Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2016-01-01-D-207 Sacubitril/Valsartan

Stand: Februar 2015

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Indikation für die Recherche bei Wirkstoff (evtl. Markenname):

Behandlung der Herzinsuffizienz (NYHA-Klasse II-IV) bei Patienten mit systolischer Dysfunktion.

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel, s. „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet“

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I. Zweckmäßige Vergleichstherapie: Kriterien der VerfO	
Sacubitril/Valsartan **Zur Behandlung der Herzinsuffizienz (NYHA-Klasse II-IV) bei Patienten mit systolischer Dysfunktion. [Anwendungsgebiet abgekürzt]**	
Kriterien gemäß 5. Kapitel § 6 Absatz 3 Satz 2 VerfO	
1. Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	siehe Anlage II Wirkstoffklassen • ACE-Hemmer (z.B. Enalapril, Lisinopril, Ramipril…) • AT1-Antagonisten • Betablocker (z.B. Bisoprolol, Metoprolol, Nevibolol • Diuretika (z.B. HTC, Chlortalidon, Triamteren/HCT, Aldosteron- Antagonisten (Eplerenon) • Digitalisglycoside • Wirkstoff Ivabradin
2. Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*nicht angezeigt*
3. Als Vergleichstherapie sollen bevorzugt Arzneimittel-anwendungen oder nicht-medikamentöse Behandlungen herangezogen werden, deren patientenrelevanter Nutzen durch den Gemeinsamen Bundesausschuss bereits festgestellt ist.	*DMP koronare Herzkrankheit Anforderungen an ein Modul „Chronische Herzinsuffizienz“ für strukturierte Behandlungsprogramme für Koronare Herzkrankheit (KHK). 2008 Abrufbar unter: https://www.g-ba.de/downloads/40-268-634/2008-06-20_DMP_KHK_Modul-HI.pdf.*
4. Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	

	⇨ *siehe Aufbereitung der Evidenz*

II. Zugelassene Arzneimittel im Anwendungsgebiet (Auswahl)

Wirkstoff	**Anwendungsgebiet** (Text aus Fachinformation)
Zu prüfendes Arzneimittel:	
Sacubitril/Valsartan	Anwendungsgebiet: Zur Behandlung einer symptomatischen, chronischen Herzinsuffizienz mit reduzierter Ejektionsfraktion angewendet (siehe Abschnitt 5.1).
ACE-Hemmer	
Enalapril *generisch*	- Behandlung der symptomatischen Herzinsuffizienz - Prävention der symptomatischen Herzinsuffizienz bei Patienten mit asymptomatischer linksventrikulärer Dysfunktion (linksventrikuläre Ejektionsfraktion [LVEF] ≤35%)
Captopril *generisch*	- „Zur Behandlung der chronischen Herzinsuffizienz mit Reduktion der systolischen ventrikulären Funktion, in **Kombination mit Diuretika und, wenn erforderlich, mit Digitalis und Betablockern**.“
Benazepril (Cibacen®) Quinapril (Accupril®)	- “Herzinsuffizienz - **zusätzlich zu Diuretika** und insbesondere bei schwerer Herzinsuffizienz auch **zu Digitalis**“
Trandolapril (Udrik®)	- „Linksventrikuläre Dysfunktion **nach Myokardinfarkt** bei klinisch stabilen Patienten mit Ejektionsfraktion <=35 %“
Fosinopril, Rami-pril,	- Behandlung der symptomatischen Herzinsuffizienz

Lisinopril *generisch* Perindopril (Coversum Arginin 2,5 mg®)	
Cilazapril (Dynorm)	- Dynorm ist für die Behandlung von chronischer Herzinsuffizienz indiziert.
AT1-Antagonisten	
Candesartan (Atacand)	Behandlung erwachsener Patienten mit Herzinsuffizienz und eingeschränkter links-ventrikulärer systolischer Funktion (links-ventrikuläre Ejektionsfraktion ≤ 40 %), **wenn Angiotensin-Converting-Enzym (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)
Losartan (Lorzaar)	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 Herzinsuffizienztherapie klinisch stabil sein.
Valsartan (Diovan)	Behandlung der symptomatischen Herzinsuffizienz bei erwachsenen Patienten, **wenn ACE-Hemmer nicht gegeben werden können** **oder zusätzlich zu einem ACE-Hemmer, wenn Beta-Blocker nicht angewendet werden können** (siehe Abschnitte 4.4 und 5.1).
Betablocker	
Metoprolol (Beloc- Zok	stabile chronische gering bis mäßig ausgeprägte Herzinsuffizienz bei eingeschränkter systolischer Ventrikelfunktion (Ejektionsfraktion ≤40 %) – **zusätzlich z**ur üblichen Standardtherapie mit ACE-Hemmern und Diuretika und ggf. Herzglykosiden (für weitere Informationen siehe 5.1).

Bisoprolol *generisch*	„Behandlung der stabilen chronischen mittelgradigen bis schweren Herzinsuffizienz […] **zusätzlich zu** […] ACE-Hemmern und Diuretika und optional Herzglykosiden“
Metoprolol Metoprolol Teva®	„stabile, leichte bis mittelschwere chronische Herzinsuffizienz […] **zusätzlich** zur üblichen Standardtherapie mit ACE-Hemmern und Diuretika und, falls erforderlich, Herzglykosiden“
Carvedilol *generisch*	Behandlung der mittelschweren bis schweren Herzinsuffizienz **zusätzlich** zur konventionellen Basistherapie mit Diuretika, ACEHemmern, Digitalis und/oder Vasodilatatoren.
Nebivolol *generisch*	Behandlung einer stabilen leichten und mittel-schweren chronischen Herzinsuffizienz **zusätzlich** zu Standardtherapien bei älteren Patienten ab 70 Jahren.
Diuretika	
HCT *generisch*	- Kardiale, hepatische und renale Ödeme - Adjuvante symptomatische Therapie der chronischen Herzinsuffizienz zusätzlich zu ACE-Hemmern.
Triamteren/ Hydrochlorothiazid *generisch*	- Kardiale, hepatogene oder nephrogene Ödeme - Chronische Herzinsuffizienz
Chlortalidon (Hygroton® 25/50 mg)	- Behandlung von kardialen, hepatischen und nephrogenen Ödemen - Manifeste Herzinsuffizienz
Eplerenon	**zusätzlich** zu einer optimalen Standardtherapie zur Verringerung des Risikos der kardiovaskulären Mortalität und -Morbidität bei erwachsenen Patienten mit (chronischer) Herzinsuffizienz der New York Heart Association (NYHA)-Klasse II und linksventrikulärer systolischer Dysfunktion (LVEF ≤

(Inspra®)	30 %) (siehe Abschnitt 5.1).
Xipamid *generisch,* Furosemid *generisch,* Amilorid HCT (Amiloretik)	- Kardiale, (renale) und hepatische Ödeme
Digitalisglycoside	
Digitoxin (Digitoxin AWD 0,07®)	Manifeste chronische Herzinsuffizienz (aufgrund systolischer Dysfunktion)
Beta-Acetyldigoxin AC01AA02	Manifeste chronische Herzinsuffizienz (aufgrund systolischer Dysfunktion)
Metildigoxin Lanitop® AC01AA08	Manifeste chronische Herzinsuffizienz (aufgrund systolischer Dysfunktion)
Sonstige	
Levosimendan	„Simdax ist zur **Kurzzeit-Behandlung bei akut dekompensierter** schwerer chronischer Herzinsuffizienz (ADHF) indiziert, wenn eine konventionelle Therapie nicht ausreichend ist und in Fällen, wo die Verabreichung von Inotropika als geeignet betrachtet wird (siehe

(Simdax®)	Abschnitt 5.1). Simdax ist für die Behandlung von Erwachsenen bestimmt
Ivabradin (Procoralan®)	Ivabradin ist indiziert bei chronischer Herzinsuffizienz der NYHA-Klasse II bis IV mit systolischer Dysfunktion, bei Patienten im 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). (!! Roter-Hand-Brief vom 10.12.2014)

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Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation „Herzinsuffizienz (NYHA-Klasse II-IV) bei Patienten mit systolischer Dysfunktion“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 09.01.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1.189 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden 98 Quellen eingeschlossen. Insgesamt ergab dies 14 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

