NATIONALE VERSORGUNGS LEITLINIEN

Nationale VersorgungsLeitlinie

Chronische Herzinsuffizienz

Recherchedokumentation
+ Evidenztabellen

Version 4

AWMF-Register-Nr. nvl-006

Träger:

Bundesärztekammer

Kassenärztliche Bundesvereinigung

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften

Inhaltsverzeichnis

1 Themenübergreifende strukturierte Recherche nach systematischen Übersichtsarbeiten

1.1 Fragestellung

Es werden systematische Übersichtsarbeiten zum Thema „Chronische Herzinsuffizien“ gesucht, die als primäre Evidenzquellen für die Aktualisierung der NVL Chronische Herzinsuffizienz dienen sollen.

- Population: erwachsene Patient*innen mit manifester chronischer oder akuter Herzinsuffizienz
- Intervention: alle
- Kontrolle: alle
- Outcome: Mortalität, Hospitalisierungen, Lebensqualität
- Sprachen: deutsch, englisch
- Publikationstyp: aggregierte Evidenz
- Zeitraum: ab 2016 (Ende Suchzeitraum systematische Suche für 2. Auflage der NVL); regelmäßige Updates über Newsletter (IQWiG) bzw. Alert (Cochrane); händische Updates (NICE, AHRQ) jährlich

Recherchequellen

Als Quellen für die strukturierte Suche nach hochwertigen systematischen Übersichtsarbeiten wurden folgende Institutionenen aufgrund ihrer evidenzbasierten Vorgehensweise, ihrer hohen Berichtsqualität, ihrer wissenschaftlichen Unabhängigkeit, eines weitergehenden Einblicks in Studiendossiers sowie ggf. ihres Bezugs zum deutschen bzw. europäischen Versorgungskontext ausgewählt:

- IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
- NICE (National Institute for Health and Care Excellence)
- Cochrane
- AHRQ

Ein- und Ausschlusskriterien

Einschluss	**E**	Einschluss: Fragestellung passend, Studientyp passend	
		Ep	noch nicht veröffentlicht (Protokoll, Berichtsplan o. Ä. vorhanden)
		Es	spezielle Patientengruppe/Subgruppe
		Esz	zurückgestellt für iteratives Vorgehen (z.B. Detailfragestellung)
Ausschluss	Aa	thematisch nicht passend: andere Erkrankung/ Fragestellung/Thema	
	Ap	Studientyp nicht passend	
	Ad	Doppelpublikation oder nicht erhältlich	
	As	Sprache nicht deutsch oder englisch	
	Az	falscher Zeitraum (veröffentlicht vor 2016)	
	Aw	zurückgezogen oder Update vorhanden	
	Av	Irrelevant für deutschen Versorgungskontext	

Treffen für eine gefundene Leitlinie mehrere Ausschlusskriterien zu, so wird das jeweils erste Kriterium in der Liste bzw. das am zutreffendste Kriterium für die Begründung des Ausschlusses angegeben.

1.2 Recherchestrategien und -ergebnisse

Die Recherchestrategien (z. B. Datenbanksuche, Schlagwortsuche, einfaches Sreening) richten sich nach den Möglichkeiten der jeweiligen Recherchequelle.

1.2.1 IQWiG

Suche am 06.02.2022 nach IQWiG-Projekten unter https://www.iqwig.de/projekte/projekte-und-ergebnisse

Aktualisierungssuche am 22.02.2023

Suchstrategie 1

Suchwort „Herzinsuffizienz“, Filter: Ergebnisse ab 2016, Bearbeitung abgeschlossen

Suchergebnisse: n=20

- A22-39: Empagliflozin (Herzinsuffizienz) – Nutzenbewertung gemäß § 35a SGB V; Bearbeitung abgeschlossen; 15.09.2022
  E
- A22-86: Empagliflozin (Herzinsuffizienz mit erhaltener Ejektionsfraktion) – Addendum zum Auftrag A22-39; Bearbeitung abgeschlossen; 15.09.2022
  E
- A22-08: Vericiguat (Herzinsuffizienz) - Addendum zum Auftrag A21-120; Bearbeitung abgeschlossen; 03.03.2022
  E
- A21-120: Vericiguat (Herzinsuffizienz) - Nutzenbewertung gemäß § 35a SGB V; Bearbeitung abgeschlossen; 03.03.2022
  E
- A21-93: Empagliflozin (Herzinsuffizienz) - Nutzenbewertung gemäß § 35a SGB V; Bearbeitung abgeschlossen; 06.01.2022
  E
- A21-148: Empagliflozin (Herzinsuffizienz) - Addendum zum Auftrag A21-93; Bearbeitung abgeschlossen; 06.01.2022
  E
- V20-05: Leitliniensynopse für die Aktualisierung des DMP Herzinsuffizienz; Bearbeitung abgeschlossen; 29.12.2021
  Aa
- A20-113: Dapagliflozin (Herzinsuffizienz) - Nutzenbewertung gemäß § 35a SGB V; Bearbeitung abgeschlossen; 20.09.2021
  E
- H21-05: Perkutan-implantierter interatrialer Shunt zur Behandlung der Herzinsuffizienz - Addendum zum Auftrag H20-06; Bearbeitung abgeschlossen; 28.06.2021
  E
- H20-08: Endovaskuläre Implantation eines Stentgrafts mit Klappenelement bei Trikuspidalklappeninsuffizienz - Bewertung gemäß §137h SGB V; Bearbeitung abgeschlossen; 26.05.2021
  Aa
- H20-06: Perkutan-implantierter interatrialer Shunt zur Behandlung der Herzinsuffizienz - Bewertung gemäß §137h SGB V; Bearbeitung abgeschlossen; 26.05.2021
  E
- A21-44: Dapagliflozin (Herzinsuffizienz) - Addendum zum Auftrag A20-113; Bearbeitung abgeschlossen; 20.05.2021
  E
- N19-01: Datengestütztes, zeitnahes Management in Zusammenarbeit mit einem ärztlichen telemedizinischen Zentrum für Patientinnen und Patienten mit einer fortgeschrittenen Herzinsuffizienz - Rapid Report; Bearbeitung abgeschlossen; 28.10.2019
  E
- N16-02: Telemonitoring mithilfe von aktiven kardialen implantierbaren Aggregaten bei ventrikulären Tachyarrhythmien sowie Herzinsuffizienz; Bearbeitung abgeschlossen; 11.07.2018
  E

- E15-04: Messung und Monitoring des pulmonalarteriellen Druckes mittels implantiertem Sensor zur Therapieoptimierung bei Herzinsuffizienz; Bearbeitung abgeschlossen; 25.01.2018
  E
- E16-02: Messung und Monitoring des pulmonalarteriellen Druckes mittels implantiertem Sensor zur Therapieoptimierung bei Herzinsuffizienz – Addendum zum Auftrag E15-04; Bearbeitung abgeschlossen; 25.01.2018
  E
- A16-29: Sacubitril/Valsartan - Addendum zum Auftrag A15-60; Bearbeitung abgeschlossen; 16.06.2016
  Az (bereits in NVL berücksichtigt)
- A15-60: Sacubitril/Valsartan - Nutzenbewertung gemäß § 35a SGB V; Bearbeitung abgeschlossen; 01.04.2016
  Az (bereits in NVL berücksichtigt)
- V14-01: Systematische Leitlinienrecherche und -bewertung sowie Extraktion relevanter Empfehlungen für ein DMP chronische Herzinsuffizienz; Bearbeitung abgeschlossen; 15.01.2016
  Aa

Suchstrategie 2

Anwendungsgebiet: „Herz und Kreislauf“, Filter: Status „Bearbeitung abgeschlosssen“, Ergebnisse ab 2016

Suchergebnisse: n=0 weitere inhaltlich relevante Treffer (ohne Duplikate gemäß Suchstrategie 1):

Suchstrategie 3

Suche am 06.02.2022 unter https://www.iqwig.de/sich-einbringen/themencheck-medizin/berichte

Aktualisierungssuche am 22.02.2023

Filter: Anwendungsgebiet „Herz und Kreislauf“

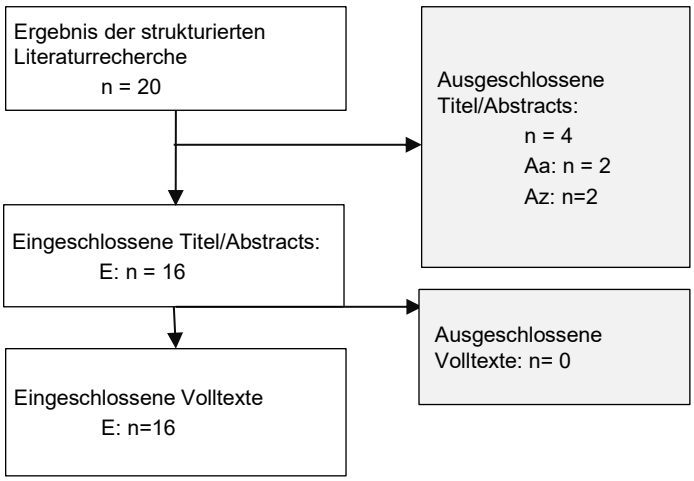
Suchergebnisse

n=1

- HT19-01: Fortgeschrittenes Lymphödem: Lassen sich durch nicht medikamentöse Verfahren die Symptome lindern?; Bearbeitung abgeschlossen; 8/2017 - 7/2018
  Aa

Flowchart

Kriterien für den Ein- und Ausschluss: siehe 1.2.



1.2.2 NICE

Suchstrategie

Suche unter https://www.nice.org.uk/guidance – NICE Guidance – Conditions and diseases – Cardiovascular conditions – Heart Failure
Suche am 06.02.2022; Aktualisierung am 22.02.2023

Suchergebnisse

NICE Guidelines (n=31)

- Acute heart failure: diagnosis and management (CG187)
  Last updated: 17 November 2021
  Az
- Chronic heart failure in adults: diagnosis and management (NG106)
  12 September 2018
  Az

Technology appraisal guidance (n=16)

- TYRX Absorbable Antibacterial Envelope for preventing infection from cardiac implantable electronic devices (terminated appraisal) (TA790)
  Product type:GuidanceProgramme:Technology appraisal guidance Published: 25 May 2022
  Aa
- Empagliflozin for treating chronic heart failure with reduced ejection fraction (TA773)
  Product type:GuidanceProgramme:Technology appraisal guidance Published: 9 March 2022
  E
- Sodium zirconium cyclosilicate for treating hyperkalaemia (TA599)
  Product type:GuidanceProgramme:Technology appraisal guidance Last updated: 24 January 2022 Published: 4 September 2019
  Aa
- Vericiguat for treating chronic heart failure with reduced ejection fraction (terminated appraisal) (TA731)
  Product type:GuidanceProgramme:Technology appraisal guidancePublished: 29 September 2021
  E
- Dapagliflozin for treating chronic heart failure with reduced ejection fraction (TA679)
  Product type:GuidanceProgramme:Technology appraisal guidancePublished: 24 February 2021
  E
- Patiromer for treating hyperkalaemia (TA623)
  Product type:GuidanceProgramme:Technology appraisal guidancePublished: 13 February 2020
  Aa
- Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (TA388)
  Product type:GuidanceProgramme:Technology appraisal guidancePublished: 27 April 2016
  Az
- Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (TA314)
  Product type:GuidanceProgramme:Technology appraisal guidancePublished: 25 June 2014
  Az
- Ivabradine for treating chronic heart failure (TA267)
  Product type:GuidanceProgramme:Technology appraisal guidancePublished: 28 November 2012
  Az
- Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID1648]
  Status:In development | In consultationProgramme:Technology appraisal guidanceConsultation end date: 1 March 2023Expected publication date: 21 June 2023
  Ep

- Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction [ID3945]
  Status:In development | In consultationProgramme:Technology appraisal guidanceConsultation end date: 1 March 2023Expected publication date: 21 June 2023
  Ep
- Rivaroxaban for treating chronic heart failure [ID1462]
  Status:Awaiting developmentProgramme:Technology appraisal guidanceExpected publication date: TBC
  Ep
- Omecamtiv mecarbil for treating chronic heart failure with reduced ejection fraction [ID3912]
  Status:Awaiting developmentProgramme:Technology appraisal guidanceExpected publication date: TBC
  Ep
- Sacubitril valsartan for treating chronic heart failure with reduced ejection fraction in people under 18 years TS ID 10350
  Status:Topic selectionProgramme:Technology appraisal guidanceExpected publication date: TBC
  Ep
- Semaglutide for treating obesity-related heart failure with preserved ejection fraction TS ID 11788
  Status:Awaiting developmentProgramme:Technology appraisal guidanceExpected publication date: TBC
  Aa
- Empagliflozin for reducing death and hospitalisation from heart failure after acute myocardial infarction TS ID 11817
  Status:Awaiting developmentProgramme:Technology appraisal guidanceExpected publication date: TBC
  Ep

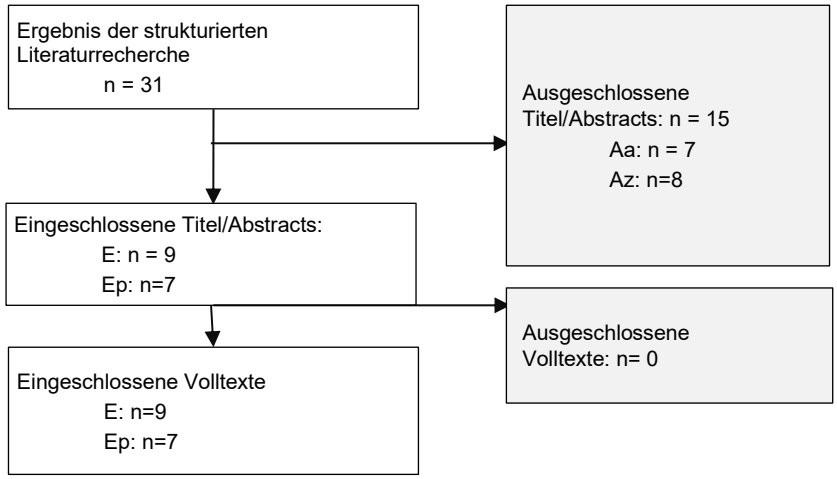
Interventional procedures guidance (n=13)

- Percutaneous implantation of pulmonary artery pressure sensors for monitoring treatment of chronic heart failure (IPG711)
  Product type:GuidanceProgramme:Interventional procedures guidancePublished: 24 November 2021
  E
- Permanent His-bundle pacemaker implantation for treating heart failure (IPG694)
  Product type:GuidanceProgramme:Interventional procedures guidancePublished: 5 May 2021
  E
- Electrical stimulation to improve muscle strength in chronic respiratory conditions, chronic heart failure and chronic kidney disease (IPG677)
  Product type:GuidanceProgramme:Interventional procedures guidancePublished: 5 August 2020
  Aa (zu speziell für NVL)
- Cardiac contractility modulation device implantation for heart failure (IPG655)
  Product type:GuidanceProgramme:Interventional procedures guidancePublished: 26 June 2019
  E
- Percutaneous mitral valve leaflet repair for mitral regurgitation (IPG649)
  Product type:GuidanceProgramme:Interventional procedures guidancePublished: 29 May 2019
  E
- Artificial heart implantation as a bridge to transplantation for end-stage refractory biventricular heart failure (IPG602)
  Product type:GuidanceProgramme:Interventional procedures guidancePublished: 20 December 2017
  E
- Normothermic extracorporeal preservation of hearts for transplantation following donation after brainstem death (IPG549)
  Product type:GuidanceProgramme:Interventional procedures guidancePublished: 24 February 2016
  Aa
- Implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation (IPG516)
  Product type:GuidanceProgramme:Interventional procedures guidancePublished: 27 March 2015
  Az

- Extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults (IPG482)
  Product type:GuidanceProgramme:Interventional procedures guidancePublished: 27 March 2014
  Az
- Percutaneous mitral valve annuloplasty (IPG352)
  Product type:GuidanceProgramme:Interventional procedures guidancePublished: 28 July 2010
  Aa
- Short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery (IPG177)
  Product type:GuidanceProgramme:Interventional procedures guidancePublished: 28 June 2006
  Az
- Partial left ventriculectomy (the Batista procedure) (IPG41)
  Product type:GuidanceProgramme:Interventional procedures guidancePublished: 25 February 2004
  Az
- Implantable Vagus Nerve Stimulator in Heart Failure
  Status:In developmentProgramme:Interventional procedures guidanceExpected publication date: TBC)
  Ep

Flowchart

Kriterien für den Ein- und Ausschluss: siehe 1.2.



1.2.3 Cochrane

Suchstrategie

Cochrane Library (laufend per Alert)

Nr.	Suchfrage	Anzahl
#1	"heart failure":ti with Cochrane Library publication date from Jan 2016 to present, in Cochrane Reviews and Cochrane Protocols	33

Suchergebnisse Reviews

- Ultrafiltration for acute heart failure
  Mehul Srivastava, Nicholas Harrison, Ana Francisca SMA Caetano, Audrey R Tan, Mandy Law
  Intervention, Review, 21 January 2022
  Aa (zu speziell für NVL)
- Beta-blockers in patients without heart failure after myocardial infarction
  Sanam Safi, Naqash J Sethi, Steven Kwasi Korang, Emil Eik Nielsen, Joshua Feinberg, Christian Gluud, Janus C Jakobsen
  Intervention, Review, 5 November 2021
  Aa
- Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction
  Nicole Martin, Karthick Manoharan, Ceri Davies, R Thomas Lumbers
  Intervention, Review, 22 May 2021
  E
- Anticoagulation versus placebo for heart failure in sinus rhythm
  Eduard Shantsila, Monika Kozieł, Gregory YH Lip
  Intervention, Review, 18 May 2021
  E
- Coenzyme Q10 for heart failure
  Tareq Al Saadi, Yazan Assaf, Medhat Farwati, Khaled Turkmani, Ahmad Al-Mouakeh, Baraa Shebli, Mohammed Khoja, Adib Essali, Mohammed E Madmani
  Intervention, Review, 3 February 2021
  E
- Ivabradine as adjuvant treatment for chronic heart failure
  Carina Benstoem, Christina Kalvelage, Thomas Breuer, Nicole Heussen, Gernot Marx, Christian Stoppe, Vincent Brandenburg
  Intervention, Review, 4 November 2020
  E
- Beta-blockers for congestive heart failure in children
  Samer Alabed, Ammar Sabouni, Suleiman Al Dakhoul, Yamama Bdaiwi
  Intervention, Review, 23 July 2020
  Aa
- mHealth education interventions in heart failure
  Sabine Allida, Huiyun Du, Xiaoyue Xu, Roslyn Prichard, Sungwon Chang, Louise D Hickman, Patricia M Davidson, Sally C Inglis
  Intervention, Review, 2 July 2020
  E
- Advance care planning for adults with heart failure
  Yuri Nishikawa, Natsuko Hiroyama, Hiroki Fukahori, Erika Ota, Atsushi Mizuno, Mitsunori Miyashita, Daisuke Yoneoka, Joey SW Kwong
  Intervention, Review, 27 February 2020
  E

- Pharmacological interventions for heart failure in people with chronic kidney disease
  Meaghan Lunney, Marinella Ruospo, Patrizia Natale, Robert R Quinn, Paul E Ronksley, Ioannis Konstantinidis, Suetonia C Palmer, Marcello Tonelli, Giovanni FM Strippoli, Pietro Ravani
  Intervention, Review, 27 February 2020
  E
- Positive airway pressure therapy for the treatment of central sleep apnoea associated with heart failure
  Shuhei Yamamoto, Takayoshi Yamaga, Kenichi Nishie, Chie Nagata, Rintaro Mori
  Intervention, Review, 4 December 2019
  Aa (zu speziell für NVL)
- Natriuretic peptide-guided treatment for the prevention of cardiovascular events in patients without heart failure
  Claire Sweeney, Fiona Ryan, Mark Ledwidge, Cristin Ryan, Ken McDonald, Chris Watson, Rebabonye B Pharithi, Joe Gallagher
  Intervention, Review, 15 October 2019
  Aa
- Exercise-based cardiac rehabilitation for adults with heart failure
  Linda Long, Ify R Mordi, Charlene Bridges, Viral A Sagar, Edward J Davies, Andrew JS Coats, Hasnain Dalal, Karen Rees, Sally J Singh, Rod S Taylor
  Intervention, Review, 29 January 2019
  E
- Disease management interventions for heart failure
  Andrea Takeda, Nicole Martin, Rod S Taylor, Stephanie JC Taylor
  Intervention, Review 8 January 2019
  E
- Stem cell therapy for chronic ischaemic heart disease and congestive heart failure
  Sheila A Fisher, Carolyn Doree, Anthony Mathur, David P Taggart, Enca Martin-Rendon
  Intervention, Review, 24 December 2016
  Az
- B-type natriuretic peptide-guided treatment for heart failure
  Julie McLellan, Carl J Heneghan, Rafael Perera, Alison M Clements, Paul P Glasziou, Karen E Kearley, Nicola Pidduck, Nia W Roberts, Sally Tyndel, F Lucy Wright, Clare Bankhead
  Intervention, Review, 22 December 2016
  Az (Update des Reviews durch Hauptautorin als Cochrane-unabhängiger Review publiziert)
- Antiplatelet versus anticoagulation treatment for patients with heart failure in sinus rhythm
  Eduard Shantsila, Gregory YH Lip
  Intervention, Review, 15 September 2016
  Az
- Pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy
  Arturo J Martí-Carvajal, Joey SW Kwong
  Intervention, Review, 8 July 2016
  Aa
- Shengmai (a traditional Chinese herbal medicine) for heart failure
  Jie Chen, Yu Yao, Haining Chen, Joey SW Kwong, Jin Chen
  Intervention, Review, 29 April 2016
  Aw (withdrawn)
- Diuretics for heart failure
  Rajaa F Faris, Marcus Flather, Henry Purcell, Philip A Poole-Wilson, Andrew JS Coats
  Intervention, Review, 4 April 2016
  Aw (withdrawn)

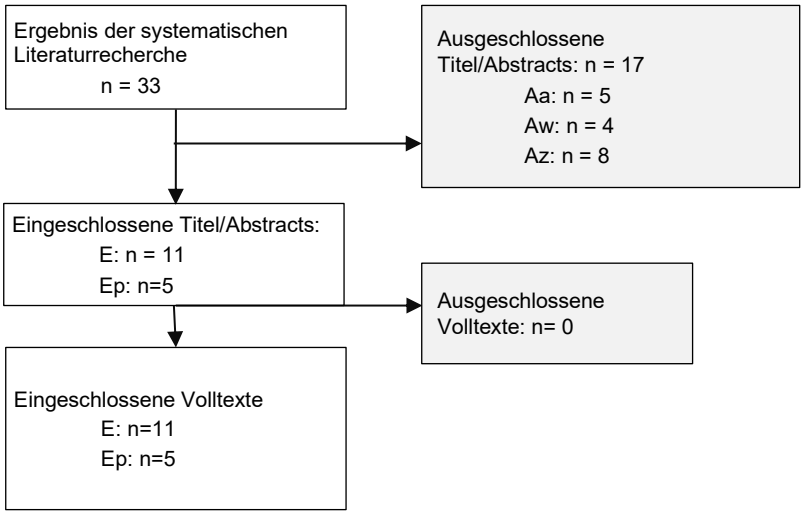
Suchergebnisse Protokolle

- Heart failure symptoms as predictors of hospital admission, readmission and all-cause mortality
  Mohammad Rizwan Ali, Suzanne C Freeman, Laura Gray, Umesh Kadam, Claire Lawson
  Prognosis, Protocol, 21 October 2022
  Ep

- Continuous infusion versus bolus injection of loop diuretics for congestive heart failure
  Juqian Zhang, Can Zhou, Mahnoor Ihsan, Andreas Tsangarides, Sarah Ahmed, Ranga Fernando, Tin Sanda Lwin, Shazmeen Surtee, Ebony Farnell, Muhammad Chaudhary, Gregory YH Lip, Ruaraidh A Hill, Rajiv Sankaranarayanan
  Intervention, Protocol, 24 August 2021
  Ep
- Beta-blockers for heart failure
  Sanam Safi, Steven Kwasi Korang, Emil Eik Nielsen, Naqash J Sethi, Joshua Feinberg, Christian Gluud, Janus C Jakobsen
  Intervention, Protocol, 2 July 2021
  Aw (withdrawn)
- Treatment for hyperkalaemia in heart failure: a network meta-analysis
  Nyuk Jet Chong, Shuhei Yamamoto, Raymond Ching Chiew Wong
  Intervention, Protocol, 29 June 2021
  Aa
- Psychological interventions for depression and anxiety in patients with coronary heart disease, heart failure or atrial fibrillation
  Chantal F Ski, Rod S Taylor, Karen McGuigan, Jeffrey D Lambert, Suzanne H Richards, David R Thompson
  Intervention, Protocol, 6 July 2020
  Ep
- LCZ696 (sacubitril/valsartan) for patients with heart failure
  Adrian V Hernandez, Vinay Pasupuleti, Maciej Banach, Agata M Bielecka-Dabrowa
  Intervention, Protocol, 14 January 2020
  Ep
- Implantable device monitoring versus usual care for managing individuals with heart failure
  Kevin Koo, Caleb Ferguson, Liang-Han Ling, John GF Cleland, Sally C Inglis
  Intervention, Protocol, 20 August 2019
  Ep
- Reduced salt intake for heart failure
  Kamal R Mahtani, Carl J Heneghan, David Nunan, Igho J Onakpoya, Nia W Roberts, FD Richard Hobbs
  Intervention, Protocol, 22 February 2018
  Aw (withdrawn)
- Yoga for improving functional capacity, quality of life and cardiovascular outcomes in people with heart failure
  Mahalaqua Nazli Khatib, Richard Kirubakaran, Shilpa Gaidhane, Anuraj H Shankar, Zahiruddin Quazi Syed
  Intervention, Protocol, 14 July 2017
  Aw (withdrawn)
- Interventions to improve evidence-based prescribing in heart failure
  Lydia AL Bazzano, Marilyn K Marshall, Robert Harrold, Kirk J Pak, Mieke L van Driel
  Intervention, Protocol, 22 August 2016
  Aw (withdrawn)
- Ivabradine as adjuvant treatment for chronic heart failure
  Carolina Mizzaci, André T Vilela, Rachel Riera
  Intervention, Protocol, 8 April 2016
  Aw (withdrawn)
- Opioids for treating dyspnoea in patients with chronic heart failure
  Fiona A Shearer, Allan D Struthers, Robin Harbour
  Intervention, Protocol, 4 April 2016
  Aw (withdrawn)
- Beta-blockers for heart failure
  John GF Cleland, Nick Freemantle, Joanne Eastaugh, Phillip J Young, Jane Harrison, Balraj S Heran, Rod S Taylor
  Intervention, Protocol, 19 January 2016
  Aw (withdrawn)

Flowchart

Kriterien für den Ein- und Ausschluss: siehe 1.2.



1.2.4 AHRQ

Suche am 06.2.2022; Aktualisierung am 22.02.2023

nach EPC Reports unter https://www.ahrq.gov/research/findings/evidence-based-reports/search.html

Suchstrategie 1

Keyword „heart failure“, Ergebnisse ab 2016

Suchergebnisse: n=0

Suchstrategie 2

Suche nach Topic “Heart and Vascular Disease”, Ergebnisse ab 2016

Suchergebnisse

Keine Ergebnisse zu Herzinsuffizienz

Flowchart

Kriterien für den Ein- und Ausschluss: siehe 1.2.

1.2.5 Zusammenfassung

	IQWiG	NICE	Cochrane	AHRQ	gesamt
E	14	8	9	0	**31**
Ep	0	7	5	0	**12**

Insgesamt wurden 31 systematische Übersichtsarbeiten bzw. Publikationen, die systematische Übersichtsarbeiten enthalten, identifiziert, die als potenziell relevant für Version 4.0 der NVL Chronische Herzinsuffizienz erachtet wurden.

Darüber hinaus wurden 12 Review-Protokolle zu relevanten Themen identifiziert.

1.3 Evidenztabellen

Die folgenden Evidenztabellen enthalten die extrahierten Studien für das Kapitel Medkamentöse Therapie in Version 4 der NVL.

Referenz	Charakteristika	Ergebnisse	methodische Qualität	Aussagesicherheit
Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction Nicole Martin, Karthick Manoharan, Ceri Davies, R Thomas Lumbers Intervention, Review, 22 May 2021	SR mit MA Suchzeitraum: 202005 P: HFpEF I: Betablocker, ACE-i, ARB, MRA C: diverse O: diverse Evidenzbasis: 41 RCT (n=23492) RoB oft unklar; nur 5x "low"	Betablocker : 10 RCT (n=3087); 5 vs. Placebo, 5 vs. Standard; Durchschnittsalter 30 bis 81 Jahre cv Mortalität RR 0,78 (95 % KI) 0,62; 0,99; NNT 25; 3 RCT, n=1046; niedrige Aussagesicherheit Gesamtmortalität RR 0,82 (95% CI 0,67; 1,00); 4 RCT, n=1105 Teilnehmer; niedrige Aussagesicherheit Hospitalisierungen, Hyperkaliämie, Lebensqualität: unklar MRA: 13 RCT, n=4459; 8 vs. Placebo, 5 vs. Standard; Durchschnittsalter 54,5 bis 80 Jahre HF-Hosp.: RR 0,82 (95 % CI 0,69; 0,98); NNT = 41; 3 RCT, n=3714; moderate Aussagesicherheit Gesamtmortalität: RR 0,91 (95% CI 0,78; 1,06); 5 RCT, n=4207 Teilnehmer;moderate Aussagesicherheit cv Mortalität: RR 0,90 (95% CI 0,74; 1,11); 3 RCT, n=4070; moderate Aussagesicherheit Lebensqualität MD 0,84 (95 % KI -2,30; 3,98); 3 RCT, n=511; niedrige Aussagesicherheit Hyperkaliämie: RR 2,11 (95 % KI 1,77; 2,51); NNH = 11; 6 RCT, n=4291; hohe Aussagesicherheit ACEi: 8 RCT, n=2061; 3 vs. Placebo, 5 vs. Standard; Durchschnittsalter 70 bis 82 Jahre cv Mortalität:RR 0,93 (95 % CI 0,61; 1,42); 2 RCT, n=945 T Gesamtmortalität: RR 1,04 (95 % CI 0,75; 1. 45); 5 RCT, n=1187 HF-Hospitalisierungen: RR 0,86, 95 % KI 0,64; 1,15); 3 RCT, n=1019 Lebensqualität: MD -0,09 (95 % KI -3,66; 3,48); 2 RCT, n=154 Aussagesicherheit niedrig (alle) ARB: 8 RCT, n=8755; 5 vs. Placebo; 3 vs. Standard; Durchschnittsalter 61 bis 75 Jahre cv Mortalität: RR 1,02 (95 % 0,90; 1,14); 3 RCT, n=7254 Gesamtmortalität: RR 1,01 (95 % CI 0. 92; 1,11); 4 RCT, n=7964 T HF-Hospitalisierungen: RR 0,92 (95% CI 0,83; 1,02); 3 RCT, n=7254 Lebensqualität: MD 0,41 (95% CI -0,86; 1,67); 3 RCT, n=3117 Hyperkaliämie: RR 1,88 (95 % KI 1,07; 3,33); 2 RCT, n=7148 Teilnehmer Aussagesicherheit hoch (alle) ARNI: 3 RCT, n=7702; 2 vs. ARB, 1 vs. Standard; Durchschnittsalter 71 bis 73 Jahre cv Mortalität: RR 0,96 (95% CI 0,79; 1,15); 1 RCT, n=4796; moderate Aussagesicherheit Gesamtmortalität: RR 0,97 (95% CI 0,84; 1,11); 3 RCT, n=7663; hohe Aussagesicherheit Lebensqualität n.s. (hohe Aussagesicherheit) HF-Hosp.: RR 0,89 (95 % KI 0,80; 1,00); 2 RCT, n=7362; moderate Aussagesicherheit Hyperkaliämie (vs. Valsartan) RR 0,88 (95 % KI 0,77; 1,01); 2 RCT, n=5054; moderate Aussagesicherheit	AMSTAR-2: high	siehe endpunktspezifische Autorenbewertung (siehe Spalte "Ergebnisse")

Referenz	Charakteristika	Ergebnisse	methodische Qualität	Aussagesicherheit
Anticoagulation versus placebo for heart failure in sinus rhythm Eduard Shantsila, Monika Kozieł, Gregory YH Lip Intervention, Review, 18 May 2021	SR mit MA Suchzeitraum: 202003 P: Herzinsuffizienz I: Antikoagulation C: divers O: divers Evidenzbasis: 3 RCT (n=5498) 1) Warfarin, Aspirin vs. keine antithrombotische Therapie 2) Warfarin vs. Placebo bei idiopathischer dilatativer Kardiomyopathie 3) Rivaroxaban vs. Placebo HF und KHK	Warfarin vs. Placebo/ keine Behandlung Gesamtmortalität: OR 0,66 (95% CI 0,36;1,18); 2 RCT, n=324 Teilnehmer; niedrige Aussagesicherheit) schwere Blutungen: OR 5,98 (95% CI 1,71; 20,93), NNH 17; 2 RCT, n=324; niedrige Aussagesicherheit Rivaroxaban vs. Placebo Gesamtmortalität: OR 0,99 (95% CI 0,87; 1,13); 1 RCT, n=5022; hohe Aussagesicherheit Schlaganfall: OR 0,67 (95% CI 0,47; 0,95); NNTB 101; 1 RCT, n=5022; moderate Aussageicherheit schwere Blutungen: OR 1,65 (95% CI 1,17; 2,33); NNH 79; 1 RCT, n=5008; moderate Aussagesicherheit "Based on the three RCTs, there is no evidence that oral anticoagulant therapy modifies mortality in people with HF in sinus rhythm."	AMSTAR-2: high	siehe endpunktspezifische Autorenbewertung (siehe Spalte "Ergebnisse")

2 ARNI und SGLT2-Inhibitoren bei HFpEF oder AHF

2.1 PICO-Frage

Fragestellung: Effektivität und Sicherheit von ARNI und SGLT2-Inhibitoren bei HFpEF oder AHF

Population: Patient*innen mit HFpEF oder AHF

Intervention: SGLT2-I und/oder ARNI

Kontrolle: Placebo,

Outcome: Mortalität, Hospitalisierungen, Lebensqualität, Sicherheit

Studientyp: RCT

Sprache: deutsch, englisch

Zeitraum: keine Einschränkung

2.2 Recherchestrategien

Die Recherche und das Titel-Abstract-Screening erfolgten im Rahmen des Living Systematic Reviews (Recherchestrategien siehe LSR-Protokoll (Verweis). Ab dem Volltext-Screening wurde die Evidenzaufbereitung im Rahmen des NVL-Programms durch das ÄZQ durchgeführt. Die getrennte Darstellung nach ARNI und SGLT2-Inhibitoren erfolgte erst mit dem Volltextscreening.

2.3 Screening

2.3.1 Kriterien für den Ein- und Ausschluss

Ein- und Ausschlusskriterien für das Titel-Abstract-Screening siehe LSR-Protokoll (Verweis)

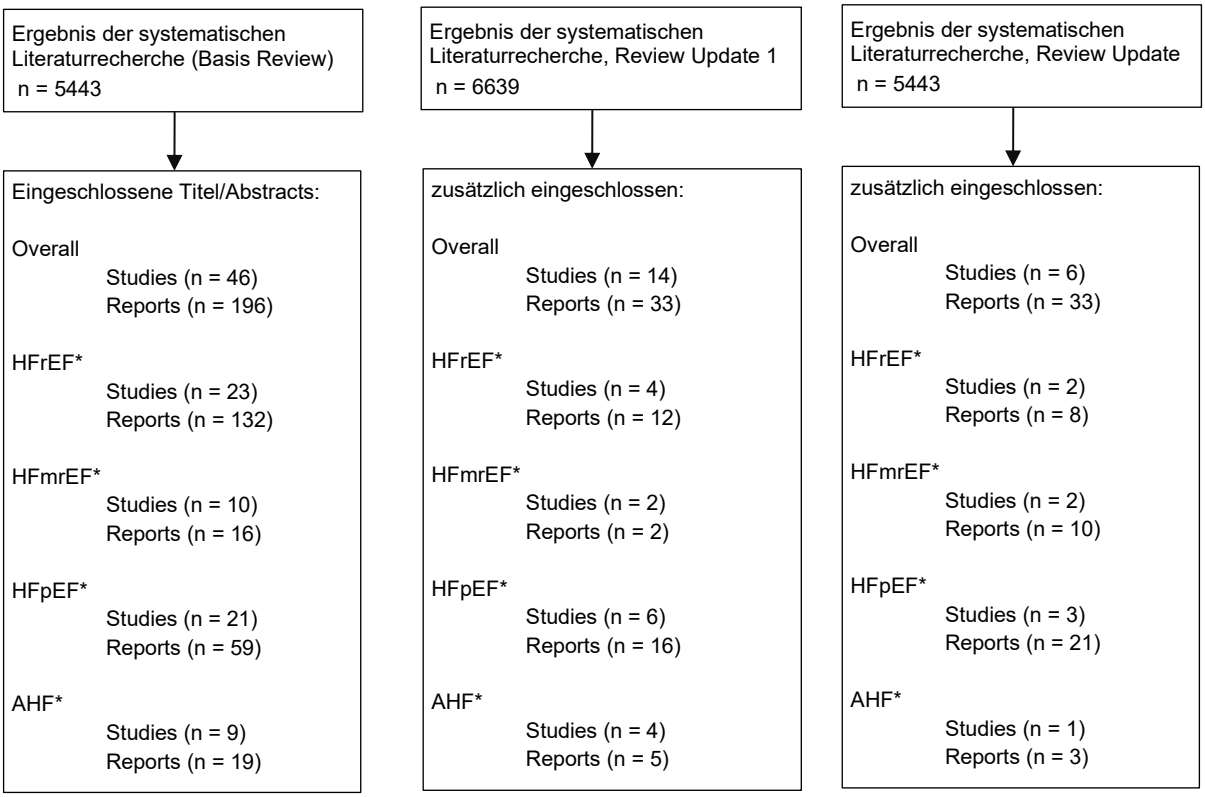
Ein- und Ausschlusskriterien für das Volltext-Screening:

Einschluss	E	Einschluss: Fragestellung passend, Studientyp passend
Ausschluss	Aa	thematisch nicht passend: andere Erkrankung/ Fragestellung/Thema
	An	Anzahl Teilnehmer <50
	Ao	Outcome nicht gemäß PICO
	Ap	Studientyp nicht passend
	Ad	Doppelpublikation oder nicht erhältlich
	As	Sprache nicht deutsch oder englisch
	Az	falscher Zeitraum (z. B. Suchzeitraum zu weit zurückliegend)
	Aw	zurückgezogen oder Update vorhanden
Treffen für eine gefundene Leitlinie mehrere Ausschlusskriterien zu, so wird das jeweils erste Kriterium in der Liste bzw. das am zutreffendste Kriterium für die Begründung des Ausschlusses angegeben.		Aq

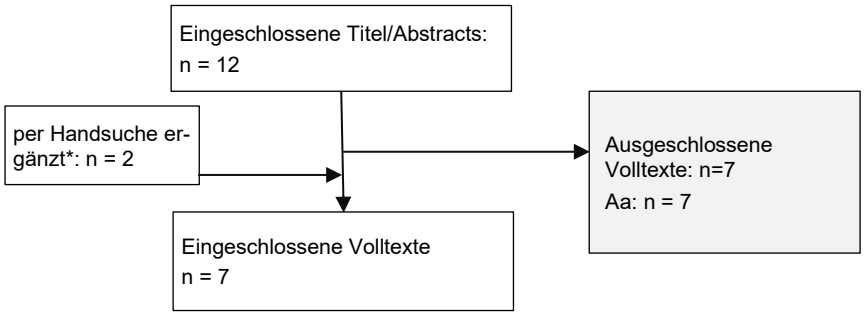
2.3.2 Flowcharts

Titel-Abstract-Screening

Details siehe LSR (Verweis)

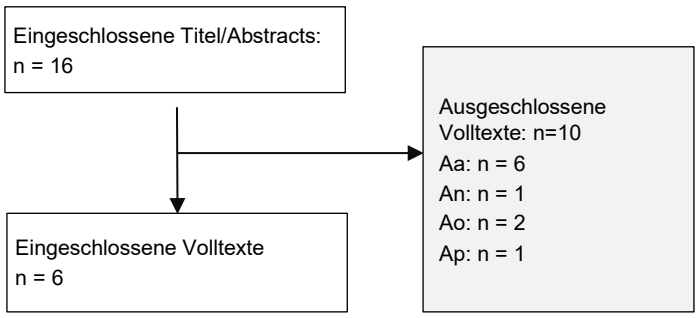


Volltextscreening – ARNI bei AHF



*Zwei Studien waren während des Titel-Abstract-Screenings aufgrund nicht passender Endpunkte ausgeschlossen wurden. Da es jedoch insgesamt nur wenig Evidenz gibt und diese beiden Studien auch von der Fachcommunity diskutiert werden, wurden sie dennoch mit berücksichtigt.

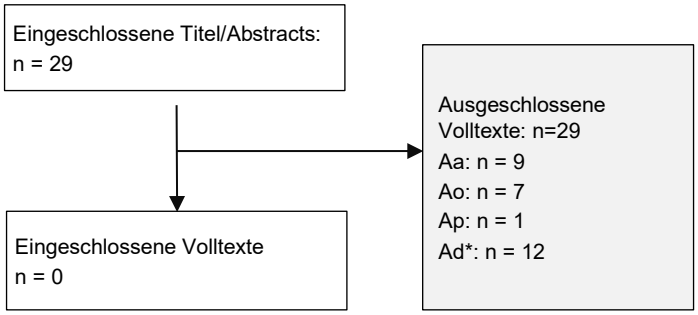
Volltextscreening: SGLT2-Inhibitoren bei AHF



Volltextscreening – ARNI bei HFmrEF

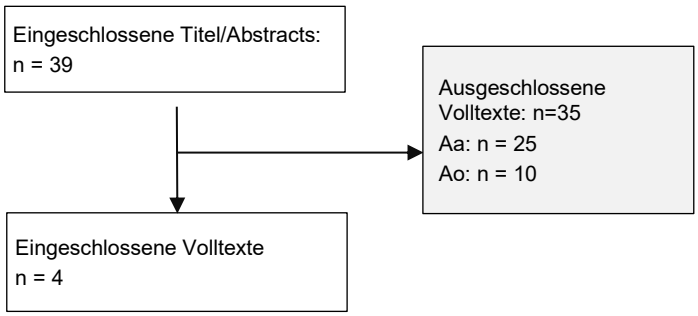
Keine Einschlüsse

Volltextscreening – SGLT2-Inhibitoren bei HFmrEF

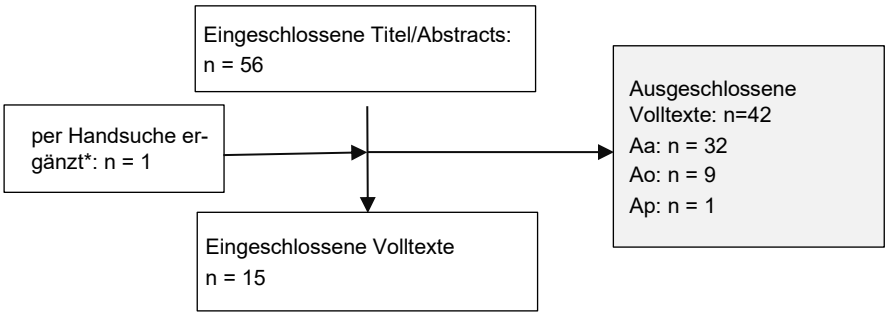


*Alle identifizierten Studien/Reports waren ebenfalls bei den Einschlüssen entweder zu HFrEF oder zu HFpEF enthalten und wurden daher als Dubletten ausgeschlossen. Studien speziell zu (ausschließlich) HFmrEF wurden nicht identifiziert.

