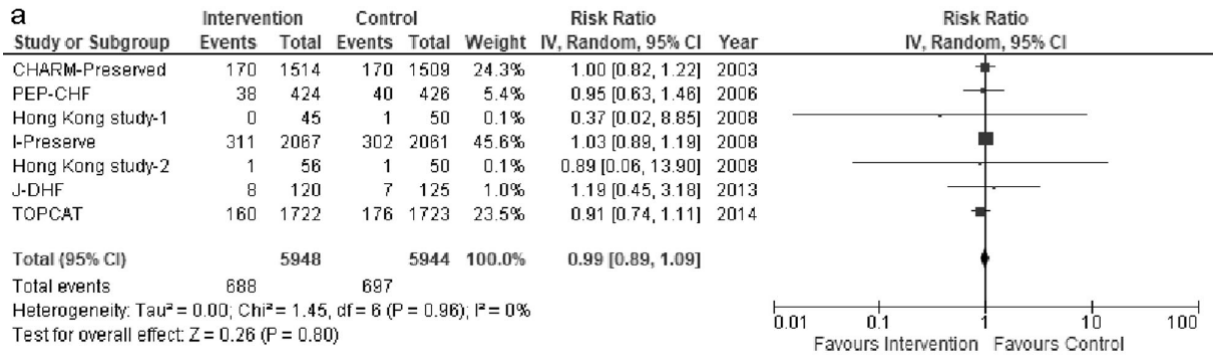
Author and year of publication	Patients (including inclusion criteria)	Intervention	Comparison	Duration of follow-up (years)
Yusuf (CHARM-Preserved) 2003	$n = 3023$; mean age, 67 years; woman, 71%; Inclusion criteria, ≧18 years, HFpEF (EF ≧ 40%), NYHA II-IV a history of hospital admission for a cardiac reason	Candesartan ($n = 1514$) HT 65% SBP (mmHg): 136.3 (before) → 129.1 (during trials)	Placebo ($n = 1509$) HT 64% SBP (mmHg): 136.3 (before) → ? (during trial	3.1 (median)
Zi 2003	$n = 74$; mean age, 78 years; woman, 65%; Inclusion criteria, >65 years, HFpEF (EF ≧ 40%), HF as defined by Framingham criteria, NYHA I-III	Quinapril ($n = 36$) HT 28% SBP (mmHg): 140.0 → 128.0	Placebo ($n = 38$) HT 32% SBP (mmHg): 135.0 → 137.0	0.5
Cleland (PEP-CHF) 2006	$n = 850$; mean age, 75 years; woman, 56%; Inclusion criteria, ≧70 years, HFpEF (EF ≧ 40%) treated with diuretics for a clinical diagnosis of CHF within 6 monthsNYHA II-IV	Perindopril ($n = 424$) HT 79% SBP (mmHg): 138.0 → 135.0	Placebo ($n = 426$) HT 79% SBP (mmHg): 140.0 → 138.0	2.1 (median)
Yip (HK-DHF) 2008	$n = 151$, mean age 74 years, woman, 62%, Inclusion criteria, >18 years, HFpEF (EF ≧ 45%), clinical history of HF within 2 months, NYHA II-IV	Ramipril/Irbesartan [$n = 101$(45/56)] HT 82%/84% SBP (mmHg): 143.0 → 141.0/ 145.0 → 137.0	Diuretics ($n = 50$) HT 80% SBP (mmHg): 145.0 → 138.0	1
Massie (I-PRESERVE) 2008	$n = 4128$, mean age 72 years, woman, 60%, ≧Inclusion criteria, 60 years, HFpEF (EF ≧ 45%), hospitalization for HF with NYHA II-IV during the previous 6 months or ongoing NYHA III or IV symptoms	Irbesartan ($n = 2067$) HT 89% SBP (mmHg): 137.0 → 133.2	Placebo ($n = 2061$) HT 88% SBP (mmHg): 136.0 → 135.8	4.1 (mean)
Deswal (RAAM-PEF) 2011	$n = 44$; mean age 70 years; woman, 6.8%; Inclusion criteria, HFpEF (EF ≧ 50%), ≧18 years, CHF with NYHA II or III for ≧2 months and BNP level ≧100	Eplerenone ($n = 21$) HT 100% SBP (mmHg): 129.7 → 126.4	Placebo ($n = 23$) HT 100% SBP (mmHg): 131 → 13(	0.5
Yamamoto K (J-DHF) 2013	$n = 245$; mean age 72 years; woman, 42%; Inclusion criteria, ≧20 years, HFpEF (EF ≧ 40%), clinical diagnosis of HF based on a slight modification of Framingham criteria	Carvedilol ($n = 120$) HT 81% SBP (mmHg): 134.0 → 131.0	Placebo ($n = 125$) HT 81% SBP (mmHg): 133.0 → 132.0	3.2 (median)
Edelmann (Aldo-DHF) 2013	$n = 422$; mean age 67 years; woman, 48%; Inclusion criteria, ≧50 years, HFpEF (EF ≧ 50%), current HF symptom consistent with NYHA II-III	Spironolactone ($n = 213$) HT 92% SBP (mmHg): 135.0 → 128.0	Placebo ($n = 209$) HT 91% SBP (mmHg): 135.0 → 137.0	1
Pitt (TOPCAT) 2014*	$n = 3445$; mean age 69 years; woman, 52%, Inclusion criteria, ≧50 years, HFpEF (EF ≧ 45%), at least one sign and one symptom of HF, or a history of hospitalization within 12 months with management of HF, or an elevated natriuretic peptide level within 60 days, NYHA I-IV	Spironolactone ($n = 1722$) HT 91% America ($n = 886$)[a] SBP (mmHg): 127.0 → 124.8 Russia ($n = 836$)* SBP (mmHg): 131.0 → 128.1	Placebo ($n = 1723$) HT 92% America ($n = 881$)[a] SBP (mmHg): 127.0 → 128.9 Russia ($n = 842$)* SBP (mmHg): 131.0 → 128.9	3.3 (mean)
Miura (SUPPORT subanalysis) 2016	$n = 709$; mean age 66 years; Woman, 29%; Inclusion criteria, HFpEF (EF ≧ 50%), hypertensive CHF, NYHA II-IV	Olmesartan ($n = 363$) (ACE and/or β blocker+ olmesartan) HT 100% SBP (mmHg): 131.5 → 123.0	Control ($n = 346$) (ACE and/or β+ not AR HT 100% SBP (mmHg): 130.1 → 125.0	4.4 (median)

Studienergebnisse:

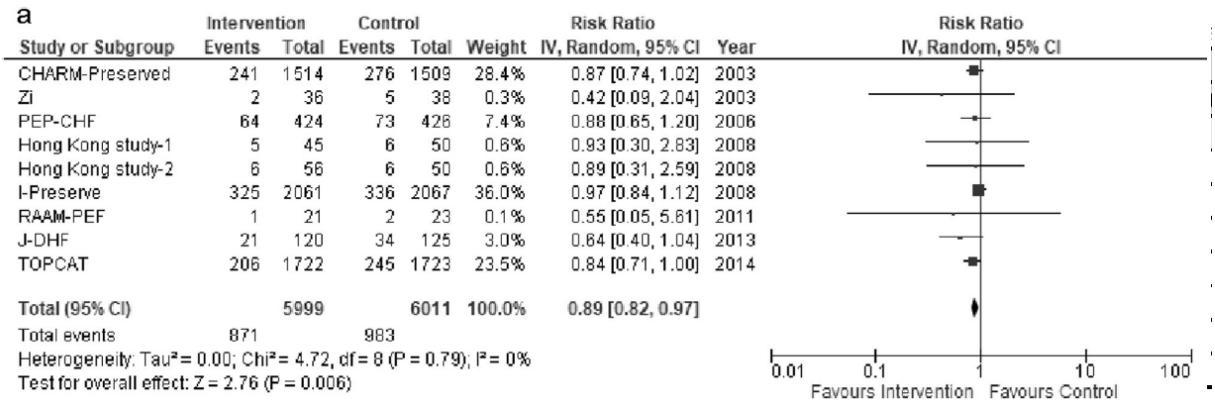
- All-cause mortality



- Cardiovascular mortality



- Heart failure hospitalization



- Worsening renal function
  - We analyzed nine RCTs that included data about the occurrence of worsening renal function, and the metaanalysis of those nine RCTs demonstrated an increased occurrence of worsening renal function in the intervention group compared to that in the control group [RR 1.52 (1.31–1.76), P < 0.00001].
- Hypotension
  - We analyzed five RCTs that included data about the occurrence of hypotension, and the meta-analysis of those five RCTs demonstrated that there was no significant occurrence of hypotension between the intervention and control groups [RR 1.36 (0.75–2.46), P=0.31].

Anmerkung/Fazit der Autoren

In general, HFpEF is defined when LVEF is ≥50%. The present study includes RCTs that having various definitions of HFpEF, i.e., LVEF ranging from >40% to >50%. Recently, HF with LVEF in the range of 40–49% has been regarded as HF with borderline EF or HF with mid-range EF (HFmrEF). Thus, it should be considered possible that not only patients with HFpEF but also those who have HF with borderline EF or HFmrEF were included in the present study.

In patients with HFpEF, SBP lowering to ~130 mmHg was related to a risk reduction of HF hospitalization. Nevertheless, careful attention should be paid to potential increases in renal dysfunction and other adverse events. Further RCTs are needed to confirm the treatment effects of intensive BP lowering in patients with HFpEF.

Kommentare zum Review

Die Meta-Analyse beinhaltet eine Studie, in der Eplerenon eingesetzt wurde. Eplerenon hat in Deutschland keine Zulassung für die vorliegende Indikation.

Khan MS et al., 2017 [8].

Renin-angiotensin blockade in heart failure with preserved ejection fraction: a systematic review and meta-analysis

- Siehe auch folgenden systematischen Review mit vergleichbaren Ergebnissen:
  - Fukuta H et al., 2017. Effect of renin-angiotensin system inhibitors on mortality in heart failure with preserved ejection fraction: a meta-analysis of observational cohort and randomized controlled studies [5].