ACEI	Angiotensin Converting Enzyme-Inhibitor
AF	Atrial Fibrillation (Vorhofflimmern)
ARB	Angiotensin Rezeptor Blocker
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DAHTA	Deutsche Agentur für Health Technology Assessment
DRI	Direct renin inhibitor
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HF	Heart failure (Herzinsuffizienz)
HFrEF	Herzinsuffizienz mit reduzierter Ejektionsfraktion
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LVEF	left ventricular ejection fraction
MRA	Mineralocorticoid receptor antagonists
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
OR	Odds Ratio

RAS	renin-angiotensin system
RR	Risk Ratio
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

G-BA, 2008: Anforderungen an strukturierte Behandlungsprogramme für Patienten mit Koronarer Herzkrankheit (KHK). [6]	**Medikamentöse Therapie:** […] Vorrangig sollen unter Berücksichtigung der Kontraindikationen, der Komorbiditäten und der Patientenpräferenzen Medikamente zur Behandlung der KHK verwendet werden, deren positiver Effekt und deren Sicherheit […] in randomisierten, kontrollierten Studien (RCT) nachgewiesen wurden. Sofern im Rahmen der individuellen Therapieplanung Wirkstoffe aus anderen Wirkstoffgruppen als die in dieser Anlage genannten verordnet werden sollen, ist die Patientin oder der Patient darüber zu informieren, ob für diese Wirkstoffe Wirksamkeitsbelege zur Risikoreduktion klinischer Endpunkte vorliegen. […] **ACE-Hemmer** sind grundsätzlich bei allen KHK-Patienten in der frühen Postinfarktphase (4 Wochen) indiziert und wenn die chronische KHK mit einer begleitenden Herzinsuffizienz oder mit asymptomatischer linksventrikulärer Dysfunktion und/oder mit der Komorbidität Hypertonie und/oder Diabetes mellitus einhergeht. Im Falle einer ACE-Hemmer-Unverträglichkeit können bei Patienten mit KHK und einer systolischen Herzinsuffizienz oder dem gleichzeitigen Vorliegen der Komorbiditäten Hypertonie und Diabetes mellitus **AT1-Rezeptorantagonisten** eingesetzt werden.

Cochrane Reviews

Hood WB, 2014 **(assessed as up-to-date 2013) [8]** **Digitalis for treatment of heart failure in patients in sinus rhythm**	1. Fragestellung To examine the effectiveness of digitalis glycosides in treating HF in patients with normal sinus rhythm. To examine the effects of digitalis in patients taking diuretics and angiotensin-converting enzyme inhibitors; in patients with varying severity and duration of disease; in patients with prior exposure to digitalis versus no prior exposure; and in patients with "HF due to systolic dysfunction" versus "HF with preserved ejection fraction."
	2. Methodik Population: This review includes adult participants of both sexes with HF, older than 18 years of age, and of any ethnic group. For the purposes of this review, the presence of an ejection fraction of 0.45 or less was considered as identifying a subgroup of individuals having "HF due to systolic dysfunction." Patients with an ejection fraction greater than 0.45 were considered to have "HF with preserved ejection fraction." All studies but two provided information about NYHA functional class, and most of the participants studied were NYHA Class II or III. Intervention: digoxin (≥ seven weeks) was the only agent employed in the 13 included studies Use of other concurrent cardiac medications, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, and beta-blocking agents, is also recorded. Komparator: Placebo Endpunkt: mortality, hospitalization, and clinical status Suchzeitraum (Aktualität der Recherche): 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 (n=7.896) Qualitätsbewertung der Studien: nach Cochrane (Heterogenität: Chi^2 und I^2)
	3. Ergebnisdarstellung The data show no evidence of a difference in mortality (OR=0,98, 95% KI 0,89-1,09) between treatment and control groups, whereas digitalis therapy is associated with lower rates of both hospitalization (OR=0,68, 95% KI 0,61-0,75) and clinical deterioration (OR=0,31, 95% KI 0,21-0,43). The largest study, in which most participants were taking angiotensinconverting enzyme inhibitors, showed a

	significant rise in “other cardiac” deaths, possibly due to arrhythmias. However collectively, these findings were based on studies done before beta-blockers, as well as angiotensin receptor blockers and aldosterone antagonists, became widely used to treat HF.
	4. Anmerkungen/Fazit der Autoren The literature indicates that digitalis may have a useful role in the treatment of patients with HF who are in normal sinus rhythm. New trials are needed to elucidate the importance of the dosage of digitalis and its usefulness in the era of beta-blockers and other agents shown to be effective in treating HF. 5. Anmerkungen FBMed: Studien zum Großteil aus den 1980er/90er Jahren
Faris RF, 2012 **(assessed as up-to-date 2011) [5]** **Diuretics for heart failure**	1. Fragestellung To assess the harms and benefits of diuretics for chronic heart failure
	2. Methodik Population: Adult participants with chronic heart failure, defined as a clinical syndrome characterised by breathlessness and fatigue that is caused by an inability of the heart to support an adequate circulation, that may limit exercise tolerance andmay lead to pulmonary congestion and peripheral oedema. Intervention: All diuretic drugs; comparisons of loop (e.g. furosemide, bumetanide), thiazides (e.g. chlorothiazide), or potassium-sparing diuretics (e.g. amiloride, triamterene) diuretics. Komparator: Placebo, or one diuretic with another active agent (e.g. ACE inhibitors, digoxin) Endpunkt Primär: i) mortality ii) morbidity Sekundär: i) effect of diuretic withdrawal on worsening of heart failure; ii) effect of diuretics on exercise capacity; iii) effect of diuretics on symptoms and quality of life; iv) haemodynamic effect of diuretics; v) neuroendocrine effect of diuretics; vii) adverse effects. Suchzeitraum (Aktualität der Recherche):2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 14 (n=525) Qualitätsbewertung der Studien: nach Cochrane (Heterogenität: Chi^2

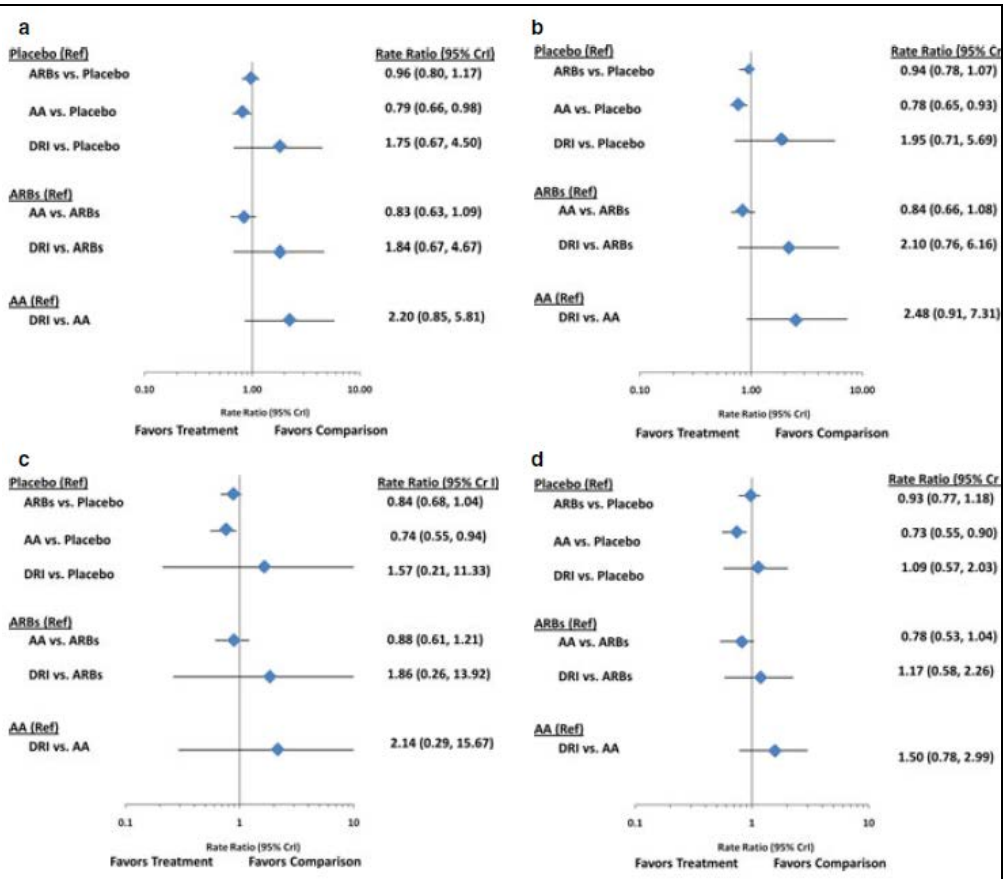
	und I^2)
	3. Ergebnisdarstellung 7 studies were placebo-controlled, and 7 compared diuretics against other agents such as ACE inhibitors or digoxin. We analysed the data for mortality and for worsening heart failure. **Mortality** data were available in 3 of the placebo-controlled trials (202 participants). Mortality was lower for participants treated with diuretics than for placebo (OR= 0,24; 95% KI 0,07 – 0,83; P = 0.02). **Hospital admission** for worsening heart failure was reduced in those taking diuretics in two trials (169 participants) (OR=0,07 ;95% KI 0,01 - 0.52; P = 0,01). In four trials comparing diuretics to **active control** (91 participants), diuretics improved **exercise capacity** in participants with CHF, difference in means WMD 0,72; 95% KI 0,40 – 1,04; P < 0.0001.
	4. Anmerkungen/Fazit der Autoren The available data from several small trials show that in patients with chronic heart failure, conventional diuretics appear to reduce the risk of death and worsening heart failure compared to placebo. Compared to active control, diuretics appear to improve exercise capacity. 5. Anmerkungen FBMed: Studien zum Großteil aus den 1980er/90er Jahren
Heran BS, 2012 **(assessed as up-to-date 2010) [7]** **Angiotensin receptor blockers for heart failure**	1. Fragestellung To assess the benefit and harm of ARBs compared with ACE inhibitors (ACEIs) or placebo on mortality, morbidity and withdrawals due to adverse effects in patients with symptomatic HF and left ventricular systolic dysfunction or preserved systolic function.
	2. Methodik Population: Men and women of all ages who had symptomatic HF with NYHA functional class II-IV. Intervention: Experimental intervention with any ARB at any dose, including candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, and other ARBs not currently marketed. Komparator: Placebo or ACE-Inhibitor Endpunkt: Primary: o Total mortality o Cardiovascular mortality