Volltextscreening: ARNI bei HFpEF



Volltextscreening: SGLT2-Inhibitoren bei HFpEF



*Eine nach dem Recherchezeitraum erschienene Metaanalyse wurde aufgrund der hohen Relevanz der Detailfragestellung per Handsuche hinzugefügt.

2.4 Evidenztabellen

2.4.1 ARNI bei akuter Herzinsuffizienz

Title	Kurztitel	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study	Wachter 2019 TRANSITION	siehe TRANSITION/Pascual-Figal 2020 - Vorab-Ergebnisse	Zieldosis bei ca. 50% der Pat. nach 10 Wochen erreicht	siehe TRANSITION/Pascual-Figal 2020	siehe TRANSITION/Pascual-Figal 2020
Initiation of sacubitril/valsartan shortly after hospitalisation for acutely decompensated heart failure in patients with newly diagnosed (de novo) heart failure: a subgroup analysis of the TRANSITION study	Senni 2020 TRANSITION	siehe TRANSITION/Pascual-Figal 2020 Subgruppenanalyse de novo HF	besseres Nutzen-Schaden-Verhältnis für Sac/Val als bei bekannter HF	siehe TRANSITION/Pascual-Figal 2020	siehe TRANSITION/Pascual-Figal 2020

Title	Kurztitel	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
NT-proBNP Response to Sacubitril/Valsartan in Hospitalized Heart Failure Patients With Reduced Ejection Fraction TRANSITION Study	Pascual-Figal 2020 TRANSITION	open-label, n=1002 P: HFrEF, stationär wg. HF I: frühzeitige (stationäre) Initiierung von Sac/Val C: mittelfristige (nach Entlassung) Initiierung von Sac/Val: O: NTpro-BNP-Ansprechen, Sicherheit, Erreichen Zieldosis	schnelles Ansprechen bzgl. NTpro-BNP sowohl vor- als auch nach Entlassung bei Ansprechen auf NT-proBNP nach 4 Wochen (ca. bei 50% der Pat.): geringerer Risiko für eine erneute Hospitalisierung wegen Herzinsuffizienz (HF) oder kardiovaskulären Todes nach 26 Wochen verbunden (Hazard Ratio: 0,57; 95% Konfidenzintervall [CI]: 0,38 bis 0,86; p ¼ 0,007).	keine Bewertung, da Studie nur für Übersicht mit aufgeführt; kein Einschluss in Evidenzsynthese, weil - keine Verblindung - kein Vergleich vs. ACE-I/ARB - keine klinischen Effektivitätsendpunkte	nicht empfehlungsbegründend, da nur Surrogat-Endpunkt (Endpunkt NT-proBNP)

Title	Kurztitel	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure	Velazquez 2019 PIONEER-HF	RCT, n=881 P: HFrEF, hospitalized for acute decompensated heart failure I: sacubitril/valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) C: enalapril (target dose, 10 mg twice daily) O: NT-proBNP, safety outcomes nach 4 und 8 Wochen	Alter 61 (IQR 51-72), 72% männlich 34,4% de novo HF (n=303) 52% ACE-I/ARB naiv (n=458) NTpro-BNT: sig. verbessert nach 8 w geometric mean of values w4 and w8 to the baseline NT-proBNP: sac/val 0.53 vs. enalapril 0.75 percent change −46.7% vs. −25.3%; ratio of change 0.71 (95% KI 0.63; 0.81) at w1 (ratio of change, 0.76 (95% CI, 0.69;0.85) exploratorisch: HF-Rehospitalisierung: 8% vs. 13% HR 0.56 (0.37 to 0.84) (nicht gepowert für diesen Endpunkt, post-hoc) Sicherheit: renal function, hyperkalemia, symptomatic hypotension, angioedema: n.s. Erreichen der Zieldosis (Woche 8): Sac/Val 55.2% Enalapril 60.8%	Selection bias Randomisierung: low Allocation concealment: low Performance bias: low Detection bias: low Attrition bias: low (drop-out ca. 15%, ausbalanciert; ITT-Analyse) Reporting bias: low andere Biasursachen: - Sponsoring: Novartis	niedrig 1) Verzerrungsrisiko: niedrig 2) Präzision: n=881, klinische Relevanz der Effekte fraglich 3) Direktheit/Übertragbarkeit: Endpunkt nicht patientenrelevant, Follow-up nicht lange genug nach Übergang in ambulanten Sektor (Zieldosis? AE? Behandlungabbruch?) -1 in Version 3.0 im Hintergrundtext, aber nicht in Evidenztabelle; nicht empfehlungsbegründend, da nur Surrogat-Endpunkt (Endpunkt NT-proBNP)
Angiotensin Receptor-Neprilysin Inhibition Based on History of Heart Failure and Use of Renin-Angiotensin System Antagonists	Ambrosy 2020 PIONEER-HF	siehe PIONEER-HF/Velazquez 2019	Ergebnisse: - Kein Unterschied de novo/CHF - Kein Unterschied ACE-I/ARB-naiv oder vorbehandelt	siehe PIONEER-HF/Velazquez 201	siehe PIONEER-HF/Velazquez 201

Title	Kurztitel	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Initiation of Angiotensin-Neprilysin Inhibition After Acute Decompensated Heart Failure: Secondary Analysis of the Open-label Extension of the PIONEER-HF Trial	DeVore2019 PIONEER-HF Extension	siehe PIONEER-HF/Velazquez 2019 Extension: 4w open-label Sac/Val (Enalapril-Arm: Switch auf Sac/Val) Extension (n=832)	Exploratorisch: HF-Rehospitalisierung/CV-Death nach insgesamt 12w: 13.0% vs. 18.1%; HR 0.69; (95% CI 0.49-0.97) (nicht gepowert für diesen Endpunkt) Randomisierung aufgehoben (Switch)! --> Vorteil bleibt trotz Switch auf Sac/Val	siehe PIONEER-HF/Velazquez 2019	siehe PIONEER-HF/Velazquez 2019
	Senni 2016 TITRATION	RCT, n=538 P: HFrEF ambulant oder stationär I: schnelle Titrierung von Sac/Val C: langsame Titrierung von Sac/Val O: Sicherheit	Alter 64 (11,39); 79% männlich Stratifizierung nach RAAS-Vorbehandlung: kein/niedrig (ACEi/ARB-naiv oder niedrige Dosis (Enalapril ≤ 10 mg/Tag bzw. Valsartan ≤ 160 mg/Tag) - Niedrige Dosis: n=251 (50,4%) - ACE-I/ARB-naiv: n=33 (6,6%) Ergebnisse: - Langsame Titrierung sicherer - Keine klinischen Endpunkte, kein Vergleich gegen ACE-I/ARB	keine Bewertung, da Studie nur für Übersicht mit aufgeführt; kein Einschluss in Evidenzsynthese, weil - kein Vergleich vs. ACE-I/ARB - keine klinischen Effektivitätsendpunkte	nicht empfehlungsbegründend, da PICO-Fragestellung nicht passt

2.4.2 ARNI bei HFpEF

Title	Kurztitel	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial	Solomon 2012 PARAMOUNT	RCT, n=301 P: HFpEF LVEF ≥ 45%, dokumentierte HI mit Symptomen (anstrengungsinduzierte Dyspnoe, Orthopnoe, paroxysmale Dyspnoe, periphere Ödeme), NT-proBNP > 400 pg/mL beim Screening, Diuretikatherapie, (eGFR) ≥ 30 mL/min per 1·73 m²; Kalium ≤ 5,2 mmol/L I: LCZ696 (50 mg bid, auftitriert bis 200 mg bid innerhalb 2-4 Wochen) C: Valsartan (40 mg bid, auftitriert bis 160mg bid innerhalb 2-4 Wochen) O: change in NT-proBNP at 12 weeks Run-in-Phase: “Eligible patients were enrolled into a 2-week, single-blind, placebo run-in period, during which time they continued their background treatments. ACE inhibitors and ARBs were required to be discontinued 24 h before randomisation. After 2 weeks, all patients who fulfilled the criteria for enrolment were randomly assigned (1:1) to treatment with either LCZ696 or valsartan.”	change in NT-proBNP at 12 weeks (n = 266) ratio of change 0,77 (95% CI 0,64–0,92), p=0,005) • blood pressure: reduced by 9,3 (SD 14)/4,9 (10) mmHg (LCZ696) and 2,9 (17)/2,1 (11) mmHg (valsartan) (p=0,001 for systolic and p=0,09 for diastolic blood pressure differences). • no significant changes: in left ventricular size or function, diastolic function, left ventricular mass, or tricuspid regurgitant velocity between treatment groups Sicherheit: - LCZ696: 22 patients (15%) ≥ 1 SAE, including 1 death; - valsartan: 30 patients (20%) ≥ 1 SAE, including 2 deaths (table 4) - patients with hypotension, renal dysfunction, or hyperkalaemia: kein Unterschied zw. Gruppen Over 36 weeks: - eGFR decrease: –1,6 vs. –5,2 mL/min per 1,73 m²; p=0,007 - urinary albumin creatinine ratio increase: 1,9 to 2,9 mg/mmol vs. 2,0 to 2,0 mg/mmol; p=0,02	Selection bias Randomisierung: low Allocation concealment: low Performance bias: low Detection bias: low Attrition bias: high (keine ITT-Analyse; nur Pat., für die Follow-up vorlag n=261 12 weeks, 241 36 weeks; primärer Endpunkt mit n=266 berechnet, drop-out 12% recht hoch für 12-wöchige Studie) Reporting bias: low andere Biasursachen: Run-in-Phase (234 von 542 Pat. ausgeschlossen) Sponsoring: Novartis	sehr niedrig 1) Verzerrungsrisiko: eher hoch (Run-in-Phase) -1 2) Präzision: Phase-II-Studie, n=301 bzw. 266 -1 3) Direktheit/Übertragbarkeit: Run-in-Phase, keine patientenrelevanten Outcomes -1

Title	Kurztitel	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction	Solomon 2019 PARAGON-HF	RCT, n=4822 P: HFpEF LVEF ≥ 45%, NYHA II-IV, elevated NT-proBNP I: 97 mg sacubitril + 103 mg of valsartan twice daily C: valsartan (target dose, 160 mg twice daily) O: hospitalizations for heart failure + cv deaths	primärer Endpunkt: RR 0.87 (95% CI 0.75; 1.01) n.s. cv deaths 8.5% vs. 8.9% HR 0.95 (95% CI, 0.79; 1.16) n.s. hospitalizations for heart failure: 690 vs. 797 RR 0.85 (95% CI 0.72; 1.00) n.s. NYHA class improvement: 15.0% vs. 12.6% OR 1.45 (95% CI 1.13; 1.86); renal function worsened: 1.4% vs. 2.7%, HR 0.50 (95% CI 0.33; 0.77) mean change KCCQ summary score at 8 months: 1.0 point (95% CI, 0.0 to 2.1) higher in the sacubitril–valsartan group. Subgruppen (primärer Endpunkt) male RR 1.03 (0.85−1.25) n=2317 female RR 0.73 (0.59−0.90) n=2479 ŽLVEF Ž≤Median (57%) 0.78 (0.64−0.95) n=2495 LVEF >Median (57%) 1.00 (0.81−1.23) n=2301 Sicherheit sacubitril–valsartan ... higher incidence of hypotension and angioedema ... lower incidence of hyperkalemia	Selection bias Randomisierung: unclear Allocation concealment: unclear Performance bias: low Detection bias: low Attrition bias: low (streng genommen kein ITT, aber Drop-out nur 1,5% + ausbalanciert) Reporting bias: low andere Biasursachen: 2 Run-in-Phasen (5743 Valsartan, davon 541 herausgefallen [340 wg. AEs), 5205 Sac-Val, davon 384 herausgefallen [262 wg. AE] --> insgesamt 16% herausgefallen Sponsoring: Novartis	niedrig 1) Verzerrungsrisiko: eher hoch (Run-in-Phase) -1 2) Präzision: große Population 3) Direktheit/Übertragbarkeit: Run-in-Phase -1
Effects of Sacubitril-Valsartan Versus Valsartan in Women Compared With Men With Heart Failure and Preserved Ejection Fraction Insights From PARAGON-HF	McMurray 2020 PARAGON-HF Subanalyse	siehe PARAGON-HF, Solomon et al. 2019 2479 women (51.7%) 2317 men (48.3%)	Baseline: Women older, more obesity, less CHD, lower eGFR, lower NT-proBNP than men primary outcome (hospitalizations for heart failure + cv deaths) women RR 0.73 (95% CI, 0.59–0.90) getriggert von Hospitalisierungen men 1.03 (95% CI, 0.84–1.25) (P interaction = 0.017) NYHA-Verbesserung, renale Endpunkte: keine genderspezifischen Unterschiede Lebensqualität KCCQ: bei Frauen weniger verbessert als bei Männern AE: keine genderspezifischen Unterschiede	siehe PARAGON-HF, Solomon et al. 2019 präspezifizierte Subgruppenanalyse	siehe PARAGON-HF, Solomon et al. 2019 präspezifizierte Subgruppenanalyse "Whereas the possible sex-related modification of the effect of treatment has several potential explanations, the present study does not provide a definite mechanistic basis for this finding."

Title	Kurztitel	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Effect of Sacubitril/Valsartan vs Standard Medical Therapies on Plasma NT-proBNP Concentration and Submaximal Exercise Capacity in Patients With Heart Failure and Preserved Ejection Fraction The PARALLAX Randomized Clinical Trial	Pieske 2021 PARALLAX	RCT, n=2572 P: HFpEF LVEF >40% I: sacubitril/valsartan C: ACE-I (n=1005), ARB (n=1110) or placebo (n=304) (stratified by prior use of a RAAS-Inhibitor) O: NT-proBNP (w12), 6MWT, NYHA, QoL (w24)	mean age, 72.6 years [SD, 8.5 years]; 1301 women [50.7%]) NT-proBNP at 12w: sac/val: adjusted geometric mean ratio to baseline 0.82 pg/mL control: adjusted geometric mean ratio to baseline 0.98 pg/mL adjusted geometric mean ratio of 0.84 (95% CI, 0.80 to 0.88; P<0,001) 6MWT at w 24: increase 9.7 m vs 12.2 m (adj. MD −2.5 m (95% CI, −8.5 to 3.5) QoL KCCQ at w24: 12.3 vs11.8; MD 0.52 (95% CI, −0.93 to 1.97) NYHA improvement at w24: 23.6% vs 24.0% ; adjusted OR 0.98 (95%CI, 0.81 to 1.18) Ergebnisse für NT-proBNP über fast alle Subgruppen konsistent (auch m/w, auch LVEF > oder <60%) Sicherheit: hypotension (14.1% vs 5.5%) albuminuria (12.3% vs 7.6%) hyperkalemia (11.6% vs 10.9%).	Selection bias Randomisierung: low Allocation concealment: low Performance bias: low, allerdings funktionelle Entblindung v.a. in Placebo-Gruppe denkbar Detection bias: low Attrition bias: low (drop-out 13%), aber drop-out wegen AE unter Sac/Val größer Reporting bias: low andere Biasursachen: keine Sponsoring: Novartis	niedrig 1) Verzerrungsrisiko: eher gering 2) Präzision: n=2572, meist sehr schmale KI auch in Subgruppen, klinische Relevanz fraglich -1 3) Direktheit/Übertragbarkeit: nur teilweise patientenrelevante Outcomes (n.s.) -1

2.4.3 SGLT2-Inhibitoren bei akuter Herzinsuffizienz

Title	Study	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Impact of dapagliflozin treatment on renal function and diuretics use in acute heart failure: a pilot study	Charaya 2022	RCT, n=102 P: acute heart failure I: dapagliflozin C: standard therapy O: kurzfristige renale Outcomes u. a.	Baseline Characteristika age 73.4±11.7 years, 57.8% men; 36% de novo HF; LVEF 44.9%±14.7%, NT-proBNP 4706 (1757; 11 244) pg/mL; eGFR 51.6±19.5 mL/min. eGFR at 48 h: −4.2 (−11.03; 2.28) mL/min vs 0.3 (−6; 6) mL/min eGFR at discharge 54.71±19.18 mL/min vs. 58.92±24.65 mL/min n.s. worsening renal function: 34.4% vs 15.2%; n.s. increase dose of loop diuretics: 14% vs 30% average doses of loop diuretics: 78.46±38.95 mg/day vs 102.82±31.26 mg/day; p=0.001) weight loss: 4100 (2950; 5750) g vs 3000 (1380; 4650) g; p=0.02 In-hospital mortality: 4 (8%) vs. 4 (7.7%) deaths 30 days after discharge: 9 (19%) vs. 12 (25%), p=0.5 rehospitalisations 14 (29%) vs. 17 (35%) "more pronounced weight loss and less need to increase diuretic therapy without significant deterioration of the renal function"	Selection bias Randomisierung: low Allocation concealment: low Performance bias: high (nicht verblindet) Detection bias: high (nicht verblindet) Attrition bias: low Reporting bias: low, andere Biasursachen: - Sponsoring: öffentlich	niedrig (primärer Endpunkt) 1) Verzerrungsrisiko: eher niedrig, da primärer Endpunkt nicht anfällig für Verzerrung (Messungen) 2) Präzision: n=100 -1 3) Direktheit/Übertragbarkeit: Surrogat -1 Studie nicht gepowert für klinische Endpunkte bzw. Follow-up zu kurz
Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF)	Damman 2020 EMPA-RESPONSE-AHF	RCT, n=80 P: acute HF patients with and without diabetes I: empagliflozin 10 mg/day 30 days C: placebo O: invisual analogue scale (VAS) dyspnoea score, diuretic response, change in NT-proBNP, length of stay	Baseline-Patientencharakteristika: Mean age 76 years; 33% were female; 47% de novo HF; median NT-proBNP 5236 pg/mL VAS dyspnoea score: n.s. diuretic response, length of stay, NT-proBNP: n.s. Sicherheit: "no adverse effects on blood pressure or renal function"	Selection bias Randomisierung: low Allocation concealment: low Performance bias: low Detection bias: low Attrition bias: low (73/80 für primären Endpunkt) Reporting bias: low, allerdings nachträglich nach anderen sig. (Komposit-)Endpunkten gesucht + berichtet andere Biasursachen: - Sponsoring: Boehringer Ingelheim	niedrig 1) Verzerrungsrisiko: niedrig 2) Präzision: n=80; -1 3) Direktheit/Übertragbarkeit: kurzes Follow-up; visual analogue scale (VAS) dyspnoea score patientenrelevant, die anderen Endpunkte nicht -1

Title	Study	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Effects of Early Empagliflozin Initiation on Diuresis and Kidney Function in Patients With Acute Decompensated Heart Failure (EMPAG-HF)	Schulze 2022 EMPAG-HF	RCT, n=60 P: acute decompensated heart failure (within 12 h); BNP >100 pg/mL or NT-proBNP >300 pg/mL I: empagliflozin 25 mg daily (in addition to standard decongestive treatments incl. loop diuretics) C: placebo O: cumulative urine output over 5 days exclusion: eGFR <30, end-stage kidney injury, "dry" AHF (no congestion)	cumulative urine output over 5 days: median 10.8 vs. 8.7 L mL; group difference estimation 2.2 L [95% CI, 8.4 to 3.6]; P=0.003) diuretic efficiency: 14.1 mL urine per milligram furosemide equivalent [95% CI, 0.6–27.7]; P=0.041) eGFR 51±19 vs. 54±17 mL/min per 1.73 m² (= not affected) total urinary protein, 492±845 vs. 503±847 mg/g creatinine; urinary α1-microglobulin, 55.4±38.6 vs. 31.3±33.6 mg/g creatinine; NTproBNP −1861 vs. −727.2 pg/mL after 5 days; quotient in slope, 0.89 [95% CI, 0.83–0.95]; P<0.001) Sicherheit: keine Unterschiede	Selection bias Randomisierung: unclear Allocation concealment: unclear Performance bias: low Detection bias: low Attrition bias: low Reporting bias: low andere Biasursachen: - Sponsoring: Boehringer Ingelheim	niedrig 1) Verzerrungsrisiko: niedrig 2) Präzision: n=60 -1 3) Direktheit/Übertragbarkeit: ausschließlich Surrogatparameter -1
The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial	Voors 2022 EMPULSE	RCT, n=530 P: acute de novo or decompensated chronic HF, alle LVEF I: empagliflozin 10 mg up to 90 d C: placebo O: clinical benefit = composite of death from any cause, np of HF events and time to first HF event, or a 5 point or greater difference in change from baseline in the KCCQ exclusion: eGFR <20	Begleitmedikation: ca. 70% ACE-I/ARB/ARNI; Betablocker ca. 80%, MRA 57% vs. 47%; Diuretika 88% vs. 77% --> nicht für alle gut ausbalanciert clinical benefit WR (win ratio) 1.36 (95% CI 1.09–1.68; P = 0.0054), mortality: 11 (4.2%) vs. 22 (8.3%) HF events: 28 (10.6%) vs. 39 (14.7%) mean change KCCQ Total Symptom Score (KCCQ-TSS) from baseline to 90 days: 36.2 (95% CI 33.3–39.1) vs. 31.7 (95% CI: 28.8–34.7) (siehe ausführlich Kosiborod 2022) Subgruppen (primärer Endpunkt clinical benefit): de novo HF 1.29 (0.89–1.89) n=175 decompensated chronic HF 1.39 (1.07–1.81) n=355 diabetic 1.47 (1.07–2.02) n=240 non-diabetic 1.30 (0.97–1.73) n=290 LVEF <40% 1.35 (1.04–1.75) n=354 LVEV >40% 1.39 (0.95–2.03) n=169 SAE 32.3% vs. 43.6% acute renal failure 7,7% vs. 12,1% Urinary tract infection 4,2% vs. 6,4%	Selection bias Randomisierung: low Allocation concealment: low Performance bias: low Detection bias: low Attrition bias: some concerns (rel. hohes Dropout: 20 vs. 23%, davon wg. AE 44 vs. 54%) Reporting bias: low, andere Biasursachen: Begleitmedikation (MRA, Diuretika) unterschiedlich Sponsoring: Boehringer Ingelheim	niedrig 1) Verzerrungsrisiko: niedrig 2) Präzision: n=530, klinische Relevanz fraglich -1 3) Direktheit/Übertragbarkeit: Endpunkt stark kombiniert, "win ratio" ungewöhnlicher Endpunkt, nur 70% der Pat. mit RAAS-Hemmern (nicht leitliniengerechte Therapie) -1

Title	Study	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Effects of Empagliflozin on Symptoms, Physical Limitations and Quality of Life in Patients Hospitalized for Acute Heart Failure - Results From the EMPULSE Trial	Kosiborod 2022 Subanalyse EMPULSE	RCT-Subanalyse Fragestellung: Lebensqualität (KCCQ) PICO siehe EMPULSE (Voors 2022)	"greater clinical benefit across the range of KCCQ-TSS" win ratio [95% CIs] from lowest to highest tertile: 1.49 [1.01-2.20], 1.37 [0.94-1.99], and 1.48 [1.00-2.20] "as early as 15 days and persisted through 90 days" nach 90 Tagen: KCCQ TSS MD 4.45 points [95% CI, 0.32-8.59], physical limitations MD 4.80 [95% CI, 0.00-9.61] quality of life MD 4.66 [95% CI, 0.32-9.01] clinical summary score MD 4.85 [95% CI, 0.77-8.92] overall summary score MD 4.40 [95% CI, 0.33-8.48],	siehe EMPULSE (Voors 2022) attrition: 451/530 Pat nach 90 Tagen mit KCCQ-Daten (85,1%); drop-out zwischen Gruppen in etwa gleich verteilt	siehe EMPULSE (Voors 2022) aufgrund 15% Drop-out Verzerrungsrisiko etwas höher
Renal effects of empagliflozin in patients hospitalized for acute heart failure: from the EMPULSE trial	Voors 2022 Subanalyse EMPULSE	RCT-Subanalyse Fragestellung: renale Effekte PICO siehe EMPULSE (Voors 2022)	eGFR at day 15: −2 ml/min/1.73 m2 (compared to placebo) day 90: n.s. acute renal failure: 7.7% vs. 12.1% clinical benefit unaffected by baseline eGFR	siehe EMPULSE (Voors 2022)	siehe EMPULSE (Voors 2022)

2.4.4 SGLT2-Inhibitoren bei HFpEF

Title	Study	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial	Nassif 2021	RCT, n=324 P: HFpEF LVEF ≥ 45%; NYHA class II–IV; HF hospitalization/urgent HF visit with iv diuretic treatment <12 months I: Dapagliflozin C: placebo O: KCCQ-Clinical Summery Score; sek.: 6MWT, KCCQ-OS u. a. nach 12 Wochen	Baseline-Patientencharakteristika: 57% weiblich, Alter ca. 70, LVEF 60%, ACE-I/ARB/ARNI 62%, Betablocker 72%, BMI 35 KCCQ-CS 5.8 points (95% CI 2.3–9.2) KCCQ total symptom score (KCCQ-TS) (5.8 points (95% CI 2.0–9.6) KCCQ physical limitations scores (5.3 points (95% CI 0.7–10.0) 6MWT: mean effect size 20.1 m (95% CI 5.6–34.7, P = 0.007)) KCCQ-OS: 4.5 points (95% CI 1.1–7.8, P = 0.009) proportion of participants with 5-point or greater improvements in KCCQ-OS: OR=1.73 (95% CI 1.05–2.85) reduced weight: mean effect size, 0.72 kg (95% CI 0.01–1.42) Adverse events: 44 (27.2%) vs. 38 (23.5%)	Selection bias Randomisierung: unclear Allocation concealment: unclear Performance bias: low Detection bias: low Attrition bias: low (Drop-out von 10% erscheint für 12 Wochen recht hoch) Reporting bias: low andere Biasursachen: - Sponsoring: AstraZeneca	moderat 1) Verzerrungsrisiko: -0,5 2) Präzision: -0,5 (kleine Effektgröße, <500 TN) 3) Direktheit/Übertragbarkeit: +/- 0

Title	Study	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction	Solomon 2022 DELIVER	RCT, n=6263 P: HFpEF LVEF >40%; NYHA class II–IV; NT-pro BNP ≥ 300 pg/mL ohne AVF oder ≥ 600 pg/mL mit AVF I: Dapagliflozin C: placebo O: composite: worsening HF (unplanned HF-hospitalization *or* urgent visit for HF) *or* cv death (time-to-event analysis)) median follow-up: 2.3 years exclusion: T1DM, eGFR <25 mL/min/1.73 m2; Bp <95 oder >160/180 mmHg; MI, unstable angina, PCI, CABG ...	age 72 (+/- 10); 44% weiblich, ca. 75% NYHA II, 25% NYHA III; LVEF median 54% (+/- 9); Syst. BP 128 +/- 15 ACE-I 37%; Diuretika 77%; ARB 36%; Sac/Val 5%, Beta-Blocker 83%; MRA 43% primary outcome 512/3131 (16.4%) vs. 610/3132 (19.5%) HR 0.82 (95% KI 0.73; 0.92) hospitalization for HF 10,5% vs. 13,3% HR 0.76 (0.55–1.07) worsening HF 11.8% vs. 14.5% HR 0.79 (95% CI, 0.69; 0.91) cv death 7.4% vs. 8.3% HR 0.88; (95% CI, 0.74; 1.05) death from any cause 15,9% vs. 16,8% HR 0.94 (95% CI, 0.83; 1.07) Change in KCCQ TSS at mo 8: win ratio 1.11 (1.03–1.21); mean change: 2.4 (1.5–3.4) Subgruppen: LVEF <=49% 207/1067 vs. 229/1049 HR 0.87 (0.72–1.04) LVEF 50-59% 174/1133 vs. 211/1123 HR 0.79 (0.65–0.97) LVEF <60% 381/2200 vs 440/2172 HR 0.83 (95% CI, 0.73; 0.95) LVEF >=60% 131/931 vs. 170/960 0.78 (0.62–0.98) Sicherheit: keine sig. Unterschiede zwischen Gruppen bzw. SAE/AE SAE Urinary tract infection 30 (1.0) vs. 32 (1.0)	Selection bias Randomisierung: low Allocation concealment: low Performance bias: low Detection bias: low Attrition bias: low Reporting bias: low andere Biasursachen: - Sponsoring: AstraZeneca	hoch (primärer Endpunkt) 1) Verzerrungsrisiko: +/- 0 2) Präzision: +/- 0 3) Direktheit/Übertragbarkeit: überwiegend NYHA II; aber für HFpEF erscheint der Anteil der Frauen recht gering v.a. schwer erkrankte Patienten eingeschlossen (hohe NTpro-BNP-Schwellenwerte = Hauptausschlussgrund) --> höhere Wahrscheinlichkeit für Events

Title	Study	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Dapagliflozin in Patients Recently Hospitalized With Heart Failure and Mildly Reduced or Preserved Ejection Fraction	Cunningham 2022 DELIVER-Subanalyse	RCT-Subanalyse Fragestellung: Effekte bei kürzlich hospitalisierten Patienten PICO siehe DELIVER (Solomon 2022)	654/6263 (10.4%) rand. during HF hospitalization or within 30 days of discharge --> higher risk of primary outcome (HR: 1.88; 95% CI: 1.60-2.21; P < 0.001) primary outcome in this subgroup: HR: 0.78; 95% CI: 0.60-1.03) n.s. (18% in patients without recent hospitalization (HR: 0.82; 95% CI: 0.72-0.94; Pinteraction = 0.71) Einzelendpunkte: Effektschätzer ähnlich, wegen mangelnder Power aber alle n.s., Pinteraction alle n.s. Sicherheit: keine Unterschiede	siehe DELIVER (Solomon 2022)	siehe DELIVER (Solomon 2022)
Dapagliflozin and New York Heart Association functional class in heart failure with mildly reduced or preserved ejection fraction: the DELIVER trial	Ostrominski 2022 DELIVER-Subanalyse	RCT-Subanalyse Fragestellung: Effekte nach/auf NYHA-Klasse PICO siehe DELIVER (Solomon 2022)	baseline NYHA class II (n = 4713) vs. III/IV (n = 1549) primary endpoint NYHA II (HR 0.81 [0.70–0.94] f NYHA III/IV HR 0.80 [0.65–0.98] for NYHA class III/IV; pinteraction = 0.921 KCCQ improvement at 32 weeks NYHA II (+1.8 [0.7–2.9] NYHA III/IV (+4.8 [2.5–7.1]) versus ; pinteraction = 0.011 improvement in NYHA class: [OR 1.32 [1.16–1.51]) improvement to NYHA class I (OR 1.43 [1.17–1.75]) benefits seen as early as 4 weeks	siehe DELIVER (Solomon 2022)	siehe DELIVER (Solomon 2022)
Efficacy and Safety of Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction According to Age: The DELIVER Trial	Peikert 2022 DELIVER-Subanalyse	RCT-Subanalyse Fragestellung: altersabhängige Effekte PICO siehe DELIVER (Solomon 2022)	338 (5.4%) <55 years, 1,007 (16.1%) 55-64 years, 2,326 (37.1%) 65-74 years, 2,592 (41.4%) ≥75 years primary outcome: pinteraction=0.95 Sicherheit: ebenfalls keine altersabhängigen Unterschiede, wobei AEs mit zunehmendem Alter häufiger auftraten	siehe DELIVER (Solomon 2022)	siehe DELIVER (Solomon 2022)

Title	Study	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Estimated Event-Free Survival Benefits with Dapagliflozin in HF with Mildly Reduced or Preserved Ejection Fraction	Vaduganathan 2022 DELIVER-Subanalyse	RCT-Subanalyse Fragestellung: Endpunkt event-free survival (prespecified analysis) in Abhängigkeit vom Alter PICO siehe DELIVER (Solomon 2022)	Primary endpoint: ccv death or worsening HF mean survival free from the primary endpoint for a 65-year-old participant 12.1y (95%CI 11.0 to 13.2) vs. 9.7 y (95%CI 8.8 to 10.7) --> Difference 2.3 (95%CI 0.9 ;3.8) (P=0.002) range: 2.0 (95%CI -0.6 to 4.6) years in a 55-year-old to 1.2 (95%CI -0.1 to 2.4) years in a 75-year-old Mean event-free survival was greater with dapagliflozin than with placebo across all 14 subgroups.	siehe DELIVER (Solomon 2022)	siehe DELIVER (Solomon 2022)
Efficacy and Safety of Dapagliflozin According to Frailty in Patients with Heart Failure: A Prespecified Analysis of the DELIVER Trial	Butt 2022 DELIVER-Subanalyse	RCT-Subanalyse Fragestellung: Effekte bei Patienten mit Frailty post hoc analysis PICO siehe DELIVER (Solomon 2022)	392 patients (50.4%) FI class 1 (FI ≤0.210; not frail), 1606 (33.9%) FI class 2 (FI 0.211 to 0.310; more frail), 744 (15.7%) FI class 3 (FI ≥0.311; most frail) event rate vs. placebo per 100 person-years not frail: -3.5 (95% CI, -5.7 to -1.2) more frail: -3.6 (CI, -6.6 to -0.5) most frail: -7.9 (CI, -13.9 to -1.9) prim. Endpunkt: alle HR 0,82 (0,73; 0,92) not frail HR 0,85 (0,68; 1,06) more frail HR 0,89 (0,74; 1,08) most frail HR 0,74 (0,61, 0,91) cv-death, all-cause-death: alle Subgruppen n.s., aber numerisch jeweils größter Effekt bei "most frail"	siehe DELIVER (Solomon 2022)	siehe DELIVER (Solomon 2022)

Title	Study	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Empagliflozin in Heart Failure with a Preserved Ejection Fraction	Anker 2021 EMPEROR-Preserved	RCT, n=5988 P: HFpEF LVEF >40%, NYHA II-IV; NT-pro BNP ≥ 300 pg/mL ohne AVF oder ≥ 900 pg/mL mit AVF I: empagliflozin (10 mg once daily C: placebo O: composite: cv death or HF-hospitalization median follow-up: 26,2 month	Baseline-Patientencharakteristika: 45% weiblich, Alter 72 J +/- 9; 82% NYHA II, 18% NYHA III, 0,3% NYHA IV; LVEF 54% +/-9; BMI 30 +/- 6; syst. BP 132 +/-16 (36% ≥140) RAAS 81% (davon Sac/Val 2%); MRA 37%; Betablocker 86%; Diuretika nicht berichtet prim. Endpunkt: 415/2997 (13.8%) vs. 511/2991 (17.1%); HR 0.79 (95% CI 0.69; 0.90) HF-hospitalizations 259 (8.6%) vs. 352 (11.8%); HR 0.71 (95% KI 0.60–0.83) CV-death 219 (7,3%) vs. 244 (8,2%); HR 0,91 (95% CI 0,76; 1,09) Gesamtmortalität*: 14,3% vs. 14,1% HR 1,00 (0,87; 1,15) Gesamthosp. (inkl. wiederholte)*: 44,8% vs. 42,4% HR 0,93(0,85; 1,01) Subgruppen (Auswahl: nur wenn Gruppen etwa gleich groß) LVEF <50% 0.71 (0.57–0.88); 50-59% HR 0.80 (0.64–0.99); >60% 0.87 (0.69–1.10) n.s. <70 y n.s. BMI >30 n.s. MRA use at baseline n.s. keine Unterschiede: Diabetes-Status, eGFR, AF, Blutdruck, Geschlecht ... Sicherheit Hypotension 311 (10.4) vs. 197 (6.6) symptomatic hypotension 257 (8.6) vs. 156 (5.2) Urinary tract infections 297 (9.9) vs. 243 (8.1) Genital infections 67 (2.2) vs. 22 (0.7)	Selection bias Randomisierung: low Allocation concealment: low Performance bias: low Detection bias: low Attrition bias: low Reporting bias: low andere Biasursachen: - Sponsoring: Boehringer Ingelheim	hoch (primärer Endpunkt) 1) Verzerrungsrisiko: +/- 0 2) Präzision: +/- 0 3) Direktheit/Übertragbarkeit: überwiegend NYHA II; aber für HFpEF erscheint der Anteil der Frauen recht gering v.a. schwer erkrankte Patienten eingeschlossen (hohe NTpro-BNP-Schwellenwerte = Hauptausschlussgrund) --> höhere Wahrscheinlichkeit für Events

Title	Study	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Empagliflozin, Health Status, and Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial	Butler 2022 EMPEROR-Preserved Subanalyse	RCT-Subanalyse Fragestellung: Lebensqualität (KCCQ), präspezifiziert PICO siehe EMPEROR-Preserved (Anker 2021)	Effekt auf primären Endpunkt sowie HF-Hospitalisierung unabhängig von Baseline-KCCQ KCCQ-clinical summary score vs. placebo: +1.03 (12w) +1.24 (32 w), +1.50 (52w) a improvement ≥5 points at 12w: OR 1.23 [95% CI, 1.10–1.37]) ≥10 points: OR 1.15 [95% CI, 1.03–1.27]), ≥15 points: OR 1.13 [95% CI, 1.02–1.26]) deterioration ≥5 points at 12w: OR 0.85 [95% CI, 0.75–0.97]) auch für total symptom score und overall summary score	generell siehe EMPEROR-Preserved (Anker 2021) für Lebensqualität-Endpunkte: drop-out (KCCQ clinical s.s.) 12w: 5662/5751 (1,5%) 32w: 5192 (10%) 52w: 4930 (14%) ausbalanciert zwischen Gruppen	moderat (sekundäre Endpunkte Lebensqualität, 12w) 1) Verzerrungsrisiko: +/- 0 2) Präzision: -1 (klinisch nicht relevante Effektgröße im direkten Vergleich) 3) Direktheit/Übertragbarkeit: +/- 0

Title	Study	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Effect of Empagliflozin on Worsening Heart Failure Events in Patients With Heart Failure and Preserved Ejection Fraction EMPEROR-Preserved Trial	Packer 2021 EMPEROR-Preserved Subanalyse	RCT-Subanalyse Fragestellung: Effekt auf spezfische Endpunkte bezüglich Verschlechterung der Herzinsuffizienz (ambulant+stationär) PICO siehe EMPEROR-Preserved (Anker 2021)	composite: cv-death or HF-hospitalization or emergency/urgent HF visit requiring intravenous treatment:432 vs. 546; HR 0.77 [95% CI, 0.67–0.87] --> statistical significance at 18 days after randomization Time to first hospitalization for any reason: 1271/2997 (42.4%) vs. 1340/2991 (44.8%) HR 0.92 (0.85–0.99) Time to first adjudicated HF-hospitalization: 259 (8.6) vs. 352 (11.8) HR 0.71 (0.60–0.83) outpatient intensification of diuretics: 482 vs. 610; HR 0.76 [95% CI, 0.67–0.86]; better NYHA: 20% to 50% more likely (significant effects at 12 weeks, maintained for at least 2 years) Subgruppen (effect on total HF hospitalizations) (Auswahl, Suppl.): LVEF <50: HR 0,57 (0,42; 0,79) LVEF 51-59: HR 0,66 (0,48; 0,91) LVEF >=60: HR 1,06 (0,76; 1,46) n.s. p Interaktion: 0,0077; Gruppengröße ausbalanciert (je ca. 2000) Baseline MRA: HR 0,90 (0,68; 1,19) n.s. no baseline MRA: HR 0,60 (0,47; 0,77)	siehe EMPEROR-Preserved (Anker 2021)	siehe EMPEROR-Preserved (Anker 2021)

Title	Study	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes	Abraham 2021 EMPERIAL (-reduced, -preserved)	RCT EMPERIAL-reduced: n=312 EMPERIAL-preserved: n=3015 Fragestellung: 6MWT, Dyspnoe P: EMPERIAL-reduced:HFrEF <=40%, EMPERIAL-preserved: HFpEF >40%; NYHA II-IV I: empagliflozin 10 mg C: placebo O: 6MWT, KCCQ, dyspnoea score (12 w)	Baseline-Charakteristika: EMPERIAL-reduced:Alter 69,5, 26% weiblich, 65% NYHA II, 35% NYHA III, LVEF median 30% EMPERIAL-preserved: Alter 74,0, 43% weiblich, 77% NYHA II, 23% NYHA III, LVEF median 53% 6MWT difference median at 12 w EMPERIAL-reduced: 13.5 m (-8.0, 42.0) vs. 18.0 m (-11.5, 54.0); MD -4.0 m (-16.0, 6.0) n.s. EMPERIAL-preserved: 10.0 m (-10.0, 32.0) vs. 5.0 m (-20.0, 33.0); MD +4.0 m (-5.0, 13.0) n.s. KCCQ-total system score: beide Studien n.s. Dyspnoe score CHQ-SAS: beide Studien n.s.	Selection bias Randomisierung: low Allocation concealment: low Performance bias: low Detection bias: low Attrition bias: low Reporting bias:low andere Biasursachen: - Sponsoring: Boehringer Ingelheim da hierarchische Testung: da primärer Endpunkt n.s., gelten die Auswertungen der sekundären Endpunkte als exploratorisch	moderat 1) Verzerrungsrisiko: +/-0 2) Präzision: keine klinisch relevanten Effekte, je <500 TN -1 3) Direktheit/Übertragbarkeit: +/-0
Early benefit with empagliflozin in heart failure with preserved ejection fraction: insights from the EMPEROR-Preserved trial	Butler 2022 EMPEROR-Preserved Subanalyse	RCT-Subanalyse Fragestellung: Frühes Ansprechen PICO siehe EMPEROR-Preserved (Anker 2021)	time to cardiovascular death or HF hospitalization day 18 HR 0.41 (95% CI 0.17–0.99) (danach alle sig. mit Verkleinerung der HR) KCCQ (CSS, TSS, OSS) significantly improved at 3 months less severe NYHA: 4w OR 1.17 (0.99–1.37) n.s.; 8w OR 1.23 (1.07–1.41) (danach alle sig. mit Vergrößerung des Effekts)	siehe EMPEROR-Preserved (Anker 2021)	siehe EMPEROR-Preserved (Anker 2021)
Empagliflozin for Heart Failure With Preserved Left Ventricular Ejection Fraction With and Without Diabetes	Filippatos 2022 EMPEROR-Preserved Subanalyse	RCT-Subanalyse Fragestellung: Effektivität in Abhängigkeit v PICO siehe EMPEROR-Preserved (Anker 2021)	primary outcome: with DM: HR 0.79 [95% CI, 0.67, 0.94] without DM: HR 0.78 [95% CI, 0.64, 0.95] i P interaction=0.92	siehe EMPEROR-Preserved (Anker 2021)	siehe EMPEROR-Preserved (Anker 2021)

Title	Study	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Mineralocorticoid Receptor Antagonists and Empagliflozin in Patients With Heart Failure and Preserved Ejection Fraction	Ferreira 2022 EMPEROR-Preserved Subanalyse	RCT-Subanalyse Fragestellung: MRA-spezifische Affekte PICO siehe EMPEROR-Preserved (Anker 2021)	2244/5988 with MRA at baseline (37.5%) primary outcome MRA HR: 0.73 [95% CI: 0.62-0.87] non-MRA: HR: 0.87 [95% CI: 0.71-1.06] n.s.; interaction P = 0.22 first and recurrent HF hospitalizations MRA HR: 0.90 [95% CI: 0.68-1.19] n.s. non-MRA HR: 0.60 [95% CI: 0.47-0.77]; interaction P = 0.038 Sicherheit: hyperkalemia or initiation of potassium binders: non-MRA HR: 0.90 [95% CI: 0.69-1.19] MRA HR: 0.74 [95% CI: 0.56-0.96]; interaction P = 0.29	siehe EMPEROR-Preserved (Anker 2021)	siehe EMPEROR-Preserved (Anker 2021)
Empagliflozin Improves Outcomes in Patients With Heart Failure and Preserved Ejection Fraction Irrespective of Age	Bohm 2022 EMPEROR-Preserved Subanalyse	RCT-Subanalyse Fragestellung: altersabhängige Effekte PICO siehe DELIVER (Solomon 2022)	<65 years [n = 1,199], 65-74 years [n = 2,214], 75-79 years [n = 1,276], ≥80 years [n = 1,299] Primary outcome, first + recurrent HF-hospitalization ≥75 years (P interaction = 0.22); >80 years (P interaction = 0.51) KCCQ, Pinteraction = 0.48 eGFR: Pinteraction = 0.32 "High age was not associated with reduced efficacy or meaningful intolerability."	siehe EMPEROR-Preserved (Anker 2021)	siehe EMPEROR-Preserved (Anker 2021)

Title	Study	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
SGLT2-inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials	Vaduganathan 2022	Metaanalyse EMPEROR-preserved, EMPEROR-reduced; DAPA-HF, DELIVER	Auswahl: LVEF-Subanalyse LVEF ≤40%: HR 0,75 (0,68; 0,83) LVEF 41-49%: HR 0,78 (0,67; 0,90) LVEF 50-59%: HR 0,79 (0,68; 0,93) LVEF ≥60%: HR 0,81 (0,69; 0,96)	AMSTAR2 nicht anwendbar (Metaanalyse, kein syst. Review) kein direktes Hersteller-Sponsoring der Metaanalyse, aber Verbindungen der Autoren zu den Herstellern trial-level data with harmonised endpoint definitions	hyptothesengenerierend (post-hoc-Analyse)

3 ARNI und SGLT2-Inhibitoren bei HFrEF

DEAL – Data extraction tables and figures

Sacubitril/valsartan and sodium-glucose cotransporter-2 inhibitors (SGLT2-I) in adults with heart failure with reduced ejection fraction: a living systematic review – Version: 3

29.11.2022

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3.1 Summary

Review Questions:
1. What is the efficacy and safety of sodium-glucose cotransporter-2 inhibitors (SGLT2-I) in adults with with reduced ejection fraction (HFrEF)?
2. What is the efficacy and safety of sacubitril/valsartan in adults with heart failure with reduced ejection fraction (HFrEF)?