Fragestellung

In an attempt to pool all the evidence quantitatively and qualitatively, we conducted this systematic review and meta-analysis of randomized clinical trials and observational studies to better understand the effect of ACE-I and ARBs on outcomes in HFpEF.

Methodik

Population:

- Patients with heart failure with preserved ejection fraction

Intervention:

- ACE-I or ARBs

Komparator:

- placebo or standard therapy

Endpunkte:

- all cause mortality
- HF hospitalization
- cardiovascular death
- total hospitalizations
- composite endpoint of HF hospitalization and all-cause mortality

Recherche/Suchzeitraum:

- Bis Januar 2016

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs, 6 Kohortenstudien
- Im Folgenden werden nur die RCTs betrachtet

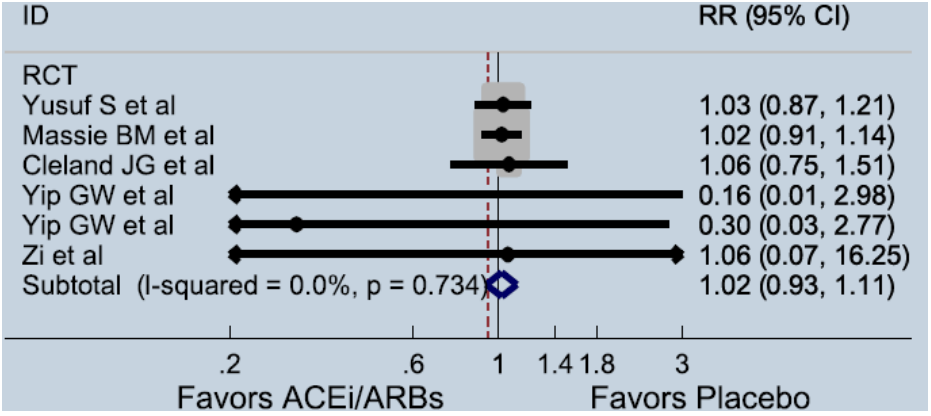
Charakteristika der Population und Qualität der Studien:

Author	Publication year	Design	Treatment	Sample	Age (years)	Follow-up (months)	Mean LVEF	HFpEF definition	Jadad score
Cleland *et al.*[6]	2006	RCT	ACE-I	424/426	75	26	64.5	40	6
Yip *et al.*[16]	2008	RCT	ACE-I	45/50	73	12	65.6	45	3
Yip *et al.*[16]	2008	RCT	ARBs	56/50	74	12	67.4	45	3
Kitzman *et al.*[23]	2010	RCT	ACE-I	35/36	69	12	65	50	6
Zi *et al.*[19]	2003	RCT	ACE-I	36/38	78	6	58.6	40	4
Massie *et al.*[7]	2008	RCT	ARBs	2067/2061	72	49	59.5	45	5
Yusuf *et al.*[5]	2003	RCT	ARBs	1514/1509	67	8	54	40	6
Parthasarathy *et al.*[22]	2009	RCT	ARBs	70/82	62	3	71	40	4

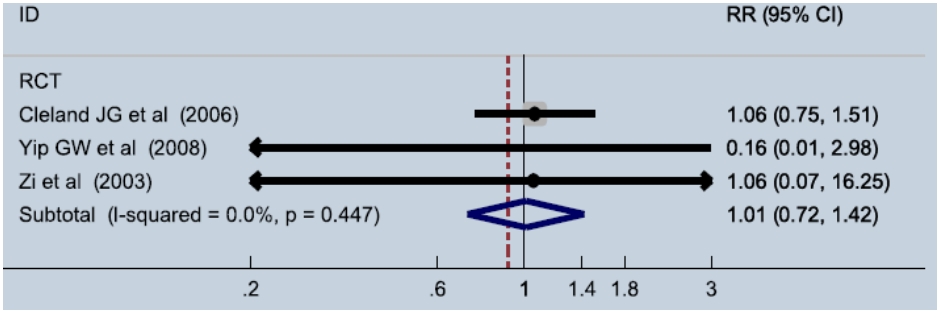
- In den RCTs wurden folgende Arzneimittel betrachtet: Candesartan (Yusuf et al.), Irbesartan (Massie et al.), Perindopril (Cleland et al.), Diuretika, Irbesartan und Ramipril (Yip et al.), Quinapril (Zi et al.), Valsartan (Parthasarathy et al.), Enalapril (Kitzman et al.).

Studienergebnisse:

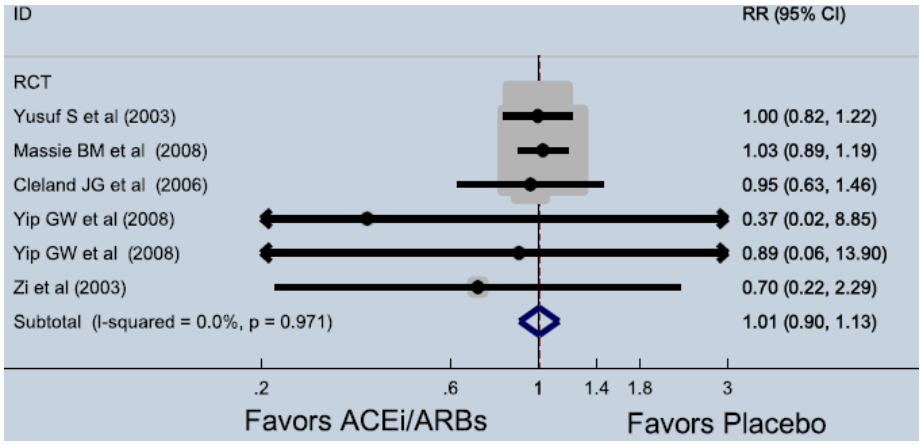
- Effect of angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (RCBs) on all-cause mortality



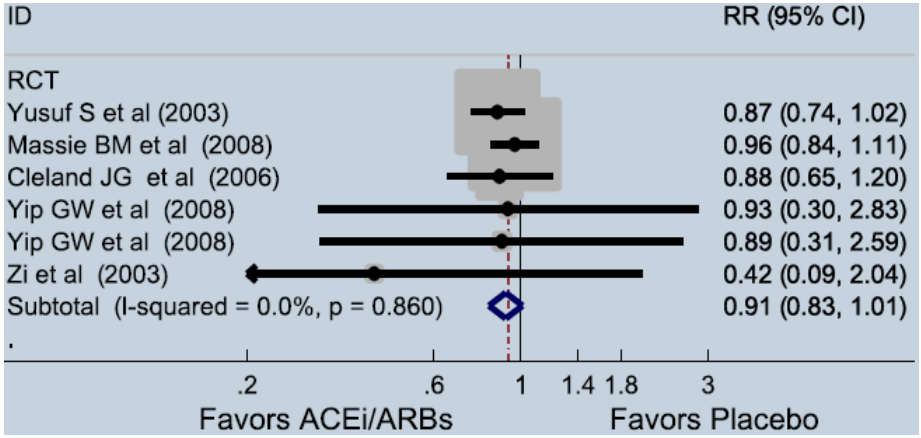
- Effect of ACE-Is on all-cause mortality



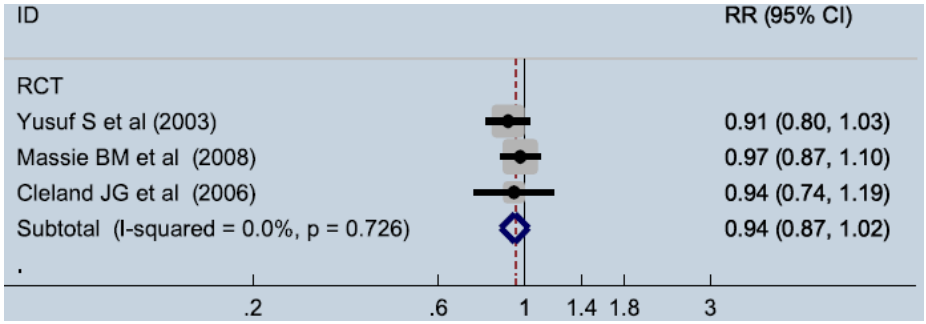
- Effect of angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (RCBs) on cardiovascular mortality



- Effect of angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (RCBs) on hospitalizations due to heart failure



- Effect of ACE-I and RCBs on hospitalizations or mortality



Anmerkung/Fazit der Autoren

The only large randomized trial (perindopril in elder people with chronic HF study) of ACE-I in patients with HFpEF did not suggest any improvement in clinical outcomes. However, it is important to recognize the many trial factors that might have caused the therapy to fail. There was a very high dropout rate of almost 40% owing to a prolonged recruitment period. Moreover, almost one-third of the patients also received open-label ACE-I after first year of follow-up. This can potentially explain the lack of ACE-I effect found in the latter part of the trial, in contrast to the positive signal earlier in the trial. The two large randomized trials of ARBs (Candesartan in Heart Failure—Assessment of Mortality and Morbidity- Preserved Trial and Irbesartan in Heart Failure with Preserved Systolic Function-Preserved Trial) had heterogeneity in the enrolled

patient population. Both trials used lower EF threshold for HFpEF and neither used diastolic function as an entry criterion. In fact, in the Candesartan in Heart Failure—Assessment of Mortality and Morbidity-Preserved Echocardiographic Substudy, nearly two-thirds of patients had no or mild diastolic dysfunction, a feature generally believed as central to the HFpEF condition. Stage of the disease may also impact results because ARB was more effective in patients who with lower natriuretic peptide levels.

Zhang Q et al., 2016 [16].

Effects of renin-angiotensin-aldosterone system inhibitors on mortality, hospitalization, and diastolic function in patients with HFpEF. A meta-analysis of 13 randomized controlled trials.

- Siehe auch folgenden systematischen Review mit vergleichbaren Ergebnissen:
  - Emdin CA et al., 2015. Meta-Analysis of Large-Scale Randomized Trials to Determine the Effectiveness of Inhibition of the Renin-Angiotensin Aldosterone System in Heart Failure [3].