	o Non-cardiovascular mortality o Cardiovascular morbidity o Myocardial infarction (MI) o Stroke o Total hospitalisations o Hospitalisations for HF (defined as a hospital o admission for worsening signs or symptoms of HF, for o complications relating to the treatment of HF, or for syncope or o arrhythmias related to HF) o Other hospitalisations Secondary: o Withdrawals due to adverse effects (WDAE) Suchzeitraum (Aktualität der Recherche):2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 22 (n=17.900; with a LVEF ≤40% [mean 2.2 years]) Qualitätsbewertung der Studien: nach Cochrane (Heterogenität: Chi^2 und I^2)
	3. Ergebnisse Placebo Kontrolle: ARBs did not reduce total **mortality** (RR 0,87; 95% KI 0,76 - 1,00) or total morbidity as measured by total **hospitalisations** (RR 0,94; 95% KI 0,88 - 1,01) compared with placebo. Aktive Kontrolle: Total mortality (RR 1,05; 95% KI 0,91 - 1,22), total hospitalisations (RR 1,00; 95% KI 0,92 - 1,08), MI (RR 1,00; 95% KI 0,62 - 1,63), and stroke (RR 1,63; 95% KI 0,77 - 3,44) **did not differ between** ARBs and ACEIs but withdrawals due to adverse effects were lower RR 0,63 95% KI 0,52 - 0,76)
	4. Anmerkungen/Fazit der Autoren In patients with symptomatic HF and systolic dysfunction or with preserved ejection fraction, ARBs compared to placebo or ACEIs do not reduce total mortality or morbidity. ARBs are better tolerated than ACEIs but do not appear to be as safe and well tolerated as placebo in terms of withdrawals due to adverse effects. Adding an ARB in combination with an ACEI does not reduce total mortality or total hospital admission but increases withdrawals due to adverse effects compared with ACEI alone.

Systematische Reviews

Agarwal, V. 2013 Effects of renin-angiotensin system blockade on mortality and hospitalizatio n in heart failure with preserved ejection fraction. [1] 5 der 6 RCTs wurden ebenfalls ausgewertet in: **Singh et al.** Safety and efficacy of rennin-angiotensin system inhibitors in heart failure with preserved ejection fraction. 2011 [13]	1. Fragestellung To examine the potential benefit of renin-angiotensin system (RAS) inhibition in heart failure with preserved ejection fraction
	2. Methodik Population: Patienten mit Herzinsuffizienz und Ejektionsfraktion ≥40 % Intervention: RAS-Inhibitor (ACE-I oder ARB [Perindopril, Candesartan,Irbesartan, Quinapril, Ramipril]) Komparator: Placebo oder Diuretika. Es wurden keine Subgruppenanalysen für Arzneimittelklassen durchgeführt Endpunkt: Mortalität, Hospitalisierung Suchzeitraum (Aktualität der Recherche): 1966-2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): Es wurden randomisierte und nicht-randomisierte Studien eingeschlossen. Es gab Sensitivitätsanalysen, in denen nur RCTs betrachtet wurden. Nur diese Ergebnisse werden hier dargestellt. Insgesamt wurden 5 RCTs eingeschlossen. Qualitätsbewertung der Studien: Since we included both randomized and observational studies in our analyses, the included studies were of variable quality. There were five studies of good quality (Jadad score C3) with low risk of bias and seven studies of low quality (Jadad score\3) with high risk of bias.
	3. Ergebnisdarstellung Gesamtmortalität, kardiovaskuläre Mortalität, Hospitalisierung: kein statistisch signifikanter Unterschied von ACE oder ARB gegenüber Standardtherapie **Ergebnisse aus Singh (2011):** Gleiche Ergebnisse hinsichtlich Gesamtmortalität, kardiovaskuläre Mortalität und Hospitalisierung (kein statistisch signifikanter Unterschied). Zusätzlich wurden hier noch folgende Endpunkte ermittelt: There was significant reduction in **worsening of heart failure** events [OR: 1,16; 95% KI: 1,03 - 1,31; p<0,05] with RASIs compared to placebo group. Treatment with RASI lead to significant improvement in **six minute walking distance** [p<0,05] and **quality of life score** in RASIs group [p=0,002] Safety analysis, as expected, revealed significantly **more**

	hyperkalemic events [OR: 0,53, KI: 0,29 – 0,95; p<0,05] and worsening of renal failure [OR: 0,65; 95% KI: 0,50 – 0,85; p<0,05] in RASI group as compared to placebo group.
	4. Anmerkungen/Fazit der Autoren In spite of the small reduction in hospitalization rates, especially with the use of ACE-Is and a trend toward decreased mortality, the inconsistency of the results between the studies along with the negative results of the larger trials allow no firm conclusions on therapy in patients with HF-PEF. For now, treatment of these patients should empirically focus on strict blood pressure control and paying attention to the other comorbidities often found in this patient population. Whether or not RAS inhibitors should be used as first-line drugs remains to be determined.
Bangalore et al. When conventional heart failure therapy is not enough: angiotensin receptor blocker, direct renin inhibitor, or aldosterone antagonist? 2013 [2]	1. Fragestellung When Conventional Heart Failure Therapy is Not Enough: Angiotensin Receptor Blocker, Direct Renin Inhibitor, or Aldosterone Antagonist?
	2. Methodik Population: HF and reduced systolic function Intervention: Standardtherapie (Diuretika, Betablocker, AT-1 Antagonisten). Subgruppenanalysen für AM-Klassen wurden durchgeführt Komparator: Placebo, head-to-head [ACEI o ARB, Captopril, Enalapril] Endpunkt: Mortalität, Hospitalisierung Suchzeitraum (Aktualität der Recherche): bis 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 16 (n=31.429) Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool. Insgesamt geringes Biasrisiko.
	3. Ergebnisdarstellung • statistisch signifikanter Vorteil von Aldosterone vs. Placebo: When compared with placebo, aldosterone antagonists reduced the rate of death (21% reduction) (Figure 3a), cardiovascular death (22% reduction) (Figure 3b), HF hospitalization (26% reduction) (Figure 3c), and the composite of cardiovascular death or HF hospitalization (27% reduction) (Figure 3d), with no difference for other efficacy outcomes (data not shown). • Kein statistisch signifikanter Unterschied beim head-to-head Vergleich • Kein statistisch signifikanter Unterschied bei ARBs



When compared with placebo (reference rate ratio of 1), ARBs increased the rate of hyperkalemia (138% increase) (Figure 4a), renal failure (126% increase) (Figure 4b), and hypotension (63% increase) (Figure 4c). Similarly, aldosterone antagonists resulted in a 110% increase in the rate of hyperkalemia, with no significant increase in the rate of either renal failure or hypotension when compared with placebo, although the point estimates suggested similar increased risk (Figure 4a–c). In addition, DRIs were associated with a 98% increase in the rate of hypotension, although there was no significant increase in the rate of either hyperkalemia or renal failure when compared with placebo although the point estimates suggested a similar increased risk (Figure 4a–c). In the head-to-head comparisons of active comparators, there was no difference for any of the safety outcomes for any combination of comparators (Figure 4a–c).