Methods: We searched MEDLINE, Cochrane Library (CENTRAL) and Web of Science (WoS) on September 21, 2022 (version 3). We included all randomized controlled trials (RCTs) on the efficacy and safety of Sodium-glucose Cotransporter-2 inhibitors (SGLT2-I) or sacubitril/valsartan in adults with heart failure with reduced ejection fraction (HFrEF). Studies that examined exclusively patients with specific co-morbidities (e.g., diabetes, myocardial infarction or functional mitral regurgitation) were excluded. Studies had to be published in a peer-reviewed journal for inclusion. We did not include trial results that were exclusively posted in trial registries, congress abstracts or any other grey literature. We used the Cochrane Risk of Bias Tool (RoB 2.0) to assess the methodological quality and the GRADE approach (via MagicAPP) to assess the certainty of evidence.

Results: We identified 30 studies reported in 156 publications:
- Sacubitril/valsartan vs. enalapril or Perindopril (n=10)
- Sacubitril/valsartan vs. valsartan (n=5)
- Sacubitril/valsartan (conservative) vs. sacubitril/valsartan (condensed) (n=1)
- Empagliflozin or dapagliflozin vs. placebo (n=12)
- Empagliflozin (low dose) vs. empagliflozin (high dose) (n=2)

The median sample size of the included studies was 165 (IQR: 89-351). Most trials were judged to raise some concerns in at least one risk of bias domain. We found evidence (high certainty) supporting the use of empagliflozin or dapagliflozin in regards to reductions in all-cause mortality, mortality due to cardiovascular causes and heart failure hospitalization. Sacubitril/valsartan vs. enalapril or perindopril showed positive effects (moderate certainty) on all-cause mortality and mortality due to cardiovascular causes. Sacubitril/valsartan increased to risk for hypotension (moderate certainty). Most of the remaining outcomes across all comparisons were of low to very low certainty of evidence.

Changes compared to the first version of this review: Two update searches were conducted in July and September 2022. Overall, 7 new studies and 24 publications were identified. Three studies added new data to the following meta-analysis:

Empagliflozin or dapagliflozin vs. placebo: Mortality (all cause), mortality (CV), hospitalization (all cause), hospitalization (heart failure), hypotension and urinary tract infection.

Sacubitril/valsartan vs. valsartan: Renal endpoint, hypotension.

Conclusion: The updates did not change the direction of effects nor the certainty of evidence.

Note: This report highlights all sections updated compared to the previous version with following descriptor:

3.2 Inclusion criteria

Table 1 Inclusion criteria.

Review version	Patient	Intervention	Comparison	Outcome	Study design	Time frame	Setting
1-3	Heart failure with reduced ejection fraction (HFrEF) *Note: We exluded studies that included exclusively patients with following conditions: Diabetes, myocardial infarction, functional mitral regurgitation or any other co-morbidities*	Sacubitril/valsartan or SGLT2-I	Any	Any	RCT	Any	Any

3.3 Evidence profile

Table 2a Evidence profile sacubitril/valsartan vs. enalapril or perindopril (n=9)

Outcome **Timeframe**	Study results and measurements	Absolute effect estimates		Certainty of the Evidence **(Quality of evidence)**
		Enalapril/Perindopril	SAC/VAL	
Mortality (all cause) (1-7)	Relative risk: 0.86 (CI 95% 0.78 - 0.94) Based on data from 9947 participants in 7 studies Follow up 5.6 - 27 months	**171** per 1000	**147** per 1000	**Moderate** Due to serious indirectness[b]
		Difference: **24 fewer per 1000** (CI 95% 38 fewer - 10 fewer)		
Mortality (CV) (3-6, 8, 9)	Relative risk: 0.81 (CI 95% 0.73 - 0.90) Based on data from 9407 participants in 6 studies Follow up 1.9 - 33.9 months	**154** per 1000	**125** per 1000	**Moderate** Due to serious indirectness[b]
		Difference: **29 fewer per 1000** (CI 95% 42 fewer - 15 fewer)		
Hospitalization (heart failure) (6, 8, 9)	Relative risk: 0.83 (CI 95% 0.63 - 1.11) Based on data from 8986 participants in 3 studies Follow up 2.8 – 33.9 months	**160** per 1000	**133** per 1000	**Very low** Due to serious risk of bias, Due to serious indirectness[b], Due to serious imprecision
		Difference: **27 fewer per 1000** (CI 95% 59 fewer - 18 more)		
Renal worsening (1, 6, 7, 9)	Relative risk: 0.89 (CI 95% 0.66 - 1.19) Based on data from 9705 participants in 4 studies Follow up 2.8 - 27 months	**30** per 1000	**27** per 1000	**Very low** Due to serious risk of bias, Due to serious indirectness[b], Due to serious imprecision
		Difference: **3 fewer per 1000** (CI 95% 10 fewer - 6 more)		
Hypotension (1, 3, 4, 6, 7, 9)	Relative risk: 1.88 (CI 95% 1.34 - 2.64) Based on data from 10078 participants in 6 studies Follow up 1.9 - 33.9 months	**110** per 1000	**207** per 1000	**Moderate** Due to serious risk of bias, Due to serious indirectness[b]
		Difference: **97 more per 1000** (CI 95% 37 more - 180 more)		
Fall (6)	Relative risk: 0.6 (CI 95% 0.22 - 1.66) Based on data from 8432 participants in 1 studies Follow up 27 months	**2** per 1000	**1** per 1000	**Very low** Due to serious risk of bias, Due to serious indirectness[b], Due to serious imprecision
		Difference: **1 fewer per 1000** (CI 95% 2 fewer - 1 more)		
Urinary tract infection (1, 6, 7)	Relative risk: 1.20 (CI 95% 0.77 - 1.88) Based on data from 9515 participants in 3 studies Follow up 2.8 - 27 months	**7** per 1000	**8** per 1000	**Very low** Due to serious risk of bias, Due to serious indirectness[b], Due to serious imprecision
		Difference: **1 more per 1000** (CI 95% 2 fewer - 6 more)		
Volume depletion (6)	Relative risk: 1.51 (CI 95% 0.25 - 9.03) Based on data from 8432 participants in 1 studies Follow up 27 months	**5** per 10.000	**8** per 10.000	**Very low** Due to serious risk of bias, Due to serious indirectness[b], Due to serious imprecision
		Difference: **3 more per 10.000** (CI 95% 4 fewer - 40 more)		
Quality of life (KCCQ) (1, 3, 4, 6, 7, 9)	Based on data from 9633[a] participants in 6 studies Follow up 1.9 - 27 months	Difference: **SMD 0.14 higher** (CI 95% 0.03 higher – 0.24 higher)		**Low** Due to serious risk of bias, Due to serious indirectness[b]

[a] Khandwalla 2019 has unclear denominator.

[b] Downgrade for indirectness due to run-in period within major studies.

Note: Studies include considerably more men than women (see 6. Study characteristics of included studies).

Table 2b Evidence profile sacubitril/valsartan vs. valsartan (n=3)

Outcome **Timeframe**	Study results and measurements	Absolute effect estimates		Certainty of the Evidence **(Quality of evidence)**
		Valsartan	SAC/VAL	
Mortality (all cause) (10, 11)	Relative risk: 1.63 (CI 95% 0.7 - 3.84) Based on data from 439 participants in 2 studies[a] Follow up 5.6 - 12 months	**48** per 1000	**78** per 1000	**Very low** Due to very serious risk of bias, Due to serious indirectness[b], Due to very serious imprecision
		Difference: **30 more per 1000** (CI 95% 14 fewer - 136 more)		
Mortality (CV) (10, 11)	Relative risk: 1.58 (CI 95% 0.63 - 3.98) Based on data from 435 participants in 2 studies[a] Follow up 5.6 - 12 months	**42** per 1000	**66** per 1000	**Very low** Due to very serious risk of bias, Due to serious indirectness[b], Due to very serious imprecision
		Difference: **24 more per 1000** (CI 95% 16 fewer - 125 more)		
Hospitalization to (heart failure) (11)	Relative risk: 1.23 (CI 95% 0.84 - 1.81) Based on data from 335 participants in 1 study Follow up 5.6 months	**214** per 1000	**263** per 1000	**Very low** Due to very serious risk of bias, Due to serious indirectness[b], Due to serious imprecision
		Difference: **49 more per 1000** (CI 95% 34 fewer - 173 more)		
Renal worsening (11-13)	Relative risk: 0.63 (CI 95% 0.24 – 1.70) Based on data from 575 participants in 3 studies Follow up 1.9 - 5.6 months	**48** per 1000	**44** per 1000	**Very low** Due to very serious risk of bias, Due to serious indirectness[b], Due to serious imprecision
		Difference: **4 fewer per 1000** (CI 95% 29 fewer - 53 more)		
Hypotension (11-13)	Relative risk: 1.33 (CI 95% 0.84 - 2.10) Based on data from 575 participants in 3 studies Follow up 1.9 - 5.6 months	**92** per 1000	**132** per 1000	**Very low** Due to very serious risk of bias, Due to serious indirectness[b], Due to serious imprecision
		Difference: **40 more per 1000** (CI 95% 13 fewer - 131 more)		
Fall (11)	Relative risk: 3.02 (CI 95% 0.12 - 73.55) Based on data from 335 participants in 1 study Follow up 5.6 months	**0** per 1000	**6** per 1000	**Very low** Due to very serious risk of bias, Due to serious indirectness[b], Due to serious imprecision
		Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)		
Diabetic ketoacidosis (11)	Relative risk: 0.34 (CI 95% 0.01 - 8.17) Based on data from 335 participants in 1 study Follow up 5.6 months	**6** per 1000	**2** per 1000	**Very low** Due to very serious risk of bias, Due to serious indirectness[b], Due to serious imprecision
		Difference: **4 fewer per 1000** (CI 95% 6 fewer - 43 more)		
Urinary tract infection (11)	Relative risk: 0.34 (CI 95% 0.01 - 8.17) Based on data from 335 participants in 1 study Follow up 5.6 months	**6** per 1000	**2** per 1000	**Very low** Due to very serious risk of bias, Due to serious indirectness[b], Due to serious imprecision
		Difference: **4 fewer per 1000** (CI 95% 6 fewer - 43 more)		
Quality of life (KCCQ) (11)	Based on data from 335 participants in 1 study Follow up 5.6 months	**0.32** Points Mean	**0.27** Points Mean	**Very Low** Due to very serious risk of bias, Due to serious indirectness[b]
		Difference: **MD 0.05 lower** (CI 95% 0.05 lower - 0.15 higher)		

[a] One zero event study. Only Mann 2022 reports events on mortality (all cause) and mortality (CV)

[b] Downgrade for *indirectness* due to run-in period within major studies

Note: Studies include considerably more men than women (see 6. Study characteristics of included studies)

Table 2c Evidence profile empagliflozin or dapagliflozin vs. placebo (n=9)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)
		Placebo	Empagliflozin or dapagliflozin	
Mortality (all cause) (14-22)	Relative risk 0.88 (CI 95% 0.79 — 0.99) Based on data from 9510 participants in 9 studies Follow up: 2.8 - 16 months. [a]	**128** per 1000	**113** per 1000	**High**
		Difference: **15 fewer per 1000** (CI 95% 27 fewer - 1 fewer)		
Mortality (CV) (15-22)	Relative risk 0.87 (CI 95% 0.77 — 0.99) Based on data from 9199 participants in 8 studies Follow up: 2.8 - 16 months. [a]	**105** per 1000	**91** per 1000	**High**
		Difference: **14 fewer per 1000** (CI 95% 24 fewer - 1 fewer)		
Hospitalization (all cause) (15, 21)	Relative risk 0.72 (CI 95% 0.07 — 7.89) Based on data from 273 participants in 2 studies Follow up: 2.8 - 3 months.	**42** per 1000	**30** per 1000	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency
		Difference: **12 fewer per 1000** (CI 95% 39 fewer — 289 more)		
Hospitalization (heart failure) (15-22)	Relative risk 0.73 (CI 95% 0.66 — 0.81) Based on data from 9195 participants in 8 studies Follow up: 2.8 - 16 months. a	**148** per 1000	**108** per 1000	**High**
		Difference: **40 fewer per 1000** (CI 95% 50 fewer - 28 fewer)		
Renal worsening (14, 16-19)	Relative risk: 0.63 (CI 95% 0.46 - 0.85) Based on data from 9113 participants in 5 studies Follow up: 2.8 - 18.2 months. a	**23** per 1000	**14** per 1000	**Moderate** Due to serious risk of bias
		Difference: **9 fewer per 1000** (CI 95% 12 fewer - 3 fewer)		
Hypotension (14-16, 18, 19, 22)	Relative risk 1.07 (CI 95% 0.88 — 1.30) Based on data from 9068 participants in 6 studies Follow up: 1.9 - 18.2 months. b	**39** per 1000	**42** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision
		Difference: **3 more per 1000** (CI 95% 5 fewer - 12 more)		
Urinary tract infection (14-16, 18-22)	Relative risk 1.02 (CI 95% 0.79 — 1.33) Based on data from 9235 participants in 8 studies Follow up: 2.8 - 16 months. [b]	**23** per 1000	**23** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision
		Difference: **0 fewer per 1000** (CI 95% 5 fewer - 8 more)		
Volume depletion (15-19)	Relative risk: 1.10 (CI 95% 0.96 - 1.26) Based on data from 8980 participants in 5 studies. [a]	**79** per 1000	**87** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision
		Difference: **8 more per 1000** (CI 95% 3 fewer - 21 more)		
Diabetic Ketoacidosis (14-22)	Relative risk 7.00 (CI 95% 0.36 — 135.44) Based on data from 9498 participants in 9 studies Follow up: 2.8 - 16 months. [c]	**0** per 1000	**1** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision
		Difference: **fewer per 1000**		
Fall (14, 16, 19)	Relative risk: 2.92 (CI 95% 1.14 - 7.49) Based on data from 8773 participants in 3 studies. [b]	**1** per 1000	**3** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision
		Difference: **2 more per 1000** (CI 95% 0 fewer - 6 more)		
Fournier Gangrene (15, 16, 19)	Relative risk: 1.0 (CI 95% 0.1 - 9.61) Based on data from 8652 participants in 3 studies.	**2** per 10.000	**2** per 10.000	**Low** Due to serious risk of bias, Due to serious imprecision
		Difference: **0 fewer per 10.000** (CI 95% 2 fewer - 17 more)		
Quality of life (KCCQ) (14-20)	Based on data from 9366 participants in 7 studies Follow up: 2.8 – 12 months.	Difference: **SMD 0.20 higher** (CI 95% 0.09 higher - 0.31 higher)		**Low** Due to serious risk of bias, Due to serious imprecision

[a] Certainty of evidence mainly based on two studies

[b] Certainty of evidence mainly based on one study

[c] Pooling was not possible, due to six zero event studies. Only McMurray 2019 reports events on diabetic ketoacidosis.

Note: Studies include considerably more men than women (see 6. Study characteristics of included studies)

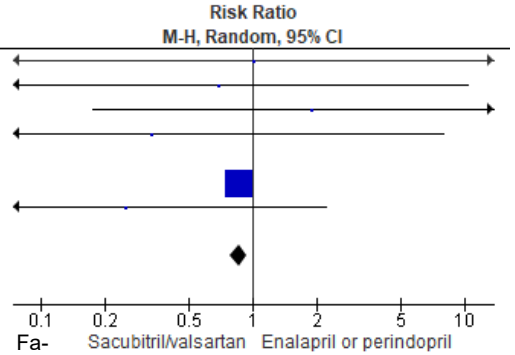
3.4 Forest Plots and Risk of Bias assessments at outcome level

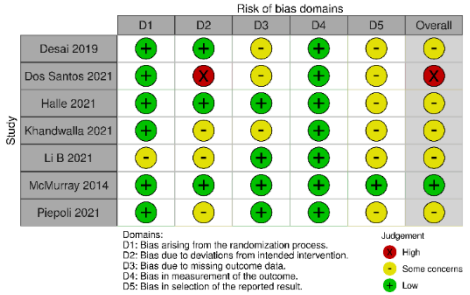
3.4.1 Figures 1a Forest Plots and Risk of Bias assessments investigating sacubitril/valsartan vs. enalapril or perindopril (n=9)

3.4.1.1 Mortality (all cause)

Study or Subgroup	Sacubitril/valsartan Events	Total	Enalapril or perindopril Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Desai 2019	1	231	1	233	0.1%	1.01 [0.06, 16.03]
DosSantos 2021	1	26	1	18	0.1%	0.69 [0.05, 10.36]
Halle 2021	2	103	1	98	0.1%	1.90 [0.18, 20.65]
Khandwalla 2021	0	70	1	70	0.1%	0.33 [0.01, 8.04]
Li B 2021	0	40	0	40		Not estimable
McMurray 2014	711	4187	835	4212	99.4%	0.86 [0.78, 0.94]
Piepoli 2021	1	309	4	310	0.2%	0.25 [0.03, 2.23]
Total (95% CI)		**4966**		**4981**	**100.0%**	**0.86 [0.78, 0.94]**
Total events	716		843			

Heterogeneity: Tau² = 0.00; Chi² = 2.02, df = 5 (P = 0.85); I² = 0%
Test for overall effect: Z = 3.40 (P = 0.0007)

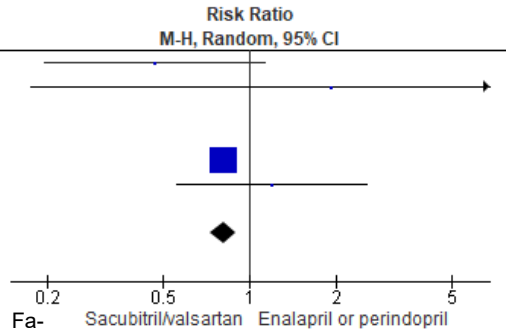


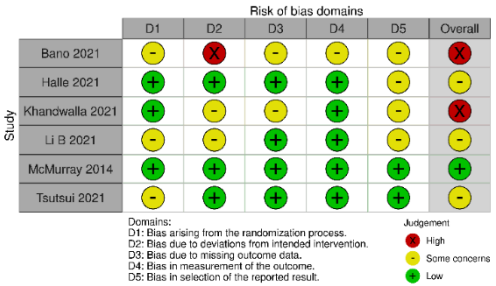


3.4.1.2 Mortality (CV)

Study or Subgroup	Sacubitril/valsartan Events	Total	Enalapril or perindopril Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bano 2021	7	181	15	183	1.3%	0.47 [0.20, 1.13]
Halle 2021	2	103	1	98	0.2%	1.90 [0.18, 20.65]
Khandwalla 2021	0	70	0	70		Not estimable
Li B 2021	0	40	0	40		Not estimable
McMurray 2014	558	4187	693	4212	96.7%	0.81 [0.73, 0.90]
Tsutsui 2021	13	111	11	112	1.8%	1.19 [0.56, 2.55]
Total (95% CI)		**4692**		**4715**	**100.0%**	**0.81 [0.73, 0.90]**
Total events	580		720			

Heterogeneity: Tau² = 0.00; Chi² = 2.96, df = 3 (P = 0.40); I² = 0%
Test for overall effect: Z = 4.06 (P < 0.0001)

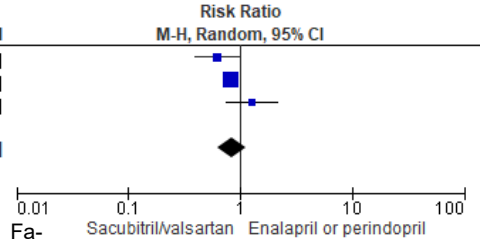


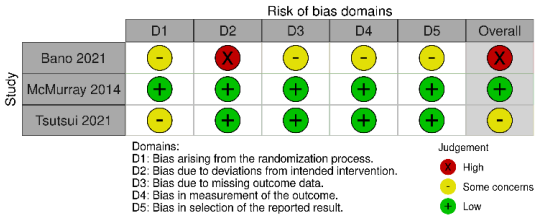


3.4.1.3 Hospitalization (heart failure)

Study or Subgroup	Sacubitril/valsartan Events	Total	Enalapril or perindopril Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bano 2021	25	181	41	183	23.9%	0.62 [0.39, 0.97]
McMurray 2014	537	4187	658	4212	56.3%	0.82 [0.74, 0.91]
Tsutsui 2021	25	111	20	112	19.7%	1.26 [0.75, 2.13]
Total (95% CI)		**4479**		**4507**	**100.0%**	**0.83 [0.63, 1.11]**
Total events	587		719			

Heterogeneity: Tau² = 0.03; Chi² = 4.09, df = 2 (P = 0.13); I² = 51%
Test for overall effect: Z = 1.25 (P = 0.21)

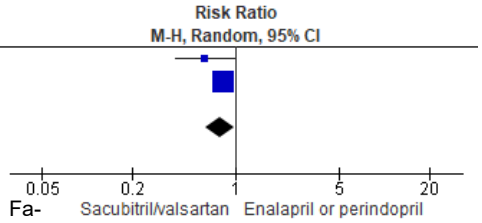




3.4.1.4 Subgroup analysis, excluding Tsutsui 2021:

Study or Subgroup	Sacubitril/valsartan Events	Total	Enalapril or perindopril Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bano 2021	25	181	41	183	19.2%	0.62 [0.39, 0.97]
McMurray 2014	537	4187	658	4212	80.8%	0.82 [0.74, 0.91]
Total (95% CI)		**4368**		**4395**	**100.0%**	**0.78 [0.62, 0.97]**
Total events	562		699			

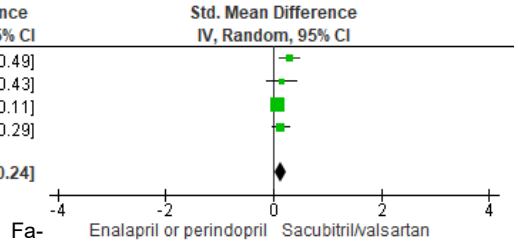
Heterogeneity: Tau² = 0.01; Chi² = 1.46, df = 1 (P = 0.23); I² = 31%
Test for overall effect: Z = 2.24 (P = 0.03)

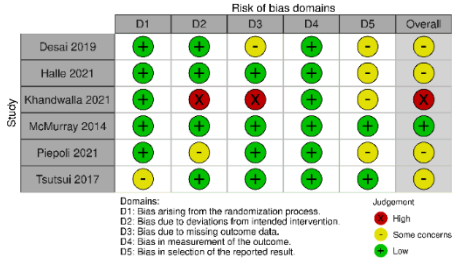


3.4.1.5 Quality of life

Study or Subgroup	Sacubitril/valsartan Mean	SD	Total	Enalapril or perindopril Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Desai 2019	8.7	14.91	216	4.2	15.12	222	18.9%	0.30 [0.11, 0.49]
Halle 2021	8.11	16.7	99	5.84	14.51	93	10.5%	0.14 [-0.14, 0.43]
McMurray 2014	-2.99	23.29	4187	-4.63	23.36	4212	47.7%	0.07 [0.03, 0.11]
Piepoli 2021	2.58	7.11	302	1.65	6.74	302	23.0%	0.13 [-0.03, 0.29]
Total (95% CI)			**4804**			**4829**	**100.0%**	**0.14 [0.03, 0.24]**

Heterogeneity: Tau² = 0.01; Chi² = 5.95, df = 3 (P = 0.11); I² = 50%
Test for overall effect: Z = 2.60 (P = 0.009)



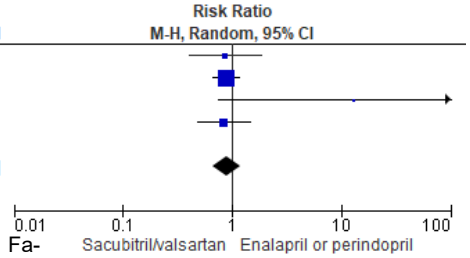


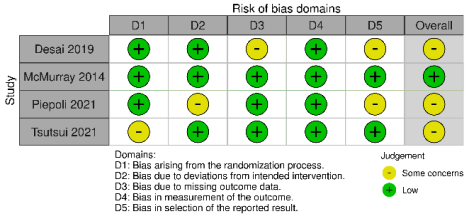
Note: Two trials (Khandwalla 2021 and Tsutsui 2017) were excluded from this analysis due to incomplete information to calculate the standardized mean difference. Mean difference including all studies are presented in Appendix 3: Additional Forest Plots.

3.4.1.6 Renal worsening (dichotomous outcome)

Study or Subgroup	Sacubitril/valsartan Events	Total	Enalapril or perindopril Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Desai 2019	12	231	14	233	13.5%	0.86 [0.41, 1.83]
McMurray 2014	94	4187	108	4212	62.3%	0.88 [0.67, 1.15]
Piepoli 2021	6	309	0	310	1.0%	13.04 [0.74, 230.51]
Tsutsui 2021	19	111	23	112	23.3%	0.83 [0.48, 1.44]
Total (95% CI)		**4838**		**4867**	**100.0%**	**0.89 [0.66, 1.19]**
Total events	131		145			

Heterogeneity: Tau² = 0.02; Chi² = 3.49, df = 3 (P = 0.32); I² = 14%
Test for overall effect: Z = 0.80 (P = 0.42)

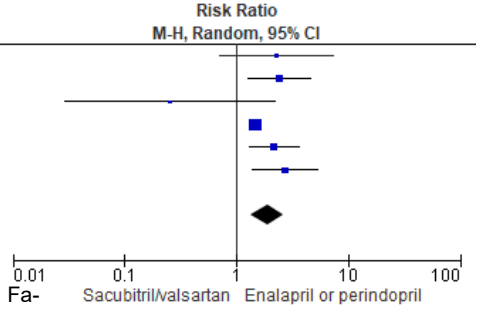


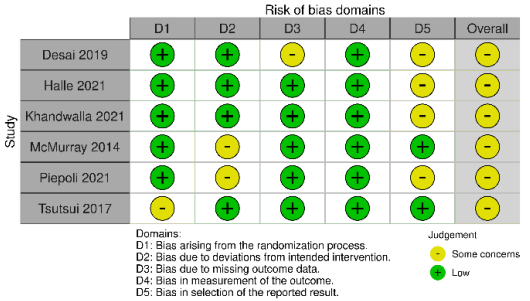


3.4.1.7 Hypotension

Study or Subgroup	Sacubitril/valsartan Events	Total	Enalapril or perindopril Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Desai 2019	9	231	4	233	7.0%	2.27 [0.71, 7.27]
Halle 2021	28	103	11	98	16.4%	2.42 [1.28, 4.59]
Khandwalla 2021	1	69	4	70	2.3%	0.25 [0.03, 2.21]
McMurray 2014	740	4203	506	4229	38.1%	1.47 [1.33, 1.63]
Piepoli 2021	43	309	20	310	21.0%	2.16 [1.30, 3.58]
Tsutsui 2021	27	111	10	112	15.3%	2.72 [1.39, 5.36]
Total (95% CI)		**5026**		**5052**	**100.0%**	**1.88 [1.34, 2.64]**
Total events	848		555			

Heterogeneity: Tau² = 0.08; Chi² = 10.16, df = 5 (P = 0.07); I² = 51%
Test for overall effect: Z = 3.66 (P = 0.0003)

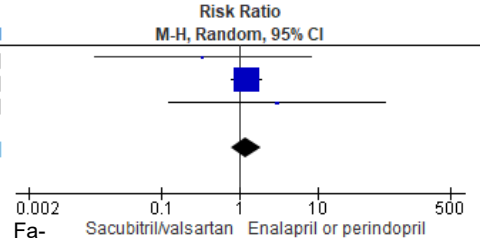


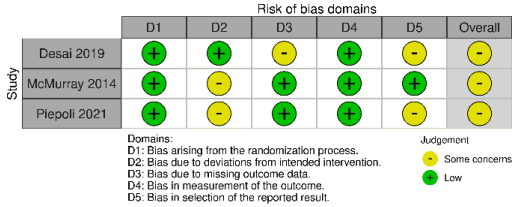


3.4.1.8 Urinary tract infection

Study or Subgroup	Sacubitril/valsartan Events	Total	Enalapril or perindopril Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Desai 2019	0	231	1	233	1.9%	0.34 [0.01, 8.21]
McMurray 2014	41	4203	34	4229	96.1%	1.21 [0.77, 1.91]
Piepoli 2021	1	309	0	310	1.9%	3.01 [0.12, 73.59]
Total (95% CI)		**4743**		**4772**	**100.0%**	**1.20 [0.77, 1.88]**
Total events	42		35			

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)



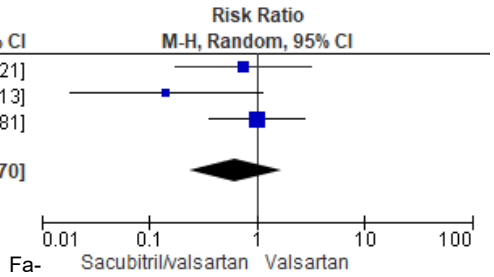


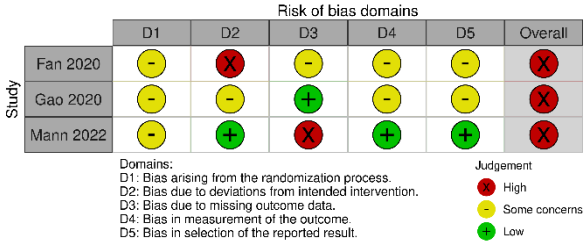
3.4.2 Figures 2b Forest Plots and Risk of Bias assessments investigating sacubitril/valsartan vs. valsartan (n=3)

3.4.2.1 Renal worsening (dichotomous outcome)

Study or Subgroup	Sacubitril/valsartan Events	Total	Valsartan Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fan 2020	3	60	4	60	32.0%	0.75 [0.18, 3.21]
Gao 2020	1	60	7	60	18.8%	0.14 [0.02, 1.13]
Mann 2022	7	167	7	168	49.2%	1.01 [0.36, 2.81]
Total (95% CI)		**287**		**288**	**100.0%**	**0.63 [0.24, 1.70]**
Total events	11		18			

Heterogeneity: Tau² = 0.24; Chi² = 2.88, df = 2 (P = 0.24); I² = 31%
Test for overall effect: Z = 0.90 (P = 0.37)

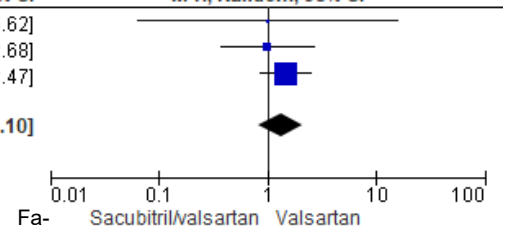


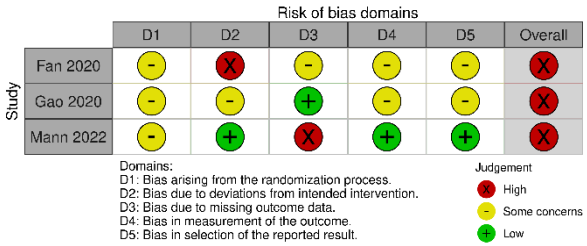


3.4.2.2 Hypotension

Study or Subgroup	Sacubitril/valsartan Events	Total	Valsartan Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fan 2020	1	60	1	60	2.8%	1.00 [0.06, 15.62]
Gao 2020	7	60	7	60	21.7%	1.00 [0.37, 2.68]
Mann 2022	29	167	20	168	75.5%	1.46 [0.86, 2.47]
Total (95% CI)		**287**		**288**	**100.0%**	**1.33 [0.84, 2.10]**
Total events	37		28			

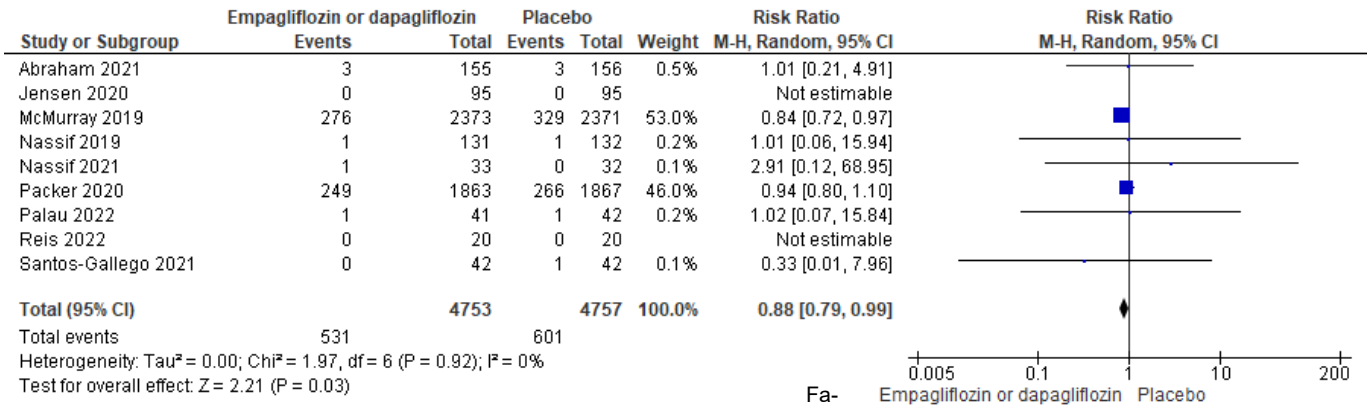
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)

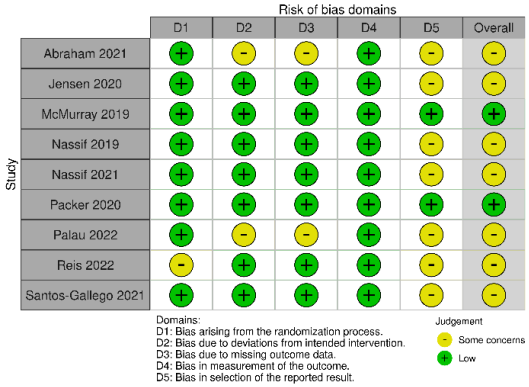




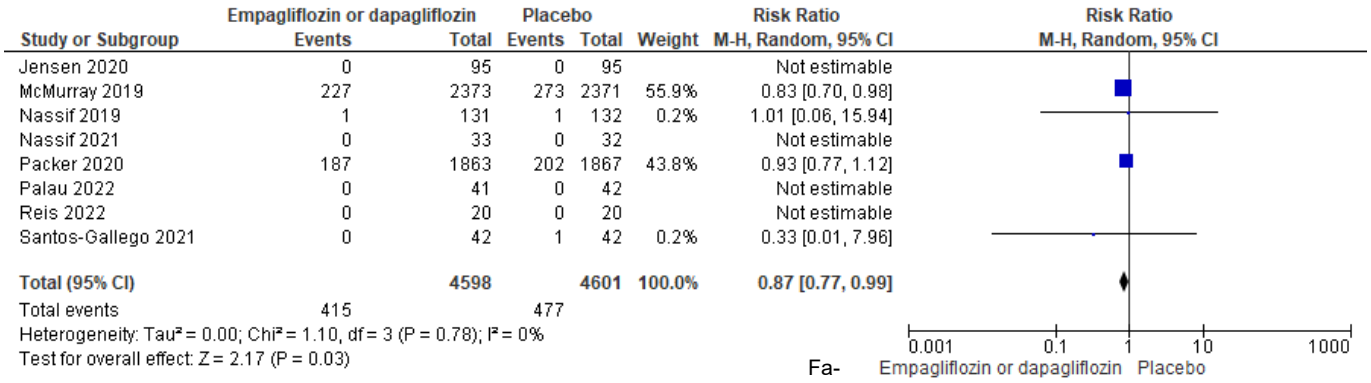
3.4.3 Figures 2c Forest Plots and Risk of Bias assessments investigating empagliflozin or dapagliflozin vs. placebo (n=10)

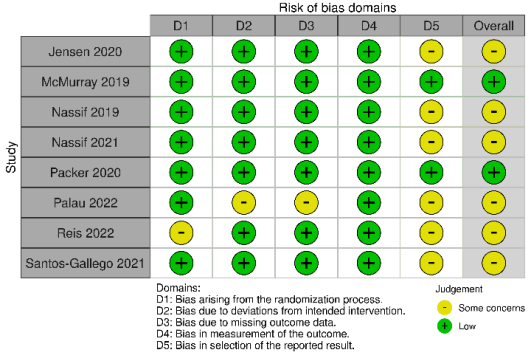
3.4.3.1 Mortality (all cause)





3.4.3.2 Mortality (CV)

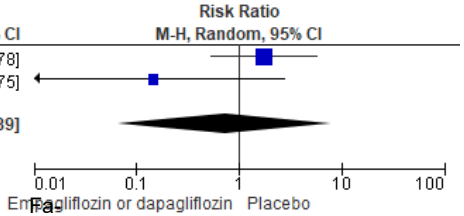


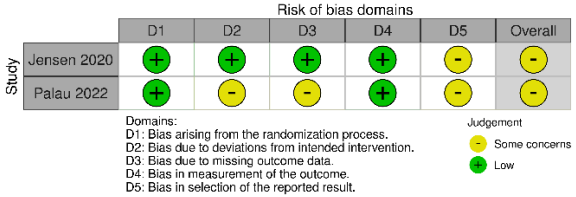


3.4.3.3 Hospitalization (all cause)

Study or Subgroup	Empagliflozin or dapagliflozin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Jensen 2020	7	95	4	95	64.4%	1.75 [0.53, 5.78]
Palau 2022	0	41	3	42	35.6%	0.15 [0.01, 2.75]
Total (95% CI)		**136**		**137**	**100.0%**	**0.72 [0.07, 7.89]**
Total events	7		7			

Heterogeneity: Tau² = 1.94; Chi² = 2.49, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 0.27 (P = 0.79)

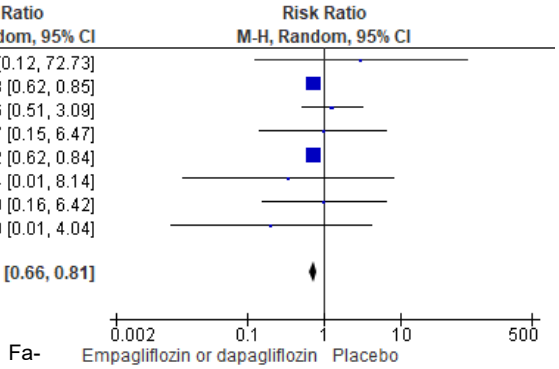


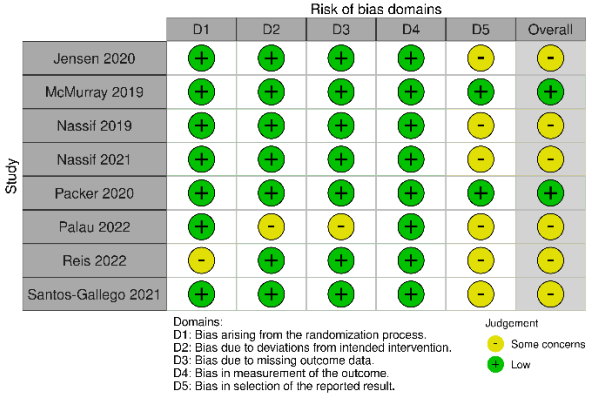


3.4.3.4 Hospitalization (heart failure)

Study or Subgroup	Empagliflozin or dapagliflozin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Jensen 2020	1	95	0	95	0.1%	3.00 [0.12, 72.73]
McMurray 2019	231	2373	318	2371	46.0%	0.73 [0.62, 0.85]
Nassif 2019	10	131	8	132	1.5%	1.26 [0.51, 3.09]
Nassif 2021	2	33	2	32	0.3%	0.97 [0.15, 6.47]
Packer 2020	246	1863	342	1867	51.5%	0.72 [0.62, 0.84]
Palau 2022	0	41	1	42	0.1%	0.34 [0.01, 8.14]
Reis 2022	2	20	2	20	0.3%	1.00 [0.16, 6.42]
Santos-Gallego 2021	0	40	2	40	0.1%	0.20 [0.01, 4.04]
Total (95% CI)		**4596**		**4599**	**100.0%**	**0.73 [0.66, 0.81]**
Total events	492		675			