Fragestellung

This meta-analysis was designed to assess the role of RAAS inhibitors on mortality, hospitalization, diastolic function, and exercise capacity in patients with HFpEF.

Methodik

Population:

- HFpEF (defined as signs or symptoms of heart failure with an EF > 40 %)

Intervention:

- RAAS inhibitors

Komparator:

- K.A:

Endpunkte:

- Mortality
- Hospitalization
- diastolic function (such as E/A velocity ratio)
- 6-min walk distance (6MWD)

Recherche/Suchzeitraum:

- Bis August 2014

Qualitätsbewertung der Studien:

- Jadad quality scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 RCTs (12,532 patients), including 6 papers on mineralocorticoid-receptor antagonists, 5 on ARBs, and 4 on ACEis.

Charakteristika der Population und Qualität der Studien:

First author (year)	Treatment	Control	Age (year)	Definition of HFPEF (LVEF, %)	Sample Size (T/C)	Follow-up (months)	Jadad score
Cleland JG (2006) [24]	Perindopril	Placebo	75.00	40	424/426	26.2	6
Deswal A (2011) [14]	Eplerenone	Placebo	70.37	50	21/23	6	3
Edelmann F (2013) [13]	Spironolactone	Placebo	67.00	50	213/209	12	7
Kitzman DW (2010) [23]	Enalapril	Placebo	69.51	50	35/36	12	6
Kurrelmeyer KM (2014) [15]	Spironolactone	Placebo	71.35	50	24/24	6	5
Mak GJ (2009) [17]	Eplerenone	Placebo	79.55	45	24/20	12	1
Massie BM (2008) [19]	Irbesartan	Placebo	72.00	45	2067/2061	49.5	5
Mottram PM (2013) [16]	Spironolactone	Placebo	62	50	2067/2061	6	5
Parthasarathy HK (2009) [20]	Valsartan	Placebo	62.13	40	70/82	3.3	4
Pitt B (2014) [12]	Spironolactone	Placebo	68.70	45	1722/1723	39.6	7
Yip GW (2008)[a] [18]	Irbesartan + diuretics	Diuretics	74.06	45	56/50	12	3
Yip GW (2008) [18]	Ramipril + diuretics	Diuretics	73.47	46	45/50	12	3
Yusuf S (2003) [22]	Candesartan	Placebo	67.15	40	1514/1509	8.5	7
Zi M (2003) [25]	Quinapril	Placebo	78	40	36/38	6	3

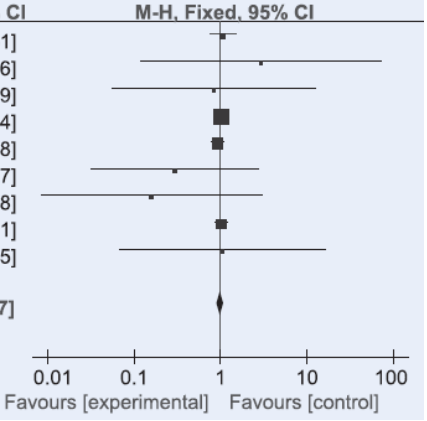
Studienergebnisse:

- all-cause mortality

a

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cleland 2006	56	424	53	426	5.2%	1.06 [0.75, 1.51]
Edelmann 2013	1	213	0	209	0.0%	2.94 [0.12, 71.86]
Mak 2009	1	24	1	20	0.1%	0.83 [0.06, 12.49]
Massie 2008	445	2067	436	2061	43.2%	1.02 [0.91, 1.14]
Pitt 2014	252	1722	274	1723	27.1%	0.92 [0.79, 1.08]
Yip 2008a	1	56	3	50	0.3%	0.30 [0.03, 2.77]
Yip 2008b	0	45	3	50	0.3%	0.16 [0.01, 2.98]
Yusuf 2003	244	1514	237	1509	23.5%	1.03 [0.87, 1.21]
Zi 2003	1	36	1	38	0.1%	1.06 [0.07, 16.25]
Total (95% CI)		**6101**		**6086**	**100.0%**	**0.99 [0.92, 1.07]**
Total events	1001		1008			

Heterogeneity: Chi² = 4.45, df = 8 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.83)

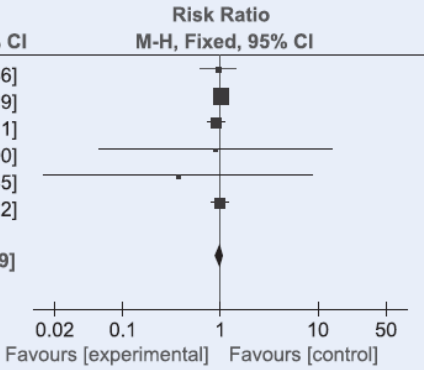


- cardiovascular (CV) mortality

b

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cleland 2006	38	424	40	426	5.8%	0.95 [0.63, 1.46]
Massie 2008	311	2067	302	2061	43.8%	1.03 [0.89, 1.19]
Pitt 2014	160	1722	176	1723	25.5%	0.91 [0.74, 1.11]
Yip 2008a	1	56	1	50	0.2%	0.89 [0.06, 13.90]
Yip 2008b	0	45	1	50	0.2%	0.37 [0.02, 8.85]
Yusuf 2003	170	1514	170	1509	24.6%	1.00 [0.82, 1.22]
Total (95% CI)		**5828**		**5819**	**100.0%**	**0.98 [0.89, 1.09]**
Total events	680		690			

Heterogeneity: Chi² = 1.31, df = 5 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)

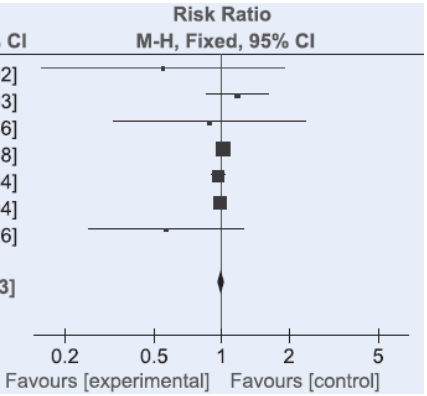


- All-cause hospitalization

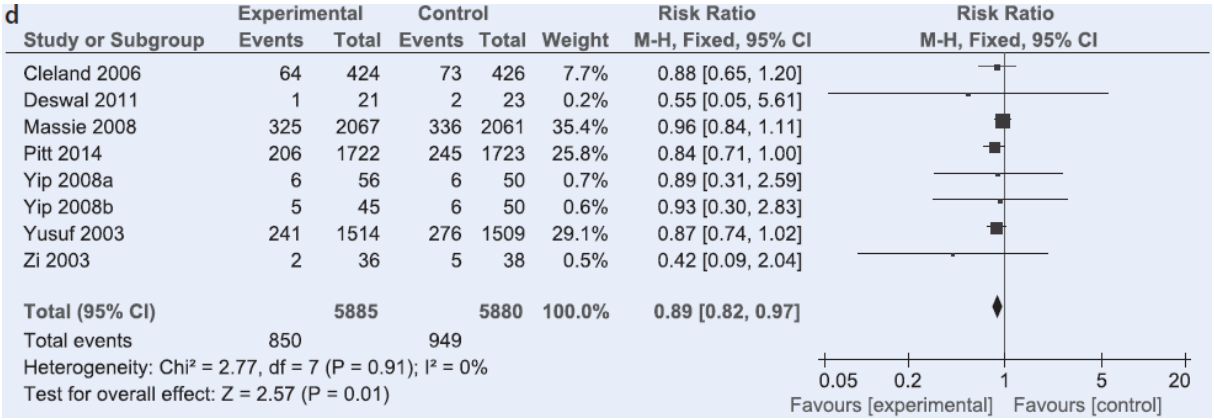
c

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Deswal 2011	3	21	6	23	0.2%	0.55 [0.16, 1.92]
Edelmann 2013	60	213	50	209	1.7%	1.18 [0.85, 1.63]
Kitzman 2010	6	35	7	36	0.2%	0.88 [0.33, 2.36]
Massie 2008	1152	2067	1126	2061	38.6%	1.02 [0.97, 1.08]
Pitt 2014	766	1722	792	1723	27.1%	0.97 [0.90, 1.04]
Yusuf 2003	912	1514	922	1509	31.6%	0.99 [0.93, 1.04]
Zi 2003	7	36	13	38	0.4%	0.57 [0.26, 1.26]
Total (95% CI)		**5608**		**5599**	**100.0%**	**0.99 [0.96, 1.03]**
Total events	2906		2916			

Heterogeneity: Chi² = 5.30, df = 6 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.76)



- Heart failure related hospitalization



- Exercise capacity
  - There is no significant effect on exercise capacity between the two groups (MD 0.65; 95 % CI −8.07 to 9.36; p = 0. 88)
- Subgruppen-Analyse

Subgroup	All-cause mortality	CV mortality	All-cause hospitalization	HF hospitalization	6MWD
	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	MD (95%CI)
Age (year)					
≥70.9	1.01 (0.91, 1.13)	1.02 (0.88, 1.17)	1.01 (0.96, 1.07)	0.94 (0.83, 1.07)	8.81 (−4.77, 22.39
<70.9	0.97 (0.87, 1.09)	0.95 (0.83, 1.10)	0.98 (0.94, 1.03)	0.86 (0.76, 0.96)	−5.07 (−16.43, 6.30)
SBP (mmHg)					
≥140	0.40 (0.12, 1.37)	UN	UN	UN	−9.31 (−30.04, 11.42)
<140	1.00 (0.92, 1.08)	0.99 (0.89, 1.09)	0.99 (0.96, 1.03)	0.89 (0.82, 0.97)	2.79 (−6.82, 12.39)
Follow-up (months)					
>8.5	0.98 (0.90, 1.07)	0.98 (0.87, 1.10)	1.00 (0.96, 1.05)	0.91 (0.82, 1.01)	−3.03 (−14.67, 8.61)
≤8.5	1.03 (0.87, 1.21)	UN	0.98 (0.92, 1.04)	0.86 (0.74, 1.01)	5.35 (−7.81, 18.50)
Drug					
MRA	0.92 (0.79, 1.08)	UN	0.98 (0.91, 1.05)	0.84 (0.71, 1.00)	−9.13 (−26.29, 8.03)
ACEI	1.01 (0.72, 1.42)	0.93 (0.61, 1.42)	0.68 (0.37, 1.26)	0.92 (0.83, 1.02)	9.18 (−6.39, 24.75)
ARB	1.02 (0.92, 1.12)	1.02 (0.90, 1.14)	1.00 (0.97, 1.05)	0.86 (0.64, 1.15)	0.30 (−13.01, 13.61)
LVEF cut-off (%)					
EF ≥45	0.97(0.89, 1.07)	0.98 (0.87, 1.11)	1.00 (0.96, 1.05)	0.91(0.82, 1.01)	−9.2 (−22.42, 4.01)
EF ≥50	UN	None	1.09 (0.81, 1.46)	UN	−9.09 (−25.11, 6.92)