4. Anmerkungen/Fazit der Autoren

Given the adverse effects and lack of consistent cardiovascular benefits, the routine addition of an ARB or DRI to ACE inhibitor therapy in HF patients should be avoided or used only in select patients who cannot tolerate aldosterone blockade. The data in aggregate seem to favor aldosterone antagonists over ARBs or DRIs as preferred add-on therapy in these patients. Regardless of which drug class is added, dual RAAS blockade will require strict monitoring of potassium and renal function

	and a careful follow-up for symptoms and signs of hypotension.
Makani et al., 2013. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomized trials. [9]	1. Fragestellung To compare the long term efficacy and adverse events of dual blockade of the renin-angiotensin system with monotherapy.
	2. Methodik Population: Patienten mit und ohne Herzinsuffizienz (Bluthochdruck, acuter Myokardinfarkt, Diabetes in Verbindung mit kardiovaskulären Erkrankungen). Für Patienten mit Herzinsuffizienz wurde eine Subgruppenanalyse durchgeführt, im Folgenden werden nur diese Ergebnisse dargestellt. Intervention: dual blockers of the renin-angiotensin system Komparator: Monotherapie Endpunkt: long term efficacy (≥1 year), safety events (≥4 weeks) Suchzeitraum (Aktualität der Recherche): 1990 bis 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 33 (n=68.405) Qualitätsbewertung der Studien: The criteria used for quality assessment were sequence generation of allocation; allocation concealment; masking of participants, staff, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias, as recommended by the Cochrane Collaboration.7 We classed studies with high or unclear risk of bias for any of the first three components to be of low quality. Von den 33 Studien wurde 18 Studien ein geringes Biasrisiko attestiert, der Rest wies ein hohes Biasrisiko auf.
	3. Ergebnisse In subgroup analysis, dual therapy showed no benefit for **all cause mortality** in the cohort with heart failure (RR: 0,92; 95% KI 0,82 - 1,03; P=0,15 bei einer Heterogeniät von I^2=67%). In subgroup analysis, dual therapy had no benefit on **cardiovascular mortality** in the cohorts both with heart failure (P=0,14 bei einer Heterogeniät von I^2=64%) and without (P=0,61). In **admission to hospital** for heart failure, there was a benefit in the cohort with heart failure (RR: 0,77; 95% KI 0,68 – 0,88; P=0,0001 bei einer Heterogeniät von I^2=66%) In subgroup analysis, the **risk of hyperkalaemia** increased significantly in both the cohort with heart failure (P=0,02 bei einer Heterogeniät von I^2=68%) and the cohort without (P<0,001).

	In subgroup analysis, the **risk of hypotension** increased significantly in the cohorts both with heart failure (P<0,001 bei einer Heterogeniät von I^2=14%) and without (P=0,002). In subgroup analysis, the **risk of renal failure** increased significantly in the cohort with heart failure (RR: 2.19; 95% KI 1,82 – 2,65; p<0,001 bei einer Heterogeniät von I^2=13%). In subgroup analysis, the **risk of withdrawal owing to drug related adverse events** increased significantly in the cohort both with heart failure (P<0,001 bei einer Heterogeniät von I^2=0%) and without (P=0,0003).
	4. Anmerkungen/Fazit der Autoren Although dual blockade of the renin-angiotensin system may have seemingly beneficial effects on certain surrogate endpoints, it failed to reduce mortality and was associated with an excessive risk of adverse events such as hyperkalaemia, hypotension, and renal failure compared with monotherapy. The risk to benefit ratio argues against the use of dual therapy. 5. Anmerkungen FBMed Die meisten Analysen waren durch eine hohe statistische Heterogenität der Studien gekennzeichnet. Einem Großteil der Studien wurde ein hohes Biasrisiko zugesprochen.
Betablocker	
Rienstra et al., 2013. Beta-Blockers and Outcome in Heart Failure and Atrial Fibrillation. [12]	1. Fragestellung To analyze the effect of beta blockade on outcome in patients with heart failure (HF) and atrial fibrillation (AF).
	2. Methodik Population: patients with AF at baseline and HF with reduced systolic left ventricular ejection fraction (LVEF) <40% Intervention: Betablocker (Carvedilol, Bisoprolol, Metoprolol und Nebivolol) Komparator: Patienten mit HF und AF ohne Betablockerbehandlung Endpunkt: Mortalität und Hospitalisierung Suchzeitraum (Aktualität der Recherche): keine Angabe Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 (n=8.680, davon 1.677 mit Vorhofflimmern) Qualitätsbewertung der Studien: The quality of the individual studies was assessed by 11 factors: 1) sufficiently specified inclusion and exclusion criteria; 2) sufficient explanation of sample selection; 3) specification of

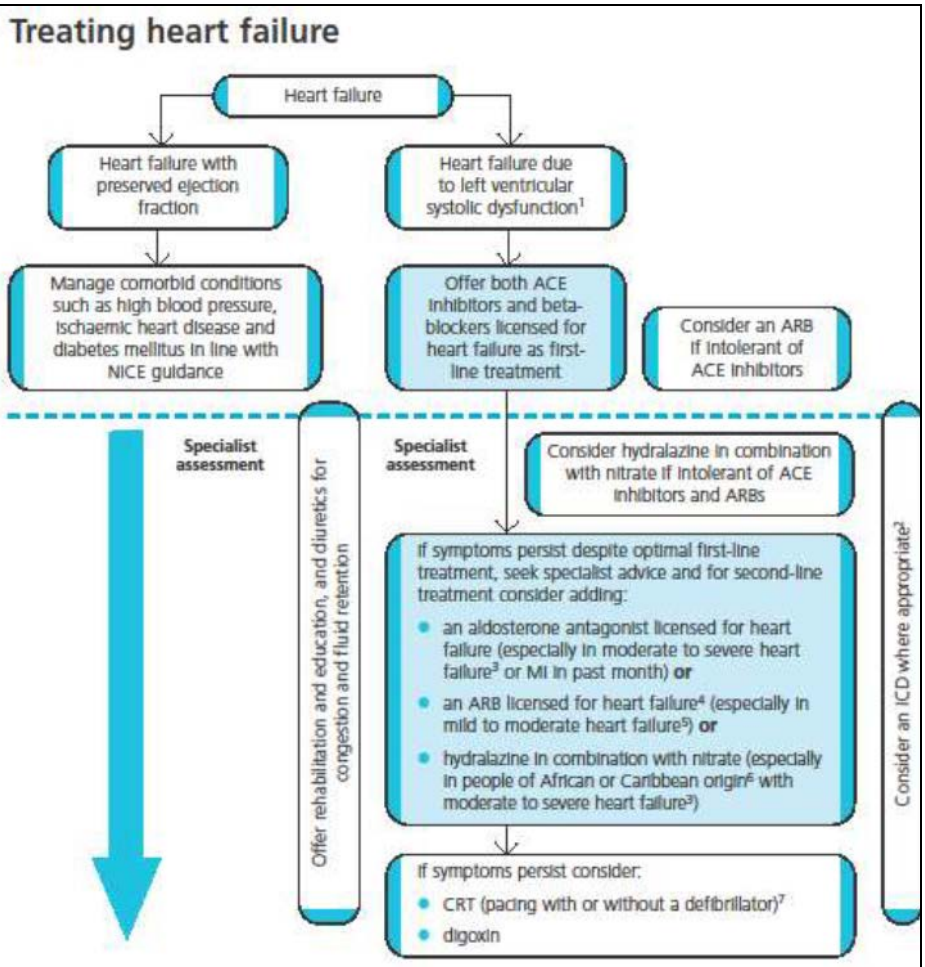
	clinical and demographic variables; 4) representation of the study sample for the mentioned patient population; 5) specification of outcome measures; 6) definition of AF; 7) assessment of the dose-response relationship between beta-blocker therapy and outcome; 8) adjustment for possible confounders in the analysis; 9) reporting of rates of patients lost to follow-up; 10) study design; and 11) duration of follow-up. Grading was as follows: good quality included 8 to 11 criteria, fair quality included 5 to 7 criteria, and poor quality included <5 criteria. Study quality was scored as “good” for all but one, the US Carvedilol-study, which was scored as “fair”.
	3. Ergebnisse In AF patients, betablockade did not reduce mortality (OR: 0,86; 95% KI 0,66 – 1,13; p= 0,28), while in sinus rhythm patients, there was a significant reduction (OR: 0,63; 95% KI 0,54 – 0,73; p < 0.0001). Interaction analysis showed significant interaction of the effects of beta-blocker therapy in AF versus that in sinus rhythm (p= 0,048). By meta-regression analysis, we did not find confounding by all relevant covariates. Betablocker therapy was not associated with a reduction in HF hospitalizations in AF (OR: 1,11; 95% KI 0,85 – 1,47; p= 0,44), in contrast to sinus rhythm (OR: 0,58; 95% KI 0,49 – 0,68; p < 0.0001). There was a significant interaction of the effects of beta-blocker therapy in AF versus that in sinus rhythm (p < 0,001).
	4. Anmerkungen / Fazit der Autoren Our findings suggest that the effect of beta-blockers on outcome in HF patients with reduced systolic LVEF who have AF is less than in those who have sinus rhythm. 5. Anmerkungen FBMed Die Studien mit Patienten mit Sinusrhythmus wiesen eine Heterogenität von I^2=55% auf für den Endpunkt „all-cause mortality“ (das I^2 für die Studien zu AF lag bei 0%). Beim Endpunkt „hospitalization risk“ verhielt es sich bezüglich der Heterogenität umgekehrt: in der AF-Gruppe lag diese bei I^2=59% und in der Sinusrhythmus-Gruppe bei I^2=5%.
Chatterjee et al., 2013. Benefits of β blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. [4]	1. Fragestellung To clarify whether any particular β blocker is superior in patients with heart failure and reduced ejection fraction or whether the benefits of these agents are mainly due to a class effect.
	2. Methodik Population: patients with heart failure and reduced ejection fraction Intervention: Betablocker (Carvedilol, Bisoprolol, Metoprolol, Atenolol, Bucindolol und Nebivolol) Komparator: Placebo, Enalapril [in 2 Studien], Metopolol [in 1 Studie])