Heterogeneity: Tau² = 0.00; Chi² = 3.33, df = 7 (P = 0.85); I² = 0%
Test for overall effect: Z = 5.70 (P < 0.00001)

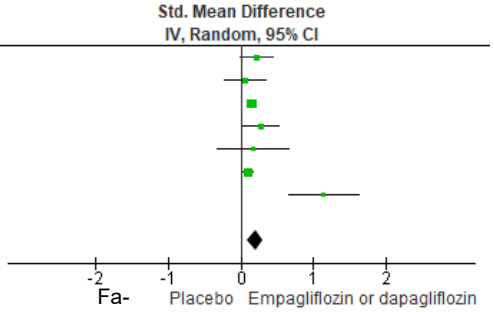


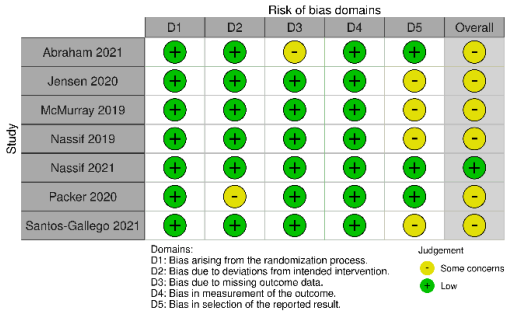


3.4.3.5 Quality of life

Study or Subgroup	Empagliflozin or dapagliflozin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abraham 2021	9.65	14.6	156	6.4	14.54	156	13.7%	0.22 [-0.00, 0.45]
Jensen 2020	1.9	12.3	94	1.2	9.4	92	10.1%	0.06 [-0.22, 0.35]
McMurray 2019	6.1	18.6	2373	3.3	19.2	2371	27.8%	0.15 [0.09, 0.21]
Nassif 2019	72.6	13.6	126	68.9	13.6	126	12.1%	0.27 [0.02, 0.52]
Nassif 2021	64.2	14.98	32	61.7	14.73	30	4.3%	0.17 [-0.33, 0.67]
Packer 2020	5.8	17.27	1863	4.1	17.28	1867	27.3%	0.10 [0.03, 0.16]
Santos-Gallego 2021	21	18	40	1.9	15	40	4.7%	1.14 [0.67, 1.62]
Total (95% CI)			**4684**			**4682**	**100.0%**	**0.20 [0.09, 0.31]**

Heterogeneity: Tau² = 0.01; Chi² = 20.71, df = 6 (P = 0.002); I² = 71%
Test for overall effect: Z = 3.48 (P = 0.0005)

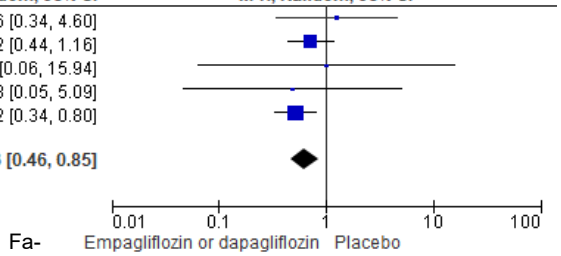


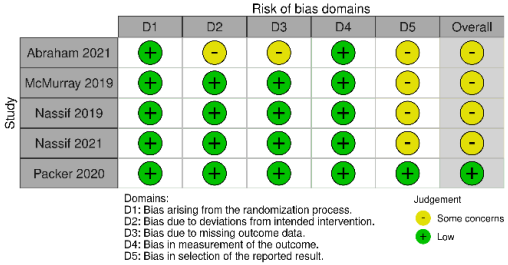


3.4.3.6 Renal worsening (dichotomous outcome)

Study or Subgroup	Empagliflozin or dapagliflozin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abraham 2021	5	155	4	156	5.7%	1.26 [0.34, 4.60]
McMurray 2019	28	2373	39	2371	41.1%	0.72 [0.44, 1.16]
Nassif 2019	1	131	1	132	1.3%	1.01 [0.06, 15.94]
Nassif 2021	1	33	2	32	1.7%	0.48 [0.05, 5.09]
Packer 2020	30	1863	58	1867	50.2%	0.52 [0.34, 0.80]
Total (95% CI)		**4555**		**4558**	**100.0%**	**0.63 [0.46, 0.85]**
Total events	65		104			

Heterogeneity: Tau² = 0.00; Chi² = 2.30, df = 4 (P = 0.68); I² = 0%
Test for overall effect: Z = 2.95 (P = 0.003)

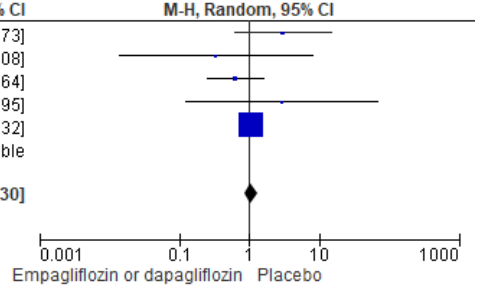


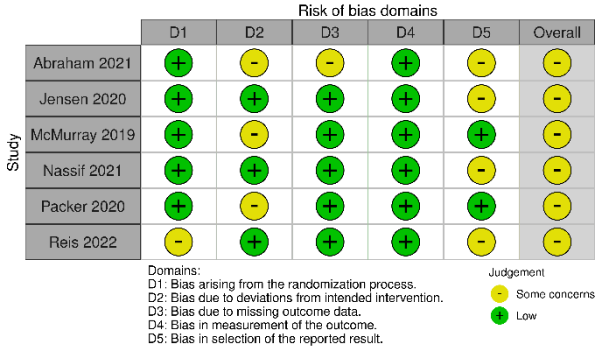


3.4.3.7 Hypotension

Study or Subgroup	Empagliflozin or dapagliflozin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abraham 2021	6	155	2	156	1.5%	3.02 [0.62, 14.73]
Jensen 2020	0	95	1	95	0.4%	0.33 [0.01, 8.08]
McMurray 2019	7	2368	11	2368	4.3%	0.64 [0.25, 1.64]
Nassif 2021	1	33	0	32	0.4%	2.91 [0.12, 68.95]
Packer 2020	176	1863	163	1863	93.4%	1.08 [0.88, 1.32]
Reis 2022	0	20	0	20		Not estimable
Total (95% CI)		**4534**		**4534**	**100.0%**	**1.07 [0.88, 1.30]**
Total events	190		177			

Heterogeneity: Tau² = 0.00; Chi² = 3.71, df = 4 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)

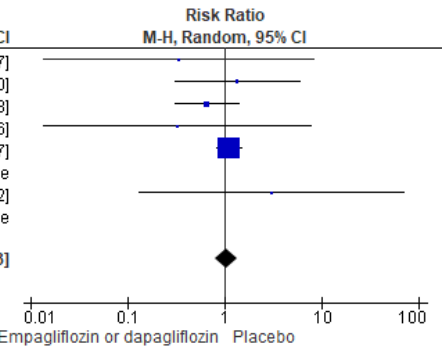


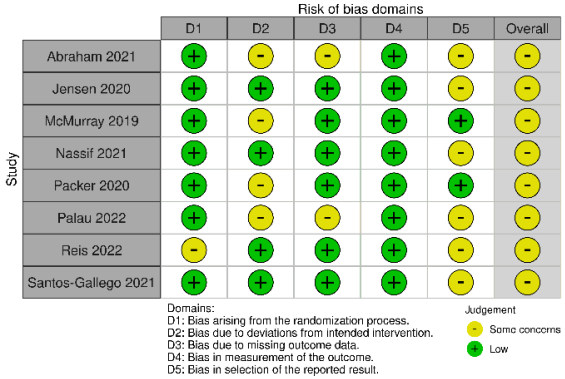


3.4.3.8 Urinary tract infection

Study or Subgroup	Empagliflozin or dapagliflozin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abraham 2021	0	155	1	156	0.7%	0.34 [0.01, 8.17]
Jensen 2020	4	95	3	95	3.2%	1.33 [0.31, 5.80]
McMurray 2019	11	2368	17	2368	12.2%	0.65 [0.30, 1.38]
Nassif 2021	0	33	1	32	0.7%	0.32 [0.01, 7.66]
Packer 2020	91	1863	83	1863	82.5%	1.10 [0.82, 1.47]
Palau 2022	0	41	0	42		Not estimable
Reis 2022	1	20	0	20	0.7%	3.00 [0.13, 69.52]
Santos-Gallego 2021	0	42	0	42		Not estimable
Total (95% CI)		**4617**		**4618**	**100.0%**	**1.02 [0.79, 1.33]**
Total events	107		105			

Heterogeneity: Tau² = 0.00; Chi² = 3.18, df = 5 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.85)

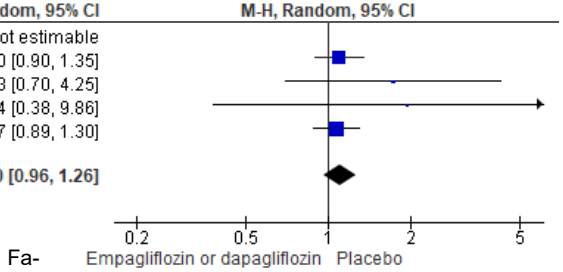


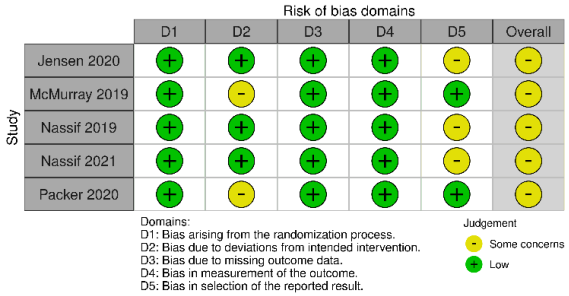


3.4.3.9 Volume depletion

Study or Subgroup	Empagliflozin or dapagliflozin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Jensen 2020	0	95	0	95		Not estimable
McMurray 2019	178	2368	162	2368	44.9%	1.10 [0.90, 1.35]
Nassif 2019	12	131	7	132	2.3%	1.73 [0.70, 4.25]
Nassif 2021	4	33	2	32	0.7%	1.94 [0.38, 9.86]
Packer 2020	197	1863	184	1863	52.1%	1.07 [0.89, 1.30]
Total (95% CI)		**4490**		**4490**	**100.0%**	**1.10 [0.96, 1.26]**
Total events	391		355			

Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 3 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.36 (P = 0.17)

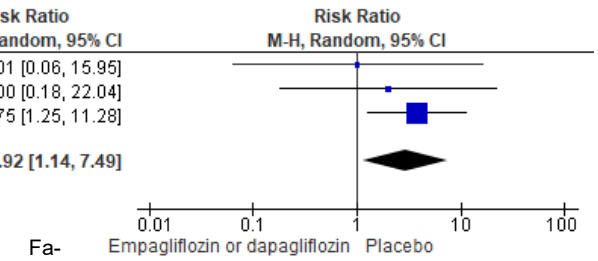


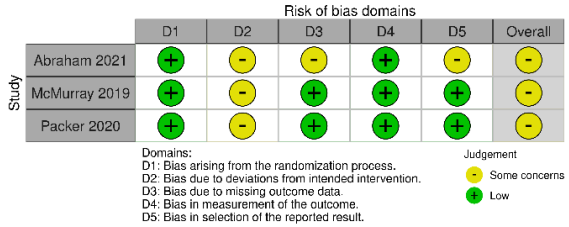


3.4.3.10 Fall

Study or Subgroup	Empagliflozin or dapagliflozin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abraham 2021	1	155	1	156	11.6%	1.01 [0.06, 15.95]
McMurray 2019	2	2368	1	2368	15.4%	2.00 [0.18, 22.04]
Packer 2020	15	1863	4	1863	73.0%	3.75 [1.25, 11.28]
Total (95% CI)		**4386**		**4387**	**100.0%**	**2.92 [1.14, 7.49]**
Total events	18		6			

Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.23 (P = 0.03)

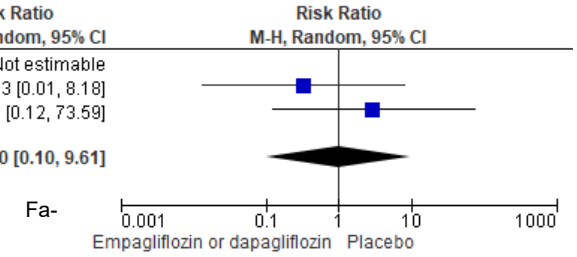


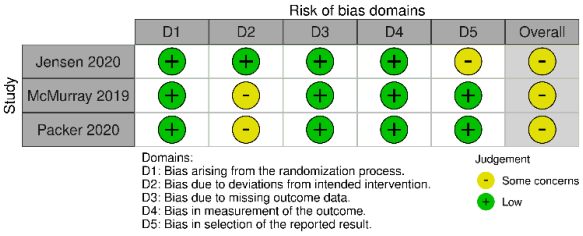


3.4.3.11 Fournier Gangrene

Study or Subgroup	Empagliflozin or dapagliflozin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Jensen 2020	0	95	0	95		Not estimable
McMurray 2019	0	2368	1	2368	50.0%	0.33 [0.01, 8.18]
Packer 2020	1	1863	0	1863	50.0%	3.00 [0.12, 73.59]
Total (95% CI)		**4326**		**4326**	**100.0%**	**1.00 [0.10, 9.61]**
Total events	1		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)





3.5 Funnel plot

Note: Not applicable (< 10 studies pooled).

3.6 Primary outcome measures

Table 3a Primary outcomes of studies investigating sacubitril/valsartan vs. enalapril or perindopril (n = 10)

Author, Study	*Outcome and follow up*	*Intervention*		*Control*		*Effect measure*
		Event or continuous measure	**Total N**	**Event or continuous measure**	**Total N**	**Effect measure + 95% CI**
Bano 2021 (8)	HF-related hospitalization in 12 months	Events: 25	181	Events: 41	183	RR: 0.61 (0.39-0.97)
Desai 2019 (1) *EVALUATE-HF*	Aortic characteristic impedance (Zc, dyne × s/cm^5), change from baseline to 2.8 months	Mean: -2.9 (-13.8-8)	203	Mean: -0.7 (-11.6-10.1)	205	MD: -2.2 (-17.6-13.2)
DosSantos 2021 (2) *NEPRIExTol*	Peak VO2 (mL/kg/min) change in percentage from baseline to 5.6 months	Mean: 13.5	NR	Mean: 12	NR	NR
Halle 2021 (3) *ACTIVITY-HF*	Peak VO2 (mL/min/kg) change from baseline to 2.8 months	Mean: 0.51 (SE:0.18)	98	Mean: 0.19 (SE: 0.19)	90	Least square mean difference: 0.32 (-0.21-0.85)
Khandwalla 2021 (4) *AWAKE-HF*	Activity counts during the most active 30 min/day, change from baseline to 1.9 months	Mean: 0.98	70	Mean: 1.04	70	Geometric mean ratio: 0.95 (0.89-1.01)
Li 2021 (5)	NR; Comparison of the LVEF (%) between two groups of Patients before and after treatment from baseline to 2.8 months	Mean: 32.12 (SD: 4.37) vs. 41.28 (SD: 4.12)	40	Mean: 31.98 (SD: 4.18) vs. 37.26 (SD: 4.33)	40	NR
McMurray 2014 (6) *PARADIGM-HF*	Death from cardiovascular causes or first hospitalization for worsening heart failure in 27 months	Events: 914	4187	Events: 1117	4212	HR: 0.8 (0.73-0.87)
Piepoli 2021 (7) *OUTSTEP-HF*	6MWT distance (meter) change from baseline to 2.8 months	Mean: 35.09 (27.85-42.32)	290	Mean: 26.11 (18.78-33.43)	294	Least square mean difference: 8.98 (-1.31-19.27)
Tsutsui 2021 (9) *PARALLEL-HF*	Composite of cardiovascular death or first heart failure hospitalization in 33.9 months	Events: 30	111	Events: 28	112	HR: 1.09 (0.65-1.82)
Zhao 2022 (23)	RV (right ventricular) function (TAPSE/sPAP) in 6 months	Mean: 0.5 (SD: 0.23)	NR	Mean: 0.39 (SD: 0.14)	NR	NR

Table 3b Primary outcomes of studies investigating sacubitril/valsartan vs. valsartan (n = 5)

Author, Study	*Outcome and follow up*	*Intervention*		*Control*		*Effect measure*
		Event or continuous measure	**Total N**	**Event or continuous measure**	**Total N**	**Effect measure + 95% CI**
Du 2022 (24)	Patient's clinical symptoms and signs (e.g., dyspnea, fatigue, and edema) from baseline to 6 months	Events: 28	30	Events: 25	30	NR
Fan 2020 (12)	LVEF (%) at baseline and 2.8 months	Mean: 34.76 (SD: 6.38) vs. 48.36 (SD: 8.15)	60	Mean: 35.17 (SD: 6.42) vs. 43.16 (SD:7.68)	60	NR
Gao 2020(13)	Positive therapeutic effect (remarkable effect = pronounced and remarkable effect on symptoms of dyspnea, edema, and no fatigue, cardiac function improved two classes or recovery to NYHA Class I; effect = obvious improvement of symptoms of dyspnea, edema, and fatigue, cardiac function improved one class but did not reach NYHA Class I) from baseline to 1.9 months	Events: 53	60	Events: 42	60	NR
Makarovskaiya 2020 (10)	Effective area of the regurgitation hole (cm^2) change from baseline to 12 months	Mean: -0.07 (SD: 0.066)	52	Mean: -0.03 (SD: 0.058)	48	MD: -0,04 (-0.07--0.011)
Mann 2022 (11) *LIFE*	Area under the curve for NT-proBNP levels (pg/mL) proportional change from baseline to 5.6 months	Median: 1.08 (0.75-1.6)	155	Median: 1.19 (0.91-1.64)	158	Ratio of change: 0.95 (0.84-1.08)

Table 3c Primary outcomes of studies investigating sacubitril/valsartan (conservative) vs. sacubitril/valsartan (condensed) (n = 1)

Author, Study	*Outcome and follow up*	*Intervention*		*Control*		*Effect measure*
		Event or continuous measure	**Total N**	**Event or continuous measure**	**Total N**	**Effect measure + 95% CI**
Senni 2016 (25) *TITRATION*	Tolerability, hypotension (renal dysfunction, hyperkalaemia, adjudicated angioedema also reported) in 2.6 months	Events: 24	247	Events: 21	251	HR: 1.19 (0.66-2.13)

Table 3d Primary outcomes of studies investigating empagliflozin vs. placebo (n = 6).

Author, Study	*Outcome and follow up*	*Intervention*		*Control*		*Effect measure*
		Event or continuous measure	**Total N**	**Event or continuous measure**	**Total N**	**Effect measure + 95% CI**
Abraham 2021 (14) *EMPERIAL-Reduced*	6MWTD change (meter) from baseline to 2.8 months	Median: 13.5 (-8-42)	156	Median: 18 (-11.5-54)	156	Difference, median: -4.0 (-16-6)
Jensen 2020 (15) *Empire HF**	NT-proBNP (pg/mL) change from baseline to 2.8 months	Median: 478 (281- 961)	94	Median: 520 (267- 1075)	92	Ratio of change: 0.98 (0.82-1.11)
Kolwelter 2021 (26) *ELSI*	Central systolic blood pressure (mmHg) change from baseline to 3 months	Mean: -4.6 (SD: 8.4)	48	Mean: -0.3 (SD: 11.8)	26	MD: -4.3 (SD: 2.6)
Nassif 2021 (18) *EMBRACE-HF*	PA diastolic pressure (mmHg) at the end of the treatment period from week 1 to 3 months 1 to 1.9 months	Mean: 21.19 vs. 20.23	33	Mean: 21.51 vs. 22.11	32	MD: 1.9 (0.1-3.6)
Packer 2020 (19) *EMPEROR-Reduced*	Composite outcome (cardiovascular death; hospitalization for heart failure) in 16 months	Events: 361	1863	Events: 462	1867	HR: 0.75 (0.65-0.86)
Santos-Gallego 2021 (20) *EMPA-TROPISM*	LV end-diastolic volume change (ml) from baseline to 6 months	Mean: -25.1 (SD:26)	40	Mean: -1.5 (SD: 25.4)	40	NR

* The Empire-HF study accounted for three of included studies (15, 27, 28). One study was identified as main study (15), the remaining two as sub-studies (27, 28). The sub-studies shared partly the same population as the main study and were not presented in the result section of this report.

Table 3e Primary outcomes of studies investigating empagliflozin low dose vs. empagliflozin high dose (n = 2).

Author, Study	*Outcome and follow up*	*Intervention*		*Control*		*Effect measure*
		Event or continuous measure	**Total N**	**Event or continuous measure**	**Total N**	**Effect measure + 95% CI**
Hao 2022a (29)	HF hospitalization and cardiovascular death in 12 months	Events: 19	150	Events: 36	150	NR
Hao 2022b (30)	Change LVEF (increase) from baseline to 3 months	Mean: 6.1 (SD: 4.3)	50	Mean: 4.1 (SD: 4.2)	50	NR

Table 3f Primary outcomes of studies investigating dapagliflozin vs. placebo (n = 4).

Author, Study	*Outcome and follow up*	*Intervention*		*Control*		*Effect measure*
		Event or continuous measure	**Total N**	**Event or continuous measure**	**Total N**	**Effect measure + 95% CI**
McMurray 2019 (16) *DAPA-HF*	Composite of worsening heart failure or death from cardiovascular causes in 18.2 months	Events: 386	2373	Events: 502	2371	HR: 0.74 (0.65-0.85)
Nassif 2019 (17) *DEFINE-HF*	Average NT-proBNP (pg/mL) at 1.4 months and 2.8 months	Mean: 1133 (1036-1238)	130	Mean: 1191 (1089-1304)	131	Adjusted ratio: 0.95 (0.84-1.08)
Palau 2022 (21) *DAPA-VO2*	Peak VO2 (ml/kg/min) at 3 months	Mean: 13.7 (13.1-14.2)	39	Mean: 12.7 (12.1-13.3)	38	Least square mean: 1.01 (0.03-1.99)
Reis 2022 (22)	Peak VO2 (ml/kg/min) difference between baseline 6 months	Mean: 3.1 (SD: NR)	20	Mean: 0.1 (SD: NR)	20	Time x Group Interaction Partial eta squared: 0.16

3.7 Study characteristics of included studies

Table 5a Study characteristics of studies investigating sacubitril/valsartan vs. enalapril or perindopril (n = 10).

Author, Study	Funding	Run-in period		Patients randomized	Dose and follow up	LVEF*	NT-pro BNP*	NYHA I	NYHA II	NYHA III	NYHA IV	eGFR*	Age*	N, female (%)
Bano 2021 (8)	Public/non profit	NR	I	200	24/26 or 49/51 mg sacubitril/valsartan twice daily for 12 months	31.21 (4.1)	1201.23 (101.34)	NR	NR	NR	NR	NR	53 (12)	93 (47%)
			C	200	2.5 or 5 mg enalapril twice daily for 12 months	31.8 (4.0)	1211.61 (99.98)	NR	NR	NR	NR	NR	55 (12)	93 (47%)
Desai 2019 (1) EVALUATE-HF	Private	NR	I	232	24/26 mg (initial), up to 97/103 mg (titrated) sacubitril/valsartan twice daily for 2.8 months	34 (10)	560 (254-1498)	33 (14%)	152 (66%)	46 (20%)	0 (0%)	70 (22)	67.8 (9.8)	61 (26%)
			C	233	2.5 mg up to 10 mg (titrated) enalapril twice daily for 2.8 months	33 (10)	595 (244-1438)	28 (12%)	161 (69%)	44 (19%)	0 (0%)	69 (20)	66.7 (8.5)	48 (21%)
DosSantos 2021 (2)	Public/non profit	NR	I	29	49/51 mg (initial), 98/103 (titrated) sacubitril/valsartan twice daily for 5.6 months	26 (23-32)	680.5 (369.5-1251.3	0 (0%)	14 (48%)	12 (41%)	0 (0%)	60 (50-60)	56 (50-63)	8 (28%)

Author, Study	Funding	Run-in period		Patients randomized	Dose and follow up	LVEF*	NT-pro BNP*	NYHA I	NYHA II	NYHA III	NYHA IV	eGFR*	Age*	N, female (%)
NEPRIExTol			C	23	10 mg (initial if 10 mg enalapril was given before), 20 mg (titrated) twice daily for 5.6 months	25 (19-34)	1052.5 (303.5-6022.5)	0 (0%)	8 (35%)	10 (43%)	0 (0%)	60 (58-60)	61 (55-67)	5 (22%)
Halle 2021 (3) ACTIVITY-HF	Private	NR	I	103	49/51 mg (initial),97/103 mg (titrated) sacubitril/valsartan twice daily for 2.8 months	31.9 (6.1)	NR	0 (0%)	0 (0%)	103 (100%)	0 (0%)	NR	66.1 (10.8)	17 (17%)
			C	98	5 mg (initial), 10 mg (titrated) enalapril twice daily for 2.8 months	32.0 (5.7)	NR	0 (0%)	1 (1%)	97 (99%)	0 (0%)	NR	67.6 (10)	21 (21%)
Khandwalla 2021 (4) AWAKE-HF	Private	NR	I	70	24/26 mg (initial), 97/103 (titrated) sacubitril/valsartan twice daily for 1.9 months	31.1 (7.9)	NR	0 (0%)	64 (91%)	6 (9%)	0 (0%)	69.3 (24.1)	62.3 (8.8)	18 (26%)
			C	70	2.5 mg (initial), 10 mg (titrated) enalapril twice daily for 1.9 months	30.6 (7.7)	NR	0 (0%)	62 (89%)	8 (11%)	0 (0%)	67.5 (19.4)	64.2 (11.6)	14 (20%)
Li 2021 (5)	Public/non profit	NR	I	40	50 mg (initial), 200 mg (titrated) sacubitril/valsartan twice daily for 2.8 months	32.12 (4.37)	NR	0 (0%)	9 (23%)	22 (55%)	9 (23%)	NR	63.2 (5.4)	17 (43%)
			C	40	4 mg perindopril tert-butylamine once daily for 2.8 months	31.98 (4.18)	NR	0 (0%)	8 (20%)	21 (53%)	11 (28%)	NR	62.8 (6.1)	16 (40%)
McMurray 2014 (6) PARADIGM-HF	Private	Yes	I	4187	100 mg (initial), 200 mg (titrated) LCZ696 twice daily for 27 months	29.6 (6.1)	1631 (885-3154)	180 (4%)	2998 (72%)	969 (23%)	33 (1%)	NR	63.8 (11.5)	879 (21%)
			C	4212	10 mg enalapril twice daily in addition to standard of care for 27 months	29.4 (6.3)	1594 (866-3305)	209 (5%)	2921 (69%)	1049 (25%)	27 (1%)	NR	63.8 (11.3)	953 (23%)
Piepoli 2021 (7) OUTSTEP-HF	Private	NR	I	310	24/26 (initial), 97/103 (titrated) sacubitril/valsartan twice daily for 2.8 months	NR	NR	0 (0%)	161 (52%)	146 (47%)	2 (1%)	NR	67.16 (11.04)	71 (23%)
			C	311	2.5 mg (initial), 10 mg (titrated) enalapril twice daily for 2.8 months	NR	NR	0 (0%)	162 (52%)	146 (47%)	2 (1%)	NR	66.62 (10.45)	61 (20%)

Author, Study	Funding	Run-in period		Patients randomized	Dose and follow up	LVEF*	NT-pro BNP*	NYHA I	NYHA II	NYHA III	NYHA IV	eGFR*	Age*	N, female (%)
Tsutsui 2021 (9) PARALLEL-HF	Private	Yes	I	112	100 mg (initial), 200 mg (titrated) sacubitril/valsartan twice daily for 33.9 months	28.6 (5.1)	837 (563-1476)	4 (4%)	101 (90%)	6 (5%)	0 (0%)	58.3 (17.6)	69 (9.7)	15 (13%)
			C	113	5 mg (initial), 10 mg (titrated) enalapril twice daily for 33.9 months	27.7 (5.5)	841 (511-1601)	4 (4%)	104 (92%)	4 (4%)	0 (0%)	57.6 (14.7)	66.7 (10.9)	16 (14%)
Zhao 2022(23)	Public/non profit	NR	I	52	50 mg (titrated) sacubitril/valsartan twice daily for 6 months	35.8 (3.94)	2899.27 (1136.33)	0 (0%)	0 (0%)	28 (54%)	24 (46%)	NR	68.65 (10.48)	29 (56%)
			C	45	10 mg enalapril once daily for 6 months	35.18 (4.73)	2814.49 (1356.44)	0 (0%)	0 (0%)	21 (47%)	24 (53%)	NR	66.71 (10.42)	25 (56%)

*Mean (SD) or Median (IQR)

Table 5b Study characteristics of studies investigating sacubitril/valsartan vs. valsartan (n = 5).

Author, Study	Funding	Run-in period		Patients randomized	Dose and follow up	LVEF*	NT-pro BNP*	NYHA I	NYHA II	NYHA III	NYHA IV	eGFR*	Age*	N, female (%)
Du 2022 (24)	NR	NR	I	30	50 mg (initial), 100 mg (titrated) sacubitril/valsartan twice daily for 6 months	30.04 (5.03)	4858.82 (512.34)	0 (0%)	NR	NR	NR	122.33 (19.14)	74.37 (3.5)	9 (30%)
			C	30	80 mg valsartan twice daily for 6 months	31.32 (4.96)	4835.43 (496.76)	0 (0%)	NR	NR	NR	123.45 (19.35)	75.97 (3.72)	11 (37%)
Fan 2020 (12)	NR	NR	I	60	100 mg (initial), 200 mg (titrated) twice daily sacubitril/valsartan for 2.8 months	34.76 (6.38)	NR	0 (%)	25 (42%)	26 (43%)	9 (15%)	NR	54.36 (8.43)	23 (38%)
			C	60	80 mg valsartan once daily for 2.8 months	35.17 (6.42)	NR	0 (%)	23 (38%)	24 (40%)	13 (22%)	NR	56.27 (8.61)	25 (42%)
Gao 2020 (13)	NR	NR	I	60	50 mg sacubitril/valsartan twice daily for 1.9 months	31.12 (6.65)	10356.94 (5447.68)	0 (%)	11 (18%)	25 (42%)	24 (40%)	NR	70.53 (7.05)	14 (23%)
			C	60	80 mg valsartan once daily for 1.9 months	30.41 (6.11)	9518.17 (5905.17)	0 (%)	14 (23%)	21 (35%)	25 (42%)	NR	70 (7.51)	18 (30%)
Makarovskaiya 2020 (10)	Public/non profit	NR	I	52	24/26 to 49/51 (initial), 97/103 (titrated) sacubitril/valsartan twice daily for 12 months	NR	NR	NR	45 (87%)	5 (10%)	NR	NR	62 (10.1)	22 (42%)

Author, Study	Funding	Run-in period		Patients randomized	Dose and follow up	LVEF*	NT-pro BNP*	NYHA I	NYHA II	NYHA III	NYHA IV	eGFR*	Age*	N, female (%)
			C	48	40 to 80 (initial), 160 mg (titrated) valsartan twice daily for 12 months	NR	NR	NR	42 (88%)	3 (6%)	NR	NR	60 (9.8)	15 (31%)
Mann 2022 (11) LIFE	Mixed	Yes	I	167	24/26 mg (inital), 97/103 mg (titrated) sacubitril/valsartan twice daily for 5.6 months	19.9 (6.2)	3449.6 (6616.2)	3 (2%)	38 (23%)	67 (40%)	59 (%35)	63.6 (24.3)	60.2 (13.4)	47 (28%)
			C	168	40 mg (ACE inhibitor/ARB naive) or 49 mg (ACE inhibitor/ARB at baseline) initial; 160 mg twice daily for 5.6 months	20.9 (6.8)	2779.4 (3115.2)	5 (3%)	37 (22%)	70 (42%)	55 (33%)	65.7 (25.9)	58.3 (13.1)	43 (26%)

*Mean (SD) or Median (IQR)

Table 5c Study characteristics of studies investigating sacubitril/valsartan (conservative) vs. sacubitril/valsartan (condensed) (n = 1).

Author, Study	Funding	Run-in period		Patients randomized	Dose and follow up	LVEF*	NT-pro BNP	NYHA I	NYHA II	NYHA III	NYHA IV	eGFR	Age*	N, female (%)
Senni 2016 (25) *TITRATION*	Private	Yes	I	247	48/52 mg (initial), 96/98 (titrated, after 2 weeks) sacubitril/valsartan twice daily for 2.6 months	29.8 8 (5.15)	NR	0 (0%)	175 (71%)	72 (29%)	0 (0%)	NR	64.2 (11.6)	56 (23%)
			C	251	24/26 mg (initial), 96/98 (titrated, after 5 weeks) sacubitril/valsartan twice daily for 2.6 months	29.6 (5.36)	NR	0 (0%)	178 (71%)	72 (29%)	1 (0%)	NR	63.8 (10.94)	50 (20%)

*Mean (SD) or Median (IQR)

Table 5d Study characteristics of studies investigating empagliflozin vs. placebo (n = 6).

Author, Study	Funding		Patients randomized	Dose and follow up	LVEF*	NT-pro BNP*	NYHA I	NYHA II	NYHA III	NYHA IV	eGFR*	Age*	N, female (%)
Abraham 2021 (14) *EMPERIAL-Reduced*	Private	I	156	10 mg empagliflozin once daily for 2.8 months	30 (24.5-35)	1458 (817-2881)	0 (%)	101 (65%)	55 (35%)	0 (0%)	56.8 (44.0-73.3)	68.7 (9.9)	35 (22%)
		C	156	Placebo for 2.8 months	30 (26-36)	1559 (830-2919)	0 (%)	101 (65%)	55 (35%)	0 (0%)	53 (42.0-74.3)	69.3 (10.6)	45 (29%)

Author, Study	Fund-ing		Patients ran-domized	Dose and follow up	LVEF*	NT-pro BNP*	NYHA I	NYHA II	NYHA III	NYHA IV	eGFR*	Age*	N, female (%)
Jensen 2020 (15) Empire HF†	Mixed	I	95	10 mg empagliflozin once daily for 2.8 months	29 (8)	582 (304-1020)	5 (5%)	72 (76%)	18 (19%)	0 (0%)	73 (57-89)	65 (10)	16 (17%)
		C	95	Placebo for 2.8 months	30 (8)	605 (322-1070)	7 (7%)	77 (81%)	11 (12%)	0 (0%)	74 (60-89)	63 (12)	12 (13%)
Kolwelter 2021 (26) ELSI	Private	I	49	10 mg empagliflozin orally once daily for 3 months	39.8 (8.3)	499 (293.3-1401.8)	0 (0%)	NR	NR	0 (0%)	75.7 (15.5)	69 (8.1)	7 (14%)
		C	26	Placebo once daily for 3 months	36.8 (9.1)	511 (189-1194.5)	0 (0%)	NR	NR	0 (0%)	74.7 (20.3)	67.4 (8.7)	1 (4%)
Nassif 2021 (18) EMBRACE-HF	Private	I	33	10 mg empagliflozin once daily for 2.8 months	46.7 (14.9)	865.5 (311-1982.5)	0 (0%)	14 (42%)	18 (55%)	NR	51.2 (19.7)	69.5 (12)	12 (36%)
		C	32	Placebo once daily for 2.8 months	40.7 (17.2)	563.5 (153-1964)	0 (0%)	16 (50%)	16 (50%)	0 (0%)	62.7 (25.5)	62.9 (13.3)	12 (38%)
Packer 2020 (19) EMPEROR-Re-duced	Private	I	1863	10 mg empagliflozin daily for 16 months	27.7 (6)	1887 (1077-3429)	0 (0%)	1399 (75%)	455 (24%)	9 (1%)	61.8 (21.7)	67.2 (10.8)	437 (23%)
		C	1867	Placebo once daily for 16 months	27.2 (6.1)	1926 (1153-3525)	0 (0%)	1401 (75%)	455 (24%)	11 (1%)	62.2 (21.5)	66.5 (11.2)	456 (24%)
Santos-Gallego 2021 (20) EMPA-TROPISM	Private	I	42	10 mg empagliflozin once daily for 6 months	36.2 (8.2)	NR	0 (0%	NR	NR	0 (0%)	80 (21)	64.2 (10.9)	15 (36%)
		C	42	10 mg placebo once daily for 6 months	36.5 (8)	NR	0 (0%)	NR	NR	0 (0%)	83 (23)	59.9 (13.1)	15 (36%)

*Mean (SD) or Median (IQR)

† The Empire-HF study accounted for three of included studies (15, 27, 28). One study was identified as main study (15), the remaining two as sub-studies (27, 28). The sub-studies shared partly the same population as the main study and were not presented in the result section of this report.

Table 5e Study characteristics of studies investigating empagliflozin low dose vs. empagliflozin high dose (n = 2).

Author, Study	Funding		Patients ran-domized	Dose and follow up	LVEF*	NT-pro BNP*	NYHA I	NYHA II	NYHA III	NYHA IV	eGFR	Age*	N, female (%)
Hao 2022a (29)	Public/ non profit	I	150	25 mg empagliflozin and 10mg placebo for 12 months (unclear frequency)	32 (4.5)	2658.8 (1029.7)	NR	104 (69%)	46 (31%)	NR	NR	68.2 (13.6)	65 (43%)

Author, Study	Funding		Patients randomized	Dose and follow up	LVEF*	NT-pro BNP*	NYHA I	NYHA II	NYHA III	NYHA IV	eGFR	Age*	N, female (%)
		C	150	10 mg empagliflozin and 25mg placebo for 12 months (unclear frequency)	31.5 (4.3)	2470 (1001.5)	NR	93 (62%)	57 (38%)	NR	NR	66.9 (12.4)	71 (47%)
Hao 2022b (30)	NR	I	50	25 mg empagliflozin per for 3 months	28.6 (3.4)	2458.3 (851.1)	NR	NR	NR	NR	NR	62.5 (9)	18 (36%)
		C	50	10 mg empagliflozin per for 3 months	27.4 (3.8)	2362.8 (813.9)	NR	NR	NR	NR	NR	63.5 (9)	23 (46%)

*Mean (SD) or Median (IQR)

Table 5f Study characteristics of studies investigating dapagliflozin or vs. placebo or standard of care (n = 4).