Anmerkung/Fazit der Autoren

primary outcome: RAAS inhibitors might reduce the rate of heart failure related hospitalization, but had no significant effect on reducing all cause or cardiovascular mortality and all cause hospitalization; (2) secondary outcome: RAAS inhibitors had a significant effect on improving the E/e' velocity ratio compared with the controls. However, the results from this meta-analysis were still not sufficient to prove the effectiveness of RRAS inhibitors on the other diastolic function parameters; and (3) tertiary outcome: RAAS inhibitors could not increase 6MWD in patients suffering from HFpEF, which indicated little effect of the RAAS inhibitors on improving the cardiopulmonary function.

According to the current guidelines, patients with EF between 40 and 50 % are defined as an intermediate group. Their features, therapy models and prognoses seem to be similar to patients with HFpEF, who were identified by an EF > 50 %. In our meta analysis, when different cut-offs (45 and 50 %) were used in the subgroup analyses, the results were similar to our original

conclusion. Thus, this meta analysis included studies using EF ≥ 40 % as the EF cut-off criterion of HFpEF.

The treatment period may not be long enough to achieve an improved diastolic function. Ten studies had a mean follow-up periods of ≤ 12 months, while only three studies had an observable mean follow-up periods > 12 months. Subgroup analysis indicated that a longer follow- up with medication might be more effective than short-term medication.

Subgroup analysis showed that the effects of the three types of RAAS inhibitors were inconsistent. Aldosterone receptor blockade reduced heart failure rehospitalization and improved the E/e' index significantly, while the ACEi subgroup had a tendency to decrease HF-related hospitalization, with no significant differences in the E/e' index compared with the control group. The ARB subgroup showed no effect in reducing HF rehospitalization in contrast to the control group. These results may be explained by the use of the other RAAS inhibitors. In the I-PRESERVE study, 40 % of the patients received ACEi and 29 % received spironolactone. Kitzman DW et al. [23] mentioned that they could not exclude the patients receiving ARB from their research. In the CHARM study [22], 19 % of the patients took ACEi and 11 % took spironolactone. The use of other RAAS inhibitors may lead to crossover effects and different results. Second, this condition can also be interpreted as an 'aldosterone breakthrough'. In clinical trials using ACEi or ARBs as the intervention, some patients' plasma aldosterone levels decreased at first and then elevated over a long period of time, which was called 'aldosterone breakthrough'.

There are several limitations in our meta- analysis. First, the inclusion of studies with a follow-up of less than one year may lead to an excessively low estimation of mortality and hospitalization. Among the 13 included studies, six studies had a follow-up of less than 1 year, with one study having a 3.3 month follow-up.

Kommentare zum Review

Die Meta-Analyse beinhaltet zwei Studien, in denen Eplerenon eingesetzt wurde. Eplerenon hat in Deutschland keine Zulassung für die vorliegende Indikation.

3.4 Leitlinien

Bundesärztekammer (BÄK) et al., 2017 [2].

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

Nationale VersorgungsLeitlinie Chronische Herzinsuffizienz, Langfassung, 2. Auflage, 2017, Version 3.

Fragestellung

Die NVL Chronische Herzinsuffizienz soll zur Verbesserung der sektorenübergreifenden Versorgung von Patienten mit chronischer Herzinsuffizienz beitragen. Dazu wird sowohl die Versorgung im gesamten ambulanten Be-reich, als auch in Teilaspekten des stationären Bereichs (Behandlung der akuten Dekompensation, invasive The-rapien) adressiert. Außerdem werden die Übergänge zwischen primärärztlicher und spezialfachärztlicher Versor-gung sowie zwischen ambulanter und stationärer Versorgung definiert.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Die erste Auflage der NVL Chronische Herzinsuffizienz basierte auf einer Leitliniensynopse nationaler und internationaler Leitlinien. Auf eine neue eigene Leitlinienrecherche und -bewertung für die 2. Auflage wurde verzichtet und auf eine aktuelle Leitliniensynopse zurückgegriffen, die vom IQWiG im Rahmen der Aktualisierung des DMP Chronische Herzinsuffizienz erstellt worden war [10]. Anstelle der in der IQWiG-Synopse enthaltenen ESC-Leitlinie von 2012 [11] wurde die Neuauflage dieser Leitlinie [12] verwendet und einer strukturierten methodischen Bewertung mithilfe von AGREE unterzogen (siehe Leitlinienreport [9]). Darüber hinaus wurden 14 ergänzende systematische Recherchen durchgeführt.
- Systematische Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.
- Diese Leitlinie wurde am 31. August 2017 durch die Träger des NVL-Programms verabschiedet und ist bis zur nächsten Überarbeitung bzw. spätestens bis Ende August 2022 gültig.

10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). Systematische Leitlinienrecherche und -bewertung sowie Extraktion relevanter Empfehlungen für ein DMP Chronische Herzinsuffizienz. Abschlussbericht. Auftrag V14-01. Version 1.0. IQWiG-Berichte; 342. 2016 [cited: 2016-03-16]. http://www.iqwig.de/download/V14-01_Abschlussbericht_Leitlinienrecherche-und-bewertung-fuer-ein-DMP-Chronische-Herzinsuffizienz.pdf.
11. 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.
12. Ponikowski P, Anker SD, Voors AA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2016: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society

of Cardiology. Developed with the special contribution Heart Failure Association (HFA) of the ESC. 2016 [cited: 2017-03-30].

Recherche/Suchzeitraum:

- Recherche: bis 2016

LoE

- Bewertung der Evidenz anhand der Level of Evidence nach Oxford Center of Evidence Based Medicine, sowie Bewertung der Evidenz mittels AMSTAR für Übersichtsarbeiten und SIGN Checkliste für Primärliteratur. Die Leitlinien wurden durch das IQWiG mit AGREE bewertet

GoR

Empfehlungsgrad	Beschreibung	Formulierung	Symbol
A	starke Empfehlung	Soll (nicht)	⇑⇑ (⇓⇓)
B	Empfehlung	Sollte (nicht)	⇑ (⇓)
0	offen	kann	⇔

Ab der 2. Auflage wird der Überarbeitungsstand der Empfehlungen mit „bestätigt“, „modifiziert“ oder „neu“ sowie dem Jahr der letzten Aktualisierung gekennzeichnet. Dabei enthalten modifizierte Empfehlungen im Vergleich zur Vorversion inhaltliche Änderungen, während bestätigte Empfehlungen nicht oder lediglich redaktionell geändert wurden.

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

Terminologie ab 2. Auflage, 2017

Ab der 2. Auflage der NVL ersetzt die an der LVEF orientierte Charakterisierung der Herzinsuffizienz die bisherigen Bezeichnungen „systolische/diastolische Herzinsuffizienz“ (Definition nach [12]):

Tabelle 2: Definition der Herzinsuffizienz mit reduzierter, geringgradig eingeschränkter sowie erhaltener linksventrikulärer Ejektionsfraktion

Herzinsuffizienz mit reduzierter linksventrikulärer Ejektionsfraktion (Heart Failure with reduced Ejection Fraction, HFrEF)	Herzinsuffizienz mit geringgradig eingeschränkter linksventrikulärer Ejektionsfraktion (heart failure with mid-range Ejection fraction, HFmrEF)	Herzinsuffizienz mit erhaltener linksventrikulärer Ejektionsfraktion (Heart Failure with preserved Ejection Fraction, 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

Obwohl nahezu die Hälfte der Patienten an einer diastolischen Herzinsuffizienz (Herzinsuffizienz bei erhaltener systolischer Funktion) leiden, sind diese Patienten in Therapiestudien bisher unterrepräsentiert oder gar ausgeschlossen. Aus diesem Grund wird die bisher existierende Evidenz für Patienten mit diastolischer Dysfunktion (Herzinsuffizienz bei erhaltener systolischer Funktion) als unzureichend eingeschätzt.