	Endpunkt: Mortalität Suchzeitraum (Aktualität der Recherche): bis 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 21 (n=23.122) Qualitätsbewertung der Studien: Risk of Bias Tool der Cochrane Collaboation. Allen Studien wurde ein geringes Biasrisiko attestiert.
	3. Ergebnisse As expected, in the overall analysis, β blockers provided credible mortality benefits in comparison with placebo or standard treatment after a median of 12 months (OR: 0,69; 95% KI 0,56 – 0,80). However, no obvious differences were found when comparing the different β blockers head to head for the risk of death, sudden cardiac death, death due to pump failure, or drug discontinuation. Accordingly, improvements in left ventricular ejection fraction were also similar irrespective of the individual study drug.
	4. Anmerkungen / Fazit der Autoren The benefits of β-blockers in patients with heart failure with reduced ejection fraction seem to be mainly due to a class effect, as no statistical evidence from current trials supports the superiority of any single agent over the others.

Leitlinien

NICE, 2010 Chronic heart failure [11]	NICE Leitlinie Update mit neuen Empfehlungen aus 2010
	Methodik Grundlage der Leitlinie: Empfehlungen der NICE Guidance aus 2003. Das National Clinical Guideline Centre for Acute and Chronic Conditions (gegründet 2009) identifiziete Bereiche dieser Leitlinie, für die ein Update notwendig war. For intervention studies, randomised controlled trials (RCTs) were the preferred sources of evidence. Cohort studies and lower levels of evidence were only considered if RCTs data was not available. Die Evidenz hinter den Empfehlungen wurde mit GRADE evaluiert. Suchzeitraum bis Oktober 2009
	Empfehlungen Die folgenden Empfehlungen sind sämtlich aus 2010, bis auf die Empfehlungen zu Diuretika, die aus 2003 übernommen wurden. Empfehlung 1 Offer both angiotensin-converting enzyme (ACE) inhibitors and beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction. Use clinical judgement when deciding which drug to start first. Empfehlung 2: ACE-Inhibitor Start ACE inhibitor therapy at a low dose and titrate upwards at short intervals (for example, every 2 weeks) until the optimal tolerated or target dose is achieved. Measure serum urea, creatinine, electrolytes and eGFR at initiation of an ACE inhibitor and after each dose increment. Empfehlung 3: Betablocker Offer beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction, including: • older adults and • patients with: – peripheral vascular disease – erectile dysfunction – diabetes mellitus – interstitial pulmonary disease and

	– chronic obstructive pulmonary disease (COPD) without reversibility. I Introduce beta-blockers in a „start low, go slow" manner, and assess heart rate, bloodpressure, and clinical status after each titration. Switch stable patients who are already taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure due to left ventricular systolic dysfunction, to a beta-blocker licensed for heart failure. Empfehlung 4: Hydralazin (alternative first-line-treatment) Seek specialist advice and consider hydralazine in combination with nitrate for patients with heart failure due to left ventricular systolic dysfunction who are intolerant of ACE inhibitors and ARBs. Empfehlung 5: Angiotensin II Rezeptor Antagonisten (alternative first-line-treatment) Consider an ARB licensed for heart failure as an alternative to an ACE inhibitor for patients with heart failure due to left ventricular systolic dysfunction who have intolerable side effects with ACE inhibitors. Monitor serum urea, electrolytes, creatinine and eGFR for signs of renal impairment or hyperkalaemia in patients with heart failure who are taking an ARB Empfehlung 6: Digoxin Digoxin is recommended for: worsening or severe heart failure due to left ventricular systolic dysfunction despite first- and second-line treatment for heart failure. Empfehlung 7: Diuretika Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in patients with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies.

	
NVL 2013: Nationale Versorgungsleitlinie (NVL): Chronische KHK [3]	Nationale Versorgungsleitlinie (NVL)
	Methodik (S3-Leitlinie) Grundlage der Leitlinie: Adaptation von Quellleitlinien aus systematischer Leitlinienrecherche und Aktualisierungsrecherchen, systematische Auswahl und Bewertung der Literatur, formale Konsensusprozesse zur Formulierung und Verabschiedung der Empfehlungen. Ergänzende systematische Recherchen nach anderen Quellen aufbereiteter Evidenz (z. B. HTA-Berichte und systematische Übersichtsarbeiten) und Primärstudien erfolgten für Fragestellungen, die in den Quell-Leitlinien nicht hinlänglich beantwortet wurden sowie zur Aktualisierung. Detaillierte Angaben sind in den zitierten Leitlinienreports zu finden. Adäquate Angabe und Verknüpfung zur Empfehlungsstärke und dem zugrundeliegendem Evidenzlevel (siehe unten) <u>Angaben zur Recherche aus dem Leitlinienreport der Herzinsuffizienz:</u> Ausgangspunkt der Leitlinienrecherche bildete die im September 2006 fertiggestellte Leitlinie der Deutschen Gesellschaft für

Allgemeinmedizin und Familienmedizin (DEGAM), da sie bereits eine umfangreiche systematische Leitlinien-Recherche (Recherchedatum 11.3.2004) enthält. Von den Ergebnissen dieser Recherche ausgehend wurde nach aktuellen oder aktualisierten Versionen der dort identifizierten Leitlinien systematisch gesucht. Falls erforderlich, wurde zusätzliche Literatur durch die beteiligten Experten eingebracht oder eine zusätzliche Literaturrecherche und Auswertung der Literatur vorgenommen

Recherchezeitraum: 2007/2008

LoE

Tabelle 1: Evidenzgraduierung der NVL Chronische KHK nach SIGN

Grad	Beschreibung Evidenzgraduierung	Beschreibung Evidenzgraduierung (seit 15.04.2013)
1++	Qualitativ hochwertige Metaanalysen, systematische Übersichten von RCTs, oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)	
1+	Gut durchgeführte Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit geringem Risiko systematischer Fehler (Bias)	Gut durchgeführte Metaanalysen, Systematische Übersichten, oder RCTs mit geringem Risiko systematischer Fehler (Bias)
1-	Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit hohem Risiko systematischer Fehler (Bias)	Metaanalysen, Systematische Übersichten, oder RCTs mit hohem Risiko systematischer Fehler (Bias)
2++	Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist	
2+	Gut durchgeführte Fall-Kontroll-Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist	
2-	Fall-Kontroll-Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und signifikantem Risiko, dass die Beziehung nicht ursächlich ist	
3	Nicht-analytische Studien, z. B. Fallberichte, Fallserien	
4	Expertenmeinung	

GoR

Tabelle 2: Einstufung von Leitlinien-Empfehlungen in Empfehlungsgrade (Grades of Recommendation)

Empfehlungs-grad	Beschreibung	Formulierung	Symbol
A	Starke Empfehlung	Soll (nicht)	⇑⇑ (⇓⇓)
B	Empfehlung	Sollte (nicht)	⇑ (⇓)
0	Offen	kann	⇔

Sonstige methodische Hinweise

Gültigkeit des Leitlinienreports zur Herzinsuffizienz ist abgelaufen.