Author, Study	Funding		Patients randomized	Dose and follow up	LVEF*	NT-pro BNP*	NYHA I	NYHA II	NYHA III	NYHA IV	eGFR*	Age*	N, female (%)
McMurray 2019 (16) *DAPA-HF*	Private	I	2373	10 mg dapagliflozin once daily for 18.2 months	31.2 (6.7)	1428 (857-2655)	0 (0%)	1606 (68%)	747 (31%)	20 (1%)	66.0 (19.6)	66.2 (11)	564 (24%)
		C	2371	Placebo once daily for 18.2 months	30.9 (6.9)	1446 (857-2641)	0 (0%)	1597 (67%)	751 (32%)	23 (1%)	65.5 (19.3)	66.5 (10.8)	545 (23%)
Nassif 2019 (17) DEFINE-HF	Private	I	131	10 mg dapagliflozin once daily for 2.8 months	27.2 (8.0)	1136 (668-2465)	0 (0%)	91 (69%)	40 (31%)	0 (0%)	66.9 (21.1)	62.2 (11)	36 (27%)
		C	132	Placebo once daily for 2.8 months	25.7 (8.2)	1136 (545-2049)	0 (0%)	82 (62%)	50(38%)	0 (0%)	71.2 (23.1)	60.4 (12)	34 (26%)
Palau 2022 (21)	Mixed	I	45	10 mg dapagliflozin once daily for 3 months	33.7 (5.3)	1085 (889-2100)	NR	41 (91%)	NR	NR	64.1 (20.7)	69.8 (62.4-74)	10 (22%)
		C	45	10 mg Placebo once daily for 3 months	34 (5.3)	1620 (889-2328)	NR	39 (87%)	NR	NR	69.4 (23)	67.3 (60.8-75.1)	11 (24%)
Reis 2022 (22)	Public/non profit	I	20	10 mg dapagliflozin once daily for 6 months	34.5 (8.9)	890.5 (426.5-1652)	0 (0%)	NR	6 (30%)	NR	68.7 (23.8)	60.3 (11.6)	3 (15%)

Author, Study	Funding		Patients randomized	Dose and follow up	LVEF*	NT-pro BNP*	NYHA I	NYHA II	NYHA III	NYHA IV	eGFR*	Age*	N, female (%)
		C	20	Maintain usual medication for a period of 6 months	33.5 (7.8)	747.4 (287.7-1490.2)	0 (0%)	NR	2 (10%)	NR	72.5 (17.1)	61.7 (14.8)	4 (20%)

*Mean (SD) or Median (IQR)

3.8 Ongoing trials

Table 6 Ongoing trials identified on clinicaltrials.gov and the International Clinical Trials Registry Platform (ICTRP) (Last search: 08.11.2022)

Registration number	Status	Title	Study start	Intervention	Control	Number of participants
ACTRN12621000187842	Not yet recruiting	Mechanisms of action of SGLT2 inhibitors in patients with heart failure with reduced ejection fraction (HFrEF)	March 8, 2021	Dapagliflozin	Placebo	36
NCT04688294	Completed	The Bio-Clinical Effects of the (sacubitril-valsartan) Combination on Patients With Chronic Heart Failure	January 1, 2020	Sacubitril/valsartan	Valsartan	60
NCT03332212	Completed	A Study That Looks at the Function of the Heart in Patients With Heart Failure Who Take Empagliflozin	March 1, 2018	Empagliflozin	Placebo	72
NCT02788656	Terminated (Inadequate Recruitment)	Pulmonary Artery Pressure Reduction With ENTresto (sacubitril/valsartan)	September, 2016	Sacubitril/valsartan + Placebo	ACEi or ARB + Placebo	4
NCT03119623	Withdrawn (Lost funding prior to study commencing)	Comparing ARNI With ACE Inhibitor on Endothelial Function	June 1, 2017	Sacubitril/valsartan	Enalapril	0
NCT04575675	Completed	dapagliflozin on Hypotensive Heart Failure Patients After sacubitril/valsartan Therapy	May 29, 2020	Dapagliflozin with standard care	Standard care	78
ChiCTR2100049834	Pending	Efficacy of dapagliflozin in the treatment of HFrEF with moderate to severe obstructive sleep apnea syndrome: a prospective, randomized controlled clinical study	September 1, 2021	Dapagliflozin	Standard optimized treatment of heart failure	30
CTRI/2020/11/029176	Open to Recruitment	Comparative study of effect of Remogliflozin and empagliflozin on parameters of heart failure.	November 20, 2020	Empagliflozin	Remogliflozin Etabonate	250
EUCTR2021-005394-66-IT	Authorised-recruitment may be ongoing or finished	Effects of dapagliflozin on cardiac deformation and clinical outcomes in heart failure with reduced and mildly reduced ejection fraction	February 21, 2022	Dapagliflozin	Standard care	88
NCT03821701	Unknown	Effect of Angiotensin-Neprilysin Inhibition (ARNI) on Prognosis of Chronic Heart Failure	June 1, 2018	Entresto	ACEI/ARB	340

Registration number	Status	Title	Study start	Intervention	Control	Number of participants
NCT04458285	Unknown	Efficacy and Safety of sacubitril/valsartan in Maintenance Hemodialysis Patients With Heart Failure	January 1, 2020	Sacubitril/valsartan	Valsartan	118
NCT03415906	Withdrawn (Difficulties in recruiting patients)	Influences of Angiotensin-neprilysin Inhibition on Sympathetic Activity in Heart Failure	December 14, 2017	Sacubitril/valsartan	Valsartan	0
NCT04782245	Not yet recruiting	Acute Reno-Cardiac Action of dapagliflozin In Advanced Heart Failure Patients on Heart Transplant Waiting List	September, 2022	Dapagliflozin	Placebo	80
NCT05152940	Recruiting	ERTU-SODIUM: Study on the Effects of Ertugliflozin on Sodium Storage, Interstitial Volume, and Plasma Volume in HFrEF	October 2022	Ertugliflozin	Placebo	28
NCT02920918	Completed	Treatment of Diabetes in Patients With Systolic Heart Failure	October 2016	Canagliflozin	Sitagliptin	36
NCT03271879	Unknown	empagliflozin Versus Placebo on the Rate of Arrhythmic Events in Heart Failure Patients	February 15, 2018	Empagliflozin	Placebo	128
NCT03298009	Withdrawn (end of contract negociations)	Impact of a Short-term Treatment With Canagliflozin (Canacardia-HF)	November 1, 2017	Canagliflozin	Placebo	0
NCT03917459	Completed	COmparing arNi and Ace For Improving Erectile Dysfunction in mEN With reduCed Ejection Fraction Heart Failure	April 16, 2019	Sacubitril/valsartan	Enalapril	27
NCT04080518	Recruiting	Hepato-renal Regulation of Water Conservation in Heart Failure Patients With SGLT-2 Inhibitor Treatment	November 11, 2019	Dapagliflozin	Placebo	40
NCT04304560	Unknown	Value of SGLT2 Inhibitor (dapagliflozin) as an Added Therapy in Diabetic Patients With Heart Failure With Reduced Ejection Fraction; Randomized Controlled Clinical Trial	March 2020	Dapagliflozin	Placebo	60
NCT04600921	Recruiting	Ertugliflozin to Reduce Arrhythmic Burden in ICD/CRT patientS (ERASe-Trial) - a Phase III Study	June 24, 2021	Ertugliflozin	Placebo	402
NCT04707261	Recruiting	Association Between dapagliflozin-induced Improvement and Anemia in Heart Failure Patients (ADIDAS)	August 6, 2021	Dapagliflozin	Placebo	1990
NCT04956809	Recruiting	Effect of dapagliflozin on Submaximal Exercise Tolerance in Heart Failure	October 22, 2021	Dapagliflozin	Placebo	27
NCT03300427	Completed	The Effects of sacubitril/valsartan on Cardiac Oxygen Consumption and Efficiency of Cardiac Work in Heart Failure Patients	July 5, 2018	Sacubitril/valsartan	Valsartan	55
NCT04023227	Recruiting	Efficacy and Safety of sacubitril/valsartan Compared With enalapril on Morbidity, Mortality, and NT-proBNP Change in Patients With CCC	December 10, 2019	Sacubitril/valsartan	Enalapril	900
NCT04696185	Recruiting	dapagliflozin After Transcatheter Aortic Valve Implantation	January 7, 2021	Dapagliflozin	Standard care	1020

Registration number	Status	Title	Study start	Intervention	Control	Number of participants
NCT04191681	Recruiting	Safety and Efficacy of ARNI After LVAD ImplanT (SEAL-IT) Study	November 8, 2019	Sacubitril/valsartan	Standard care	50
NCT04206865	Withdrawn (New study initiated)	Comparison of ARNI to Alternate Oral Vasodilator Therapies in Patients With Low Cardiac Output	November 25, 2019	Sacubitril/valsartan	Standard Oral Vasodilators	0
NCT02787798	Terminated (Today Entresto treatment has marketing authorization and is available for all patients, that is the reason why study was halted prematurely.)	Evaluation of the Entresto Effect on Sympathic Nervous System in Patient With Heart Failure	October 2016	Sacubitril/valsartan	Placebo	4
NCT03977116	Completed	Sodium-glucose Co-transporter 2 Inhibitors Effects in Failing Heart Patients	January 1, 2017	SLGT2	Placebo	100
NCT05278962	Recruiting	HF Patients With LAVDs Being Treated With SGLT2i	September 8, 2022	SGLT2i	No SGLT2i	44
NCT04591639	Recruiting	The DAPA-MEMRI Trial	August 19, 2020	Dapagliflozin	Placebo	160
NCT04633005	Recruiting	Polypill Strategy for Heart Failure With Reduced Ejection Fraction	November 15, 2021	Polypill (incl. empagliflozin, beta-blocker and mineralocorticoid antagonist)	Guideline-directed medical therapy	175
NCT03168568	Completed	Differential Vascular and Endocrine Effects of valsartan/sacubitril in Heart Failure With Reduced Ejection Fraction	May 4, 2017	Sacubitril/valsartan or placebo	Valsartan or placebo	79
NCT03005184	Withdrawn (Study is being redesigned and submitted as a new study.)	Mechanism(s) Underlying Cardiovascular Effects of ARB/NEP Inhibition - Aim 2	September 17	Sacubitril/valsartan + Icatibant	Sacubitril/valsartan +Placebo, Enalapril+Placebo, enalapril+Icatibant	0
NCT04113109	Recruiting	Mechanisms Underlying Hypotensive Response to ARB/NEP Inhibition - Aim 2	November 1, 2019	Sacubitril/valsartan + Icatibant	Sacubitril/valsartan + Placebo	80
IRCT20210809052117N1	Pending	Effect of Empagliflozin on clinical and echocardiographic parameters in patient with reduced LVEF heart failure	June 28, 2022	Empagliflozin	Placebo	44
NCT05580510	Not yet recruiting	" Evaluation of Safety and Efficacy of Empagliflozin and Sacubitril/Valsartan for CHF With Reduced Ejection Fraction in ACHD "	February 6, 2023	Sacubitril/valsartan + Empagliflozin	Empagliflozin	160

Registration number	Status	Title	Study start	Intervention	Control	Number of participants
NCT05550441	Not yet recruiting	Effect of Dapagliflozin on VT in Patients With Heart Failure.	November 15, 2022	Dapagliflozin	Placebo	120
ChiCTR2100052426	Pending	Impact of Dapagliflozin on the sympathetic activity in chronic heart failure with reduced ejection fraction: Rationale and design of the randomized, double-blind, palcebo controlled trial	November 1, 2021	Dapagliflozin	Placebo	120
NCT03877237	Completed	DETERMINE-reduced - Dapagliflozin Effect on Exercise Capacity Using a 6-minute Walk Test in Patients With Heart Failure With Reduced Ejection Fraction	April 9, 2019	Dapagliflozin	Placebo	313

3.9 Excluded trials after full-text screening

Note: Overall, 491 publications were excluded. Details on excluded references and reasons for exclusion are available in Appendix 1: Excluded studies and reasons for exclusion.

3.10 Limitations

Table 8 Limitations in the living systematic review process

Limitations	Description
Heterogenic outcomes	Outcome definitions (e.g. adverse events, serious adverse events, renal worsening, and hypotension) are different between studies. This complicates comparability
No grey literature included	To date, we did not search grey literature. This might lead to an unexplored publication bias

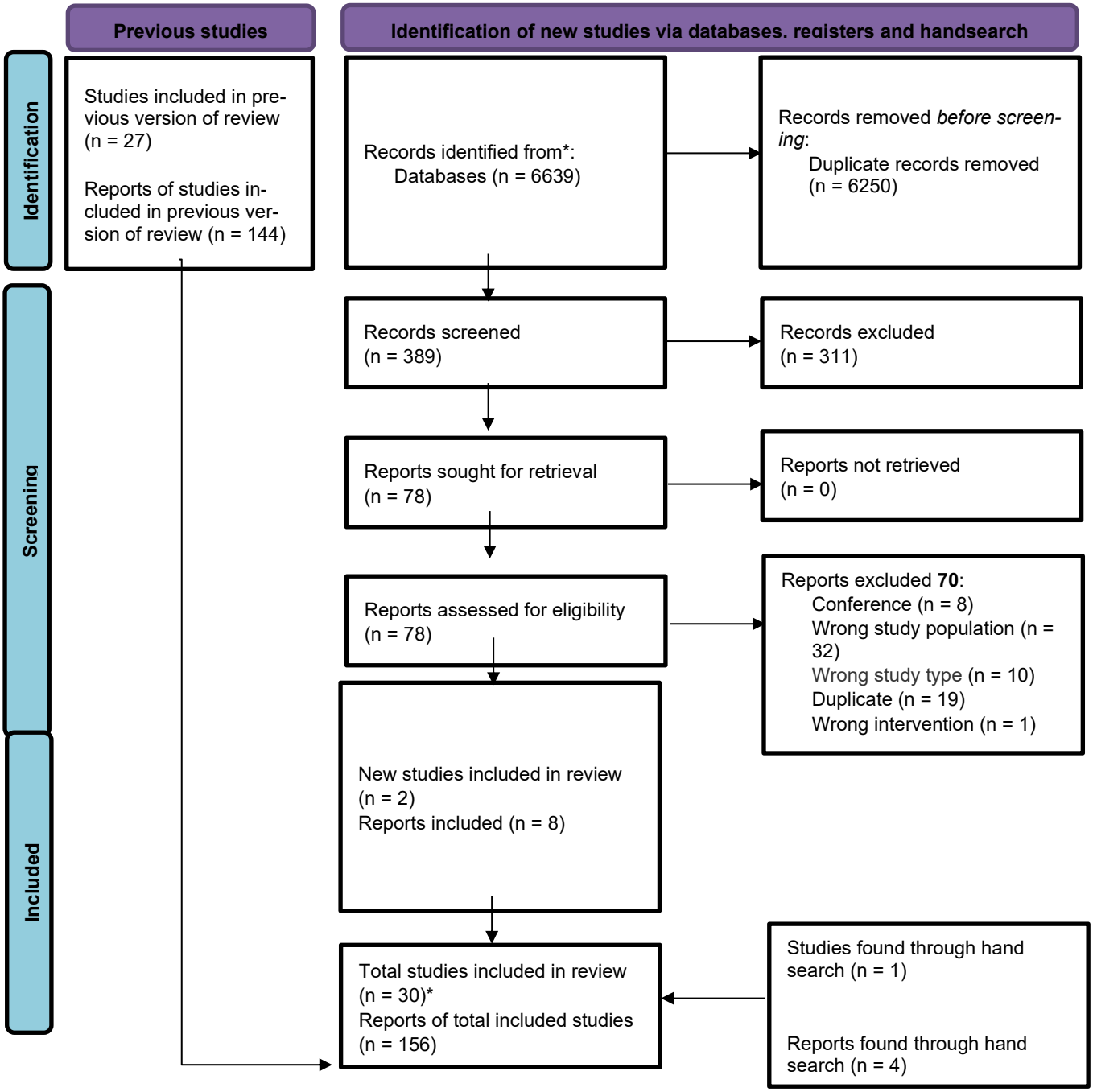
3.11 Protocol updates - list of changes

Table 9 Protocol updates – list of changes (compared to the original protocol: CRD42022311172)

Protocol changes (from Version 1 onwards)	Description/Justification
- Limitation on heart failure with reduced ejection fraction (HFrEF)	- Inclusion criteria to broad for the scope of the DEAL-Project
- Studies that focus next to HFrEF exclusively on any other co-morbidity (e.g. Diabetes) were excluded.	- Out of scope. Studies do not represent the general population with HFrEF

3.12 PRISMA

Figure 3 PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases



* The Empire-HF study accounted for three included studies (15, 27, 28). One study was identified as main study (15), the remaining two as sub-studies (27, 28). The sub-studies shared partly the same population as the main study and were not presented in the result section of this report.

3.13 Search strategy

Table 10a Search strategy for randomized controlled trials in MEDLINE (Ovid), searched 21.09.2022.

#	Searches
1	exp Heart Failure/
2	((heart or cardiac or myocardial or decompensated) adj2 failure).ti,ab,kf.
3	HFrEF.ti,ab,kf.
4	HFmrEF.ti,ab,kf.
5	HFpEF.ti,ab,kf.
6	or/1-5
7	LCZ 696.mp.
8	LCZ696.mp.
9	Entresto.mp.
10	(sacubitril adj2 valsartan).mp.
11	or/7-10
12	exp Sodium-Glucose Transporter 2 Inhibitors/
13	Sodium Glucose Transporter 2 Inhibitor$.mp.
14	Sodium-glucose cotransporter-2 inhibitor$.mp.
15	SGLT2i.mp.
16	SGLT2-I.mp.
17	SGLT 2 Inhibitor$.mp.
18	SGLT2 Inhibitor$.mp.
19	Gliflozin$.mp.
20	Canagliflozin$.mp.
21	dapagliflozin$.mp.
22	Empagliflozin$.mp.
23	Ertugliflozin$.mp.
24	Ipragliflozin$.mp.
25	Licogliflozin$.mp.
26	Remogliflozin Etabonate.mp.
27	Sergliflozin Etabonate.mp.
28	Sotagliflozin$.mp.
29	Tofogliflozin$.mp.
30	or/12-29
	n = 2808

Table 10b Search strategy for randomized controlled trials in CENTRAL (Cochrane Library), searched 21.09.2022.

#	Searches
1	MESH DESCRIPTOR Heart Failure EXPLODE ALL TREES
2	(((heart or cardiac or myocardial or decompensated) adj2 failure)):TI,AB,KY
3	HFrEF
4	HFmrEF
5	HFpEF
6	#1 OR #2 OR #3 OR #4 OR #5
7	LCZ 696
8	LCZ696
9	Entresto
10	(sacubitril adj2 valsartan)

#	Searches
11	#7 OR #8 OR #9 OR #10
12	MESH DESCRIPTOR Sodium-Glucose Transporter 2 Inhibitors EXPLODE ALL TREES
13	Sodium Glucose Transporter 2 Inhibitor*
14	Sodium-glucose cotransporter-2 inhibitor*
15	SGLT2i
16	SGLT2-I
17	SGLT 2 Inhibitor*
18	SGLT2 Inhibitor*
19	Gliflozin*
20	Canagliflozin*
21	dapagliflozin*
22	Empagliflozin*
23	Ertugliflozin*
24	Ipragliflozin*
25	Licogliflozin*
26	Remogliflozin Etabonate
27	Sergliflozin Etabonate
28	Sotagliflozin*
29	Tofogliflozin*
30	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
31	#6 AND #11
32	#6 AND #30
	n = 1509

Table 10c Search strategy for randomized controlled trials Web of Science, searched 21.09.2022.

#	Searches
	n = 2322
39	#31 AND #37
38	#30 AND #37
37	#35 OR #36
36	(TI=(medline OR medlars OR embase OR pubmed OR cochrane OR (scisearch OR psychinfo OR psycinfo) OR (psychlit OR psyclit) OR cinahl OR ((hand NEAR/2 search?) OR (manual? NEAR/2 search?)) OR ("electronic database*" OR "bibliographic database*" OR "computeri$ed database*" OR "online database*") OR (pooling OR pooled OR "mantel haenszel") OR (peto OR dersimonian OR "der simonian" OR "fixed effect")) OR AB=(medline OR medlars OR embase OR pubmed OR cochrane OR (scisearch OR psychinfo OR psycinfo) OR (psychlit OR psyclit) OR cinahl OR ((hand NEAR/2 search*) OR (manual* NEAR/2 search*)) OR ("electronic database*" OR "bibliographic database*" OR "computeri$ed database*" OR "online database*") OR (pooling OR pooled OR "mantel haenszel") OR (peto OR dersimonian OR "der simonian" OR "fixed effect"))) OR ALL=("retraction of publication" OR "retracted publication")
35	TI="Systematic Review" OR AB= "Systematic Review"
34	#31 AND #32
33	#30 AND #32
32	TS= (randomly OR randomised OR randomized OR "random allocat*" OR RCT OR CCT OR "double blind*" OR "single blind" OR trial)
31	#6 AND #29
30	#6 AND #10
29	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
28	ALL=(Sergliflozin Etabonate)
27	ALL=(Tofogliflozin*)
26	ALL=(Sotagliflozin*)
25	ALL=(Remogliflozin Etabonate)
24	ALL=(Licogliflozin*)
23	ALL=(Ipragliflozin*)
22	ALL=(Ertugliflozin*)
21	ALL=(Empagliflozin*)
20	ALL=(dapagliflozin*)
19	ALL=(Canagliflozin*)

#	Searches
18	ALL=(Gliflozin*)
17	ALL="SGLT2 Inhibitor*"
16	ALL="SGLT 2 Inhibitor*"
15	ALL=SGLT2-I
14	ALL=SGLT2i
13	ALL="Sodium-glucose cotransporter-2 inhibitor*"
12	ALL="Sodium Glucose Transporter 2 Inhibitor*"
11	#7 OR #8 OR #9 OR #10
10	TS=(sacubitril NEAR/2 valsartan)
9	ALL=Entresto
8	ALL=LCZ696
7	ALL="LCZ 696"
6	#1 OR #2 OR #3 OR #4 OR #5
5	TS=HFpEF
4	TS=HFmrEF
3	TS=HFrEF
2	TS=((heart OR cardiac OR myocardial OR decompensated) NEAR/2 failure)
1	TS=("Heart Failure")

3.14 Abbreviations

6MWT	6 minutes walking test
C	Control
eGFR	Estimated Glomerular Filtration Rate
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
I	Intervention
LVEF	Left ventricular ejection fraction
MD	Mean difference
NR	Not reported
NT-pro BNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association (NYHA) Functional Classification
Peak VO2	peak oxygen consumption
RR	Relative risk or risk ratio
SGLT2-I	Sodium-glucose Cotransporter-2 inhibitors
SMD	Standardized mean difference

Included studies

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26. Kolwelter J, Bosch A, Jung S, Stabel L, Kannenkeril D, Ott C, et al. Effects of the sodium-glucose cotransporter 2 inhibitor empagliflozin on vascular function in patients with chronic heart failure. ESC Heart Failure. 2021.

27. Omar M, Jensen J, Frederiksen PH, Kistorp C, Videbæk L, Poulsen MK, et al. Effect of Empagliflozin on Hemodynamics in Patients With Heart Failure and Reduced Ejection Fraction. J Am Coll Cardiol. 2020;76(23):2740-51.

28. Jensen J, Omar M, Kistorp C, Tuxen C, Gustafsson I, Køber L, et al. Effects of empagliflozin on estimated extracellular volume, estimated plasma volume, and measured glomerular filtration rate in patients with heart failure (Empire HF Renal): a prespecified substudy of a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2021;9(2):106-16.

29. Hao Z, Zhang Y. Comparison of 10 mg and 25 mg of Empagliflozin in Patients With Heart Failure With Reduced Ejection Fraction. Can J Cardiol. 2022;38(10):1641-2.

30. Hao Z, Zhang Y. Different Doses of Empagliflozin in Patients with Heart Failure with Reduced Ejection Fraction. Int Heart J. 2022;63(5):852-6.

Note: All primary and secondary publications of included studies are available in Appendix 2: Included studies

3.15 Appendix 1: Excluded studies and reasons for exclusion

3.15.1 Version 1 (Basis Review)

1. Long-term maintenance of efficacy of dapagliflozin in patients with type 2 diabetes mellitus and cardiovascular disease. Diabetes, Obesity and Metabolism 2016, 18(8) Exclusion reason: Wrong study type.
2. Empagliflozin reduces mortality and hospitalisation for heart failure irrespective of cardiovascular risk score at baseline. European Heart Journal 2018, 39 Exclusion reason: Conference
3. Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure. Circulation 2019 Exclusion reason: Wrong study type.
4. Impact of sacubitril-valsartan compared to angiotensin inhibition on ventricular tachycardia burden in heart failure patients with reduced ejection fraction and implantable defibrillator. European Journal of Heart Failure 2019, 21 Exclusion reason: Conference.
5. Clinical predictors of NT-proBNP response to early initiation of sacubitril/valsartan after hospitalisation for decompensated heart failure: An analysis of the TRANSITION study. European Heart Journal 2019, 40 Exclusion reason: Conference.
6. Short-term changes in albuminuria and risk of cardiovascular outcomes in type 2 diabetes: A post hoc analysis of the EMPA-REG outcome trial. Journal of the American Society of Nephrology 2019, 30 Exclusion reason: Wrong study population.
7. HEART FAILURE OUTCOMES IN PATIENTS WITH DIABETES WITH AND WITHOUT ATRIAL FIBRILLATION - DATA FROM THE EMPA-REG OUTCOME STUDY. Canadian Journal of Cardiology 2019, 35(10) Exclusion reason: Wrong study population.
8. Heart Failure Outcomes in Patients with Diabetes With and Without Atrial Fibrillation â?? Data From the EMPA-REG OUTCOME Study. Heart Lung and Circulation 2019, 28 Exclusion reason: Wrong study population.
9. Effects of SGLT2 inhibitors in type 2 diabetes, comparing women to men. Diabetes, obesity & metabolism 2019 Exclusion reason: Wrong study type.
10. Effect of dapagliflozin on cardiovascular outcomes in patients with type 2 diabetes according to baseline renal function and albuminuria status: Insights from DECLARE-TIMI 58. European Heart Journal 2019, 40 Exclusion reason: Wrong study population.
11. Consistent cardiovascular (CV) benefits from empagliflozin across the spectrum of CV risk factor control: Post hoc analysis from EMPA-REG OUTCOME. Diabetes 2019, 68 Exclusion reason: Wrong study population.
12. EFFECT OF SACUBITRIL/VALSARTAN VS. ENALAPRIL ON CHANGES IN BACKGROUND MEDICAL THERAPY OVER TIME IN THE PARADIGM-HF TRIAL. Journal of the American College of Cardiology 2020, 75(11) Exclusion reason: Conference.
13. Does sacubitril-valsartan have an antiarrhythmic or a pro-arrhythmic effect in patients with heart failure? Kardiologicka Revue 2020, 22(2) Exclusion reason: Wrong study type.
14. Angiotensin-Neprilysin Inhibition and Renal Outcomes in Heart Failure. Circulation 2020, 142(SUPPL 3) Exclusion reason: Conference.
15. Tissue Sodium Content Increases with Severity of Chronic Heart Failure. Circulation 2020, 142(SUPPL 3) Exclusion reason: Conference.
16. EMPEROR-Reduced trial. SGLT-2 inhibitor empagliflozin is also effective in heart failure. Krankenhauspharmazie 2020, 41(12) Exclusion reason: Wrong study type.
17. Effects of Dapagliflozin on Physical and Social Activity Limitations in Patients with Heart Failure and Reduced Ejection Fraction: An Analysis of DAPA-HF. Circulation 2020, 142(SUPPL 3)Exclusion reason: Conference.
18. The effect of dapagliflozin across the spectrum of baseline risk: A post-hoc analysis of DAPA-HF. European Heart Journal 2020, 41(SUPPL 2) Exclusion reason: Conference.
19. Consistent cardiovascular (CV) benefit of empagliflozin over the spectrum of CV risk factor control in EMPA-REG OUTCOME. Metabolism: Clinical and Experimental 2020, 104Exclusion reason: Conference.
20. THE ASSOCIATION BETWEEN POLYVASCULAR DISEASE AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES: A SUB-ANALYSIS OF EMPA-REG OUTCOME. Journal of the American College of Cardiology 2020, 75(11) Exclusion reason: Wrong study population.
21. APPLICATION OF THE TIMI HEART FAILURE RISK SCORE TO THE EMPA-REG OUTCOME POPULATION. Journal of the American College of Cardiology 2020, 75(11) Exclusion reason: Conference.
22. The Dapagliflozin And Prevention of Adverse outcomes in Heart Failure trial (DAPA-HF) in context. European heart journal 2020Exclusion reason: Wrong study type.
23. Erratum: Effect of Empagliflozin as an Add-On Therapy on Decongestion and Renal Function in Patients with Diabetes Hospitalized for Acute Decompensated Heart Failure: A Prospective Randomized Controlled Study (Circ Heart Fail. (2021) 14 (e007048) DOI: 10. Circulation: Heart Failure 2021Exclusion reason: Wrong study population.
24. Renal and cardiovascular effects of SGLT2inhibition in combination with loopdiuretics in patients with type 2 diabetesand chronic heart failure: The RECEDECHF trial. Scottish Medical Journal 2021, 66(2) Exclusion reason: Conference.
25. Abraham W, Anker S, Salsali A, Peil B, Zeller C, Brun M et al: Design of the effect of empaglifozin on exercise ability and HF-symptoms, in patients with chronic he art failure (EMPERIAL) trials of empagliflozin in patients with chronic heart failure with reduced or preserved ejection fraction. Diabetologie und Stoffwechsel 2019, 14 Exclusion reason: Conference.
26. Ademi Z, Pfeil AM, Hancock E, Trueman D, Haroun RH, Deschaseaux C et al: Cost-effectiveness of sacubitril/valsartan in chronic heart-failure patients with reduced ejection fraction. Swiss medical weekly 2017, 147 Exclusion reason: Wrong study type.
27. Ambrosy A, Braunwald E, Morrow D, Devore A, McCague K, Duffy C et al: Angiotensin receptor-neprilysin inhibition in patients with De novo acute decompensated heart failure: A prespecified subgroup analysis of the PIONEER-HF trial. European Heart Journal 2019, 40 Exclusion reason: Conference.
28. Ambrosy AP, Braunwald E, Morrow DA, DeVore AD, McCague K, Meng XY et al: Angiotensin Receptor-Neprilysin Inhibition Based on History of Heart Failure and Use of Renin-Angiotensin System Antagonists. Journal of the American College of Cardiology 2020, 76(9) Exclusion reason: Wrong study population.
29. Ambrosy AP, DeVore A, Morrow D, Braunwald E, Duffy C, McCague K et al: PRIOR EXPOSURE TO A CONVENTIONAL RENIN-ANGIOTENSIN SYSTEM ANTAGONIST AND ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITION IN ACUTE DECOMPENSATED HEART FAILURE: A PRESPECIFIED SUBGROUP ANALYSIS OF THE PIONEER-HF TRIAL. Journal of the American College of Cardiology 2019, 73(9) Exclusion reason: Conference.
30. Angermann CE, Santos-Gallego CG, Requena-Ibanez JA, Sehner S, Zeller T, Maack C et al: Effects of Empagliflozin on Iron Metabolism in Non-Diabetic Patients With Heart Failure. Substudy of the EMPATROPISM Randomized Trial. Circulation 2021, 144(25) Exclusion reason: Conference.
31. Anker S, Zannad F, Butler J, Filippatos G, Salsali A, Kimura K et al: Design and rationale of the EMPEROR trials of, empagliflozin 10 mg once daily, in patients with chronic heart failure with reduced ejection fraction (EMPEROR-Reduced) or preserved ejection fraction (EMPEROR-Preserved). Diabetologie und Stoffwechsel 2019, 14 Exclusion reason: Conference.
32. Anker SD: Empagliflozin in Heart Failure With a Preserved Ejection Fraction >= 50% - Results From the EMPEROR-Preserved Clinical Trial. Circulation 2021, 144(25) Exclusion reason: Conference.
33. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M et al: Empagliflozin in Heart Failure with a Preserved Ejection Fraction. New England Journal of Medicine 2021, 385(16):1451-1461Exclusion reason: Wrong study population;:
34. Anker SD, Ponikowski P, Wanner C, Pfarr E, Hauske S, Peil B et al: Kidney Function After Initiation And Discontinuation Of Empagliflozin (EMPA) In Heart Failure (HF) Patients (Pts) With And Without Type 2 Diabetes (T2D): Insights From The Emperial Trials. Journal of Cardiac Failure 2020, 26(12) Exclusion reason: Conference.
35. Autoren Anker SD, Butler J, Filippatos GS, Marx N, Schnaidt SY, Ofstad AP et al: Effect of empagliflozin on cardiovascular and kidney outcomes in patients with heart failure by baseline diabetes status-results from the EMPEROR-reduced trial. Diabetologie und Stoffwechsel 2021, 16(SUPPL 1) Exclusion reason: Conference.
36. Autoren Zannad F, Butler J, Filippatos GS, Pocock S, Jamal W, Schnee J et al: Cardiovascular and kidney outcomes with empagliflozin in heart failure. Diabetologie und Stoffwechsel 2021, 16(SUPPL 1) Exclusion reason: Conference.
37. Aziz MIA, Wu D-C, Ng K, Lin L: Cost-effectiveness of sacubitril/valsartan in heart failure. International Journal of Technology Assessment in Health Care Conference: 14th Annual Meeting of the Health Technology Assessment International, HTAi 2017 Italy 2017, 33(Supplement 1)Exclusion reason: Conference.
38. Bates ER: In HFpEF, adding empagliflozin to usual care reduced a composite of CV death or HF hospitalization at a median 26 mo. Annals of Internal Medicine 2022, 175(1) Exclusion reason: Wrong study type.
39. Benjamin Munoz Calvo B, Ganan-Gomez C, Quiles-Recuenco A, Calvo-Llorente B, Mendo-Pedrajas I, Navarro-Lopez J et al: Sacubitril-valsartan treatment furtherly improves response to intermittent parenteral levosimendan in ambulatory patients with advanced heart failure with reduced ejection fraction. European Journal of Heart Failure 2019, 21Exclusion reason: Conference.
40. Berardi C, Braunwald E, Morrow DA, Mulder HS, Duffy CI, O'Brien TX et al: Angiotensin-Neprilysin Inhibition in Black Americans: Data From the PIONEER-HF Trial. JACC Heart failure 2020, 8(10) Exclusion reason: Wrong study population; Philipp Kapp (2022-05-03 20:36:37)(Select): PIONEER-HF.

41. Berg DD, Braunwald E, DeVore AD, Lala A, Pinney SP, Duffy CI et al: Efficacy and Safety of Sacubitril/Valsartan by Dose Level Achieved in the PIONEER-HF Trial. JACC Heart failure 2020, 8(10) Exclusion reason: Wrong study population.
42. Berg DD, Samsky MD, Velazquez EJ, Duffy CI, Gurmu Y, Braunwald E et al: Efficacy and Safety of Sacubitril/Valsartan in High-Risk Patients in the PIONEER-HF Trial. Circulation Heart failure 2021, 14(2) Exclusion reason: Wrong study population.
43. Berg DD, Velazquez EJ, Duffy CI, Gurmu Y, Braunwald E, Morrow DA: Efficacy and safety of sacubitril/valsartan in acute decompensated heart failure in high-risk patients in the pioneer-hf trial. Circulation 2019, 140 Exclusion reason: Conference.
44. Beusekamp JC, Tromp J, Boorsma EM, Heerspink HJL, Damman K, Voors AA et al: Effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on potassium handling in patients with acute heart failure. European Journal of Heart Failure 2021, 23(6) Exclusion reason: Wrong study population.
45. Bhatt AS, Claggett BL, Packer M, Lefkowitz MP, Zile MR, McMurray JJV et al: Treatment Effects of Sacubitril/Valsartan Compared With Valsartan by Ejection Fraction in Patients With Recent Hospitalization. Journal of Cardiac Failure 2021, 27(9) Exclusion reason: Wrong study population.
46. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK et al: Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. The New England journal of medicine 2021, 384(2) Exclusion reason: Wrong study population.
47. Biering-Sorensen T SACBZMPBP-KEVASVLMPMMJJV: The angiotensin receptor neprilysin inhibitor (arni), sacubitril/valsartan, improves left ventricular myocardial deformation in heart failure with preserved ejection fraction (paramount trial). Journal of the American College of Cardiology 2018, 71(11)E xclusion reason: Conference.
48. Bohm M, Refsgaard J, Ramires FJA, Rouleau JL, Solomon SD, Swedberg K et al: Effect of the angiotensin receptor neprilysin inhibitor LCZ696 compared with enalapril according to systolic blood pressure in PARADIGM-HF NOVARTIS Pharmaceuticals. European journal of heart failure 2015, 17 Exclusion reason: Conference.
49. Bohm M, Slawik J, Brueckmann M, Mattheus M, George JT, Ofstad AP et al: Efficacy of empagliflozin on heart failure and renal outcomes in patients with atrial fibrillation: data from the EMPA-REG OUTCOME trial. European Journal of Heart Failure 2019 Exclusion reason: Wrong study population.
50. Bonora BM, Vigili de Kreutzenberg S, Avogaro A, Fadini GP: Effects of the SGLT2 inhibitor dapagliflozin on cardiac function evaluated by impedance cardiography in patients with type 2 diabetes. Secondary analysis of a randomized placebo-controlled trial. Cardiovascular diabetology 2019, 18(1) Exclusion reason: Wrong study population.
51. Bonura R, Alabrese R, Simone G, De Rosa F, Demola PL, Garibaldi S et al: Sacubitril/valsartan in advanced heart failure: Is it a just matter of contractility or are there effects on pulmonary circulation.monocentric experience fromreal life. European Heart Journal, Supplement 2019, 21(SUPPL J) Exclusion reason: Wrong study type.
52. Bonura R, Alabrese R, Simone G, De Rosa F, Luigi Demola P, Garibaldi S et al: Sacubitril/valsartan in advanced heart failure: Is it a just matter of contractility or are there effects on pulmonary circulation.monocentric experience from real life. Giornale Italiano di Cardiologia 2019, 20(12) Exclusion reason: Wrong study type.
53. Boorsma EM, Beusekamp JC, Ter Maaten JM, Figarska SM, Danser AHJ, van Veldhuisen DJ et al: Effects of empagliflozin on renal sodium and glucose handling in patients with acute heart failure. European journal of heart failure 2021, 23(1) Exclusion reason: Wrong study population.
54. Briasoulis A, Kuno T, Ueyama H: Efficacy of Sacubitril-Valsartan in Patients With Reduced Left Ventricular Ejection Fraction. American Journal of Cardiology 2021, 153Exclusion reason: Conference.
55. Brown A, Gandy S, McCrimmon R, Struthers A, Lang CC: A randomised controlled trial of dapagliflozin on left ventricular hypertrophy in patients with type two diabetes. the dapa-lvh trial. Circulation 2019, 140 Exclusion reason: Conference.
56. Brown AJM, Gandy S, McCrimmon R, Struthers A, Lang C: Dapagliflozin improves left ventricular myocardial longitudinal function in people with type 2 diabetes. European Heart Journal 2020, 41(SUPPL 2) Exclusion reason: Wrong study population.
57. Burgdorf C, Brockmoller J, Strampe H, Januszewski M, Remppis BA: Reduction of Pulmonary Hypertension After Transition to Sacubitril/Valsartan in Patients With Heart Failure With Preserved Ejection Fraction. Frontiers in Cardiovascular Medicine 2021, 8 Exclusion reason: Wrong study type.
58. Butler J: Empagliflozin, Health Status, and Quality of Life in Patients With Heart Failure and Preserved Ejection: The EMPEROR-Preserved Trial. Circulation 2021, 144(25) Exclusion reason: Conference.
59. Butler J, Filippatos G, Jamal Siddiqi T, Brueckmann M, Bohm M, Chopra VK et al: Empagliflozin, Health Status, and Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial. Circulation 2022, 145(3) Exclusion reason: Wrong study population.
60. Butler J PMFGZFSAKKSJZCPSGJBMASD: Design and rationale of the EMPagliflozin outcomE tRial in patients with chrOnic heaRt failure (EMPEROR-Preserved). European journal of heart failure 2018, 20 Exclusion reason: Conference.
61. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U et al: Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. The New England journal of medicine 2020, 383(15) Exclusion reason: Wrong study population.
62. Cannon J, Boytsov S, Senni M, Rouleau JL, Solomon SD, Swedberg K et al: Dementia-related adverse effects in the prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). European journal of heart failure 2015, 17 Exclusion reason: Conference.
63. Carbone S, Billingsley HE, Canada JM, Bressi E, Rotelli B, Kadariya D et al: The effects of canagliflozin compared to sitagliptin on cardiorespiratory fitness in type 2 diabetes mellitus and heart failure with reduced ejection fraction: TheCANA-HFstudy. Diabetes-Metabolism Research and Reviews 2020, 36(8) Exclusion reason: Wrong study population.
64. Chanchal Chandramouli C, Asali S, Kassim S, Hussein Z, Chopra V, Li J et al: Asian diabetes outcome prevention trial (ADOPT). European Journal of Heart Failure 2019, 21 Exclusion reason: Conference.
65. Chandra A, Vaduganathan M, Lewis EF, Claggett BL, Rizkala AR, Wang W et al: Health-Related Quality of Life in HeartÂ Failure With Preserved EjectionÂ Fraction: The PARAGON-HF Trial. JACC Heart failure 2019Exclusion reason: Duplicate.
66. Chandra A, Vaduganathan M, Lewis EF, Claggett BL, Rizkala AR, Wang WY et al: Health-Related Quality of Life in Heart Failure With Preserved Ejection Fraction The PARAGON-HF Trial. Jacc-Heart Failure 2019, 7(10) Exclusion reason: Wrong study population.
67. Chen C, Wu X, Li Y, Peng Y: Study on the application effect of bisoprolol combined with sacubitril valsartan sodium tablets in the cardiac rehabilitation of patients with acute myocardial infarction combined with left heart failure after percutaneous coronary intervention (PCI). Annals of Palliative Medicine 2021, 10(5) Exclusion reason: Wrong study type.
68. Chen CH, Ramparsad NT, Greenlaw N, Jhund PS, Shi VC, Rouleau JL et al: Pulse pressure and outcomes in heart failure with reduced ejection fraction: Insights from PARADIGM-HF. European Heart Journal 2016, 37 Exclusion reason: Conference.
69. Cheung DG, Aizenberg D, Gorbunov V, Hafeez K, Chen CW, Zhang J: Efficacy and safety of sacubitril/valsartan in patients with essential hypertension uncontrolled by olmesartan: A randomized, double-blind, 8-week study. Journal of Clinical Hypertension 2018, 20(1) Exclusion reason: Wrong study population.
70. Colombo G, Casella R, Cazzaniga A, Casiraghi C, Gruppo di Autoformazione M: Dapagliflozin in patients with heart failure and reduced ejection fraction. Internal & Emergency Medicine 2020, 15(3) Exclusion reason: Wrong study type.
71. Corentin Curinier C SKDAMCSCFDASSVABCRCFPMG: Evaluation of the sST2-guided optimization of medical treatments of patients admitted for HF, to prevent readmission: The STADE-HF study. European journal of heart failure 2017, 19 Exclusion reason: Conference.
72. Costanzo MR: Similar Yet Different: Examining the Effects of Sacubitril/Valsartan by Race in the PIONEER-HF Trial. JACC Heart Failure 2020, 8(10) Exclusion reason: Wrong study type.
73. Cowan L, Adamson C, Docherty K, Inzucchi S, Koeber L, Kosiborod M et al: Elevated markers of liver function are associated with poorer outcomes in HFREF: An analysis of DAPA-HF. European Heart Journal 2021, 42(SUPPL 1) Exclusion reason: Conference.
74. Cunningham JW, Claggett BL, O'Meara E, Prescott MF, Pfeffer MA, Shah SJ et al: Effect of Sacubitril/Valsartan on Biomarkers of Extracellular Matrix Regulation in Patients With HFpEF. Journal of the American College of Cardiology 2020, 76(5) Exclusion reason: Wrong study population.
75. Cunningham JW, Vaduganathan M, Claggett BL, Zile MR, Anand IS, Packer M et al: Effects of Sacubitril/Valsartan on N-Terminal Pro-B-Type Natriuretic Peptide in Heart Failure With Preserved Ejection Fraction. JACC Heart failure 2020, 8(5) Exclusion reason: Wrong study population.
76. Damman K, Andersen K, Belohlavek J, Lefkowitz MP, Rouleau JL, Solomon SD et al: Angiotensin receptor neprilysin inhibition and renal function and in heart failure: Results from PARADIGM-HF. European heart journal 2015, 36 Exclusion reason: Conference.
77. Damman K, Beusekamp JC, Boorsma EM, Swart HP, Smilde TDJ, Elvan A et al: Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). European journal of heart failure 2020, 22(4) Exclusion reason: Wrong study population.
78. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP et al: Renal Effects and Associated Outcomes During Angiotensin-Neprilysin Inhibition in Heart Failure. JACC: Heart Failure 2018, (no pagination) Exclusion reason: Duplicate..
79. de Boer RA, Núñez J, Kozlovski P, Wang Y, Proot P, Keefe D: Effects of the dual sodium-glucose linked transporter inhibitor, licogliflozin vs placebo or empagliflozin in patients with type 2 diabetes and heart failure. British journal of clinical pharmacology 2020, 86(7) Exclusion reason: Wrong study population.
80. Desai AS, Claggett B, McMurray JJV, Packer M, Rouleau J, Swedberg K et al: Factors associated with dropout during the run-in period prior to randomization in PARADIGM-HF. European heart journal 2015, 36Exclusion reason: Conference.
81. Desai AS, Cleland J, Vaduganathan M, Claggett B, Barkoudah E, Finn PV et al: MODE OF DEATH IN PATIENTS WITH HEART FAILURE AND LEFT VENTRICULAR EJECTION FRACTIONâ?¥45%: INSIGHTS FROM PARAGON-HF. Journal of the American College of Cardiology 2020, 75(11) Exclusion reason: Conference.