Medikamentöse Therapie bei Herzinsuffizienz mit erhaltener linksventrikulärer Ejektionsfraktion (HFpEF)

6-22 neu 2017 Wenn bei Patienten mit Herzinsuffizienz mit erhaltener linksventrikulärer Ejektionsfraktion Komorbiditäten vorliegen, sollen diese gemäß der jeweiligen Leitlinie behandelt werden. Expertenkonsens	⇑⇑
6-23 neu 2017 Patienten mit Herzinsuffizienz und erhaltener linksventrikulärer Ejektionsfraktion und Zeichen einer Flüssigkeitsretention sollen symptomorientiert Diuretika empfohlen werden. Quellleitlinie [12]	⇑⇑

Die Evidenzlage zur medikamentösen Therapie von Patienten mit Herzinsuffizienz mit erhaltener linksventrikulärer Ejektionsfraktion (HFpEF) ist unzureichend, da diese Patienten in den meisten großen randomisierten Studien zur chronischen Herzinsuffizienz ausgeschlossen wurden [185] und in keiner randomisierten Studie mit diesen Patienten bisher ein klarer Nutzen hinsichtlich Mortalität, Morbidität und verbesserter Symptomatik nachgewiesen werden konnte:

- ACE-Hemmer: PEP-CHF (Perindopril) [222]; Komposit-Endpunkt kardiovaskuläre Mortalität und kardiovaskulär bedingte Hospitalisierungen nicht signifikant (35% vs. 37%, p = 0,30);
- ARB: CHARM-Preserved (Candesartan) [266]; Komposit-Endpunkt kardiovaskuläre Mortalität und Herzinsuffizienz-bedingte Hospitalisierungen nicht signifikant (22% vs. 24%, adjustierter p = 0,051); I-PRESERVE (Irbesartan) [267]: kombinierter Endpunkt Gesamtmortalität und Herzinsuffizienz-bedingte Hospitalisierungen nicht signifikant (36% vs. 37%, p = 0,35);
- MRA: Aldo-DHF (Spironolacton)[268]; diastolische Funktion signifikant verbessert (E/e' MD -1,5; p < 0,001), keine signifikante Änderung der maximalen Belastungsfähigkeit (peak VO2 p = 0,81), Mortalität und Hospitalisierungen nicht berichtet; TOPCAT (Spironolacton) [269]: Komposit-Endpunkt kardiovaskulärer Tod, überlebter Herzstillstand oder Herzinsuffizienz-bedingte Hospitalisierungen nicht signifikant (19% vs. 20%, p = 0,14);
- ARNI: PARAMOUNT (Sacubitril/Valsartan) [270]; signifikante Reduktion NT-proBNP (0,77, p = 0,005), Mortalität, Morbidität und Hospitalisierungen nicht berichtet;
- Digitalisglykoside: DIG-PEF (Digoxin) [271]: Komposit-Endpunkt Herzinsuffizienz-bedingte Mortaliät und Herzinsuffizienz-bedingte Hospitalisierungen nicht signifikant (21% vs 24%, p = 0,14);
- Phosphodiesterase-5-Hemmer: RELAX (Sildenafil) [272]: keine Veränderung der maximalen Belastungsfähigkeit (peak VO2 p = 0 ,90).

Aufgrund der unzureichenden Evidenzlage sprechen die Autoren keine Empfehlung zur spezifischen medikamentösen Therapie der HFpEF aus. Die Therapieempfehlungen für die HFpEF orientieren sich daher an der Behandlung prognostisch relevanter Komorbiditäten. Dabei spielt die arterielle Hypertonie die größte Rolle.

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 (siehe Kapitel 1.2 Formen der chronischen Herzinsuffizienz).

185. 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.
222. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001;357(9266):1385-90.
266. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362(9386):777-81.
267. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction. N Engl J Med 2008.
268. Edelmann F, Wachter R, Schmidt AG, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA 2013;309(8):781-91. DOI: 10.1001/jama.2013.905.
269. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370(15):1383-92. DOI: 10.1056/NEJMoa1313731.
270. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012;380(9851):1387-95. DOI: 10.1016/S0140-6736(12)61227-6.
271. Ahmed A, Rich MW, Fleg JL, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation 2006;114(5):397-403. DOI: 10.1161/CIRCULATIONAHA.106.628347.
272. Heart Failure Clinical Research Network (HFN), Redfield MM, Chen HH, et al. 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(12):1268-77. DOI: 10.1001/jama.2013.2024.

Medikamentöse Therapie bei Herzinsuffizienz mit reduzierter linksventrikulärer Ejektionsfraktion (HFrEF)

Die Empfehlungen für Patienten mit HFrEF sind aus Sicht der Leitlinienersteller auch auf Patienten mit geringgradig eingeschränkter linksventrikulärer Ejektionsfraktion (LVEF 40-49%) (HFmrEF) anwendbar und werden daher im Folgenden dargestellt.

Im Mittelpunkt der medikamentösen Therapie der 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.

Tabelle 21: Medikamentöse Stufentherapie nach NYHA-Klassen bei Herzinsuffizienz mit reduzierter LVEF

		NYHA I (asymptomatische LV-Dysfunktion)	NYHA II	NYHA III	NYHA IV (nur 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
	Mineralokortikoid-rezeptorantagonisten		indiziert*	indiziert	indiziert
	Ivabradin		bei Betarezeptoren-blocker-Intoleranz oder additiv bei Patienten mit Herzfrequenz ≥ 75/min	bei Betarezeptoren-blocker-Intoleranz oder additiv bei Patienten mit Herzfrequenz ≥ 75/min	bei Betarezeptoren-blocker-Intoleranz oder additiv bei Patienten mit Herzfrequenz ≥ 75/min
	Sacubitril/Valsartan		als ACE-Hemmer/ARB-Ersatz bei persistierender Symptomatik**	als ACE-Hemmer/ARB-Ersatz bei persistierender Symptomatik**	als ACE-Hemmer/ARB-Ersatz bei persistierender Symptomatik**
symptomverbessernd	Diuretika		bei Flüssigkeitsretention	indiziert	indiziert
	Digitalisglykoside			bei Sinusrhythmus als Reservemittel (mit niedrigem Zielserumspiegel)	bei Sinusrhythmus als Reservemittel (mit niedrigem Zielserumspiegel)
		bei nicht beherrschbarem tachyarrhythmischem Vorhofflimmern			

* bei persistierender Symptomatik unter leitliniengerechter Kombinationstherapie mit ACE-Hemmern/ARB und Betarezeptorenblockern

** trotz leitliniengerechter Kombinationstherapie mit ACE-Hemmern/ARB, Betarezeptorenblockern und Mineralokortikoid-Rezeptorantagonisten

Empfohlene Basismedikation

Empfehlungen/Statements	Empfehlungsgrad
6-5 modifiziert 2017 Allen symptomatischen sowie asymptomatischen Patienten mit einer nachgewiesenen reduzierten Ejektionsfraktion und fehlenden Kontraindikationen sollen ACE-Hemmer empfohlen werden. Quellleitlinien [12; 13], Literatur [186-190]	⇑⇑

Internationale Leitlinien empfehlen übereinstimmend den Einsatz von ACE-Hemmern bei allen Patienten mit Herzinsuffizienz mit reduzierter LVEF (HFrEF) [12; 13]. In RCTs [186; 187; 191; 192] und Metaanalysen [193; 194] 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 Hospitalisierungs-rate senken sowie die Symptomatik und Belastungstoleranz verbesser. Bei herzinsuffizienten Patienten nach Myokardinfarkt senken ACE-Hemmer darüber hinaus die Re-Infarktrate [187; 191; 192].

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 [195]. In Abhängigkeit vom Mortalitätsrisiko schwanken die Effektmaße in den ausgewerteten Studien deshalb erheblich:

• CONSENSUS 1987 [188]: NYHA IV, Follow-up 6 Monate, Enalapril vs. Placebo, Mortalität: ARR 15%, NNT 6 Monate = 7;

• SOLVD 1991 [189]: ~ 90% Patienten NYHA II oder III, Follow-up 3,5 Jahre, Enalapril vs. Placebo, Mortalität: ARR 4,5%, NNT 42 Monate = 22;

• SOLVD 1992 [190]: 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.

12. Ponikowski P, Anker SD, Voors AA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2016: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology. Developed with the special contribution Heart Failure Association (HFA) of the ESC. 2016 [cited: 2017-03-30].
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.
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.
187. Pfeffer MA, Braunwald E, Moye 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(10):669-77. http://www.ncbi.nlm.nih.gov/pubmed/1386652.
188. 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. http://www.ncbi.nlm.nih.gov/pubmed/2883575.
189. 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. http://www.ncbi.nlm.nih.gov/pubmed/2057034.
190. 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.
191. Cleland JG, Erhardt L, Murray G, et al. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial 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.
192. 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.
193. 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.
194. 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.
195. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: 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

Empfehlungen/Statements	Empfehlungs-grad
6-7 bestätigt 2017 Patienten mit symptomatischer Herzinsuffizienz (NYHA II-IV), die ACE-Hemmer nicht tolerieren, sollen Angiotensinrezeptorblocker empfohlen werden. Quellleitlinien [12; 13], Literatur [202-204]	⇑⇑

Die Ergebnisse der Primärstudien zu Angiotensinrezeptorblockern (ARB, auch: AT1-Rezeptorblocker, Angiotensin-II-Rezeptorantagonisten) bei HFrEF sind inkonsistent:

• ARB verbunden mit höherer Gesamtmortalität (nicht statistisch signifikant): zwei RCTs zu Candesartan (RE-SOLVD) bzw. Losartan (ELITE II) im Vergleich zu ACE-Hemmern (Enalapril bzw. Captopril) bei symptomatischen Herzinsuffizienzpatienten [202; 205];

• ARB vergleichbar effektiv bezüglich Gesamtmortalität: zwei RCTs zu Losartan (OPTIMAAL) bzw. Valsartan (VALIANT) im Vergleich zu Captopril bei Postinfarktpatienten mit linksventrikulärer Dysfunktion und/oder Herzinsuffizienzzeichen [203; 206];

• ARB effektiver bezüglich des kombinierten Endpunktes kardiovaskuläre Mortalität und Herzinsuffizienz-bedingte Hospitalisierung: RCT zu Candesartan (CHARM) bei ACE-Hemmer-intoleranten Patienten mit symptomatischer HFrEF im Vergleich zu Placebo [204] sowie Subgruppenanalysen der Val-HeFT Studie [207].

Während eine Metaanalyse einen knapp statistisch signifikanten Mortalitätsbenefit für ARB gegenüber Placebo zeigen konnte [208], ergaben zwei weitere Metaanalysen keinen Benefit bezüglich Mortalität und Hospitalisierungen, verglichen mit Placebo oder ACE-Hemmern [209; 210]. Aufgrund dieser Evidenzlage werden ARB als Mittel der zweiten Wahl bei ACE-Hemmer-Unverträglichkeit empfohlen.