	Freitext/Empfehlungen/Hinweise Empfehlung 1 Patientinnen/Patienten mit KHK und Herzinsuffizienz sollen lebenslang mit einem Betablocker behandelt werden (Reduktion der Sterblichkeit gesichert für Bisoprolol, Carvedilol, Metoprolol-Succinat). **Starke Empfehlung (Grad A)**
McKelvie, 2012 **Canadian Cardiovascular Society (CCS) [10]** The 2012 Canadian Cardiovascular Society Heart Failure Management Guidelines Update: Focus on Acute and Chronic Heart Failure	The 2012 CCS HF **Consensus Update** objectives are to provide an overall review of HF management and recommendations. The Guidelines deal with the areas of (1) **acute HF (AHF)** and (2) **chronic stable HF**.
	Methodik Grundlage der Leitlinie The recommendations follow the Grading of Recommendations Assessment, Development, and Evaluation (**GRADE**). The GRADE system offers 2 grades of recommendations: “Strong” (desirable effects clearly outweigh undesirable effects or clearly do not) and “Weak.” When trade-offs are less certain, either because of low-quality evidence or because evidence suggests desirable and undesirable effects are closely balanced, **weak recommendations become mandatory**. Also new this year is the inclusion of values and preferences that complement the GRADE system of recommendations. – Update: Update der Leitlinie aus 2006, hier mit dem Fokus auf akute und chronische Herzinsuffizienz – Suchzeitraum und Angaben zur Recherche unbekannt – Evidenzgrundlage ist im Fließtext verknüpft und transparent dargestellt. To ensure high quality and transparency, the CCS has adopted the GRADE Scale for rating the strength of recommendations and the quality of evidence. **ALL recommendations** will begin with **we recommend** (where strength and quality are strong) and we suggest (where strength and quality of evidence is not strong). **For strength of recommendations**, we will use **strong and conditional** as qualifiers. **For quality of evidence**, we will use the words **very low, low, moderate, or high**.

Empfehlungen

Heart failure with preserved ejection fraction

Empfehlung 1

We recommend systolic/diastolic hypertension be controlled according to the hypertension guidelines to prevent and treat HF-PEF (Strong Recommendation, High- Quality Evidence).

Empfehlung 2

We recommend diuretics be used to control symptoms from pulmonary congestion and peripheral edema (Strong Recommendation, High-Quality Evidence).

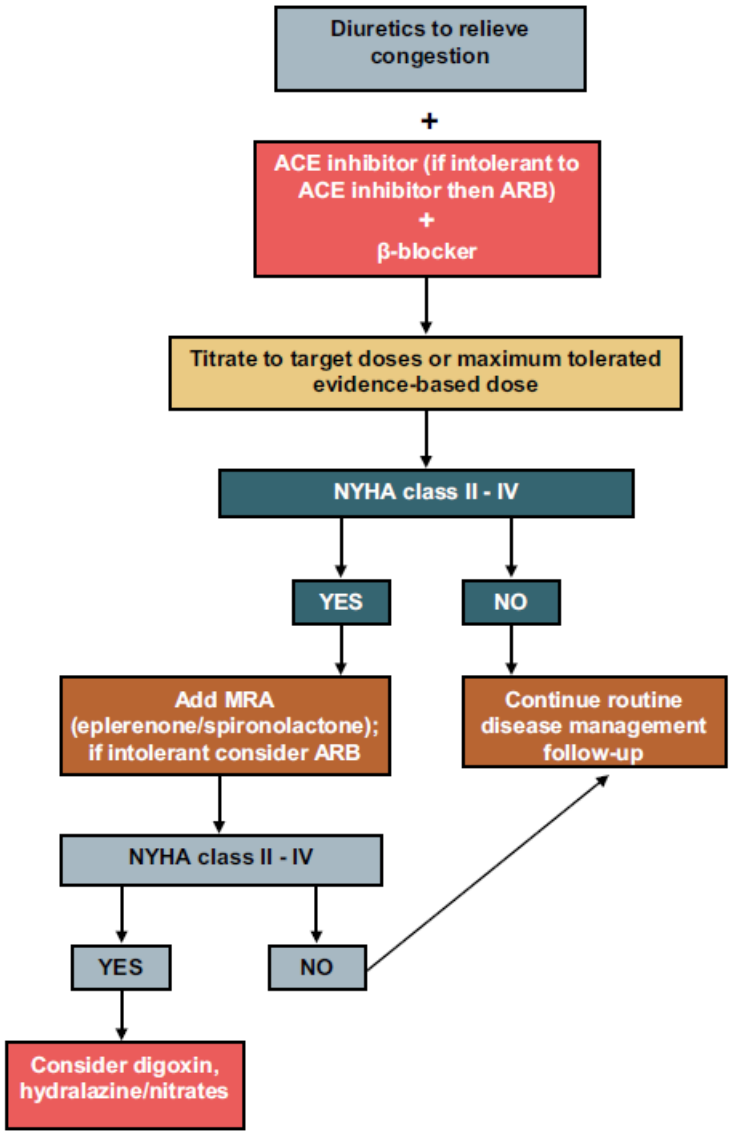


Figure 2. Pharmacologic management options for symptomatic heart failure with reduced ejection fraction (≤ 40%). ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

	Heart failure with reduced ejection fraction **ACE inhibitor** Empfehlung 1. We recommend an ACE inhibitor be used in all patients as soon as safely possible after a MI and be continued indefinitely if EF < 40% or if HF complicates a MI (Strong Recommendation, High-Quality Evidence). Empfehlung 2. We recommend ACE inhibitors be used in all asymptomatic patients with an EF < 35% (Strong Recommendation, Moderate-Quality Evidence). Empfehlung 3 We recommend ACE inhibitors be used in all symptomatic HF patients and EF < 40%. (Strong Recommendation,High-Quality Evidence). **ARB** Empfehlung 1 We recommend an ARB be used in patients who cannot tolerate an ACE inhibitor (Strong Recommendation,High-Quality Evidence). Empfehlung 2 We recommend an ARB be added to an ACE inhibitor for patients with NYHA class II-IVHF and EF<40% deemedat increased risk of HF events despite optimal treatment with an ACE inhibitor and -blocker as tolerated (Strong Recommendation, Moderate-Quality Evidence). Empfehlung 3 We recommend an ARB be considered instead of an ACE inhibitor for patients with acute MI with HF or an EF <40% who cannot tolerate an ACE inhibitor (Strong Recommendation, Moderate-Quality Evidence). Empfehlung 4 We recommend ARBs be considered as adjunctive therapy to ACE inhibitors when -blockers are either contraindicated or not tolerated after careful attempts at initiation (Weak Recommendation, Low-Quality Evidence). Empfehlung 5 We recommend routine combination of an ACE inhibitor, ARB, and MRA not be used for patients with current or previous symptoms of HF and REF (Strong Recommendation, Low-Quality Evidence).