82. Desai AS, Shah AM, Mitchell GF, Claggett BL, Fang JC, Abbas CA et al: Effects of sacubitril-valsartan compared with enalapril on pulmonary artery pressure in patients with heart failure and reduced ejection fraction. Circulation 2019, 140 Exclusion reason: Conference.
83. Desai AS, Solomon SD, Shah AM, Claggett BL, Fang JC, Izzo J et al: Effects of Sacubitril-valsartan Compared with Enalapril on Arterial Hemodynamics, Cardiac Remodeling, and Quality of Life in Patients with Heart Failure and Reduced Ejection Fraction. Journal of Cardiac Failure 2019, 25(11) Exclusion reason: Conference.
84. Desai AS, Vaduganathan M, Cleland JG, Claggett BL, Barkoudah E, Finn P et al: Mode of Death in Patients With Heart Failure and Preserved Ejection Fraction: Insights From PARAGON-HF Trial. Circulation: Heart Failure 2021, 14(12) Exclusion reason: Wrong study population.
85. DeVore A, Morrow D, Braunwald E, Duffy CI, Ambrosy AP, McCague K et al: EFFECT OF SACUBITRIL/VALSARTAN INITIATION ON 30-DAY READMISSIONS AFTER A HOSPITALIZATION FOR ACUTE DECOMPENSATED HEART FAILURE: A SECONDARY ANALYSIS OF THE PIONEER-HF TRIAL. Journal of the American College of Cardiology 2019, 73(9) Exclusion reason: Conference.
86. DeVore A, Morrow D, Braunwald E, Duffy CI, Ambrosy AP, McCague K et al: EFFECT OF SACUBITRIL/VALSARTAN INITIATION ON 300-DAY READMISSIONS AFTER A HOSPITALIZATION FOR ACUTE DECOMPENSATED HEART FAILURE: A SECONDARY ANALYSIS OF THE PIONEER-HF TRIAL. Journal of the American College of Cardiology 2019, 73(9) Exclusion reason: Conference.
87. DeVore AD, Braunwald E, Morrow DA, Duffy CI, Ambrosy AP, Chakraborty H et al: Initiation of Angiotensin-Neprilysin Inhibition After Acute Decompensated Heart Failure: Secondary Analysis of the Open-label Extension of the PIONEER-HF Trial. JAMA cardiology 2020, 5(2) Exclusion reason: Wrong study type; Philipp Kapp (2022-04-08 22:11:35)(Select): open label extension.
88. Dewan P, Jhund PS, Bengtsson O, Demets DL, Inzucchi SE, Kober L et al: The effect of dapagliflozin in patients with HFrEF and COPD: A post-hoc analysis of DAPA-HF. European Heart Journal 2020, 41(SUPPL 2) Exclusion reason: Conference.
89. Dixon DL, Billingsley HE, Canada JM, Trankle C, Kadariya D, Cooke R et al: Effect of Canagliflozin Compared to Sitagliptin on Serum Lipids in Patients with Type 2 Diabetes Mellitus and Heart Failure with Reduced Ejection Fraction. Journal of cardiovascular pharmacology 2021 Exclusion reason: Wrong study population.
90. Dixon DL, Billingsley HE, Canada JM, Trankle CR, Kadariya D, Cooke R et al: Effect of Canagliflozin Compared With Sitagliptin on Serum Lipids in Patients with Type 2 Diabetes Mellitus and Heart Failure with Reduced Ejection Fraction: A Post-Hoc Analysis of the CANA-HF Study. Journal of Cardiovascular Pharmacology 2021, 78(3) Exclusion reason: Wrong study population.
91. Docherty K, Inzucchi SE, Kober L, Kosiborod M, Langkilde AM, Martinez F et al: The Effect of Dapagliflozin on Anemia in Patients with Heart Failure and Reduced Ejection Fraction: An Analysis of DAPA-HF. Circulation 2020, 142(SUPPL 3) Exclusion reason: Conference.
92. Docherty K, Inzucchi SE, Kosiborod MN, Kober L, Langkilde AM, Martinez F et al: Does Background T2D Therapy Modify the Benefits of Dapagliflozin in Heart Failure? Analysis of the DAPA-HF Trial. Diabetes 2020, 69 Exclusion reason: Conference.
93. Docherty K, Jackson A, Inzucchi SE, Jhund P, Kober L, Kosiborod M et al: CONSISTENT BENEFIT OF DAPAGLIFLOZIN ACCORDING TO BACKGROUND THERAPY IN PATIENTS WITH HFREF: AN ANALYSIS OF THE DAPA-HF TRIAL. Journal of the American College of Cardiology 2020, 75(11) Exclusion reason: Conference.
94. Docherty KF, Campbell RT, Brooksbank KJM, Dreisbach JG, Forsyth P, Godeseth RL et al: Effect of Neprilysin Inhibition on Left Ventricular Remodeling in Patients With Asymptomatic Left Ventricular Systolic Dysfunction Late After Myocardial Infarction. Circulation 2021, 144(3) Exclusion reason: Wrong study population.
95. Docherty KF, Campbell RT, Brooksbank KJM, Dreisbach JG, Forsyth P, Godeseth RL et al: The Effect of Neprilysin Inhibition on Left Ventricular Remodeling in Patients with Asymptomatic Left Ventricular Systolic Dysfunction Late After Myocardial Infarction. Circulation 2021 Exclusion reason: Duplicate.
96. Docherty KF, Campbell RT, Brooksbank KJM, Godeseth RL, Forsyth P, McConnachie A et al: A Randomized Trial Comparing The Effect Of Sacubitril/Valsartan To Valsartan On Left Ventricular Remodeling In Patients With Asymptomatic Left Ventricular Systolic Dysfunction After Myocardial Infarction. Journal of Cardiac Failure 2020, 26(12) Exclusion reason: Wrong study population.
97. Docherty KF, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, Bengtsson O et al: Efficacy and safety of dapagliflozin in black, compared to white, patients with heart failure with reduced ejection fraction: Results from DAPA-HF. European Journal of Heart Failure 2021, 23(SUPPL 2) Exclusion reason: Conference.
98. Docherty KF, Vaduganathan M, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA et al: Acute changes in estimated glomerular filtration rate following initiation of dapagliflozin in patients with heart failure and reduced ejection fraction: Insights from DAPA-HF. European Journal of Heart Failure 2021, 23(SUPPL 2) Exclusion reason: Conference.
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3.15.2 Version 2 (Review Update 1)

1. Erratum: correction to: renal and Cardiovascular Effects of SGLT2 Inhibition in Combination with Loop Diuretics in Patients with Type 2 Diabetes and Chronic Heart Failure: the RECEDE-CHF Trial (Circulation (2020) 142 (1713-1724) DOI: 10.1161/CIRCULATIONAH. Circulation 2020 Exclusion reason: Wrong study type.
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91. Pascual-Figal D, Bao W, Senni M, Wachter R, Behlolavek J, Chakrabarti A et al: Clinical predictors of NT-proBNP response to early initiation of sacubitril/valsartan after hospitalisation for decompensated heart failure: An analysis of the TRANSITION study. European Heart Journal 2019, 40 Exclusion reason: Conference.
92. Pascual-Figal D, Witte KK, Wachter R, Belohlavek J, Straburzynska-Migaj E, Fonseca C et al: Rehospitalisations during 26 weeks of follow up from initiation of sacubitril/valsartan after acute decompensated heart failure: an analysis of the TRANSITION study. European heart journal 2019, 40 Exclusion reason: Conference.
93. Pathak P: Angiotensin Receptor-Neprilysin Inhibitor in Acute Myocardial Infarction. Journal of the Association of Physicians of India 2022, 70(4) Exclusion reason: Conference.
94. Peikert A, Vaduganathan M, Mc Causland F, Claggett BL, Chatur S, Packer M et al: Effects of sacubitril/valsartan versus valsartan on renal function in patients with and without diabetes and heart failure with preserved ejection fraction: insights from PARAGON-HF. European Journal of Heart Failure Exclusion reason: Duplicate.
95. Peikert A, Vaduganathan M, McCausland F, Claggett B, Chatur S, Packer M et al: EFFECTS OF SACUBITRIL/VALSARTAN VERSUS VALSARTAN ON RENAL FUNCTION IN PATIENTS WITH TYPE 2 DIABETES AND HEART FAILURE WITH PRESERVED EJECTION FRACTION: PARAGON-HF. Journal of the American College of Cardiology 2022, 79(9) Exclusion reason: Conference.
96. Sakai T, Miura S: Effect of sodium-glucose cotransporter 2 inhibitor on vascular endothelial function and diastolic function in patients with heart failure with preserved ejection fraction (hfpef). Circulation 2017, 136 Exclusion reason: Conference.
97. Sayeed S, Fudim M, Xu H, Matsouaka R, Heidenreich PA, Yancy CW et al: Representativeness of the PIONEER-HF Clinical Trial Population in Patients Hospitalized with Heart Failure. Journal of cardiac failure 2019, 25(8) Exclusion reason: Conference.
98. Senni M, McMurray JJV, Anand I, Charney A, Sarkar A, Shi V: Target dose of sacubritil/varsartan achieved in most patients with hfref irrespective of baseline sbp. Journal of cardiac failure 2016, 22 Exclusion reason: Conference.
99. Singh JSS, Mordi I, Mohan M, Gandy SJ, Pearson E, Houston JG et al: Research into the effect of sodium-glucose linked transporter 2 inhibition on left ventricular remodeling in patients with heart failure and diabetes mellitus. Diabetes 2018, 67 Exclusion reason: Conference.
100. Slawson DC: No Improved Patient-Oriented Outcomes With Sacubitril/Valsartan in Adults With Heart Failure and Preserved Ejection Fraction. American Family Physician 2022, 105(6) Exclusion reason: Wrong study type.
101. Solomon SD, Vaduganathan M, Claggett BL, de Boer RA, DeMets D, Hernandez AF et al: Baseline Characteristics of Patients With HF With Mildly Reduced and Preserved Ejection Fraction: DELIVER Trial. JACC Heart failure 2022, 10(3) Exclusion reason: Wrong study population.
102. Spertus JA, Birmingham MC, Nassif M, Damaraju CV, Abbate A, Butler J et al: The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. Nature medicine 2022, 28(4) Exclusion reason: Wrong study population.
103. Straburzynska-Migaj E, Senni M, Wachter R, Belohlavek J, Fonseca C, Witte K et al: Initiation of sacubitril/valsartan in patients with renal impairment early after acute decompensated heart failure in the TRANSITION study. European journal of heart failure 2021, 23(SUPPL 2) Exclusion reason: Conference.
104. Tamura H, Kondo Y, Ito K, Hasebe M, Satoh S, Terauchi Y: Comparison of the effects of empagliflozin and glimepiride on endothelial function in patients with type 2 diabetes: a randomized controlled study. PloS one 2022, 17(2) Exclusion reason: Wrong study population.
105. Tanaka A, Imai T, Suzuki M, Hiramitsu S, Takahashi N, Kadokami T et al: Mediators of the effects of canagliflozin on N-terminal pro-brain natriuretic peptide concentration: An exploratory mediation analysis of the randomized CANDLE trial. Diabetes Obesity & Metabolism 2022, 24(5) Exclusion reason: Wrong study population.
106. Thiele K, Rau M, Hartmann NK, Moller M, Mollmann J, Jankowski J et al: Empagliflozin reduces markers of acute kidney injury in patients with acute decompensated heart failure. ESC heart failure 2022, 25 Exclusion reason: Wrong study population.
107. Trueman D, Kapetanakis V, Briggs A, Lewis E, Rouleau J, Solomon SD et al: Better health-related quality of life in patients treated with sacubitril/valsartan compared with enalapril, irrespective of NYHA class: analysis of EQ-5D in PARADIGM-HF. European heart journal 2017, 38 Exclusion reason: Conference.
108. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J et al: The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nature Medicine 2022, 28(3) Exclusion reason: Wrong study population.
109. Wang Q, Zhuo C, Xia Q, Jiang J, Wu B, Zhou D et al: Sacubitril/Valsartan Can Reduce Atrial Fibrillation Recurrence After Catheter Ablation in Patients with Persistent Atrial Fibrillation. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2022 Exclusion reason: Wrong study population.
110. Yang L, Zhang M, Hao Z, Wang N: Sacubitril/valsartan attenuates atrial structural remodelling in atrial fibrillation patients. ESC heart failure 2022 Exclusion reason: Wrong study population.
111. Yao J, Liu D: Clinical Effect of Qili Qiangxin Capsule Combined with Sacubitril-Valsartan in Patients with Chronic Heart Failure. Journal of Healthcare Engineering 2022, 2022 Exclusion reason: Wrong study population.
112. Yu H, Tang W, Greasley PJ, Penland RC, Boulton DW, Hallow KM: Predicted Cardiac Hemodynamic Consequences of the Renal Actions of SGLT2i in the DAPA-HF Study Population: a Mathematical Modeling Analysis. Journal of clinical pharmacology 2020 Exclusion reason: Wrong study type.
113. Zheng H: Cardiovascular benefits of digoxin and empagliflozin in patients with chronic heart failure: the DIG trial revisited. American journal of medicine 2022 Exclusion reason: Wrong study type.

3.15.3 Version 3 (Review Update 2)

1. Adamson C, Docherty KF, Heerspink HJL, de Boer RA, Damman K, Inzucchi SE et al: Initial Decline (Dip) in Estimated Glomerular Filtration Rate After Initiation of Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction: Insights From DAPA-HF. Circulation, 146(6) Exclusion reason: Duplicate.
2. Adamson C, Kondo T, Jhund P, de Boer RA, Honorio JWC, Claggett B et al: Dapagliflozin for heart failure according to body mass index: the DELIVER trial. European Heart Journal Exclusion reason: Wrong study population; Philipp Kapp.
3. Aktas MK, Goldenberg I, Zareba W, Vidula H, Brueckmann M, Zeller C et al: HF-567-01 THE BENEFIT OF AN IMPLANTABLE CARDIOVERTER DEFIBRILLATOR IN HEART FAILURE PATIENTS TREATED WITH EMPAGLIFLOZIN: AN ANALYSIS FROM THE EMPEROR-REDUCED TRIAL. Heart rhythm 2022, 19(5) Exclusion reason: Conference.
4. Amerena J: Effects of Empagliflozin in Women and Men With Heart Failure and Preserved Ejection Fraction: results From the EMPEROR-Preserved Trial. Heart lung and circulation 2022, 31 Exclusion reason: Conference.
5. Amerena J: Empagliflozin in Heart Failure With a Preserved Ejection Fraction ≥50%: results From the EMPEROR-Preserved Clinical Trial. Heart lung and circulation 2022, 31 Exclusion reason: Conference.
6. Anker SD, Siddiqi TJ, Filippatos G, Zannad F, Ferreira JP, Pocock SJ et al: Outcomes with empagliflozin in heart failure with preserved ejection fraction using DELIVER-like endpoint definitions. European Journal of Heart Failure, 24(8) Exclusion reason: Wrong study population.
7. Berg DD, Docherty KF, Sattar N, Jarolim P, Welsh P, Jhund PS et al: Serial Assessment of High-Sensitivity Cardiac Troponin and the Effect of Dapagliflozin in Patients With Heart Failure With Reduced Ejection Fraction: An Analysis of the DAPA-HF Trial. Circulation, 145(3) Exclusion reason: Duplicate.
8. Bohm M, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Abdin A et al: Empagliflozin Improves Outcomes in Patients With Heart Failure and Preserved Ejection Fraction Irrespective of Age. Journal of the American College of Cardiology, 80(1) Exclusion reason: Wrong study population.
9. Bohm M, Butler J, Mahfoud F, Filippatos G, Ferreira JP, Pocock SJ et al: Heart failure outcomes according to heart rate and effects of empagliflozin in patients of the EMPEROR-Preserved Trial. European Journal of Heart Failure 2022, 10 Exclusion reason: Wrong study population.
10. Butler J, Filippatos G, Jamal Siddiqi T, Brueckmann M, Bohm M, Chopra VK et al: Empagliflozin, Health Status, and Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial. Circulation, 145(3) Exclusion reason: Duplicate.
11. Butler J, Filippatos G, Jamal Siddiqi T, Pedro Ferreira J, Brueckmann M, Bocchi E et al: Effects of Empagliflozin in Women and Men With Heart Failure and Preserved Ejection Fraction. Circulation Exclusion reason: Wrong study population.
12. Butler J, Green JB, Rosenstock J, Emperor Trial C, Investiga: Impact of empagliflozin on insulin use in patients with heart failure with preserved ejection fraction (HFpEF) and type 2 diabetes: sub-analysis from EMPEROR-Preserved trial. Diabetologia 2022, 65(SUPPL 1) Exclusion reason: Conference.
13. Butler J, Siddiqi TJ, Filippatos G, Ferreira JP, Pocock SJ, Zannad F et al: Early benefit with empagliflozin in heart failure with preserved ejection fraction: insights from the EMPEROR-Preserved trial. European Journal of Heart Failure, 24(2) Exclusion reason: Duplicate.

14. Butt JH, Dewan P, Docherty K, Inzucchi S, Ponikowski P, Martinez F et al: Efficacy and safety of dapagliflozin according to frailty in heart failure with reduced ejection fraction: a post hoc analysis of the DAPA-HF trial. European Journal of Heart Failure 2022, 24 Exclusion reason: Duplicate.
15. Butt JH, Dewan P, Jhund PS, Anand IS, Atar D, Ge J et al: Sacubitril/Valsartan and Frailty in Patients With Heart Failure and Preserved Ejection Fraction. Journal of the American College of Cardiology, 80(12) Exclusion reason: Wrong study population.
16. Butt JH, Jhund PS, Belohlavek J, de Boer RA, Chiang CE, Desai AS et al: Efficacy and Safety of Dapagliflozin According to Frailty in Patients with Heart Failure: A Prespecified Analysis of the DELIVER Trial. Circulation 2022, 27 Exclusion reason: Wrong study population.
17. Butt JH, Kondo T, Jhund PS, Comin-Colet J, de Boer RA, Desai AS et al: Dapagliflozin, atrial fibrillation, and heart failure with mildly reduced or preserved ejection fraction in DELIVER. Journal of the American College of Cardiology 2022, 13 Exclusion reason: Wrong study population.
18. Chandra A, Vaduganathan M, Lewis EF, Claggett BL, Rizkala AR, Wang W et al: Health-Related Quality of Life in Heart Failure With Preserved Ejection Fraction: The PARAGON-HF Trial. JACC Heart Failure, 7(10) Exclusion reason: Duplicate.
19. Chatur S, Vaduganathan M, Peikert A, Claggett BL, McCausland FR, Skali H et al: Longitudinal trajectories in renal function before and after heart failure hospitalization among patients with heart failure with preserved ejection fraction in the PARAGON-HF trial. European Journal of Heart Failure Exclusion reason: Wrong study population.
20. Correale M, Mallardi A, Tricarico L, Mazzeo P, Ferraretti A, Diella C et al: Remodelling is inversely proportional to left ventricular dimensions in a real-life population of patients with chronic heart failure after therapy with sacubitril/valsartan. Acta Cardiologica, 77(5) Exclusion reason: Wrong study type.
21. Cunningham JW, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS, Jhund PS et al: Dapagliflozin in Patients Recently Hospitalized With Heart Failure and Mildly Reduced or Preserved Ejection Fraction. Journal of the American College of Cardiology 2022, 26 Exclusion reason: Wrong study population.
22. Docherty KF, Campbell RT, Brooksbank KJM, Dreisbach JG, Forsyth P, Godeseth RL et al: Effect of Neprilysin Inhibition on Left Ventricular Remodeling in Patients With Asymptomatic Left Ventricular Systolic Dysfunction Late After Myocardial Infarction. Circulation, 144(3) Exclusion reason: Wrong study population.
23. Docherty KF, Jhund PS, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA et al: Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. European Heart Journal, 41(25) Exclusion reason: Duplicate.
24. Ejiri K, Miyoshi T, Kihara H, Hata Y, Nagano T, Takaishi A et al: Effects of luseogliflozin and voglibose on high-risk lipid profiles and inflammatory markers in diabetes patients with heart failure. Scientific Reports, 12(1) Exclusion reason: Wrong study population.
25. Feng M, He B, Wang B, Chen X, Chu H: Clinical Study of Heart Failure with Left Ventricular Ejection Fraction Regimen Treated with Entresto. Contrast Media & Molecular Imaging, 2022 Exclusion reason: Wrong study population.
26. Ferreira JP, Zannad F, Butler J, Filipattos G, Ritter I, Schuler E et al: Empagliflozin and serum potassium in heart failure: an analysis from EMPEROR-Pooled. European Heart Journal, 43(31) Exclusion reason: Wrong study type.
27. Ferreira JP, Zannad F, Pocock SJ, Anker SD, Butler J, Filippatos G et al: Interplay of Mineralocorticoid Receptor Antagonists and Empagliflozin in Heart Failure: eMPEROR-Reduced. Journal of the American College of Cardiology 2021, 77(11) Exclusion reason: Duplicate.
28. Ferry A: Dapagliflozin for patients with heart failure and reduced ejection fraction. JAAPA, 35(9) Exclusion reason: Wrong study type.
29. Harper AR, Bakhai A: Sacubitril/valsartan: clinical evidence from PARADIGM-HF. Primary care cardiovascular journal (PCCJ) 2016 Exclusion reason: Wrong study type.
30. Jhund PS, Ponikowski P, Docherty KF, Gasparyan SB, Bohm M, Chiang CE et al: Dapagliflozin and Recurrent Heart Failure Hospitalizations in Heart Failure With Reduced Ejection Fraction: An Analysis of DAPA-HF. Circulation, 143(20) Exclusion reason: Duplicate.
31. Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Bohm M et al: Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction: Results of DAPA-HF. Circulation, 143(4) Exclusion reason: Duplicate.
32. Kolwelter J, Bosch A, Jung S, Stabel L, Kannenkeril D, Ott C et al: Effects of the sodium-glucose cotransporter 2 inhibitor empagliflozin on vascular function in patients with chronic heart failure. ESC heart failure, 8(6) Exclusion reason: Duplicate.
33. Kosiborod MN, Angermann CE, Collins SP, Teerlink JR, Ponikowski P, Biegus J et al: Effects of Empagliflozin on Symptoms, Physical Limitations, and Quality of Life in Patients Hospitalized for Acute Heart Failure: Results From the EMPULSE Trial. Circulation, 146(4) Exclusion reason: Duplicate; Philipp Kapp (2022-10-06 19:15:40)(Select): Duplicate.
34. Lee MMY, Gillis KA, Brooksbank KJM, Allwood-Spiers S, Barrientos PH, Wetherall K et al: Effect of Empagliflozin on Kidney Biochemical and Imaging Outcomes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure with Reduced Ejection Fraction (SUGAR-DM-HF). Circulation 2022, 146(4) Exclusion reason: Wrong study population.
35. Li BH, Fang KF, Lin PH, Zhang YH, Huang YX, Jie H: Effect of sacubitril valsartan on cardiac function and endothelial function in patients with chronic heart failure with reduced ejection fraction. Clinical Hemorheology & Microcirculation, 77(4) Exclusion reason: Duplicate.
36. McDowell K, Welsh P, Docherty KF, Morrow DA, Jhund PS, de Boer RA et al: Dapagliflozin reduces uric acid concentration, an independent predictor of adverse outcomes in DAPA-HF. European Journal of Heart Failure, 24(6) Exclusion reason: Duplicate.
37. McMurray JJV, Jackson AM, Lam CSP, Redfield MM, Anand IS, Ge J et al: Effects of Sacubitril-Valsartan Versus Valsartan in Women Compared With Men With Heart Failure and Preserved Ejection Fraction: Insights From PARAGON-HF. Circulation, 141(5) Exclusion reason: Duplicate.
38. Myhre PL, Vaduganathan M, Claggett BL, Miao ZM, Jhund PS, de Boer RA et al: Influence of NT-proBNP on Efficacy of Dapagliflozin in Heart Failure With Mildly Reduced or Preserved Ejection Fraction. JACC Heart Failure 2022, 27 Exclusion reason: Wrong study population.
39. Naser N, Kulic M, Jatic Z: Our Experience With Sacubitril/Valsartan in Chronic Heart Failure Management - HFrEF in the Ambulatory Setting. Medicinski Arhiv, 76(2) Exclusion reason: Wrong study type.
40. Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE et al: Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial. Circulation, 140(18) Exclusion reason: Duplicate.
41. Ostrominski JW, Vaduganathan M, Claggett BL, de Boer RA, Desai AS, Dobreanu D et al: Dapagliflozin and New York Heart Association functional class in heart failure with mildly reduced or preserved ejection fraction: the DELIVER trial. European Journal of Heart Failure Exclusion reason: Wrong study population.
42. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ et al: Empagliflozin in Patients With Heart Failure, Reduced Ejection Fraction, and Volume Overload: eMPEROR-Reduced Trial. Journal of the American College of Cardiology 2021, 77(11) Exclusion reason: Duplicate.
43. Peikert A, Martinez FA, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS et al: Efficacy and Safety of Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction According
to Age: The DELIVER Trial. Circulation: Heart Failure 2022, 27 Exclusion reason: Wrong study population.
44. Peters AE, Ogunniyi MO, Hegde SM, Bianco C, Ghafghazi S, Hernandez AF et al: A multicenter program for electronic health record screening for patients with heart failure with preserved ejection fraction: Lessons from the DELIVER-EHR initiative. Contemporary Clinical Trials Exclusion reason: Wrong study type.
45. Pocock SJ, Ferreira JP, Packer M, Zannad F, Filippatos G, Kondo T et al: Biomarker-driven prognostic models in chronic heart failure with preserved ejection fraction: the EMPEROR-Preserved trial. European Journal of Heart Failure Exclusion reason: Wrong study population.
46. Sardar S: The SGLT2 Inhibitor Empagliflozin in Patients Hospitalized for Acute Heart Failure a Multinational Randomized Trial (The EMPULSE Trial). Journal of the Practice of Cardiovascular Sciences 2022, 8(2) Exclusion reason: Wrong study type.
47. Schulze PC, Bogoviku J, Westphal J, Aftanski P, Haertel F, Grund S et al: Effects of Early Empagliflozin Initiation on Diuresis and Kidney Function in Patients With Acute Decompensated Heart Failure (EMPAG-HF). Circulation, 146(4) Exclusion reason: Wrong study population..
48. Selvaraj S, Fu Z, Jones P, Kwee LC, Windsor SL, Ilkayeva O et al: Metabolomic Profiling of the Effects of Dapagliflozin in Heart Failure With Reduced Ejection Fraction: DEFINE-HF. Circulation, 146(11) Exclusion reason: Duplicate.
49. Senni M, Alemayehu WG, Sim D, Edelmann F, Butler J, Ezekowitz J et al: Efficacy and Safety of Vericiguat in Patients with Heart Failure with Reduced Ejection Fraction Treated with Sacubitril/Valsartan: insights from the VICTORIA Trial. European Journal of Heart Failure 2022 Exclusion reason: Wrong intervention.
50. Senni M, Trimarco B, Emdin M, De Biase L: [Sacubitril/valsartan, a new and effective treatment for heart failure with reduced ejection fraction]. Giornale Italiano Di Cardiologia, 18(1) Exclusion reason: Wrong study type.
51. Sezai A, Tanaka A, Imai T, Kida K, Sekino H, Murohara T et al: Comparing the Effects of Canagliflozin vs. Glimepiride by Body Mass Index in Patients with Type 2 Diabetes and Chronic Heart Failure: A Subanalysis of the CANDLE Trial. Biomedicines 2022, 10(7) Exclusion reason: Wrong study population.
52. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF et al: Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. New England Journal of Medicine 2022, 27 Exclusion reason: Wrong study population.

53. Tan J, Hecker T, Ilyas F, Jones L, Wollaston F, Swan A et al: Acute Effects of Dapagliflozin on Myocardial Work in Type 2 Diabetics With Heart Failure With Reduced Ejection Fraction: a Crossover Trial. Heart lung and circulation 2022, 31 Exclusion reason: Conference.
54. Tanaka A, Imai T, Shimabukuro M, Nakamura I, Matsunaga K, Ozaki Y et al: Effect of canagliflozin on white blood cell counts in patients with type 2 diabetes and heart failure: A subanalysis of the randomized CANDLE trial. Journal of Diabetes Investigation 2022, 16 Exclusion reason: Wrong study population.
55. Tanaka A, Imai T, Shimabukuro M, Taguchi I, Sezai A, Toyoda S et al: Association between serum insulin levels and heart failure-related parameters in patients with type 2 diabetes and heart failure treated with canagliflozin: a post-hoc analysis of the randomized CANDLE trial. Cardiovascular Diabetology 2022, 21(1) Exclusion reason: Wrong study population.
56. Teerlink J, Voors A, Collins S, Kosiborod M, Biegus J, Ferreira J et al: Empagliflozin in Patients Hospitalised for De Novo Versus Decompensated Chronic Heart Failure: insights From the EMPULSE Trial. Heart lung and circulation 2022, 31 Exclusion reason: Conference.
57. Thiele K, Rau M, Hartmann NK, Moller M, Mollmann J, Jankowski J et al: Empagliflozin reduces markers of acute kidney injury in patients with acute decompensated heart failure. ESC heart failure, 9(4) Exclusion reason: Wrong study population.
58. Vaduganathan M, Claggett BL, Jhund P, de Boer RA, Hernandez AF, Inzucchi SE et al: Estimated Event-Free Survival Benefits with Dapagliflozin in HF with Mildly Reduced or Preserved Ejection Fraction. Journal of the American College of Cardiology 2022, 24 Exclusion reason: Wrong study population.
59. Voors AA, Damman K, Teerlink JR, Angermann CE, Collins SP, Kosiborod M et al: Renal effects of empagliflozin in patients hospitalized for acute heart failure: from the EMPULSE trial. European Journal of Heart Failure 2022, 06 Exclusion reason: Wrong study population.
60. Wang C, Qin Y, Zhang X, Yang Y, Wu X, Liu J et al: Effect of Dapagliflozin on Indicators of Myocardial Fibrosis and Levels of Inflammatory Factors in Heart Failure Patients. Disease Markers, 2022 Exclusion reason: Wrong study type.
61. Wang G, Liu X, Guo Z, Zhang J, Zuo S, Sun S et al: Effect of Entresto on Clinical Symptoms, Ventricular Remodeling, Rehabilitation, and Hospitalization Rate in Patients with Both Acute Myocardial Infarction and Acute Heart Failure. Evidence-Based Complementary & Alternative Medicine: eCAM, 2022 Exclusion reason: Wrong study population.
62. Witte KK, Wachter R, Senni M, Belohlavek J, Straburzynska-Migaj E, Fonseca C et al: Influence of diabetes on sacubitril/valsartan titration and clinical outcomes in patients hospitalized for heart failure. ESC heart failure 2022, 20 Exclusion reason: Wrong study population.
63. Wolsk E, Jurgens M, Schou M, Ersboll M, Hasbak P, Kjaer A et al: Randomized Controlled Trial of the Hemodynamic Effects of Empagliflozin in Patients With Type 2 Diabetes at High Cardiovascular Risk: The SIMPLE Trial. Diabetes 2022, 71(4) Exclusion reason: Wrong study population.
64. Wu J, Shi N, Ren J, Mou G: EFFECTS OF SACUBITRIL/VALSARTAN ON CARDIAC FUNCTION, VENTRICULAR REMODELING AND SERUM NT-PROBNP, CTNT, ICAM-1 IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND HEART FAILURE. Acta medica mediterranea 2022, 38(2) Exclusion reason: Wrong study population; Philipp Kapp (2022-10-06 02:09:36)(Included): Exclude?; Gina Bantle (2022-09-26 21:31:51)(Select): Sacubitril/Valsartan (Acute?) heart failure.
65. Wu WJ, Zhang SY, Liu C, Shen JB, Wang N, Wang Q et al: [Impact of empagliflozin on peak oxygen uptake in HFmrEF patients: a randomized controlled trial]. Chung-Hua Hsin Hsueh Kuan Ping Tsa Chih [Chinese Journal of Cardiology], 50(7) Exclusion reason: Wrong study population.
66. Young KG, McGovern AP, Hopkins R, Raya D, Sattar NA, Holman RR et al: Precision medicine in type 2 diabetes: integrating trial and real-world evidence can provide accurate estimates of heart failure benefit when initiating SGLT2-inhibitors. Diabetologia 2022, 65(SUPPL 1) Exclusion reason: Conference.
67. Yousef Z: EMPAGLIFLOZIN IN HEART FAILURE WITH A PRESERVED EJECTION FRACTION ≥50%: RESULTS FROM THE EMPEROR-PRESERVED CLINICAL TRIAL. Heart (British Cardiac Society) 2022, 108 Exclusion reason: Conference.
68. Zannad F, Ferreira JP, Pocock SJ, Zeller C, Anker SD, Butler J et al: Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function: Insights From EMPEROR-Reduced. Circulation, 143(4) Exclusion reason: Duplicate; Gina Bantle (2022-09-28 22:27:20)(Select): Dublette.
69. Zhang H, Liu Z: Effects of Dapagliflozin in Combination with Metoprolol Sustained-Release Tablets on Prognosis and Cardiac Function in Patients with Acute Myocardial Infarction after PCI. Computational & Mathematical Methods in Medicine, 2022 Exclusion reason: Wrong study population.
70. Zheng H: Cardiovascular Benefits of Digoxin and Empagliflozin in Patients with Chronic Heart Failure: The DIG Trial Revisited. American Journal of Medicine, 135(6) Exclusion reason: Wrong study type.

3.16 Appendix 2: Included studies

Typ	Acronym	Title	Authors	Year	Journal	Volume	Issue	DOI
Design	EMPERIAL	Design of the EMPERIAL-reduced trial of empagliflozin in patients with chronic heart failure with reduced ejection fraction	Abraham Wt, Ponikowski P. Anker S. D. Salsali A. Peil B. Brun M. Brueckmann M. Lindenfeld J.	2018	European journal of heart failure 2018;20():			
Primäre Publikation	EMPERIAL	Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes	Abraham, W. T.; Lindenfeld, J.; Ponikowski, P.; Agostoni, P.; Butler, J.; Desai, A. S.; Filippatos, G.; Gniot, J.; Fu, M.; Gullestad, L.; Howlett, J. G.; Nicholls, S. J.; Redon, J.; Schenkenberger, I.; Silva-Cardoso, J.; Stork, S.; Wranicz, J. K.; Savarese, G.; Brueckmann, M.; Jamal, W.; Nordaby, M.; Peil, B.; Ritter, I.; Ustyugova, A.; Zeller, C.; Salsali, A.; Anker, S. D.	2021	European Heart Journal	42	6	10.1093/eurheartj/ehaa943
Sekundäre Publikation	EMPERIAL	Kidney Function After Initiation and Discontinuation of Empagliflozin in Patients With Heart Failure With and Without Type 2 Diabetes: Insights From the EMPERIAL Trials	Anker, S. D.; Ponikowski, P.; Wanner, C.; Pfarr, E.; Hauske, S.; Peil, B.; Salsali, A.; Ritter, I.; Koitka-Weber, A.; Brueckmann, M.; Lindenfeld, J.; Abraham, W. T.; Emperial Investigators; National, Coordinators	2021	Circulation	144	15	
Primäre Publikation	Empire HF_Main	Twelve weeks of treatment with empagliflozin in patients with heart failure and reduced ejection fraction: A double-blinded, randomized, and placebo-controlled trial	Jensen, J.; Omar, M.; Kistorp, C.; Poulsen, M. K.; Tuxen, C.; Gustafsson, I.; Køber, L.; Gustafsson, F.; Faber, J.; Fosbøl, E. L.; Bruun, N. E.; Brønd, J. C.; Forman, J. L.; Videbæk, L.; Møller, J. E.; Schou, M.	2020	American heart journal	228		10.1016/j.ahj.2020.07.011
Design	Empire HF_Main	Empagliflozin in heart failure patients with reduced ejection fraction: a randomized clinical trial (Empire HF)	Jensen, J.; Omar, M.; Kistorp, C.; Poulsen, M. K.; Tuxen, C.; Gustafsson, I.; Køber, L.; Gustafsson, F.; Fosbøl, E.; Bruun, N. E.; Videbæk, L.; Frederiksen, P. H.; Møller, J. E.; Schou, M.	2019	Trials	20	1	10.1186/s13063-019-3474-5
Sekundäre Publikation	Empire HF_Main	Associations of Empagliflozin With Left Ventricular Volumes, Mass, and Function in Patients With Heart Failure and Reduced Ejection Fraction: A Substudy of the Empire HF Randomized Clinical Trial	Omar, M.; Jensen, J.; Ali, M.; Frederiksen, P. H.; Kistorp, C.; Videbaek, L.; Poulsen, M. K.; Tuxen, C. D.; Moller, S.; Gustafsson, F.; Kober, L.; Schou, M.; Moller, J. E.	2021	JAMA Cardiology	6	7	
Sekundäre Publikation	Empire HF_Renal_Metabolic	Effects of empagliflozin on estimated extracellular volume, estimated plasma volume, and measured glomerular filtration rate in patients with heart failure (Empire HF Renal): a prespecified substudy of a double-blind, randomised, placebo-controlled trial	Jensen, J.; Omar, M.; Kistorp, C.; Tuxen, C.; Gustafsson, I.; Køber, L.; Gustafsson, F.; Faber, J.; Malik, M. E.; Fosbøl, E. L.; Bruun, N. E.; Forman, J. L.; Jensen, L. T.; Møller, J. E.; Schou, M.	2021	The lancet. Diabetes & endocrinology	9	2	10.1016/S2213-8587(20)30382-X
Sekundäre Publikation	Empire HF_Renal_Metabolic	Metabolic Effects of Empagliflozin in Heart Failure: A Randomized, Double-Blind, and Placebo-Controlled Trial (Empire HF Metabolic)	Jensen, J.; Omar, M.; Kistorp, C.; Tuxen, C.; Gustafsson, I.; Kober, L.; Gustafsson, F.; Faber, J.; Forman, J. L.; Moller, J. E.; Schou, M.	2021	Circulation	143	22	
Sekundäre Publikation	Empire HF_Blood Volume_Hemodynamics	Effect of Empagliflozin on Blood Volume Redistribution in Patients With Chronic Heart Failure and Reduced Ejection Fraction: An Analysis from the Empire HF Randomized Clinical Trial	Omar, M.; Jensen, J.; Burkhoff, D.; Frederiksen, P. H.; Kistorp, C.; Videbaek, L.; Poulsen, M. K.; Gustafsson, F.; Kober, L.; Borlaug, B. A.; Schou, M.; Moller, J. E.	2021	Circulation: Heart Failure	8		
Sekundäre Publikation	Empire HF_Blood Volume_Hemodynamics	Effect of Empagliflozin on Hemodynamics in Patients With Heart Failure and Reduced Ejection Fraction	Omar, M.; Jensen, J.; Frederiksen, P. H.; Kistorp, C.; Videbæk, L.; Poulsen, M. K.; Möller, S.; Ali, M.; Gustafsson, F.; Køber, L.; Borlaug, B. A.; Schou, M.; Møller, J. E.	2020	Journal of the American College of Cardiology	76	23	10.1016/j.jacc.2020.10.005
Primäre Publikation	EMPA-TROPISM	Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction	Santos-Gallego, C. G.; Vargas-Delgado, A. P.; Requena-Ibanez, J. A.; Garcia-Ropero, A.; Mancini, D.; Pinney, S.; Macaluso, F.; Sartori, S.; Roque, M.; Sabatel-Perez, F.; Rodriguez-Cordero, A.; Zafar, M. U.; Fergus, I.; Atallah-Lajam, F.; Contreras, J. P.; Varley, C.; Moreno, P. R.; Abascal, V. M.; Lala, A.; Tamler, R.; Sanz, J.; Fuster, V.; Badimon, J. J.; Empa-Tropism Investigators	2021	Journal of the American College of Cardiology	77	3	10.1016/j.jacc.2020.11.008
Sekundäre Publikation	EMPA-TROPISM	Mechanistic Insights of Empagliflozin in Nondiabetic Patients With HFrEF: From the EMPA-TROPISM Study	Requena-Ibáñez, J. A.; Santos-Gallego, C. G.; Rodriguez-Cordero, A.; Vargas-Delgado, A. P.; Mancini, D.; Sartori, S.; Atallah-Lajam, F.; Giannarelli, C.; Macaluso, F.; Lala, A.; Sanz, J.; Fuster, V.; Badimon, J. J.	2021	JACC. Heart failure	9	8	10.1016/j.jchf.2021.04.014
Sekundäre Publikation	EMPA-TROPISM	Empagliflozin improves quality of life in nondiabetic HFrEF patients. Sub-analysis of the EMPATROPISM trial	Requena-Ibanez, J. A.; Santos-Gallego, C. G.; Rodriguez-Cordero, A.; Vargas-Delgado, A. P.; Badimon, J. J.	2022	Diabetes & Metabolic Syndrome	16	2	