202. 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.
203. 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.
204. 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.
205. 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.
206. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial 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.
207. 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.
208. Lee VC, Rhew DC, Dylan M, et al. Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. Ann Intern Med 2004;141(9):693-704. http://www.ncbi.nlm.nih.gov/pubmed/15520426.
209. Jong P, Demers C, McKelvie RS, et al. Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. J Am Coll Cardiol 2002;39(3):463-70. http://www.ncbi.nlm.nih.gov/pubmed/11823085.
210. Heran BS, Musini VM, Bassett K, et al. Angiotensin receptor blockers for heart failure. Cochrane Database Syst Rev 2012;4:CD003040. DOI: 10.1002/14651858.CD003040.pub2. http://www.ncbi.nlm.nih.gov/pubmed/22513909.

Empfehlungen/Statements	Empfehlungs-grad
6-9 bestätigt 2017 Allen klinisch-stabilen*, symptomatischen Patienten (NYHA II-IV) mit nachgewiesener Herzinsuffizienz und Fehlen von Kontraindikationen sollen Betarezeptorenblocker (Bisoprolol, Carvedilol oder Metoprololsuccinat) empfohlen werden, Patienten über 70 Jahren alternativ auch Nebivolol. Quellleitlinien [12; 13], Literatur [213-217]	⇑⇑

* Als „klinisch stabil“ sollen Patienten gelten, die unter Diuretikatherapie über 1-2 Wochen konstantes Körpergewicht haben und auch sonst keine Zeichen einer Dekompensation aufweisen.

Zum Nutzen von Betarezeptorenblockern bei chronischer Herzinsuffizienz liegen RCTs und Metaanalysen vor [194]. 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 [213-215; 218]. Subgruppenanalysen der CIBIS II-Studie ergaben zudem keine unterschiedlichen Ergebnisse für ausgewertete Subgruppen (z. B. Alter, Geschlecht, NYHA-Stadium, EF) [219].

Für den Betarezeptorenblocker Nebivolol wurde bei älteren Herzinsuffizienzpatienten (> 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 [217].

Einen Klasseneffekt gibt es bei Betarezeptorenblockern offenbar nicht, da bei anderen Betarezeptorenblockern keine Mortalitätsreduktion bzw. eine Erhöhung der Sterblichkeit beobachtet wurde [220; 221].

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) [213]: NYHA III-IV, EF 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) [214]: NYHA II-IV, EF 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) [215]: NYHA III und IV: schwere HI (≥ 2 Monate Ruhedyspnoe oder bei minimaler Belastung, EF < 25%), EF durchschnittlich 19,9%, Follow-up 10,4 Mon., Carvedilol vs. Kontrollen, Basistherapie ACE-Hemmer oder ARB + Diuretika + Digoxin: ARR = 5,5%, NNT 10,4 Monate = 18
- Carvedilol (US Carvedilol HF 1996) [216]: NYHA II-III, EF durchschnittlich 23%, Follow-up 6,5 Monate,Carvedilol, Basistherapie ACE-Hemmer + Diuretika + Digoxin: ARR = 4,6%, NNT 6,5 Monate = 22; für den kombinierten Endpunkt Tod oder Hospitalisierung: ARR = 8,8%, NNT 6,5 Monate = 11
- Nebivolol (SENIORS) [217]: HI Einweisung oder EF < 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 [223].

Ob die Behandlung zuerst mit ACE-Hemmern oder Betarezeptorenblocker oder mit beiden gleichzeitig begonnen wird, ist individuell zu entscheiden [225].

194. 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.
213. 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.
214. 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 failure (MERIT-HF). MERIT-HF Study Group. JAMA 2000;283(10):1295-302. http://www.ncbi.nlm.nih.gov/pubmed/10714728.
215. 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.
216. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996;334(21):1349-55. http://www.ncbi.nlm.nih.gov/pubmed/8614419.

217. Flather MD, Shibata MC, Coats AJ, 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. http://www.ncbi.nlm.nih.gov/pubmed/15642700.
218. 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.
219. 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.
220. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001;344(22):1659-67. http://www.ncbi.nlm.nih.gov/pubmed/11386264.
221. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003;362(9377):7-13. http://www.ncbi.nlm.nih.gov/pubmed/12853193.
222. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001;357(9266):1385-90. http://www.ncbi.nlm.nih.gov/pubmed/11356434.
223. Kaiser T, Jennen E, Sawicki PT. Entscheidungsgrundlage zur evidenzbasierten Diagnostik und Therapie bei Disease Management Programmen für Herzinsuffizienz bei systolischer linksventrikulärer Dysfunktion. 2., überarbeitete Version. Köln: DIeM; 2003.
224. Kotecha D, Holmes J, Krum H, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet 2014;384(9961):2235-43. DOI: 1016/S0140-6736(14)61373-8. http://www.ncbi.nlm.nih.gov/pubmed/25193873.
225. 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
6-12 modifiziert 2017 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. Quellleitlinie [12], Literatur [230-233]	⇑⇑
6-13 neu 2017 Auch Patienten mit Diabetes, eingeschränkter Nierenfunktion oder grenzwertiger Hyperkaliämie sollten Mineralokortikoidrezeptorantagonisten erhalten, wenn Nut-zen und Schaden kritisch abgewogen werden Expertenkonsens, basierend auf [230-232]	⇑

Der Nutzen von Mineralokortikoidrezeptorantagonisten (MRA, auch: Aldosteronantagonisten) bei chronischer Herzinsuffizienz wurde in mehreren randomisierten Studien belegt:

• Spironolacton 12,5-50 mg/Tag (RALES) [230]: NYHA III/IV, LVEF ≤ 35%, n = 1 663; Follow-up 24 Monate; Gesamtsterblichkeit signifikant reduziert (ARR 11%, NNT = 9); Rate der Krankenhauseinweisungen aufgrund der Herzinsuffizienz signifikant reduziert (ARR 29%, NNT = 4);

• Eplerenon 25-50 mg/Tag (EPHESUS) [231]: 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 kardiovaskulärer Ereignisse signifikant reduziert (ARR 3%, NNT = 34);

• Spironolacton [233]: 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) [232]: 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

Herzinsuffizienz-bedingte Hospitalisierung signifikant reduziert (ARR 7,7%, NNT = 13), Gesamtmortalität reduziert (ARR 3%, NNT = 33);

• Metaanalyse NYHA I//II, n = 3 929 [234]: 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)).

In den 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 sehen die Autoren der Leitlinie keine Hinweise, dass diese Patienten nicht von MRA profitieren können und empfehlen deshalb die gründliche Prüfung der Indikation.

Bei der Auswahl des MRA ist der jeweilige Zulassungsstatus zu beachten (CAVE: Off-Label-Use, siehe Hinweis Kapitel 6.1 Allgemeine Empfehlungen zur medikamentösen Therapie). 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).

230. 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.
231. 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.
232. 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.
233. 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.
234. 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.

Empfehlungen/Statements	Empfehlungs-grad
6-15 bestätigt 2017 Patienten mit Herzinsuffizienz und reduzierter Ejektionsfraktion, die Zeichen einer Flüssigkeitsretention aufweisen, sollen Diuretika empfohlen werden. Quellleitlinie [12]	⇑⇑

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 unverzichtbar.

Die Dosierung der Schleifendiuretika orientiert sich an der Symptomatik und der Nierenfunktion. Zur Durchbrechung einer Diuretika-Resistenz eignet sich eine Kombinationsbehandlung mit Thiazid und Schleifendiuretikum (sequenzielle Nephronblockade). Da diese jedoch zu starken Kalium- und Magnesiumverlusten führen kann, ist insbesondere die Indikation für eine

dauerhafte Nephronblockade streng zu prüfen. Die engmaschige Kontrolle der Elektrolytwerte im Verlauf ist wichtig.

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.

Ponikowski P et al., 2016 [11].

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

- 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. [12] 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.
- Konsensusprozesse dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt.

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.

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.

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.

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.

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]

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.

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]

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]

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.
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.
301. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–1392.
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, Du¨ngen H-D, Fro¨hling S, Wachter R, Stahrenberg R, Binder L, To¨pper A, Lashki DJ, Schwarz S, Herrmann-Lingen C, Lo¨ ffler 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.

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

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

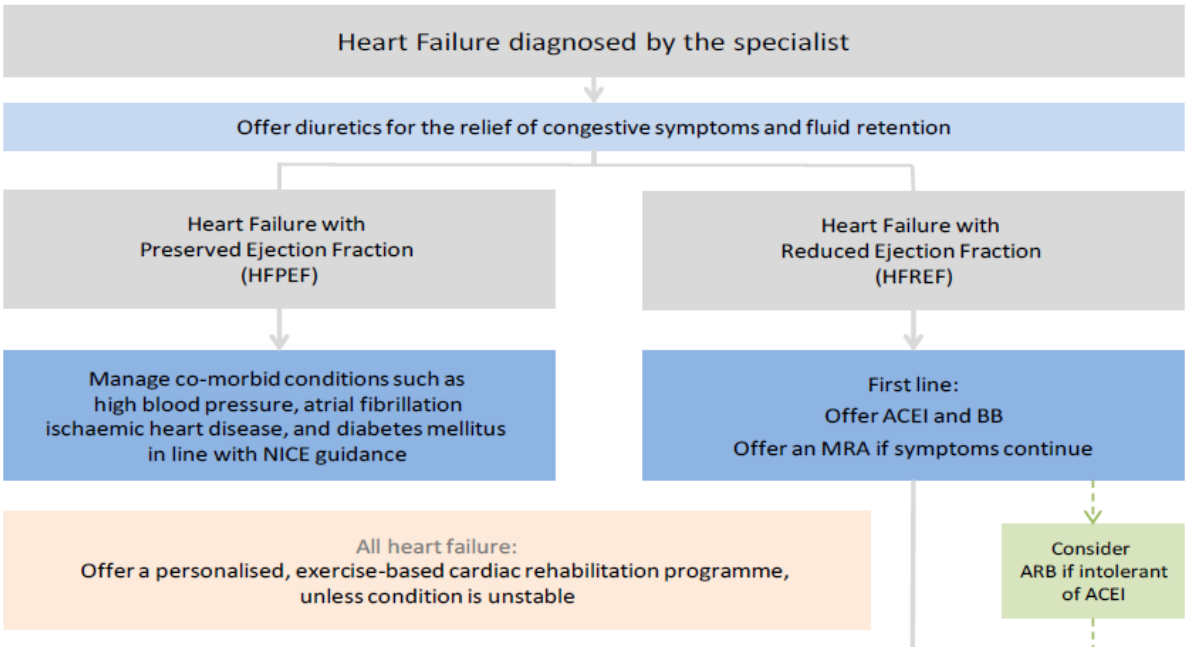
The Guideline Development Group (GDG) agreed on the following definitions:

- 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)

Therapeutic algorithm



Diuretics

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]

Mineralocorticoid Receptor Antagonists in HFPEF

Keine Empfehlung für Mineralcorticoid Rezeptor Antagonisten bei Patienten mit HFPEF

A search was conducted for randomised controlled trials comparing the effectiveness of mineralocorticoid receptor antagonists with placebo in people with heart failure with preserved ejection fraction (HFPEF) on current standard first line treatment. Two studies (reported in 11 publications) were included in the review: Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist Trial (TOPCAT)[94, 199, 259, 265, 306-310] and Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF).[108, 109].