	MRA Empfehlung 1 We recommend an MRA such as eplerenone be considered for patients > 55 years with mild to moderate HF during standard HF treatments with EF ≤ 30% (or ≤ 35% if QRS duration > 130 ms) and recent (6 months) hospitalization for CV disease or with elevated BNP or NT-proBNP levels (Strong Recommendation, High- Quality Evidence). Empfehlung 2 We recommend an MRA such as eplerenone be considered in patients after an MI with EF ≤ 30% and HF or EF ≤ 30% alone in the presence of diabetes (Strong Recommendation, High-Quality Evidence). Empfehlung 3 We recommend an MRA such as spironolactone be considered for patients with an EF <30% and severe chronic HF (NYHA IIIB-IV) despite optimization of other recommended treatments (Strong Recommendation, High-Quality Evidence). (Values and preferences. The above recommendations place a high value on an understanding that among a given drug class, only drugs proven to be beneficial in large trials can be used because their effective target doses capable of modifying clinical outcome are known, and less value on individual response. If a drug with proven mortality or morbidity benefits is not tolerated by the patient, other concomitant drugs with less proven benefit can be carefully re-evaluated to determine whether their dose can be reduced or the drug discontinued to allow for better tolerance of the drug with proven benefit. These values and preferences also apply to the recommendations of other classes of drugs discussed below. Furthermore, because there are still no data on outcome-modifying pharmacologic treatment in HF-PEF, the above recommendations apply predominantly to patients with HF-REF.) **ß-Blocker** Empfehlung 1. We recommend all HF patients with an EF≤40% receive a ß-blocker proven to be beneficial in clinical trials (Strong Recommendation, High-Quality Evidence). Empfehlung 2. We recommend NYHA class IV patients be stabilized before initiation of a ß-blocker (Strong Recommendation, High-Quality Evidence).

	Empfehlung 3. We recommend therapy be initiated at a low dose and titrated to the target dose used in large trials or the maximum tolerated dose if less than the target dose (Strong Recommendation, Moderate-Quality Evidence). Empfehlung 4. We recommend a ß-blocker not be generally introduced to patients with symptomatic hypotension despite adjustment of other therapies, patients with severe reactive airways disease, symptomatic bradycardia, or with significant atrioventricular block without a permanent pacemaker; stable chronic obstructive pulmonary disease is not a contraindication for use of_ blockade (Strong Recommendation, Moderate-Quality Evidence). (Values and preferences. These recommendations place a very high value on the understanding that only ß-blockers that have been shown to improve clinical outcomes should be used.) **Diuretics** Empfehlung 1 We recommend a loop diuretic, such as furosemide, for most patients with HF and congestive symptoms. When acute congestion is cleared, the lowest dose should be used that is compatible with stable signs and symptoms (Strong Recommendation, Low-Quality Evidence). Empfehlung 2 We recommend that for patients with persistent volume overload despite optimal medical therapy and increases in loop diuretics, cautious addition of a second diuretic (a thiazide or low dose metolazone) may be considered as long as it is possible to closely monitor morning weight, renal function, and serum potassium (Weak Recommendation, Moderate-Quality Evidence). (Values and preferences. These recommendations place a high value on the understanding that diuretics have not been shown to improve survival like the ACE inhibitors and -blockers but are frequently required to relieve congestion.) **Digoxin** Empfehlung 1 We recommend digoxin in patients in sinus rhythm who continue to have moderate to severe symptoms, despite optimized HF therapy to relieve symptoms and reduce hospitalizations (Strong Recommendation, Moderate- Quality Evidence).

	Empfehlung 2 We recommend digoxin in patients with chronic atrial fibrillation (AF) and poor control of ventricular rate despite optimal -blocker therapy, or when -blockers cannot be used (Strong Recommendation, Low-Quality Evidence). (Values and preferences. These recommendations place a high value on the understanding that the use of cardiac glycosides in chronic HF remains controversial. Digoxin can cause atrial and ventricular arrhythmias particularly in the presence of hypokalemia. Not all glycosides and not all preparations have been studied in terms of efficacy and safety.) **Isosorbide dinitrate and hydralazine** Empfehlung 1 We recommend the combination of isosorbide dinitrate and hydralazine be considered in addition to standard therapy for black Canadians with HF-REF (Strong Recommendation, Moderate-Quality Evidence) and may be considered for others including non-black HF patients unable to tolerate an ACE inhibitor or ARB because of intolerance, hyperkalemia, or renal dysfunction (Strong Recommendation, Low-Quality Evidence). (Values and preferences. Adverse effects such as headache, nausea, dizziness, and hypotension are common and frequently require a reduction in dose or discontinuation.)
Yancy CW, 2013 **American College of Cardiology Foundation (ACCF) American Heart Association Task Force on Practice Guidelines (AHA) [14]** 2013 ACCF/AHA Guideline for the Management of Heart Failure	This guideline covers multiple management issues for the adult patient with HF.
	Methodik – Suchzeitraum An extensive evidence review was conducted through October 2011 and includes selected other references through April 2013. Searches were extended to studies, reviews, and other evidence conducted in human subjects and that were published in English from PubMed, EMBASE, Cochrane, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to this guideline. Empfehlungen sind direkt mit Angaben zur Qualität der Evidenz und mit Literaturstellen verknüpft. LoE und GoR siehe Anhang Tab. 1
	Empfehlungen

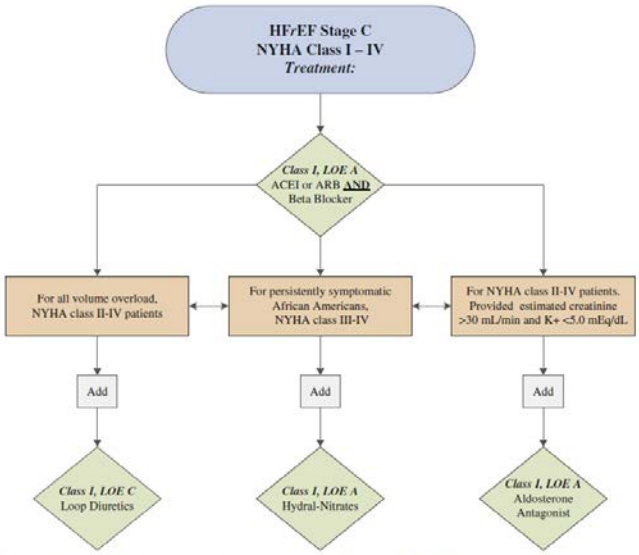


Figure 1. Stage C HFrEF: evidence-based, guideline-directed medical therapy. ACEI indicates angiotensin-converting enzyme inhibito ARB, angiotensin-receptor blocker; HFrEF, heart failure with reduced ejection fraction; Hydral-Nitrates, hydralazine and isosorbide dinitra LOE, Level of Evidence; and NYHA, New York Heart Association.

Für die Beschreibung Class I – Class III siehe Anhang Tab. 1

Diuretics

Empfehlung 1
Class I: Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (Level of Evidence: C)

Ohne Angabe des LoE machen die Autoren folgenden Hinweis: Diuretics should generally be combined with an ACE inhibitor, beta blocker, and aldosterone antagonist.

ACE inhibitor

Empfehlung 1
Class1: ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. (Level of Evidence: A)

ARB

Empfehlung 1
Class I: ARBs are recommended in patients with HFrEF with current or prior symptoms who are ACE inhibitor intolerant, unless contraindicated, to reduce morbidity and mortality. (Level of Evidence: A)

Empfehlung 2
Class IIa: ARBs are reasonable to reduce morbidity and mortality as alternatives to ACE inhibitors as first-line therapy for patients with HFrEF, especially for patients already taking ARBs for other

	indications, unless contraindicated. (Level of Evidence: A) Empfehlung 3 Class IIb: Addition of an ARB may be considered in persistently symptomatic patients with HFrEF who are already being treated with an ACE inhibitor and a beta blocker in whom an aldosterone antagonist is not indicated or tolerated. (Level of Evidence: A) Empfehlung 4 Class III, Harm: Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with HFrEF. (Level of Evidence: C) **ß-Blocker** Empfehlung 1 Class I: Use of 1 of the 3 beta blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (Level of Evidence: A) **Aldosterone receptor antagonist** Empfehlung 1 Class I: Aldosterone receptor antagonists (or mineralocorticoid receptor antagonists) are recommended in patients with NYHA class II–IV HF and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be 2.5 mg/dL or less in men or 2.0 mg/dL or less in women (or estimated glomerular filtration rate >30 mL/min/1.73 m2), and potassium should be less than 5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (Level of Evidence: A) Empfehlung 2 Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF of 40% or less who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated (446). (Level of Evidence: B) Empfehlung 3 Class III, Harm: Inappropriate use of aldosterone receptor antagonists is potentially harmful because of life-threatening hyperkalemia or renal insufficiency when serum creatinine is greater than 2.5 mg/dL in men or greater than 2.0 mg/dL in women (or estimated glomerular filtration

rate <30 mL/min/1.73m2), and/or potassium greater than 5.0 mEq/L. (Level of Evidence: B)