Typ	Acronym	Title	Authors	Year	Journal	Volume	Issue	DOI
Primäre Publikation	EMPEROR-Reduced	Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure	Packer, Milton; Anker, Stefan D.; Butler, Javed; Filippatos, Gerasimos; Pocock, Stuart J.; Carson, Peter; Januzzi, James; Verma, Subodh; Tsutsui, Hiroyuki; Brueckmann, Martina; Jamal, Waheed; Kimura, Karen; Schnee, Janet; Zeller, Cordula; Cotton, Daniel; Bocchi, Edimar; Böhm, Michael; Choi, Dong-Ju; Chopra, Vijay; Chuquiure, Eduardo; Giannetti, Nadia; Janssens, Stefan; Zhang, Jian; Gonzalez Juanatey, Jose R.; Kaul, Sanjay; Brunner-La Rocca, Hans-Peter; Merkely, Bela; Nicholls, Stephen J.; Perrone, Sergio; Pina, Ileana; Ponikowski, Piotr; Sattar, Naveed; Senni, Michele; Seronde, Marie-France; Spinar, Jindrich; Squire, Iain; Taddei, Stefano; Wanner, Christoph; Zannad, Faiez	2020	New England Journal of Medicine	383	15	10.1056/NEJMoa2022190
Design	EMPEROR-Reduced	Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial	Packer, M.; Butler, J.; Filippatos, G. S.; Jamal, W.; Salsali, A.; Schnee, J.; Kimura, K.; Zeller, C.; George, J.; Brueckmann, M.; Anker, S. D.; Zannad, F.; Perrone, S.; Nicholls, S.; Janssens, S.; Bocchi, E.; Giannetti, N.; Verma, S.; Jian, Z.; Spinar, J.; Seronde, M. F.; Bohm, M.; Merkely, B.; Chopra, V.; Senni, M.; Taddei, S.; Tsutsui, H.; Choi, D. J.; Chuquiure, E.; La Rocca, H. P. B.; Ponikowski, P.; Juanatey, J. R. G.; Squire, I.; Januzzi, J.; Pina, I.; Pocock, S. J.; Carson, P.; Doehner, W.; Miller, A.; Haas, M.; Pehrson, S.; Komajda, M.; Anand, I.; Teerlink, J.; Rabinstein, A.; Steiner, T.; Kamel, H.; Tsivgoulis, G.; Lewis, J.; Freston, J.; Kaplowitz, N.; Mann, J.; Petrie, M.; Bernstein, R.; Cheung, A.; Green, J.; Kaul, S.; Ping, C. L. S.; Lip, G.; Marx, N.; McCullough, P.; Mehta, C.; Rosenstock, J.; Sattar, N.; Scirica, B.; Wanner, C.; Welty, F. K.; Parhofer, K. G.; Clayton, T.; Pedersen, T. R.; Lees, K. R.; Konstam, M. A.; Greenberg, B.; Palmer, M.; E. MPEROR-Reduced Trial Comm Investi; Executive, Comm; Natl, Coordinators; Consulting, Statistician; Clinical Events, Comm; Sci Excellence, Comm; Data Monitoring, Comm	2019	European Journal of Heart Failure	21	10	10.1002/ejhf.1536
Sekundäre Publikation	EMPEROR-Reduced	Empagliflozin in the treatment of heart failure with reduced ejection fraction in addition to background therapies and therapeutic combinations (EMPEROR-Reduced): a post-hoc analysis of a randomised, double-blind trial	Verma, S.; Dhingra, N. K.; Butler, J.; Anker, S. D.; Ferreira, J. P.; Filippatos, G.; Januzzi, J. L.; Lam, C. S. P.; Sattar, N.; Peil, B.; Nordaby, M.; Brueckmann, M.; Pocock, S. J.; Zannad, F.; Packer, M.; E. MPEROR-Reduced Trial Comm Investi	2022	Lancet Diabetes & Endocrinology	10	1	10.1016/s2213-8587(21)00292-8
Sekundäre Publikation	EMPEROR-Reduced	Concentration-dependent clinical and prognostic importance of high-sensitivity cardiac troponin T in heart failure and a reduced ejection fraction and the influence of empagliflozin: the EMPEROR-Reduced trial	Packer, M.; Januzzi, J. L.; Ferreira, J. P.; Anker, S. D.; Butler, J.; Filippatos, G.; Pocock, S. J.; Brueckmann, M.; Jamal, W.; Cotton, D.; Iwata, T.; Zannad, F.; E. MPEROR-Reduced Trial Comm Inves	2021	European Journal of Heart Failure	23	9	10.1002/ejhf.2256
Sekundäre Publikation	EMPEROR-Reduced	Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial	Packer, M.; Anker, S. D.; Butler, J.; Filippatos, G.; Ferreira, J. P.; Pocock, S. J.; Rocca, H. B.; Janssens, S.; Tsutsui, H.; Zhang, J.; Brueckmann, M.; Jamal, W.; Cotton, D.; Iwata, T.; Schnee, J.; Zannad, F.; E. MPEROR-Reduced Trial Committees; Investigators,	2021	European heart journal	42	6	
Sekundäre Publikation	EMPEROR-Reduced	Interplay of Mineralocorticoid Receptor Antagonists and Empagliflozin in Heart Failure: EMPEROR-Reduced	Ferreira, J. P.; Zannad, F.; Pocock, S. J.; Anker, S. D.; Butler, J.; Filippatos, G.; Brueckmann, M.; Jamal, W.; Steubl, D.; Schueler, E.; Packer, M.	2021	Journal of the American College of Cardiology	77	11	10.1016/j.jacc.2021.01.044
Sekundäre Publikation	EMPEROR-Reduced	Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function: Insights From EMPEROR-Reduced	Zannad, F.; Ferreira, J. P.; Pocock, S. J.; Zeller, C.; Anker, S. D.; Butler, J.; Filippatos, G.; Hauske, S. J.; Brueckmann, M.; Pfarr, E.; Schnee, J.; Wanner, C.; Packer, M.	2021	Circulation	143	4	
Sekundäre Publikation	EMPEROR-Reduced	Regional and ethnic influences on the response to empagliflozin in patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial	Lam, C. S. P.; Ferreira, J. P.; Pfarr, E.; Sim, D.; Tsutsui, H.; Anker, S. D.; Butler, J.; Filippatos, G.; Pocock, S. J.; Sattar, N.; Verma, S.; Brueckmann, M.; Schnee, J.; Cotton, D.; Zannad, F.; Packer, M.	2021	European heart journal	42	43	10.1093/eurheartj/ehab360
Sekundäre Publikation	EMPEROR-Reduced	Impact of anaemia and the effect of empagliflozin in heart failure with reduced ejection fraction: findings from EMPEROR-Reduced	Ferreira, J. P.; Anker, S. D.; Butler, J.; Filippatos, G.; Iwata, T.; Salsali, A.; Zeller, C.; Pocock, S. J.; Zannad, F.; Packer, M.	2021	European Journal of Heart Failure	26		
Sekundäre Publikation	EMPEROR-Reduced	Empagliflozin in Patients With Heart Failure, Reduced Ejection Fraction, and Volume Overload	Packer, M.; Anker, S. D.; Butler, J.; Filippatos, G.; Ferreira, J. P.; Pocock, S. J.; Sattar, N.; Brueckmann, M.; Jamal, W.; Cotton, D.; Iwata, T.; Zannad, F.; E. MPEROR-Reduced Trial Comm Investi	2021	Journal of the American College of Cardiology	77	11	10.1016/j.jacc.2021.01.033

Typ	Acronym	Title	Authors	Year	Journal	Volume	Issue	DOI
Sekundäre Publikation	EMPEROR-Reduced	Empagliflozin Improves Cardiovascular and Renal Outcomes in Heart Failure Irrespective of Systolic Blood Pressure	Bohm, M.; Anker, S. D.; Butler, J.; Filippatos, G.; Ferreira, J. P.; Pocock, S. J.; Mahfoud, F.; Brueckmann, M.; Jamal, W.; Ofstad, A. P.; Schuler, E.; Ponikowski, P.; Wanner, C.; Zannad, F.; Packer, M.; Emperor Reduced Trial Comm Invest	2021	Journal of the American College of Cardiology	78	13	10.1016/j.jacc.2021.07.049
Sekundäre Publikation	EMPEROR-Reduced	Effect of Empagliflozin on the Clinical Stability of Patients With Heart Failure and a Reduced Ejection Fraction The EMPEROR-Reduced Trial	Packer, M.; Anker, S. D.; Butler, J.; Filippatos, G.; Ferreira, J. P.; Pocock, S. J.; Carson, P.; Anand, I.; Doehner, W.; Haass, M.; Komajda, M.; Miller, A.; Pehrson, S.; Teerlink, J. R.; Brueckmann, M.; Jamal, W.; Zeller, C.; Schnaidt, S.; Zannad, F.; E. MPEROR-Reduced Trial Comm Investi	2021	Circulation	143	4	10.1161/circulationaha.120.051783
Sekundäre Publikation	EMPEROR-Reduced	Erratum: Correction to: Effect of Empagliflozin on the Clinical Stability of Patients With Heart Failure and a Reduced Ejection Fraction: The EMPEROR-Reduced Trial (Circulation (2021) 143 4 (326-336))		2021	Circulation	143	4	10.1161/CIR.0000000000000954
Sekundäre Publikation	EMPEROR-Reduced	Novel biomarker-driven prognostic models to predict morbidity and mortality in chronic heart failure: the EMPEROR-Reduced trial	Pocock, S. J.; Ferreira, J. P.; Gregson, J.; Anker, S. D.; Butler, J.; Filippatos, G.; Gollop, N. D.; Iwata, T.; Brueckmann, M.; Januzzi, J. L.; Voors, A. A.; Zannad, F.; Packer, M.	2021	European Heart Journal	42	43	10.1093/eurheartj/ehab579
Sekundäre Publikation	EMPEROR-Reduced	Emperor reduced ? cardiac and renal targets with empagliflozin in patients with heart failure with reduced ejection fraction	Spinar, J.; Spinarova, L.; Vitovec, J.	2020	Kardiologicka Revue	22	3	
Sekundäre Publikation	EMPEROR-Reduced	EMPEROR-Reduced trial: Empagliflozin in patients with heart failure and low ejection fraction	Spinar, J.; Spinarova, L.; Vitovec, J.	2020	Intervencni a Akutni Kardiologie	19	4	
Sekundäre Publikation	EMPEROR-Reduced	EMPEROR reduced - empagliflozin in patients with heart failure and reduced ejection fraction	Spinar, J.; Spinarova, L.; Vitovec, J.	2021	Vnitrni Lekarstvi	67	1	
Sekundäre Publikation	EMPEROR-Reduced	Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status Results From the EMPEROR-Reduced Trial	Anker, S. D.; Butler, J.; Filippatos, G.; Khan, M. S.; Marx, N.; Lam, C. S. P.; Schnaidt, S.; Ofstad, A. P.; Brueckmann, M.; Jamal, W.; Bocchi, E. A.; Ponikowski, P.; Perrone, S. V.; Januzzi, J. L.; Verma, S.; Bohm, M.; Ferreira, J. P.; Pocock, S. J.; Zannad, F.; Packer, M.; E. MPEROR-Reduced Trial Comm Investi	2021	Circulation	143	4	10.1161/circulationaha.120.051824
Sekundäre Publikation	EMPEROR-Reduced	Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status - Results from the EMPEROR-Reduced Trial	Anker, S. D.; Butler, J.; Filippatos, G.; Khan, M. S.; Marx, N.; Lam, C. S. P.; Schnaidt, S.; Ofstad, A. P.; Brueckmann, M.; Jamal, W.; Bocchi, E.; Ponikowski, P.; Perrone, S. V.; Januzzi, J. L.; Verma, S.; Bohm, M.; Ferreira, J. P.; Pocock, S. J.; Zannad, F.; Packer, M.	2020	Circulation			10.1161/CIRCULATIONAHA.120.051824
Sekundäre Publikation	EMPEROR-Reduced	Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial	Butler, J.; Anker, S. D.; Filippatos, G.; Khan, M. S.; Ferreira, J. P.; Pocock, S. J.; Giannetti, N.; Januzzi, J. L.; Pina, I. L.; Lam, C. S. P.; Ponikowski, P.; Sattar, N.; Verma, S.; Brueckmann, M.; Jamal, W.; Vedin, O.; Peil, B.; Zeller, C.; Zannad, F.; Packer, M.; E. MPEROR-Reduced Trial Comm Investi	2021	European Heart Journal	42	13	10.1093/eurheartj/ehaa1007
Sekundäre Publikation	EMPEROR-Reduced	Prognostic Importance of NT-proBNP and Effect of Empagliflozin in the EMPEROR-Reduced Trial	Januzzi, J. L.; Zannad, F.; Anker, S. D.; Butler, J.; Filippatos, G.; Pocock, S. J.; Ferreira, J. P.; Sattar, N.; Verma, S.; Vedin, O.; Schnee, J.; Iwata, T.; Cotton, D.; Packer, M.; Emperor Reduced Trial Comm Invest	2021	Journal of the American College of Cardiology	78	13	10.1016/j.jacc.2021.07.046
Primäre Publikation	DAPA-HF	Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction	McMurray, John J.V.; Solomon, Scott D.; Inzucchi, Silvio E.; Køber, Lars; Kosiborod, Mikhail N.; Martinez, Felipe A.; Ponikowski, Piotr; Sabatine, Marc S.; Anand, Inder S.; Bělohlávek, Jan; Böhm, Michael; Chiang, Chern-En; Chopra, Vijay K.; de Boer, Rudolf A.; Desai, Akshay S.; Diez, Mirta; Drozdz, Jaroslaw; Dukát, Andrej; Ge, Junbo; Howlett, Jonathan G.; Katova, Tzvetana; Kitakaze, Masafumi; Ljungman, Charlotta E.A.; Merkely, Béla; Nicolau, Jose C.; O'Meara, Eileen; Petrie, Mark C.; Vinh, Pham N.; Schou, Morten; Tereshchenko, Sergey; Verma, Subodh; Held, Claes; DeMets, David L.; Docherty, Kieran F.; Jhund, Pardeep S.; Bengtsson, Olof; Sjöstrand, Mikaela; Langkilde, Anna-Maria	2019	New England Journal of Medicine	381	21	10.1056/NEJMoa1911303
Design	DAPA-HF	A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF)	McMurray, J. J. V.; DeMets, D. L.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Langkilde, A. M.; Martinez, F. A.; Bengtsson, O.; Ponikowski, P.; Sabatine, M. S.; Sjostrand, M.; Solomon, S. D.; Dapa-Hf Comm Investigators	2019	European Journal of Heart Failure	21	5	10.1002/ejhf.1432

Typ	Acronym	Title	Authors	Year	Journal	Volume	Issue	DOI
Sekundäre Publikation	DAPA-HF	Dapagliflozin and Diuretic Use in Patients With Heart Failure and Reduced Ejection Fraction in DAPA-HF	Jackson, A. M.; Dewan, P.; Anand, I. S.; B. lohlávek J; Bengtsson, O.; de Boer, R. A.; Böhm, M.; Boulton, D. W.; Chopra, V. K.; DeMets, D. L.; Docherty, K. F.; Dukát, A.; Greasley, P. J.; Howlett, J. G.; Inzucchi, S. E.; Katova, T.; Køber, L.; Kosiborod, M. N.; Langkilde, A. M.; Lindholm, D.; Ljungman, C. E. A.; Martinez, F. A.; O'Meara, E.; Sabatine, M. S.; Sjöstrand, M.; Solomon, S. D.; Tereshchenko, S.; Verma, S.; Jhund, P. S.; McMurray, J. J. V.	2020	Circulation	142	11	10.1161/CIRCULATIONAHA.120.047077
Sekundäre Publikation	DAPA-HF	Dapagliflozin reduces uric acid concentration, an independent predictor of adverse outcomes in DAPA-HF	McDowell, K.; Welsh, P.; Docherty, K. F.; Morrow, D. A.; Jhund, P. S.; de Boer, R. A.; O'Meara, E.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.; Hammarstedt, A.; Langkilde, A. M.; Sjostrand, M.; Lindholm, D.; Solomon, S. D.; Sattar, N.; Sabatine, M. S.; McMurray, J. J. V.	2022	European Journal of Heart Failure	22		
Sekundäre Publikation	DAPA-HF	Dapagliflozin in HFrEF Patients Treated With Mineralocorticoid Receptor Antagonists: An Analysis of DAPA-HF	Shen, L.; Kristensen, S. L.; Bengtsson, O.; Böhm, M.; de Boer, R. A.; Docherty, K. F.; Inzucchi, S. E.; Katova, T.; Køber, L.; Kosiborod, M. N.; Langkilde, A. M.; Lindholm, D.; Martinez, M. F. A.; O'Meara, E.; Nicolau, J. C.; Petrie, M. C.; Ponikowski, P.; Sabatine, M. S.; Schou, M.; Sjöstrand, M.; Solomon, S. D.; Jhund, P. S.; McMurray, J. J. V.	2021	JACC. Heart failure	9	4	10.1016/j.jchf.2020.11.009
Sekundäre Publikation	DAPA-HF	Dapagliflozin and atrial fibrillation in heart failure with reduced ejection fraction: insights from DAPA-HF	Butt, J. H.; Docherty, K. F.; Jhund, P. S.; de Boer, R. A.; Bohm, M.; Desai, A. S.; Howlett, J. G.; Inzucchi, S. E.; Kosiborod, M. N.; Martinez, F. A.; Nicolau, J. C.; Petrie, M. C.; Ponikowski, P.; Bengtsson, O.; Langkilde, A. M.; Schou, M.; Sjostrand, M.; Solomon, S. D.; Sabatine, M. S.; McMurray, J. J. V.; Kober, L.	2021	European Journal of Heart Failure			10.1002/ejhf.2381
Sekundäre Publikation	DAPA-HF	Efficacy and Safety of Dapagliflozin in Heart Failure With Reduced Ejection Fraction According to Age: Insights From DAPA-HF	Martinez, F. A.; Serenelli, M.; Nicolau, J. C.; Petrie, M. C.; Chiang, C. E.; Tereshchenko, S.; Solomon, S. D.; Inzucchi, S. E.; Køber, L.; Kosiborod, M. N.; Ponikowski, P.; Sabatine, M. S.; DeMets, D. L.; Dutkiewicz-Piasecka, M.; Bengtsson, O.; Sjöstrand, M.; Langkilde, A. M.; Jhund, P. S.; McMurray, J. J. V.	2020	Circulation	141	2	10.1161/CIRCULATIONAHA.119.044133
Sekundäre Publikation	DAPA-HF	Extrapolating Long-term Event-Free and Overall Survival With Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction: An Exploratory Analysis of a Phase 3 Randomized Clinical Trial	Docherty, K. F.; Jhund, P. S.; Claggett, B.; Ferreira, J. P.; Bengtsson, O.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Langkilde, A. M.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Sjostrand, M.; Solomon, S. D.; McMurray, J. J. V.; Dapa-Hf Investigators; Committees,	2021	JAMA Cardiology	6	11	
Sekundäre Publikation	DAPA-HF	Effect of Dapagliflozin in DAPA-HF According to Background Glucose-Lowering Therapy	Docherty, K. F.; Jhund, P. S.; Bengtsson, O.; DeMets, D. L.; Inzucchi, S. E.; Køber, L.; Kosiborod, M. N.; Langkilde, A. M.; Martinez, F. A.; Sabatine, M. S.; Sjöstrand, M.; Solomon, S. D.; McMurray, J. J. V.; Dapa-Hf Investigators; Committees,	2020	Diabetes care	43	11	10.2337/dc20-1402
Sekundäre Publikation	DAPA-HF	Effects of dapagliflozin in heart failure with reduced ejection fraction and chronic obstructive pulmonary disease: an analysis of DAPA-HF	Dewan, P.; Docherty, K. F.; Bengtsson, O.; de Boer, R. A.; Desai, A. S.; Drozdz, J.; Hawkins, N. M.; Inzucchi, S. E.; Kitakaze, M.; Køber, L.; Kosiborod, M. N.; Langkilde, A. M.; Lindholm, D.; Martinez, F. A.; Merkely, B.; Petrie, M. C.; Ponikowski, P.; Sabatine, M. S.; Schou, M.; Sjöstrand, M.; Solomon, S. D.; Verma, S.; Jhund, P. S.; McMurray, J. J. V.	2021	European journal of heart failure	23	4	10.1002/ejhf.2083
Sekundäre Publikation	DAPA-HF	Efficacy and safety of sodium-glucose co-transporter 2 inhibition according to left ventricular ejection fraction in DAPA-HF	Dewan, P.; Solomon, S. D.; Jhund, P. S.; Inzucchi, S. E.; Køber, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.; DeMets, D. L.; Sabatine, M. S.; Bengtsson, O.; Sjöstrand, M.; Langkilde, A. M.; Anand, I. S.; B. lohlávek J; Chopra, V. K.; Dukát, A.; Kitakaze, M.; Merkely, B.; O'Meara, E.; Schou, M.; Vinh, P. N.; McMurray, J. J. V.; Dapa-Hf Investigators; Committees,	2020	European journal of heart failure	22	7	10.1002/ejhf.1867
Sekundäre Publikation	DAPA-HF	Dapagliflozin and the incidence of type 2 diabetes in patients with heart failure and reduced ejection fraction: An exploratory analysis from DAPA-HF	Inzucchi, S. E.; Docherty, K. F.; Kober, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Solomon, S. D.; Verma, S.; Belohlavek, J.; Bohm, M.; Chiang, C. E.; de Boer, R. A.; Diez, M.; Dukat, A.; Ljungman, C. E. A.; Bengtsson, O.; Langkilde, A. M.; Sjostrand, M.; Jhund, P. S.; McMurray, J. J. V.	2021	Diabetes Care	44	2	10.2337/dc20-1675
Sekundäre Publikation	DAPA-HF	Effects of dapagliflozin in DAPA-HF according to background heart failure therapy	Docherty, K. F.; Jhund, P. S.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.; DeMets, D. L.; Sabatine, M. S.; Bengtsson, O.; Sjostrand, M.; Langkilde, A. M.; Desai, A. S.; Diez, M.; Howlett, J. G.; Katova, T.; Ljungman, C. E. A.; O'Meara, E.; Petrie, M. C.; Schou, M.; Verma, S.; Vinh, P. N.; Solomon, S. D.; McMurray, J. J. V.	2020	European Heart Journal	41	25	

Typ	Acronym	Title	Authors	Year	Journal	Volume	Issue	DOI
Sekundäre Publikation	DAPA-HF	Effect of Dapagliflozin in Patients With HFrEF Treated With Sacubitril/Valsartan: The DAPA-HF Trial	Solomon, S. D.; Jhund, P. S.; Claggett, B. L.; Dewan, P.; Køber, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Inzucchi, S. E.; Desai, A. S.; Bengtsson, O.; Lindholm, D.; Sjostrand, M.; Langkilde, A. M.; McMurray, J. J. V.	2020	JACC. Heart failure	8	10	
Sekundäre Publikation	DAPA-HF	Efficacy and Safety of Dapagliflozin in Men and Women With Heart Failure With Reduced Ejection Fraction: A Prespecified Analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure Trial	Butt, J. H.; Docherty, K. F.; Petrie, M. C.; Schou, M.; Kosiborod, M. N.; O'Meara, E.; Katova, T.; Ljungman, C. E. A.; Diez, M.; Ogunniyi, M. O.; Langkilde, A. M.; Sjostrand, M.; Lindholm, D.; Bengtsson, O.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Solomon, S. D.; Jhund, P. S.; McMurray, J. J. V.; Kober, L.	2021	JAMA Cardiology	6	6	
Sekundäre Publikation	DAPA-HF	Efficacy and Safety of Dapagliflozin in Heart Failure With Reduced Ejection Fraction According to N-Terminal Pro-B-Type Natriuretic Peptide: Insights From the DAPA-HF Trial	Butt, J. H.; Adamson, C.; Docherty, K. F.; de Boer, R. A.; Petrie, M. C.; Inzucchi, S. E.; Kosiborod, M. N.; Maria Langkilde, A.; Lindholm, D.; Martinez, F. A.; Bengtsson, O.; Schou, M.; O'Meara, E.; Ponikowski, P.; Sabatine, M. S.; Sjostrand, M.; Solomon, S. D.; Jhund, P. S.; McMurray, J. J. V.; Kober, L.	2021	Circulation: Heart Failure	14	12	
Sekundäre Publikation	DAPA-HF	Efficacy of dapagliflozin in heart failure with reduced ejection fraction according to body mass index	Adamson, C.; Jhund, P. S.; Docherty, K. F.; Belohlavek, J.; Chiang, C. E.; Diez, M.; Drozdz, J.; Dukat, A.; Howlett, J.; Ljungman, C. E. A.; Petrie, M. C.; Schou, M.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Solomon, S. D.; Bengtsson, O.; Langkilde, A. M.; Lindholm, D.; Sjostrand, M.; McMurray, J. J. V.	2021	European Journal of Heart Failure	23	10	
Sekundäre Publikation	DAPA-HF	Effect of dapagliflozin on anaemia in DAPA-HF	Docherty, K. F.; Curtain, J. P.; Anand, I. S.; Bengtsson, O.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Langkilde, A. M.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Schou, M.; Sjostrand, M.; Solomon, S. D.; Jhund, P. S.; McMurray, J. J. V.; Dapa-Hf Investigators; Committees,	2021	European Journal of Heart Failure	23	4	
Sekundäre Publikation	DAPA-HF	Efficacy and safety of dapagliflozin according to aetiology in heart failure with reduced ejection fraction: insights from the DAPA-HF trial	Butt, J. H.; Nicolau, J. C.; Verma, S.; Docherty, K. F.; Petrie, M. C.; Inzucchi, S. E.; Schou, M.; Kosiborod, M. N.; Langkilde, A. M.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Sjöstrand, M.; Solomon, S. D.; Bengtsson, O.; Jhund, P. S.; McMurray, J. J. V.; Køber, L.	2021	European journal of heart failure	23	4	10.1002/ejhf.2124
Sekundäre Publikation	DAPA-HF	Patient Characteristics, Clinical Outcomes, and Effect of Dapagliflozin in Relation to Duration of Heart Failure: Is It Ever Too Late to Start a New Therapy?	Yeoh, S. E.; Dewan, P.; Jhund, P. S.; Inzucchi, S. E.; Køber, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Solomon, S. D.; Bengtsson, O.; Sjöstrand, M.; Langkilde, A. M.; McMurray, J. J. V.; Dapa-Hf Investigators; Committees,	2020	Circulation. Heart failure	13	12	10.1161/CIRCHEARTFAILURE.120.007879
Sekundäre Publikation	DAPA-HF	Efficacy of Dapagliflozin in Black Versus White Patients With Heart Failure and Reduced Ejection Fraction	Docherty, K. F.; Ogunniyi, M. O.; Anand, I. S.; Desai, A. S.; Diez, M.; Howlett, J. G.; Nicolau, J. C.; O'Meara, E.; Verma, S.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Lindholm, D.; Martinez, F. A.; Bengtsson, O.; Ponikowski, P.; Sabatine, M. S.; Sjostrand, M.; Solomon, S. D.; Langkilde, A. M.; Jhund, P. S.; McMurray, J. J. V.	2021	JACC: Heart Failure			10.1016/j.jchf.2021.08.006
Sekundäre Publikation	DAPA-HF	Efficacy of Dapagliflozin in Black Versus White Patients With Heart Failure and Reduced Ejection Fraction	Docherty, K. F.; Ogunniyi, M. O.; Anand, I. S.; Desai, A. S.; Diez, M.; Howlett, J. G.; Nicolau, J. C.; O'Meara, E.; Verma, S.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Lindholm, D.; Martinez, F. A.; Bengtsson, O.; Ponikowski, P.; Sabatine, M. S.; Sjostrand, M.; Solomon, S. D.; Langkilde, A. M.; Jhund, P. S.; McMurray, J. J. V.	2022	JACC Heart Failure	10	1	
Sekundäre Publikation	DAPA-HF	Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction Results of DAPA-HF	Jhund, P. S.; Solomon, S. D.; Docherty, K. F.; Heerspink, H. J. L.; Anand, I. S.; Bohm, M.; Chopra, V.; de Boer, R. A.; Desai, A. S.; Ge, J. B.; Kitakaze, M.; Merkley, B.; O'Meara, E.; Shou, M.; Tereshchenko, S.; Verma, S.; Vinh, P. N.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Bengtsson, O.; Langkilde, A. M.; Sjostrand, M.; McMurray, J. J. V.	2021	Circulation	143	4	10.1161/circulationaha.120.050391
Sekundäre Publikation	DAPA-HF	Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes	Petrie, M. C.; Verma, S.; Docherty, K. F.; Inzucchi, S. E.; Anand, I.; Belohlavek, J.; Bohm, M.; Chiang, C. E.; Chopra, V. K.; de Boer, R. A.; Desai, A. S.; Diez, M.; Drozdz, J.; Dukat, A.; Ge, J. B.; Howlett, J.; Katova, T.; Kitakaze, M.; Ljungman, C. E. A.; Merkely, B.; Nicolau, J. C.; O'Meara, E.; Vinh, P. N.; Schou, M.; Tereshchenko, S.; Kober, L.; Kosiborod, M. N.; Langkilde, A. M.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Sjostrand, M.; Solomon, S. D.; Johanson, P.; Greasley, P. J.; Boulton, D.; Bengtsson, O.; Jhund, P. S.; McMurray, J. J. V.	2020	Jama-Journal of the American Medical Association	323	14	10.1001/jama.2020.1906

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Sekundäre Publikation	DAPA-HF	Dapagliflozin and Recurrent Heart Failure Hospitalizations in Heart Failure With Reduced Ejection Fraction: An Analysis of DAPA-HF	Jhund, P. S.; Ponikowski, P.; Docherty, K. F.; Gasparyan, S. B.; Bohm, M.; Chiang, C. E.; Desai, A. S.; Howlett, J.; Kitakaze, M.; Petrie, M. C.; Verma, S.; Bengtsson, O.; Langkilde, A. M.; Sjostrand, M.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Martinez, F. A.; Sabatine, M. S.; Solomon, S. D.; McMurray, J. J. V.	2021	Circulation	143	20	
Sekundäre Publikation	DAPA-HF	Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF	Curtain, J. P.; Docherty, K. F.; Jhund, P. S.; Petrie, M. C.; Inzucchi, S. E.; Køber, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Bengtsson, O.; Langkilde, A. M.; Sjöstrand, M.; Solomon, S. D.; McMurray, J. J. V.	2021	European heart journal	42	36	10.1093/eurheartj/ehab560
Sekundäre Publikation	DAPA-HF	Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients With Heart Failure and Reduced Ejection Fraction: Results From the DAPA-HF Trial	Kosiborod, M. N.; Jhund, P. S.; Docherty, K. F.; Diez, M.; Petrie, M. C.; Verma, S.; Nicolau, J. C.; Merkely, B.; Kitakaze, M.; DeMets, D. L.; Inzucchi, S. E.; Køber, L.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Solomon, S. D.; Bengtsson, O.; Lindholm, D.; Niklasson, A.; Sjöstrand, M.; Langkilde, A. M.; McMurray, J. J. V.	2020	Circulation	141	2	10.1161/CIRCULATIONAHA.119.044138
Sekundäre Publikation	DAPA-HF	Effect of dapagliflozin according to baseline systolic blood pressure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF)	Serenelli, M.; Bohm, M.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Solomon, S. D.; DeMets, D. L.; Bengtsson, O.; Sjostrand, M.; Langkilde, A. M.; Anand, I. S.; Chiang, C. E.; Chopra, V. K.; de Boer, R. A.; Diez, M.; Dukat, A.; Ge, J. B.; Howlett, J. G.; Katova, T.; Kitakaze, M.; Ljungman, C. E. A.; Verma, S.; Docherty, K. F.; Jhund, P. S.; McMurray, J. J. V.; Dapa-Hf Investigators Comm	2020	European Heart Journal	41	36	10.1093/eurheartj/ehaa496
Sekundäre Publikation	DAPA-HF	Serial Assessment of High-Sensitivity Cardiac Troponin and the Effect of Dapagliflozin in Patients With Heart Failure With Reduced Ejection Fraction: An Analysis of the DAPA-HF Trial	Berg, D. D.; Docherty, K. F.; Sattar, N.; Jarolim, P.; Welsh, P.; Jhund, P. S.; Anand, I. S.; Chopra, V.; de Boer, R. A.; Kosiborod, M. N.; Nicolau, J. C.; O'Meara, E.; Schou, M.; Hammarstedt, A.; Langkilde, A. M.; Lindholm, D.; Sjostrand, M.; McMurray, J. J. V.; Sabatine, M. S.; Morrow, D. A.	2022	Circulation	145	3	
Sekundäre Publikation	DAPA-HF	Time to Clinical Benefit of Dapagliflozin and Significance of Prior Heart Failure Hospitalization in Patients With Heart Failure With Reduced Ejection Fraction	Berg, D. D.; Jhund, P. S.; Docherty, K. F.; Murphy, S. A.; Verma, S.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Langkilde, A. M.; Martinez, F. A.; Bengtsson, O.; Ponikowski, P.; Sjostrand, M.; Solomon, S. D.; McMurray, J. J. V.; Sabatine, M. S.	2021	JAMA Cardiology	6	5	
Sekundäre Publikation	DAPA-HF	Effect of Dapagliflozin on Outpatient Worsening of Patients With Heart Failure and Reduced Ejection Fraction: A Prespecified Analysis of DAPA-HF	Docherty, K. F.; Jhund, P. S.; Anand, I.; Bengtsson, O.; Böhm, M.; de Boer, R. A.; DeMets, D. L.; Desai, A. S.; Drozdz, J.; Howlett, J.; Inzucchi, S. E.; Johanson, P.; Katova, T.; Køber, L.; Kosiborod, M. N.; Langkilde, A. M.; Lindholm, D.; Martinez, F. A.; Merkely, B.; Nicolau, J. C.; O'Meara, E.; Ponikowski, P.; Sabatine, M. S.; Sjöstrand, M.; Solomon, S. D.; Tereshchenko, S.; Verma, S.; McMurray, J. J. V.	2020	Circulation	142	17	10.1161/CIRCULATIONAHA.120.047480
Primäre Publikation	DEFINE-HF	Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction	Nassif, M. E.; Windsor, S.; Tang, F.; Khariton, Y.; Husain, M.; Inzucchi, S.; McGuire, D.; Pitt, B.; Scirica, B.; Austin, B.; Drazner, M.; Fong, M.; Givertz, M.; Gordon, R.; Jermyn, R.; Katz, S.; Lamba, S.; Lanfear, D.; LaRue, S.; Lindenfeld, J.; Malone, M.; Margulies, K.; Mentz, R.; Kannan Mutharasan, R.; Pursley, M.; Umpierrez, G.; Kosiborod, M.; Malik, A.; Wenger, N.; Ogunniyi, M.; Vellanki, P.; Murphy, B.; Newman, J.; Hartupee, J.; Gupta, C.; Goldsmith, M.; Baweja, P.; Montero, M.; Gottlieb, S.; Costanzo, M. R.; Hoang, T.; Warnock, A.; Allen, L.; Tang, W.; Chen, H.; Cox, J.	2019	Circulation	140	18	10.1161/CIRCULATIONAHA.119.042929
Sekundäre Publikation	DEFINE-HF	Dapagliflozin effects on lung fluid volumes in patients with heart failure and reduced ejection fraction: Results from the DEFINE-HF trial	Nassif, M. E.; Windsor, S. L.; Tang, F. M.; Husain, M.; Inzucchi, S. E.; McGuire, D. K.; Pitt, B.; Scirica, B. M.; Austin, B.; Fong, M. W.; LaRue, S. J.; Umpierrez, G.; Hartupee, J.; Khariton, Y.; Malik, A. O.; Ogunniyi, M. O.; Wenger, N. K.; Kosiborod, M. N.	2021	Diabetes Obesity & Metabolism	23	6	10.1111/dom.14352
Primäre Publikation	ELSI	Effects of the sodium-glucose cotransporter 2 inhibitor empagliflozin on vascular function in patients with chronic heart failure	Kolwelter, J.; Bosch, A.; Jung, S.; Stabel, L.; Kannenkeril, D.; Ott, C.; Bramlage, P.; Schiffer, M.; Achenbach, S.; Schmieder, R. E.	2021	ESC Heart Failure			10.1002/ehf2.13622
Sekundäre Publikation	ELSI	Effect of empagliflozin on ketone bodies in patients with stable chronic heart failure	Pietschner, R.; Kolwelter, J.; Bosch, A.; Striepe, K.; Jung, S.; Kannenkeril, D.; Ott, C.; Schiffer, M.; Achenbach, S.; Schmieder, R. E.	2021	Cardiovascular Diabetology	20	1	10.1186/s12933-021-01410-7

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Einzelpublikation	NA	Empagliflozin Effects on Pulmonary Artery Pressure in Patients With Heart Failure Results From the EMBRACE-HF Trial	Nassif, M. E.; Qintar, M.; Windsor, S. L.; Jermyn, R.; Shavelle, D. M.; Tang, F. M.; Lamba, S.; Bhatt, K.; Brush, J.; Civitello, A.; Gordon, R.; Jonsson, O.; Lampert, B.; Pelzel, J.; Kosiborod, M. N.	2021	Circulation	143	17	10.1161/circulationaha.120.052503
Primäre Publikation	PARADIGM_HF	Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure	McMurray, John J.V.; Packer, Milton; Desai, Akshay S.; Gong, Jianjian; Lefkowitz, Martin P.; Rizkala, Adel R.; Rouleau, Jean L.; Shi, Victor C.; Solomon, Scott D.; Swedberg, Karl; Zile, Michael R.	2014	New England Journal of Medicine	371	11	10.1056/NEJMoa1409077
Design	PARADIGM_HF	Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact	McMurray, J. J.; Packer, M.; Desai, A. S.; Gong, J.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J.; Shi, V. C.; Solomon, S. D.; Swedberg, K.; Zile, M. R.; Paradigm-Hf Committees; Investigators,	2013	European journal of heart failure 2013;15(9):	15	9	
Sekundäre Publikation	PARADIGM_HF	Effect of sacubitril/valsartan on recurrent events in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)	Mogensen, U. M.; Gong, J. J.; Jhund, P. S.; Shen, L.; Kober, L.; Desai, A. S.; Lefkowitz, M. P.; Packer, M.; Rouleau, J. L.; Solomon, S. D.; Claggett, B. L.; Swedberg, K.; Zile, M. R.; Mueller-Velten, G.; McMurray, J. J. V.	2018	European Journal of Heart Failure	20	4	10.1002/ejhf.1139
Sekundäre Publikation	PARADIGM_HF	Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial	Packer, M.; Claggett, B.; Lefkowitz, M. P.; McMurray, J. J. V.; Rouleau, J. L.; Solomon, S. D.; Zile, M. R.	2018	The Lancet Diabetes & Endocrinology	6	7	
Sekundäre Publikation	PARADIGM_HF	Estimated 5-Year Number Needed to Treat to Prevent Cardiovascular Death or Heart Failure Hospitalization With Angiotensin Receptor-Neprilysin Inhibition vs Standard Therapy for Patients With Heart Failure With Reduced Ejection Fraction: An Analysis of Dat	Srivastava, P. K.; Claggett, B. L.; Solomon, S. D.; McMurray, J. J. V.; Packer, M.; Zile, M. R.; Desai, A. S.; Rouleau, J. L.; Swedberg, K.; Fonarow, G. C.	2018	JAMA cardiology	3	12	
Sekundäre Publikation	PARADIGM_HF	Outcomes and Effect of Treatment According to Etiology in HFrEF: An Analysis of PARADIGM-HF	Balmforth, C.; Simpson, J.; Shen, L.; Jhund, P. S.; Lefkowitz, M.; Rizkala, A. R.; Rouleau, J. L.; Shi, V.; Solomon, S. D.; Swedberg, K.; Zile, M. R.; Packer, M.; McMurray, J. J. V.	2019	JACC. Heart failure	7	6	
Sekundäre Publikation	PARADIGM_HF	Dementia-related adverse events in PARADIGM-HF and other trials in heart failure with reduced ejection fraction	Cannon, J. A.; Shen, L.; Jhund, P. S.; Kristensen, S. L.; Kober, L.; Chen, F. B.; Gong, J. J.; Lefkowitz, M. P.; Rouleau, J. L.; Shi, V. C.; Swedberg, K.; Zile, M. R.; Solomon, S. D.; Packer, M.; McMurray, J. J. V.; Paradigm Hf Investigators Comm	2017	European Journal of Heart Failure	19	1	10.1002/ejhf.687
Sekundäre Publikation	PARADIGM_HF	Clinical Characteristics and Outcomes of Patients With Heart Failure With Reduced Ejection Fraction and Chronic Obstructive Pulmonary Disease: Insights From PARADIGM-HF	Ehteshami-Afshar, S.; Mooney, L.; Dewan, P.; Desai, A. S.; Lang, N. N.; Lefkowitz, M. P.; Petrie, M. C.; Rizkala, A. R.; Rouleau, J. L.; Solomon, S. D.; Swedberg, K.; Shi, V. C.; Zile, M. R.; Packer, M.; McMurray, J. J. V.; Jhund, P. S.; Hawkins, N. M.	2021	Journal of the American Heart Association	10	4	
Sekundäre Publikation	PARADIGM_HF	Comparing LCZ696 with enalapril according to baseline risk using the MAGGIC and EMPHASIS-HF risk scores: an analysis of mortality and morbidity in PARADIGM-HF	Simpson, J.; Jhund, P. S.; Silva Cardoso, J.; Martinez, F.; Mosterd, A.; Ramires, F.; Rizkala, A. R.; Senni, M.; Squire, I.; Gong, J.; Lefkowitz, M. P.; Shi, V. C.; Desai, A. S.; Rouleau, J. L.; Swedberg, K.; Zile, M. R.; McMurray, J. J. V.; Packer, M.; Solomon, S. D.; Paradigm-Hf Investigators; Committees,	2015	Journal of the American College of Cardiology	66	19	
Sekundäre Publikation	PARADIGM_HF	Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF	Böhm, M.; Young, R.; Jhund, P. S.; Solomon, S. D.; Gong, J.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J. L.; Shi, V. C.; Swedberg, K.; Zile, M. R.; Packer, M.; McMurray, J. J. V.	2017	European heart journal	38	15	
Sekundäre Publikation	PARADIGM_HF	Sacubitril/Valsartan and Sudden Cardiac Death According to Implantable Cardioverter-Defibrillator Use and Heart Failure Cause: A PARADIGM-HF Analysis	Rohde, L. E.; Chatterjee, N. A.; Vaduganathan, M.; Claggett, B.; Packer, M.; Desai, A. S.; Zile, M.; Rouleau, J.; Swedberg, K.; Lefkowitz, M.; Shi, V.; McMurray, J. J. V.; Solomon, S. D.	2020	JACC Heart Failure	8	10	
Sekundäre Publikation	PARADIGM_HF	Serum potassium in the PARADIGM-HF trial	Ferreira, J. P.; Mogensen, U. M.; Jhund, P. S.; Desai, A. S.; Rouleau, J. L.; Zile, M. R.; Rossignol, P.; Zannad, F.; Packer, M.; Solomon, S. D.; McMurray, J. J. V.	2020	European journal of heart failure	22	11	
Sekundäre Publikation	PARADIGM_HF	Sacubitril/valsartan reduces serum uric acid concentration, an independent predictor of adverse outcomes in PARADIGM-HF	Mogensen, U. M.; Køber, L.; Jhund, P. S.; Desai, A. S.; Senni, M.; Kristensen, S. L.; Dukát, A.; Chen, C. H.; Ramires, F.; Lefkowitz, M. P.; Prescott, M. F.; Shi, V. C.; Rouleau, J. L.; Solomon, S. D.; Swedberg, K.; Packer, M.; McMurray, J. J. V.; Paradigm-Hf Investigators; Committees,	2018	European journal of heart failure	20	3	
Sekundäre Publikation	PARADIGM_HF	B-Type Natriuretic Peptide During Treatment With Sacubitril/Valsartan: The PARADIGM-HF Trial	Myhre, P. L.; Vaduganathan, M.; Claggett, B.; Packer, M.; Desai, A. S.; Rouleau, J. L.; Zile, M. R.; Swedberg, K.; Lefkowitz, M.; Shi, V.; McMurray, J. J. V.; Solomon, S. D.	2019	Journal of the American College of Cardiology	73	11	