Study	Intervention and comparison	Population	Outcomes	Comments
Aldo-DHF Edelmann 2013[108, 109]	Intervention: Spironolactone (25 mg / day) Comparison: Placebo	n=422 People aged ≥ 50 years with chronic NYHA class II or III heart failure, preserved LVEF ≥ 50%, and evidence of diastolic dysfunction/atrial fibrillation. 72% on BB, 77% on ACEI or ARB.	• Mortality • Quality of life (SF-36 Physical Functioning, Minnesota Living with Heart Failure Questionnaire) • Hospitalisation • Adverse events (gynaecomastia, hyperkalaemia, renal function) • NYHA class	Length of follow up: 1 year. SF-36 global self-assessment, Patient Health Questionnaire – depression scale, and Hospital Anxiety and Depression Scale were also reported in study but have not been extracted as validated quality of life measures were also reported.
TOPCAT Pitt 2014[94, 199, 259, 265, 306-310]	Intervention: Spironolactone (15 – 45 mg / day) Comparison: Placebo	n=3445 People aged ≥ 50 years with symptomatic heart failure and LVEF ≥ 45%. 78% on BB, 84% on ACEI or ARB.	• Mortality • Quality of life (EQ5D-VAS, Kansas City Cardiomyopathy Questionnaire) • Hospitalisation • Adverse events (gynaecomastia, hyperkalaemia, renal function)	Length of follow up: 3.3 years. McMaster Overall Treatment Evaluation instrument was also used to assess quality of life but was not been extracted as validated quality of life measures were also reported.

Heart failure with preserved ejection fraction (HFpEF) is associated with myocardial stiffness and reduced ventricular filling. The mechanism for this is incompletely understood but cell hypertrophy and interstitial fibrosis can be found in myocardial biopsies of patients with HFpEF.

A number of drugs affecting parts of the renin-angiotensin pathway have been developed and shown to be effective in the treatment of heart failure with reduced ejection fraction (HFREF). Many have also been investigated in HFpEF but have not shown similar benefits so currently none of these drugs are recommended for treatment of patients with HFpEF. The mineralocorticoid aldosterone, the neurohormone produced as the final product of the renin-angiotensin system is known to promote myocyte hypertrophy and fibrosis. Inhibition through mineralocorticoid receptor antagonism has been hypothesised to counteract the underlying pathological process causing HFpEF. Spironolactone and eplerenone are mineralocorticoid receptors antagonists (MRAs) licensed for treatment of people with HFREF. New studies have investigated the role of MRAs in patients with HFpEF. The aim of this review was to examine the clinical and cost-effectiveness of MRAs in people with HFpEF.

There was moderate quality evidence estimating 13 fewer deaths per 1000 patients and high quality evidence estimating 12 fewer hospitalisations per 1000 patients per year in people taking mineralocorticoid receptor antagonists (MRAs). The committee noted that although the confidence intervals were mostly indicating beneft there was also indication of increased mortality and hospitalisation. There was also moderate quality evidence (from a smaller study that did not report number of events) that suggested an increase in the number of patients hospitalised for any cause in the intervention group compared to the placebo group, though this evidence was imprecise. Based on the body of evidence, the committee concluded that it was

unclear whether MRAs have a clinical benefit, a clinical harm, or no effect on mortality and hospitalisation in this population.

The committee discussed the clinically important harm of MRAs on renal function (estimate of 77 more patients experiencing worsening renal function per 1000 in the intervention group) and hyperkalaemia (estimate of 87 more per 1000). They also noted the increased risk of gynaecomastia in patients taking spironolactone (estimate of 17 more per 1000), and that all of these effect estimates were subject to a high risk of bias likely to underestimate the effect. The committee also acknowledged that the use of MRAs had no clinically important impact on quality of life or NYHA class.

The committee was aware that post hoc analyses of the principle trial (TOPCAT) suggested a considerable degree of heterogeneity within the population recruited and that MRAs might have differential effects in the different groups. Due to the uncertainties around any possible benefit of MRAs on mortality and hospitalisations in this population, a lack of alternative treatments and the clinically important risk of deteriorating renal function and hyperkalaemia, the committee was uncertain about the affect of MRAs in HFPEF but aware they were used in clinical practice. Therefore it was decided not to make a clinical recommendation on the use of MRAs in this population pending further evidence.

94. Desai AS, Lewis EF, Li R, Solomon SD, Assmann SF, Boineau R et al. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. American Heart Journal. 2011; 162(6):966-972.e10
108. Edelmann F, Schmidt AG, Gelbrich G, Binder L, Herrmann-Lingen C, Halle M et al. Rationale and design of the 'aldosterone receptor blockade in diastolic heart failure' trial: a double-blind, randomized, placebo-controlled, parallel group study to determine the effects of spironolactone on exercise capacity and diastolic function in patients with symptomatic diastolic heart failure (Aldo-DHF). European Journal of Heart Failure. 2010; 12(8):874-82
109. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: The Aldo-DHF randomized controlled trial. JAMA. 2013; 309(8):781-791
199. Lewis EF, Kim HY, Claggett B, Spertus J, Heitner JF, Assmann SF et al. Impact of spironolactone on longitudinal changes in health-related quality of life in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. Circulation: Heart Failure. 2016; 9(3):e001937
259. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation. 2015; 131(1):34-42
265. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B et al. Spironolactone for heart failure with preserved ejection fraction. New England Journal of Medicine. 2014; 370(15):1383-92
306. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, Liu L et al. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. Circulation. 2015; 132(5):402-14
307. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, O'Meara E et al. Cardiac structure and function and prognosis in heart failure with preserved ejection fraction: findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. Circulation: Heart Failure. 2014; 7(5):740-51
308. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Deswal A, Anand IS et al. Prognostic importance of changes in cardiac structure and function in heart failure with preserved ejection fraction and the impact of spironolactone. Circulation: Heart Failure. 2015; 8(6):1052-8
309. Shah AM, Shah SJ, Anand IS, Sweitzer NK, O'Meara E, Heitner JF et al. Cardiac structure and function in heart failure with preserved ejection fraction: baseline findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial. Circulation: Heart Failure. 2014; 7(1):104-15
310. Shah SJ, Heitner JF, Sweitzer NK, Anand IS, Kim HY, Harty B et al. Baseline characteristics of patients in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. Circulation: Heart Failure. 2013; 6(2):184-92

Yancy CW et al., 2017 [14].

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 [15]. 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.

Fragestellung

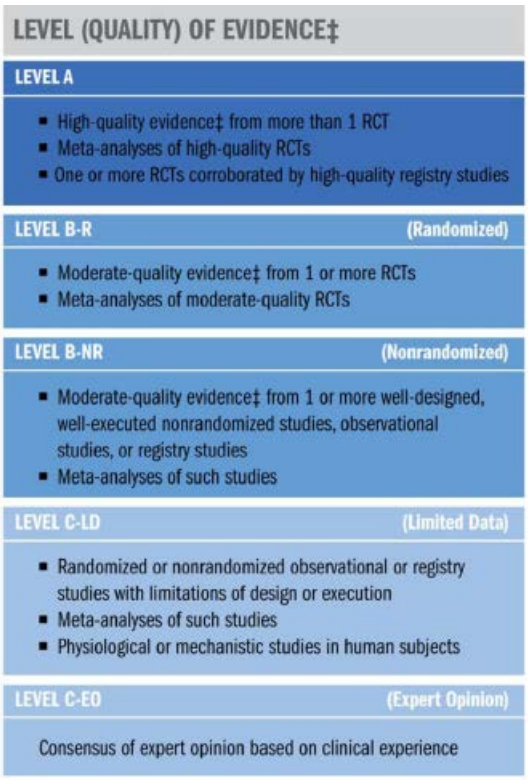
The scope of the focused update includes revision to the sections on biomarkers; new therapies indicated for stage C HF with reduced ejection fraction (HFrEF); updates on HF with preserved ejection fraction (HFpEF); new data on important comorbidities, including sleep apnea, anemia, and hypertension;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

Methodik

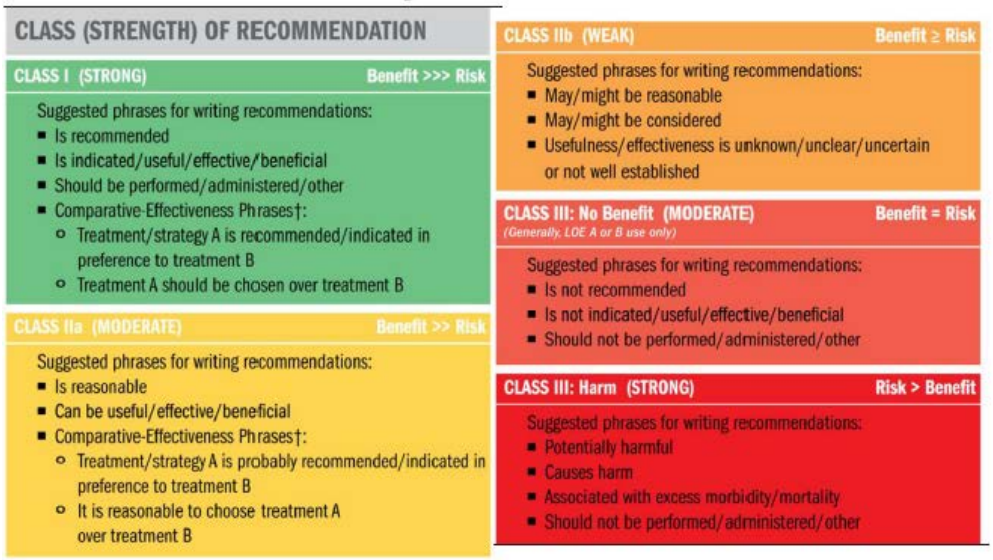
Grundlage der Leitlinie

- 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



CoR (Class of Recommendation)



Sonstige methodische Hinweise

- Keine systematische Suche.
- Auswahl und Bewertung der Evidenz nicht dargelegt.
- Konsensusprozess nicht dargelegt.