Isosorbide dinitrate and hydralazine

Empfehlung 1

Class IIa: A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated. (Level of Evidence: B)

Digoxin

Empfehlung 1
Class I: Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (Level of Evidence: B)

Recommendations	COR	LOE
Diuretics		
Diuretics are recommended in patients with HF*r*EF with fluid retention	I	C
ACE inhibitors		
ACE inhibitors are recommended for all patients with HF*r*EF	I	A
ARBs		
ARBs are recommended in patients with HF*r*EF who are ACE inhibitor intolerant	I	A
ARBs are reasonable as alternatives to ACE inhibitors as first-line therapy in HF*r*EF	IIa	A
Addition of an ARB may be considered in persistently symptomatic patients with HF*r*EF on GDMT	IIb	A
Routine *combined* use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful	III: Harm	C
Beta blockers		
Use of 1 of the 3 beta blockers proven to reduce mortality is recommended for all stable patients	I	A
Aldosterone receptor antagonists		
Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV who have LVEF ≤35%	I	A
Aldosterone receptor antagonists are recommended in patients following an acute MI who have LVEF ≤40% with symptoms of HF or DM	I	B
Inappropriate use of aldosterone receptor antagonists may be harmful	III: Harm	B
Hydralazine and isosorbide dinitrate		
The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with NYHA class III–IV HF*r*EF on GDMT	I	A
A combination of hydralazine and isosorbide dinitrate can be useful in patients with HF*r*EF who cannot be given ACE inhibitors or ARBs	IIa	B
Digoxin		
Digoxin can be beneficial in patients with HF*r*EF	IIa	B

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 08.01.2015**

#	Suchfrage
1	MeSH descriptor: [Heart Failure] explode all trees
2	Cardiac or Myocardial or heart:ti
3	left next sided:ti or systolic or chronic or congestive:ti
4	failure or decompensation:ti
5	#2 AND #3 AND #4
6	#1 OR #5
7	#6 from 2010 to 2015

SR, HTAs in Medline (PubMed) am 09.01.2015

#	Suchfrage
1	"heart failure, systolic/drug therapy"[MeSH Terms]
2	Cardiac[Title/Abstract] OR Myocardial[Title/Abstract] OR heart[Title/Abstract]
3	(left[Title/Abstract] AND sided[Title/Abstract]) OR congestive[Title/Abstract] OR systolic[Title/Abstract] OR chronic[Title/Abstract]
4	failure[Title/Abstract] OR decompensation[Title/Abstract]
5	(((((drug[Title/Abstract]) OR drug therap*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract]
6	#2 AND #3 AND #4 AND #5
7	#1 OR #6
8	(((#7) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]))) OR ((#7) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
9	(#8) AND ("2010/01/01"[PDAT] : "2015/01/09"[PDAT])

Leitlinien in Medline (PubMed) am 09.01.2015

#	Suchfrage
1	"Heart Failure"[Mesh Terms]
2	Cardiac[Title/Abstract] OR Myocardial[Title/Abstract] OR heart[Title/Abstract]
3	(left[Title/Abstract] AND sided[Title/Abstract]) OR congestive[Title/Abstract] OR systolic[Title/Abstract] OR chronic[Title/Abstract]
4	failure[Title/Abstract] OR decompensation[Title/Abstract]
5	#2 AND #3 AND #4
6	#1 OR #5
7	((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference,

	NIH[Publication Type]) OR guideline*[Title]
8	#6 AND #7
9	(#8) AND ("2010/01/01"[PDAT] : "2015/01/09"[PDAT])

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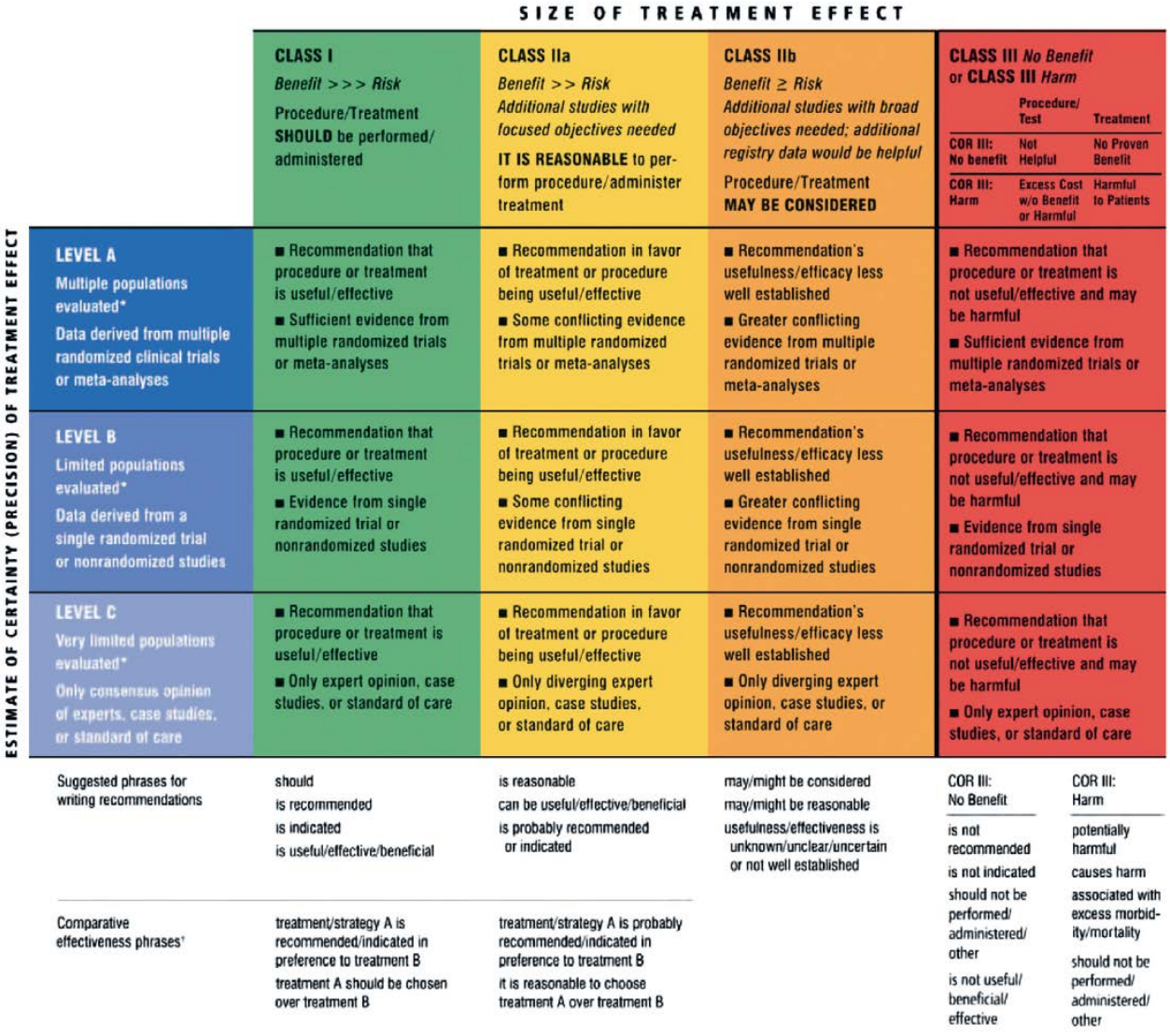
Anhang:

Tabelle 1: Aus Yancy CW, 2013 ACCF/AHA Guideline for the Management of Heart Failure, Klassifikation der Empfehlungen und Level of Evidencel



ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT			
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *No Benefit* or **CLASS III** *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

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

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

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

Tabelle 2: Aus Yancy CW, 2013 ACCF/AHA Guideline for the Management of Heart Failure,
Vergleich der Klassifikationen der Herzinsuffizienz: ACCF/AHA Stages vs. NYHA Functional Classification

ACCF/AHA Stages of HF (38)		NYHA Functional Classification (46)	
A	At high risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; and NYHA, New York Heart Association.