Definitions of HFrEF and HFpEF

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.

Pharmacological Treatment for Stage C HFpEF

Recommendations for Stage C HF*p*EF

COR	LOE	Recommendations	Comment/Rationale
I	B	**Systolic and diastolic blood pressure should be controlled in patients with HF*p*EF in accordance with published clinical practice guidelines to prevent morbidity (164,165).**	2013 recommendation remains current.
I	C	**Diuretics should be used for relief of symptoms due to volume overload in patients with HF*p*EF.**	2013 recommendation remains current.
IIa	C	**Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HF*p*EF despite GDMT.**	2013 recommendation remains current.
IIa	C	**Management of AF according to published clinical practice guidelines in patients with HF*p*EF is reasonable to improve symptomatic HF.**	2013 recommendation remains current (Section 9.1 in the 2013 HF guideline).
IIa	C	**The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HF*p*EF.**	2013 recommendation remains current.
IIb See Online Data Supplement C.	B-R	**In appropriately selected patients with HF*p*EF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations (83,166,167).**	**NEW:** Current recommendation reflects new RCT data.

Mechanistic studies have suggested that mineralocorticoid receptor antagonists can improve measures of diastolic function in patients with HFpEF, possibly by a similar effect on remodeling (83,168).

The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial (166) investigated the effects of spironolactone on a combined endpoint of death, aborted cardiac death, and HF hospitalization in patients with HFpEF. A small reduction (HR=0.89) in this composite endpoint did not reach statistical significance, although HF hospitalization was reduced (HR=0.83); known side effects of hyperkalemia and rising creatinine were seen more commonly in the treatment group (166). An unusual amount of regional variation was seen in this trial, prompting a post-hoc analysis (167) that showed that rates of the primary endpoint were 4-fold lower in Russia/Georgia than in North America and South America (the Americas). Rates in the Americas were comparable to those in other HFpEF trials (169,170). The post-hoc analysis showed efficacy in the Americas (HR=0.83) but not in Russia/Georgia (HR=1.10). Moreover, a sample of the Russia/Georgia population, despite having been in the active treatment arm, had nondetectable levels of the metabolite of spironolactone. These post-hoc analyses have significant limitations, but they suggest that in appropriately selected patients with symptomatic HFpEF (with ejection fraction [EF] ≥45%, elevated BNP level or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min creatinine <2.5 mg/dL, and potassium <5.0 mEq/L), particularly in those with elevated

BNP levels, use of spironolactone might be considered with close monitoring of potassium and renal function. Confirmatory studies are required.

With regard to the use of mineralocorticoid receptor antagonists, creatinine should be <2.5 mg/dL in men or <2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min) and potassium should be <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing represents best practices at initiation and during follow-up thereafter to minimize risk of hyperkalemia and worsening renal function.

IIb	B	The use of ARBs might be considered to decrease hospitalizations for patients with HF*p*EF (169).	2013 recommendation remains current.
III: No Benefit See Online Data Supplement C.	B-R	Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HF*p*EF is ineffective (171,172).	NEW: Current recommendation reflects new data from RCTs.

Nitrate therapy can reduce pulmonary congestion and improve exercise tolerance in patients with HFrEF. However, the NEAT-HFpEF (Nitrate's Effect on Activity Tolerance in Heart FailureWith Preserved Ejection Fraction) trial (171) randomized 110 patients with EF ≥50% on stable HF therapy, not including nitrates, and with activity limited by dyspnea, fatigue, or chest pain, to either isosorbide mononitrate or placebo and found no beneficial effects on activity levels, QoL, exercise tolerance, or NT-proBNP levels. On the basis of this trial, routine use of nitrates in patients with HFpEF is not recommended. This recommendation does not apply to patients with HFpEF and symptomatic CAD for whom nitrates may provide symptomatic relief. Phosphodiesterase-5 inhibition augments the nitric oxide system by upregulating cGMP activity. The RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) trial (172) randomized 216 patients with EF ≥50% on stable HF therapy and with reduced exercise tolerance (peak observed Vo2 <60% of predicted) to phosphodiesterase-5 inhibition with sildenafil or placebo. This study did not show improvement in oxygen consumption or exercise tolerance.

164. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–52.
165. Levy D, Larson MG, Vasan RS, et al. The progression from hypertension to congestive heart failure. JAMA 1996;275:1557–62.
166. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–92.
167. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;131:34–42.
168. Edelmann F, Wachter R, Schmidt AG, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA 2013;309:781–91.
169. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–81.
170. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456–67.
171. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. N Engl J Med 2015;373:2314–24.
172. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2013;309:1268–77.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 5 of 12, May 2019) am 15.05.2019

#	Suchfrage
1	MeSH descriptor: [Heart Failure] explode all trees
2	((cardiac OR heart OR myocardial) NEAR/3 (failure* OR decompensat*)):ti
3	#1 OR #2
4	#3 with Cochrane Library publication date from May 2014 to May 2019, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 15.05.2019

#	Suchfrage
1	"heart failure/therapy"[MeSH Major Topic]
2	((cardiac[Title] OR heart[Title] OR myocardial[Title]) AND (failure*[Title] OR decompensat*[Title]))
3	(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])
4	#1 OR (#2 AND #3)
5	(#4) 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 studies[pt] OR validation studies[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]))))))
6	(#5) AND ("2014/05/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 15.05.2019

#	**Suchfrage**
1	heart failure[MeSH Major Topic]
2	((cardiac[Title] OR heart[Title] OR myocardial[Title]) AND (failure*[Title] OR decompensat*[Title]))
3	(#1 OR #2)
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR guideline*[ti] OR recommendation*[ti])
5	(#4) AND ("2014/05/01"[PDAT] : "3000"[PDAT])
6	(#5) NOT retracted publication[ptyp]

Referenzen

1. **Bavishi C, Chatterjee S, Ather S, Patel D, Messerli FH.** Beta-blockers in heart failure with preserved ejection fraction: a meta-analysis. Heart Fail Rev 2015;20(2):193-201.

2. **Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF).** Nationale VersorgungsLeitlinie Chronische Herzinsuffizienz, Langfassung, 2. Auflage, Version 3 [online]. AWMF-Register-Nr.: nvl-006. Berlin (GER): Ärztliches Zentrum für Qualität in der Medizin; 2017. [Zugriff: 16.05.2019]. URL: https://www.leitlinien.de/mdb/downloads/nvl/herzinsuffizienz/herzinsuffizienz-2aufl-vers3-lang.pdf.

3. **Emdin CA, Callender T, Cao J, McMurray JJ, Rahimi K.** Meta-analysis of large-scale randomized trials to determine the effectiveness of inhibition of the renin-angiotensin aldosterone system in heart failure. Am J Cardiol 2015;116(1):155-161.

4. **Fukuta H, Goto T, Wakami K, Ohte N.** The effect of beta-blockers on mortality in heart failure with preserved ejection fraction: A meta-analysis of observational cohort and randomized controlled studies. Int J Cardiol 2017;228:4-10.

5. **Fukuta H, Goto T, Wakami K, Ohte N.** Effect of renin-angiotensin system inhibitors on mortality in heart failure with preserved ejection fraction: a meta-analysis of observational cohort and randomized controlled studies. Heart Fail Rev 2017;22(6):775-782.

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: 17.05.2019]. 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. **Kawano H, Fujiwara A, Kai H, Kumagai E, Okamoto R, Shibata R, et al.** Effects of blood pressure lowering in patients with heart failure with preserved ejection fraction: a systematic review and meta-analysis. Hypertens Res 2019;42(4):504-513.

8. **Khan MS, Fonarow GC, Khan H, Greene SJ, Anker SD, Gheorghiade M, et al.** Renin-angiotensin blockade in heart failure with preserved ejection fraction: a systematic review and meta-analysis. ESC Heart Fail 2017;4(4):402-408.

9. **Martin N, Manoharan K, Thomas J, Davies C, Lumbers RT.** Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. Cochrane Database of Systematic Reviews [online]. 2018(6):Cd012721. URL: http://dx.doi.org/10.1002/14651858.CD012721.pub2.

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: 16.05.2019]. (NICE Guideline; Band 106). URL: https://www.nice.org.uk/guidance/ng106/evidence/full-guideline-pdf-6538850029.

11. **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.

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

13. **Xiang Y, Shi W, Li Z, Yang Y, Wang SY, Xiang R, et al.** Efficacy and safety of spironolactone in the heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction: A meta-analysis of randomized clinical trials. Medicine (Baltimore) 2019;98(13):e14967.

14. **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.

15. **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.

16. **Zhang Q, Chen Y, Liu Q, Shan Q.** Effects of renin-angiotensin-aldosterone system inhibitors on mortality, hospitalization, and diastolic function in patients with HFpEF. A meta-analysis of 13 randomized controlled trials. Herz 2016;41(1):76-86.

17. **Zheng SL, Chan FT, Nabeebaccus AA, Shah AM, McDonagh T, Okonko DO, et al.** Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Heart 2018;104(5):407-415.