Typ	Acronym	Title	Authors	Year	Journal	Volume	Issue	DOI
Sekundäre Publikation	PARADIGM_HF	Efficacy of Sacubitril/Valsartan Relative to a Prior Decompensation: The PARADIGM-HF Trial	Solomon, S. D.; Claggett, B.; Packer, M.; Desai, A.; Zile, M. R.; Swedberg, K.; Rouleau, J.; Shi, V.; Lefkowitz, M.; McMurray, J. J. V.	2016	JACC. Heart failure	4	10	
Sekundäre Publikation	PARADIGM_HF	Geographic variations in the PARADIGM-HF heart failure trial	Kristensen, S. L.; Martinez, F.; Jhund, P. S.; Arango, J. L.; Belohlavek, J.; Boytsov, S.; Cabrera, W.; Gomez, E.; Hagege, A. A.; Huang, J.; Kiatchoosakun, S.; Kim, K. S.; Mendoza, I.; Senni, M.; Squire, I. B.; Vinereanu, D.; Wong, R. C. C.; Gong, J. J.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J. L.; Shi, V. C.; Solomon, S. D.; Swedberg, K.; Zile, M. R.; Packer, M.; McMurray, J. J. V.	2016	European Heart Journal	37	41	10.1093/eurheartj/ehw226
Sekundäre Publikation	PARADIGM_HF	Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial	Vardeny, O.; Claggett, B.; Packer, M.; Zile, M. R.; Rouleau, J.; Swedberg, K.; Teerlink, J. R.; Desai, A. S.; Lefkowitz, M.; Shi, V.; McMurray, J. J.; Solomon, S. D.; Prospective Comparison of, Arni with Acei to Determine Impact on Global Mortality; Morbidity in Heart Failure, Investigators	2016	European journal of heart failure	18	10	
Sekundäre Publikation	PARADIGM_HF	Reduced Risk of Hyperkalemia During Treatment of Heart Failure With Mineralocorticoid Receptor Antagonists by Use of Sacubitril/Valsartan Compared With Enalapril A Secondary Analysis of the PARADIGM-HF Trial	Desai, A. S.; Vardeny, O.; Claggett, B.; McMurray, J. J. V.; Packer, M.; Swedberg, K.; Rouleau, J. L.; Zile, M. R.; Lefkowitz, M.; Shi, V.; Solomon, S. D.	2017	Jama Cardiology	2	1	10.1001/jamacardio.2016.4733
Sekundäre Publikation	PARADIGM_HF	Influence of Sacubitril/Valsartan (LCZ696) on 30-Day Readmission After Heart Failure Hospitalization	Desai, A. S.; Claggett, B. L.; Packer, M.; Zile, M. R.; Rouleau, J. L.; Swedberg, K.; Shi, V.; Lefkowitz, M.; Starling, R.; Teerlink, J.; McMurray, J. J. V.; Solomon, S. D.; Paradigm-Hf Investigators	2016	Journal of the American College of Cardiology	68	3	
Sekundäre Publikation	PARADIGM_HF	Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients	Desai, A. S.; McMurray, J. J. V.; Packer, M.; Swedberg, K.; Rouleau, J. L.; Chen, F.; Gong, J.; Rizkala, A. R.; Brahimi, A.; Claggett, B.; Finn, P. V.; Hartley, L. H.; Liu, J.; Lefkowitz, M.; Shi, V.; Zile, M. R.; Solomon, S. D.	2015	European heart journal	36	30	
Sekundäre Publikation	PARADIGM_HF	Renal Effects and Associated Outcomes During Angiotensin-Neprilysin Inhibition in Heart Failure	Damman, K.; Gori, M.; Claggett, B.; Jhund, P. S.; Senni, M.; Lefkowitz, M. P.; Prescott, M. F.; Shi, V. C.; Rouleau, J. L.; Swedberg, K.; Zile, M. R.; Packer, M.; Desai, A. S.; Solomon, S. D.; McMurray, J. J. V.	2018	JACC. Heart failure	6	6	
Sekundäre Publikation	PARADIGM_HF	Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure	Zile, M. R.; Claggett, B. L.; Prescott, M. F.; McMurray, J. J. V.; Packer, M.; Rouleau, J. L.; Swedberg, K.; Desai, A. S.; Gong, J. J.; Shi, V. C.; Solomon, S. D.	2016	Journal of the American College of Cardiology	68	22	10.1016/j.jacc.2016.09.931
Sekundäre Publikation	PARADIGM_HF	Liver function and prognosis, and influence of sacubitril/valsartan in patients with heart failure with reduced ejection fraction	Suzuki, K.; Claggett, B.; Minamisawa, M.; Packer, M.; Zile, M. R.; Rouleau, J.; Swedberg, K.; Lefkowitz, M.; Shi, V.; McMurray, J. J. V.; Zucker, S. D.; Solomon, S. D.	2020	European journal of heart failure	22	9	
Sekundäre Publikation	PARADIGM_HF	Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in Heart Failure with Reduced Ejection Fraction: The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (	Solomon, S. D.; Claggett, B.; Desai, A. S.; Packer, M.; Zile, M.; Swedberg, K.; Rouleau, J. L.; Shi, V. C.; Starling, R. C.; Kozan, Ö; Dukat, A.; Lefkowitz, M. P.; McMurray, J. J.	2016	Circulation. Heart failure	9	3	
Sekundäre Publikation	PARADIGM_HF	Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial	Vardeny, O.; Claggett, B.; Kachadourian, J.; Desai, A. S.; Packer, M.; Rouleau, J.; Zile, M. R.; Swedberg, K.; Lefkowitz, M.; Shi, V.; McMurray, J. J. V.; Solomon, S. D.	2019	European journal of heart failure	21	3	
Sekundäre Publikation	PARADIGM_HF	Incidence, Predictors, and Outcomes Associated With Hypotensive Episodes Among Heart Failure Patients Receiving Sacubitril/Valsartan or Enalapril: The PARADIGM-HF Trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin-	Vardeny, O.; Claggett, B.; Kachadourian, J.; Pearson, S. M.; Desai, A. S.; Packer, M.; Rouleau, J.; Zile, M. R.; Swedberg, K.; Lefkowitz, M.; Shi, V.; McMurray, J. J. V.; Solomon, S. D.	2018	Circulation: Heart Failure	11	4	
Sekundäre Publikation	PARADIGM_HF	Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF	Jhund, P. S.; Fu, M.; Bayram, E.; Chen, C. H.; Negrusz-Kawecka, M.; Rosenthal, A.; Desai, A. S.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J. L.; Shi, V. C.; Solomon, S. D.; Swedberg, K.; Zile, M. R.; McMurray, J. J. V.; Packer, M.; Paradigm-Hf Investigators Comm	2015	European Heart Journal	36	38	10.1093/eurheartj/ehv330
Sekundäre Publikation	PARADIGM_HF	Prognostic Implications of Congestion on Physical Examination Among Contemporary Patients With Heart Failure and Reduced Ejection Fraction: PARADIGM-HF	Selvaraj, S.; Claggett, B.; Pozzi, A.; McMurray, J. J. V.; Jhund, P. S.; Packer, M.; Desai, A. S.; Lewis, E. F.; Vaduganathan, M.; Lefkowitz, M. P.; Rouleau, J. L.; Shi, V. C.; Zile, M. R.; Swedberg, K.; Solomon, S. D.	2019	Circulation	140	17	
Sekundäre Publikation	PARADIGM_HF	Growth differentiation factor-15 is not modified by sacubitril/valsartan and is an independent marker of risk in patients with heart failure and reduced ejection fraction: the PARADIGM-HF trial	Bouabdallaoui, N.; Claggett, B.; Zile, M. R.; McMurray, J. J. V.; O'Meara, E.; Packer, M.; Prescott, M. F.; Swedberg, K.; Solomon, S. D.; Rouleau, J. L.; Paradigm-Hf Investigators; Committees,	2018	European journal of heart failure	20	12	

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Sekundäre Publikation	PARADIGM_HF	Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure	Packer, M.; McMurray, J. J.; Desai, A. S.; Gong, J.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J. L.; Shi, V. C.; Solomon, S. D.; Swedberg, K.; Zile, M.; Andersen, K.; Arango, J. L.; Arnold, J. M.; B. Iohlávek J; Böhm, M.; Boytsov, S.; Burgess, L. J.; Cabrera, W.; Calvo, C.; Chen, C. H.; Dukat, A.; Duarte, Y. C.; Erglis, A.; Fu, M.; Gomez, E.; Gonzàlez-Medina, A.; Hagège, A. A.; Huang, J.; Katova, T.; Kiatchoosakun, S.; Kim, K. S.; Kozan, Ö; Llamas, E. B.; Martinez, F.; Merkely, B.; Mendoza, I.; Mosterd, A.; Negrusz-Kawecka, M.; Peuhkurinen, K.; Ramires, F. J.; Refsgaard, J.; Rosenthal, A.; Senni, M.; Sibulo, A. S.; Silva-Cardoso, J.; Squire, I. B.; Starling, R. C.; Teerlink, J. R.; Vanhaecke, J.; Vinereanu, D.; Wong, R. C.; Paradigm-Hf Investigators; Coordinators,	2015	Circulation	131	1	
Sekundäre Publikation	PARADIGM_HF	The effects of sacubitril/valsartan on coronary outcomes in PARADIGM-HF	Mogensen, U. M.; Kober, L.; Kristensen, S. L.; Jhund, P. S.; Gong, J. J.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J. L.; Shi, V. C.; Swedberg, K.; Zile, M. R.; Solomon, S. D.; Packer, M.; McMurray, J. J. V.; Paradigm-Hf Investigators	2017	American Heart Journal	188		10.1016/j.ahj.2017.02.034
Sekundäre Publikation	PARADIGM_HF	Angioedema in heart failure patients treated with sacubitril/valsartan (LCZ696) or enalapril in the PARADIGM-HF study	Shi, V.; Senni, M.; Streefkerk, H.; Modgill, V.; Zhou, W. C.; Kaplan, A.	2018	International Journal of Cardiology	264		10.1016/j.ijcard.2018.03.121
Sekundäre Publikation	PARADIGM_HF	Effects of Sacubitril/Valsartan on Physical and Social Activity Limitations in Patients With Heart Failure: A Secondary Analysis of the PARADIGM-HF Trial	Chandra, A.; Lewis, E. F.; Claggett, B. L.; Desai, A. S.; Packer, M.; Zile, M. R.; Swedberg, K.; Rouleau, J. L.; Shi, V. C.; Lefkowitz, M. P.; Katova, T.; McMurray, J. J. V.; Solomon, S. D.	2018	JAMA cardiology	3	6	
Sekundäre Publikation	PARADIGM_HF	Effects of Sacubitril/Valsartan on Biomarkers of Extracellular Matrix Regulation in Patients With HFrEF	Zile, M. R.; O'Meara, E.; Claggett, B.; Prescott, M. F.; Solomon, S. D.; Swedberg, K.; Packer, M.; McMurray, J. J. V.; Shi, V.; Lefkowitz, M.; Rouleau, J.	2019	Journal of the American College of Cardiology	73	7	
Sekundäre Publikation	PARADIGM_HF	Effect of sacubitril/valsartan vs. enalapril on changes in heart failure therapies over time: the PARADIGM-HF trial	Bhatt, A. S.; Vaduganathan, M.; Claggett, B. L.; Liu, J. K.; Packer, M.; Desai, A. S.; Lefkowitz, M. P.; Rouleau, J. L.; Shi, V. C.; Zile, M. R.; Swedberg, K.; Vardeny, O.; McMurray, J. J. V.; Solomon, S. D.	2021	European Journal of Heart Failure	23	9	10.1002/ejhf.2259
Sekundäre Publikation	PARADIGM_HF	Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial	Seferovic, J. P.; Claggett, B.; Seidelmann, S. B.; Seely, E. W.; Packer, M.; Zile, M. R.; Rouleau, J. L.; Swedberg, K.; Lefkowitz, M.; Shi, V. C.; Desai, A. S.; McMurray, J. J. V.; Solomon, S. D.	2017	The lancet. Diabetes & endocrinology	5	5	
Sekundäre Publikation	PARADIGM_HF	Efficacy and safety of sacubitril/valsartan compared with enalapril in patients with chronic heart failure and reduced ejection fraction: Results from PARADIGM-HF India sub-study	Jain, A. R.; Aggarwal, R. K.; Rao, N. S.; Billa, G.; Kumar, S.	2020	Indian heart journal	72	6	
Sekundäre Publikation	PARADIGM_HF	Importance of Clinical Worsening of Heart Failure Treated in the Outpatient Setting Evidence From the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF)	Okumura, N.; Jhund, P. S.; Gong, J. J.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J. L.; Shi, V. C.; Swedberg, K.; Zile, M. R.; Solomon, S. D.; Packer, M.; McMurray, J. J. V.; Paradigm-Hf Investigators Comm	2016	Circulation	133	23	10.1161/circulationaha.115.020729
Sekundäre Publikation	PARADIGM_HF	Independent Prognostic Value of Serum Soluble ST2 Measurements in Patients With Heart Failure and a Reduced Ejection Fraction in the PARADIGM-HF Trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart	O'Meara, E.; Prescott, M. F.; Claggett, B.; Rouleau, J. L.; Chiang, L. M.; Solomon, S. D.; Packer, M.; McMurray, J. J. V.; Zile, M. R.	2018	Circulation: Heart Failure	11	5	
Sekundäre Publikation	PARADIGM_HF	Effects of Sacubitril/Valsartan in the PARADIGM-HF Trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) According to Background Therapy	Okumura, N.; Jhund, P. S.; Gong, J. J.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J. L.; Shi, V. C.; Swedberg, K.; Zile, M. R.; Solomon, S. D.; Packer, M.; McMurray, J. J. V.	2016	Circulation-Heart Failure	9	9	10.1161/circheartfailure.116.003212
Sekundäre Publikation	PARADIGM_HF	Influenza Vaccination in Patients With Chronic Heart Failure: The PARADIGM-HF Trial	Vardeny, O.; Claggett, B.; Udell, J. A.; Packer, M.; Zile, M.; Rouleau, J.; Swedberg, K.; Desai, A. S.; Lefkowitz, M.; Shi, V.; McMurray, J. J. V.; Solomon, S. D.; Paradigm-Hf Investigators	2016	JACC. Heart failure	4	2	
Sekundäre Publikation	PARADIGM_HF	Health-Related Quality of Life Outcomes in PARADIGM-HF	Lewis, E. F.; Claggett, B. L.; McMurray, J. J. V.; Packer, M.; Lefkowitz, M. P.; Rouleau, J. L.; Liu, J. K.; Shi, V. C.; Zile, M. R.; Desai, A. S.; Solomon, S. D.; Swedberg, K.	2017	Circulation-Heart Failure	10	8	10.1161/circheartfailure.116.003430
Sekundäre Publikation	PARADIGM_HF	Effect of sacubitril/valsartan on investigator-reported ventricular arrhythmias in PARADIGM-HF	Curtain, J. P.; Jackson, A. M.; Shen, L.; Jhund, P. S.; Docherty, K. F.; Petrie, M. C.; Castagno, D.; Desai, A. S.; Rohde, L. E.; Lefkowitz, M. P.; Rouleau, J. L.; Zile, M. R.; Solomon, S. D.; Swedberg, K.; Packer, M.; McMurray, J. J. V.	2021	European Journal of Heart Failure	30		

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Primäre Publikation	EVALUATE-HF	Effect of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial	Desai, A. S.; Solomon, S. D.; Shah, A. M.; Claggett, B. L.; Fang, J. C.; Izzo, J.; McCague, K.; Abbas, C. A.; Rocha, R.; Mitchell, G. F.; Martinez-Castrillon, M.; Beato, J.; Shah, V.; Pianko, L.; Bouza, M.; Alhaddad, M.; Kashani, A.; Sampognaro, G.; Stahl, L.; Lehman, J.; Lebhar, S.; Napoli, M.; Consuegra, A. T.; Gonzalez, H.; Lloret, R.; Ariani, M.; Azizad, M.; Shah, A.; Henderson, D.; Covalesky, J.; Brabham, D.; Chane, M.; Sanchez, E.; Vega, R.; Clay, A.; McClure, J.; Sogade, F.; Ortiz-Munoz, L.; Lewis, T.; Zequeira, A. G.; Shah, R.; Lepor, N.; Gonzalez, M.; Tidman, R.; Berman, J.; Lorenz, D.; Nanna, M.; Greene, T.; Portnay, E.; Bernstein, M.; Somodevilla, G.; Grodman, R.; Gaffney, M.; Park, H.; Dor, I.; Aslam, S.; Jackson, R.; Perez, G.; Martinez, L.; Gandelman, G.; Dy, J.; Salacata, A.; Abadier, R.; Steuter, J.; Mahmood, S.; Betton, H.; Vora, K.; Tallaj, J.; Weinstein, D.; Alhosaini, H.; Everett, J.; Rosenberg, M.; Dunlap, S.; Akinboboy, O.; Walia, J.; Lyandres, Y.; Harris, B.; Abo-Auda, W.; Stearns, Z.; Kazemi, N.; Bradley, A.; Megna, L.; Taylor, J.; Innasimuthu, A.; Waggoner, L. D.; Moraes, D.; Jani, S.; Chronos, N.; Joshi, N.; Radin, M.; Suleman, A.; Grena, P.; Agrawal, S.; Holmberg, M.; Evaluate-Hf Investigators	2019	Jama-Journal of the American Medical Association	322	11	10.1001/jama.2019.12843
Sekundäre Publikation	EVALUATE-HF	Hemodynamic Effects of Sacubitril-Valsartan Versus Enalapril in Patients With Heart Failure in the EVALUATE-HF Study: Effect Modification by Left Ventricular Ejection Fraction and Sex	Mitchell, G. F.; Solomon, S. D.; Shah, A. M.; Claggett, B. L.; Fang, J. C.; Izzo, J.; Abbas, C. A.; Desai, A. S.; Evaluate-Hf Investigators*	2021	Circulation. Heart failure	14	3	
Primäre Publikation	TITRIATION	Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens	Senni, M.; McMurray, J. J. V.; Wachter, R.; McIntyre, H. F.; Reyes, A.; Majercak, I.; Andreka, P.; Shehova-Yankova, N.; Anand, I.; Yilmaz, M. B.; Gogia, H.; Martinez-Selles, M.; Fischer, S.; Zilahi, Z.; Cosmi, F.; Gelev, V.; Galve, E.; Gomez-Doblas, J. J.; Nociar, J.; Radomska, M.; Sokolova, B.; Volterrani, M.; Sarkar, A.; Reimund, B.; Chen, F. B.; Charney, A.	2016	European Journal of Heart Failure	18	9	10.1002/ejhf.548
Sekundäre Publikation	TITRIATION	Impact of systolic blood pressure on the safety and tolerability of initiating and up-titrating sacubitril/valsartan in patients with heart failure and reduced ejection fraction: insights from the TITRATION study	Senni, M.; McMurray, J. J. V.; Wachter, R.; McIntyre, H. F.; Anand, I. S.; Duino, V.; Sarkar, A.; Shi, V.; Charney, A.	2018	European journal of heart failure	20	3	
Primäre Publikation	LIFE	Effect of Treatment With Sacubitril/Valsartan in Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial	Mann, D. L.; Givertz, M. M.; Vader, J. M.; Starling, R. C.; Shah, P.; McNulty, S. E.; Anstrom, K. J.; Margulies, K. B.; Kiernan, M. S.; Mahr, C.; Gupta, D.; Redfield, M. M.; Lala, A.; Lewis, G. D.; DeVore, A. D.; Desvigne-Nickens, P.; Hernandez, A. F.; Braunwald, E.; Life Investigators	2022	JAMA Cardiology	7	1	
Design	LIFE	Sacubitril/Valsartan in Advanced Heart Failure With Reduced Ejection Fraction: Rationale and Design of the LIFE Trial	Mann, D. L.; Greene, S. J.; Givertz, M. M.; Vader, J. M.; Starling, R. C.; Ambrosy, A. P.; Shah, P.; McNulty, S. E.; Mahr, C.; Gupta, D.; Redfield, M. M.; Lala, A.; Lewis, G. D.; Mohammed, S. F.; Gilotra, N. A.; DeVore, A. D.; Gorodeski, E. Z.; Desvigne-Nickens, P.; Hernandez, A. F.; Braunwald, E.; Life Investigators	2020	JACC. Heart failure	8	10	
Primäre Publikation	PARALLEL-HF	Efficacy and Safety of Sacubitril/Valsartan in Japanese Patients With Chronic Heart Failure and Reduced Ejection Fraction - Results From the PARALLEL-HF Study	Tsutsui, H.; Momomura, S. I.; Saito, Y.; Ito, H.; Yamamoto, K.; Sakata, Y.; Desai, A. S.; Ohishi, T.; Iimori, T.; Kitamura, T.; Guo, W. N.; Parallel-Hf Investigators	2021	Circulation Journal	85	5	10.1253/circj.CJ-20-0854
Design	PRALELL-HF	Efficacy and safety of sacubitril/valsartan (LCZ696) in Japanese patients with chronic heart failure and reduced ejection fraction: Rationale for and design of the randomized, double-blind PARALLEL-HF study	Tsutsui, H.; Momomura, S.; Saito, Y.; Ito, H.; Yamamoto, K.; Ohishi, T.; Okino, N.; Guo, W. N.	2017	Journal of Cardiology	70	3-4	10.1016/j.jjcc.2016.11.011
Primäre Publikation	AWAKE-HF	The AWAKE-HF Study: Sacubitril/Valsartan Impact on Daily Physical Activity and Sleep in Heart Failure	Khandwalla, R. M.; Grant, D.; Birkeland, K.; Heywood, J. T.; Fombu, E.; Owens, R. L.; Steinhubl, S. R.; Awake-Hf Study Investigators	2021	American Journal of Cardiovascular Drugs	21	2	10.1007/s40256-020-00440-y
Sekundäre Publikation	AWAKE-HF	Sleep Outcomes From AWAKE-HF: A Randomized Clinical Trial of Sacubitril/Valsartan vs Enalapril in Patients With Heart Failure and Reduced Ejection Fraction	Owens, R. L.; Birkeland, K.; Heywood, J. T.; Steinhubl, S. R.; Dorn, J.; Grant, D.; Fombu, E.; Khandwalla, R.; Awake-Hf Study Investigators	2021	Journal of Cardiac Failure	27	12	10.1016/j.cardfail.2021.07.021
Design	AWAKE-HF	Activity Sensors to Evaluate the Effect of Sacubitril/Valsartan on Quality-of-Life in Heart Failure: rational and design of the AWAKE-HF study	Khandwalla, R. M.; Birkeland, K.; Heywood, J. T.; Steinhubl, S.; McCague, K.; Fombu, E.; Grant, D.; Riebman, J. B.; Owens, R. L.	2019	ESC heart failure	6	6	
Primäre Publikation	OUTSTEP-HF	OUTSTEP-HF: randomised controlled trial comparing short-term effects of sacubitril/valsartan versus enalapril on daily physical activity in patients with chronic heart failure with reduced ejection fraction	Piepoli, M. F.; Hussain, R. I.; Comin-Colet, J.; Dosantos, R.; Ferber, P.; Jaarsma, T.; Edelmann, F.	2021	European journal of heart failure	23	1	

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Design	OUTSTEP-HF	Rationale and study design of OUTSTEP-HF: a randomised controlled study to assess the effect of sacubitril/valsartan and enalapril on physical activity measured by accelerometry in patients with heart failure with reduced ejection fraction	Edelmann, F.; Jaarsma, T.; Comin-Colet, J.; Schorr, J.; Ecochard, L.; Hussain, R. I.; Piepoli, M. F.	2020	European journal of heart failure	9		
Einzelpublikation	NA	A randomized clinical trial on the short-term effects of 12-week sacubitril/valsartan vs. enalapril on peak oxygen consumption in patients with heart failure with reduced ejection fraction: results from the ACTIVITY-HF study	Halle, M.; Schobel, C.; Winzer, E. B.; Bernhardt, P.; Mueller, S.; Sieder, C.; Lecker, L. S. M.	2021	European Journal of Heart Failure	23	12	
Einzelpublikation	NA	Comparison of Sacubitril/Valsartan Versus Enalapril in the Management of Heart Failure	Bano, S.; Bai, P.; Kumar, S.; Kumar, N.; Ali, A.; Pariya, F.; Versha, F.; Khalid, D.; Khalid, H.; Rizwan, A.	2021	Cureus	13	7	
Einzelpublikation	NA	The results of the use of angiotensin receptor inhibitors and neprilisin in secondary functional mitral regurgitation in outpatient practice	Makarovskaiya, M. V.; Ryazanov, A. S.; Kapitonov, K. I.; Kudryavtsev, A. A.	2020	Vestnik Rossiiskoi Akademii Meditsinskikh Nauk	75	5	
Einzelpublikation	NA	Effect of sacubitril valsartan on cardiac function and endothelial function in patients with chronic heart failure with reduced ejection fraction	Li, B. H.; Fang, K. F.; Lin, P. H.; Zhang, Y. H.; Huang, Y. X.; Jie, H.	2021	Clinical Hemorheology & Microcirculation	77	4	
Einzelpublikation	NA	Sacubitril/valsartan versus enalapril on exercise capacity in patients with heart failure with reduced ejection fraction: A randomized, double-blind, active-controlled study	Dos Santos, M. R.; Alves, M. N. N.; Jordão, C. P.; Pinto, C. E. N.; Correa, K. T. S.; de Souza, F. R.; da Fonseca, G. W. P.; Tomaz Filho, J.; Costa, M.; Pereira, R. M. R.; Negrão, C. E.; Barretto, A. C. P.	2021	American heart journal	239		
Einzelpublikation	NA	Comparison of the efficacy of Sacubitril/valsartan and valsartan in the treatment of patients with heart failure	Fan, H.; Zhang, L.; Li, Y.; Wang, Y.	2020	Pharmacy Services and Research	4	251 - 254	10.5428/pcar20200403
Einzelpublikation	NA	Dapagliflozin Impact on the Exercise Capacity of Non-Diabetic Heart Failure with Reduced Ejection Fraction Patients	Reis, J.; Teixeira, A. R.; Goncalves, A. V.; Moreira, R. I.; Silva, T. P.; Timoteo, A. T.; Ferreira, R. C.	2022	Journal of Clinical Medicine	11	10	10.3390/jcm11102935
Sekundäre Publikation	DEFINE-HF	Metabolomic Profiling of the Effects of Dapagliflozin in Heart Failure with Reduced Ejection Fraction: DEFINE-HF	Selvaraj, S.; Fu, Z.; Jones, P.; Kwee, L. C.; Windsor, S. L.; Ilkayeva, O.; Newgard, C. B.; Margulies, K. B.; Husain, M.; Inzucchi, S. E.; McGuire, D. K.; Pitt, B.; Scirica, B. M.; Lanfear, D. E.; Nassif, M. E.; Javaheri, A.; Mentz, R. J.; Kosiborod, M. N.; Shah, S. H.	2022	Circulation	23		
Sekundäre Publikation	DAPA-HF	Initial Decline ("dip") in Estimated Glomerular Filtration Rate Following Initiation of Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction: insights from DAPA-HF	Adamson, C.; Docherty, K. F.; Heerspink, H. J. L.; de Boer, R. A.; Damman, K.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Martinez, F. A.; Petrie, M. C.; et al.,	2022	Circulation			10.1161/CIRCULATIONAHA.121.058910
Sekundäre Publikation	DAPA-HF	Efficacy and Safety of Dapagliflozin According to Frailty in Heart Failure With Reduced Ejection Fraction : a Post Hoc Analysis of the DAPA-HF Trial	Butt, J. H.; Dewan, P.; Merkely, B.; Belohlavek, J.; Drozdz, J.; Kitakaze, M.; Inzucchi, S. E.; Kosiborod, M. N.; Martinez, F. A.; Tereshchenko, S.; et al.,	2022	Annals of internal medicine			10.7326/M21-4776
Einzelpublikation	DAPA-VO2	Short-term effects of dapagliflozin on maximal functional capacity in heart failure with reduced ejection fraction (DAPA-VO2): a randomized clinical trial	Palau, P.; Amiguet, M.; Dominguez, E.; Sastre, C.; Mollar, A.; Seller, J.; Pinilla, J. M. G.; Larumbe, A.; Valle, A.; Doblas, J. J. G.; de la Espriella, R.; Minana, G.; Mezcua, A. R.; Santas, E.; Bodi, V.; Sanchis, J.; Pascual-Figal, D.; Gorriz, J. L.; Bayes-Genis, A.; Nunez, J.; Dapa-Vo Investigators		European Journal of Heart Failure			10.1002/ejhf.2560
Sekundäre Publikation	EMPIRE-HF	The effect of empagliflozin on contractile reserve in heart failure: Prespecified sub-study of a randomized, double-blind, and placebo-controlled trial	Jensen, J.; Omar, M.; Ali, M.; Frederiksen, P. H.; Kistorp, C.; Tuxen, C.; Andersen, C. F.; Larsen, J. H.; Ersboll, M. K.; Kober, L.; Gustafsson, F.; Faber, J.; Forman, J. L.; Moller, J. E.; Schou, M.	2022	American Heart Journal	250		
Sekundäre Publikation	EMPIRE-HF	The effect of empagliflozin on growth differentiation factor 15 in patients with heart failure: a randomized controlled trial (Empire HF Biomarker)	Omar, M.; Jensen, J.; Kistorp, C.; Højlund, K.; Videbæk, L.; Tuxen, C.; Larsen, J. H.; Andersen, C. F.; Gustafsson, F.; Køber, L.; et al.,	2022	Cardiovascular diabetology	21	1	10.1186/s12933-022-01463-2
Sekundäre Publikation	EVALUATE-HF	Changes in cardiac biomarkers in association with alterations in cardiac structure and function, and health status in heart failure with reduced ejection fraction: the EVALUATE-HF trial	Myhre, P. L.; Claggett, B. L.; Shah, A. M.; Prescott, M. F.; Ward, J. H.; Fang, J. C.; Mitchell, G. F.; Solomon, S. D.; Desai, A. S.		European Journal of Heart Failure			10.1002/ejhf.2541
Einzelpublikation	NA	Comparison of 25 mg and 10 mg of Empagliflozin in Heart Failure with Reduced Ejection Fraction	Hao, Z.; Zhang, Y.	2022	Canadian Journal of Cardiology		09	
Sekundäre Publikation	EMPEROR-Reduced	Early changes in estimated glomerular filtration rate post-initiation of empagliflozin in EMPEROR-Reduced	Zannad, F.; Ferreira, J. P.; Gregson, J.; Kraus, B. J.; Mattheus, M.; Hauske, S. J.; Butler, J.; Filippatos, G.; Wanner, C.; Anker, S. D.; Pocock, S. J.; Packer, M.; E. MPEROR-Reduced Trial Committees; Investigators,	2022	European Journal of Heart Failure	16		

Typ	Acronym	Title	Authors	Year	Journal	Volume	Issue	DOI
Sekundäre Publikation	DAPA-HF	Relationship of Dapagliflozin With Serum Sodium: Findings From the DAPA-HF Trial	Yeoh, S. E.; Docherty, K. F.; Jhund, P. S.; Petrie, M. C.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Bengtsson, O.; Boulton, D. W.; Greasley, P. J.; Langkilde, A. M.; Sjostrand, M.; Solomon, S. D.; McMurray, J. J. V.	2022	Jacc-Heart Failure	10	5	10.1016/j.jchf.2022.01.019
Einzelpublikation	NR	The Difference between Sacubitril Valsartan and Valsartan on Vascular Endothelial Function, APN, MMP-9, and BNP Levels in Patients with Hypertension and Chronic Heart Failure	Du, H.; Li, X.; Zhao, W.; Jiang, N.	2022	Journal of healthcare engineering			10.1155/2022/9494981
Einzelpublikation	NR	Different Doses of Empagliflozin in Patients with Heart Failure with Reduced Ejection Fraction	Hao, Z.; Zhang, Y.	2022	International Heart Journal	14		
Einzelpublikation	NR	The comparative effects of sacubitril/valsartan versus enalapril on pulmonary hypertension due to heart failure with a reduced ejection fraction	Zhao, Y.; Tian, L. G.; Zhang, L. X.; Ma, T.; Di, L.; Wang, Y. B.; Gu, X. S.; Wang, D. D.; Gao, S.; Wang, H. Y.	2022	Pulmonary Circulation	12	3	10.1002/pul2.12034
Sekundäre Publikation	DAPA-HF	Effects of Dapagliflozin According to the Heart Failure Collaboratory Medical Therapy Score: insights From DAPA-HF	Butt, J. H.; Dewan, P.; DeFilippis, E. M.; Biering-Sørensen, T.; Docherty, K. F.; Jhund, P. S.; Kosiborod, M. N.; Martinez, F. A.; Bengtsson, O.; Johansen, N. D.; et al.,	2022	JACC. Heart failure	10	8	10.1016/j.jchf.2022.03.009
Sekundäre Publikation	EMPIRE HF	Effect of Empagliflozin on Multiple Biomarkers in Heart Failure: Insights From the Empire Heart Failure Trial	Jensen, J.; Omar, M.; Kistorp, C.; Tuxen, C.; Poulsen, M. K.; Faber, J.; Kober, L.; Gustafsson, F.; Moller, J. E.; Schou, M.		Circulation: Heart Failure	15	8	
Sekundäre Publikation	DAPA-HF	Liver tests and outcomes in heart failure with reduced ejection fraction: findings from DAPA-HF	Adamson, C.; Cowan, L. M.; de Boer, R. A.; Diez, M.; Drozdz, J.; Dukat, A.; Inzucchi, S. E.; Kober, L.; Kosiborod, M. N.; Ljungman, C. E. A.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Lindholm, D.; Bengtsson, O.; Boulton, D. W.; Greasley, P. J.; Langkilde, A. M.; Sjostrand, M.; Solomon, S. D.; McMurray, J. J. V.; Jhund, P. S.		European Journal of Heart Failure			10.1002/ejhf.2649
Sekundäre Publikation	DAPA-HF	Iron Deficiency in Heart Failure and Effect of Dapagliflozin: Findings From DAPA-HF	Docherty, K. F.; Welsh, P.; Verma, S.; De Boer, R. A.; O'Meara, E.; Bengtsson, O.; Kober, L.; Kosiborod, M. N.; Hammarstedt, A.; Langkilde, A. M.; Lindholm, D.; Little, D. J.; Sjostrand, M.; Martinez, F. A.; Ponikowski, P.; Sabatine, M. S.; Morrow, D. A.; Schou, M.; Solomon, S. D.; Sattar, N.; Jhund, P. S.; McMurray, J. J. V.; Dapa-Hf, Investigators; Committees,		Circulation			
Sekundäre Publikation	EMPEROR-Reduced	Uric acid and sodium-glucose cotransporter-2 inhibition with empagliflozin in heart failure with reduced ejection fraction: the EMPEROR-reduced trial	Doehner, W.; Anker, S. D.; Butler, J.; Zannad, F.; Filippatos, G.; Ferreira, J. P.; Salsali, A.; Kaempfer, C.; Brueckmann, M.; Pocock, S. J.; Januzzi, J. L.; Packer, M.		European Heart Journal			10.1093/eurheartj/ehac320
Sekundäre Publikation	LIFE	Tolerability of Sacubitril/Valsartan in Patients With Advanced Heart Failure	Vader, J. M.; Givertz, M. M.; Starling, R. C.; McNulty, S. E.; Anstrom, K. J.; Desvigne-Nickens, P.; Hernandez, A. F.; Braunwald, E.; Mann, D. L.; Invest, Botlibl	2022	Jacc-Heart Failure	10	7	10.1016/j.jchf.2022.04.013
Sekundäre Publikation	PARADIGM_HF	Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: insights from Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial	Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, Martinez F, Starling RC, Desai AS, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, McMurray JJ, Packer M	2016	Circ Heart Fail	9:e002560.		
Sekundäre Publikation	PARADIGM_HF	Baseline characteristics and treatment of patients in Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial	McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz M, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Committees Investigators.	2014	Eur J Heart Fail	16		
Sekundäre Publikation	EMPA-TROPISM	Rationale and design of the EMPA-TROPISM Trial (ATRU-4): are the “cardiac benefits” of empagliflozin independent of its hypoglycemic activity?	Santos-Gallego CG, Garcia-Ropero A, Mancini D, et al	2019	Cardiovasc Drugs Ther	33		
Einzelpublikation	NR	The Impact of Sacrubitril/Valsartan on Clinical Treatment and hs-cTnT and NT-ProBNP Serum Levels and the Left Ventricular Function in Patients with Chronic Heart Failure	Yang Gao, Changtai Xing, Wenjun Hao, Hongwei Zhao, Lili Wang, Bo Luan, Aijie Hou,	2020	International Heart Journal	61	1	

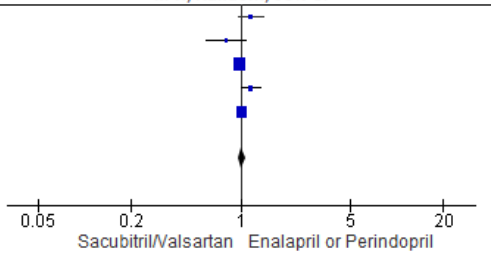
3.17 Appendix 3: Additional Forest Plots

3.17.1 Sacubitril/Valsartan vs Enalapril or Perindopril

Adverse events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Halle 2021	77	103	63	98	7.8%	1.16 [0.97, 1.40]
Khandwalla 2021	35	69	44	70	3.5%	0.81 [0.60, 1.08]
McMurray 2014	3419	4203	3503	4229	42.3%	0.98 [0.96, 1.00]
Piepoli 2021	177	309	153	310	11.1%	1.16 [1.00, 1.35]
Tsutsui 2021	109	111	108	112	35.4%	1.02 [0.97, 1.06]
Total (95% CI)		**4795**		**4819**	**100.0%**	**1.02 [0.96, 1.08]**
Total events	3817		3871			

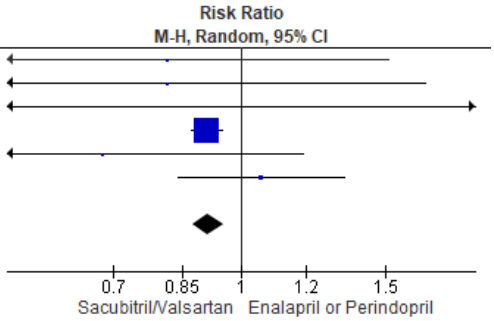
Heterogeneity: Tau² = 0.00; Chi² = 11.38, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 0.68 (P = 0.50)



Serious adverse events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Desai 2019	17	231	21	233	0.5%	0.82 [0.44, 1.51]
Halle 2021	12	103	14	98	0.4%	0.82 [0.40, 1.68]
Khandwalla 2021	0	69	1	70	0.0%	0.34 [0.01, 8.16]
McMurray 2014	1937	4203	2142	4229	95.1%	0.91 [0.87, 0.95]
Piepoli 2021	19	309	28	310	0.6%	0.68 [0.39, 1.19]
Tsutsui 2021	64	111	61	112	3.4%	1.06 [0.84, 1.34]
Total (95% CI)		**5026**		**5052**	**100.0%**	**0.91 [0.87, 0.95]**
Total events	2049		2267			

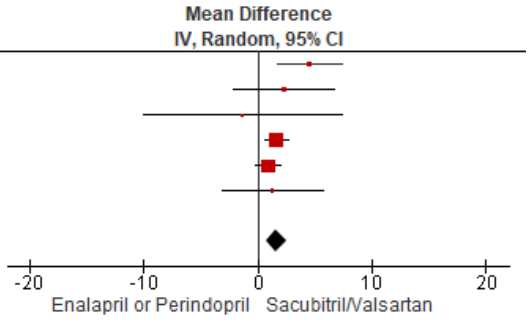
Heterogeneity: Tau² = 0.00; Chi² = 3.24, df = 5 (P = 0.66); I² = 0%
Test for overall effect: Z = 4.19 (P < 0.0001)



Quality of life

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Desai 2019	4.5	1.44	8.9%	4.50 [1.68, 7.32]
Halle 2021	2.27	2.26	3.8%	2.27 [-2.16, 6.70]
Khandwalla 2021	-1.3	4.42	1.0%	-1.30 [-9.96, 7.36]
McMurray 2014	1.64	0.51	44.4%	1.64 [0.64, 2.64]
Piepoli 2021	0.93	0.58	38.0%	0.93 [-0.21, 2.07]
Tsutsui 2021	1.27	2.25	3.8%	1.27 [-3.14, 5.68]
Total (95% CI)			**100.0%**	**1.60 [0.72, 2.48]**

Heterogeneity: Tau² = 0.19; Chi² = 5.90, df = 5 (P = 0.32); I² = 15%
Test for overall effect: Z = 3.57 (P = 0.0004)

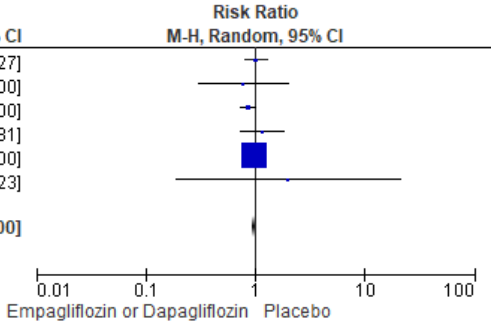


3.17.2 Empagliflozin or Dapagliflozin vs Placebo

Adverse events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Abraham 2021	74	155	74	156	2.0%	1.01 [0.80, 1.27]
Jensen 2020	7	95	9	95	0.1%	0.78 [0.30, 2.00]
McMurray 2019	286	2368	333	2368	5.1%	0.86 [0.74, 1.00]
Nassif 2021	19	33	16	32	0.5%	1.15 [0.73, 1.81]
Packer 2020	1420	1863	1463	1863	92.2%	0.97 [0.94, 1.00]
Santos-Gallego 2021	2	42	1	42	0.0%	2.00 [0.19, 21.23]
Total (95% CI)		**4556**		**4556**	**100.0%**	**0.97 [0.93, 1.00]**
Total events	1808		1896			

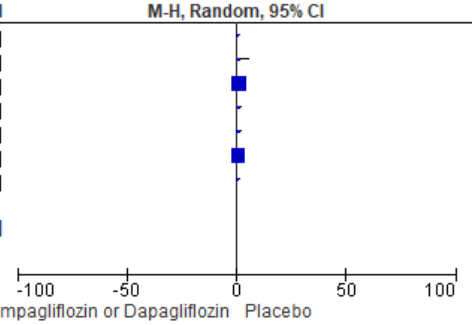
Heterogeneity: Tau² = 0.00; Chi² = 4.36, df = 5 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.03 (P = 0.04)



Serious adverse events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Abraham 2021	21	155	27	156	0.9%	0.78 [0.46, 1.32]
Jensen 2020	6	95	4	95	0.2%	1.50 [0.44, 5.15]
McMurray 2019	895	2368	994	2368	49.8%	0.90 [0.84, 0.97]
Nassif 2019	30	131	24	132	1.1%	1.26 [0.78, 2.03]
Nassif 2021	8	33	9	32	0.4%	0.86 [0.38, 1.95]
Packer 2020	772	1863	896	1863	47.6%	0.86 [0.80, 0.93]
Santos-Gallego 2021	3	42	8	42	0.2%	0.38 [0.11, 1.32]
Total (95% CI)		**4687**		**4688**	**100.0%**	**0.88 [0.84, 0.93]**
Total events	1735		1962			

Heterogeneity: Tau² = 0.00; Chi² = 5.56, df = 6 (P = 0.47); I² = 0%
Test for overall effect: Z = 4.92 (P < 0.00001)

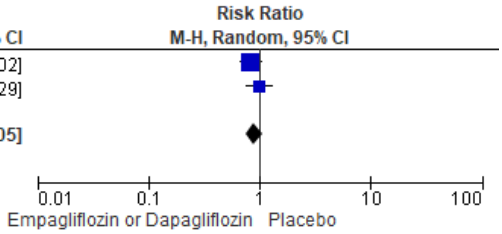


3.17.3 Subgroup Analysis for Empagliflozin or Dapagliflozin vs Placebo

Patients with no chronic kidney disease in mortality (all cause):

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
McMurray 2019	133	1410	161	1406	59.6%	0.82 [0.66, 1.02]
Packer 2020	96	879	96	867	40.4%	0.99 [0.76, 1.29]
Total (95% CI)		**2289**		**2273**	**100.0%**	**0.89 [0.74, 1.05]**
Total events	229		257			

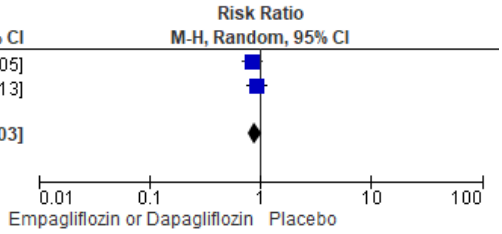
Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 1 (P = 0.31); I² = 5%
Test for overall effect: Z = 1.37 (P = 0.17)



Patients with chronic kidney disease in mortality (all cause):

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
McMurray 2019	143	962	168	964	49.1%	0.85 [0.70, 1.05]
Packer 2020	153	981	168	997	50.9%	0.93 [0.76, 1.13]
Total (95% CI)		**1943**		**1961**	**100.0%**	**0.89 [0.77, 1.03]**
Total events	296		336			

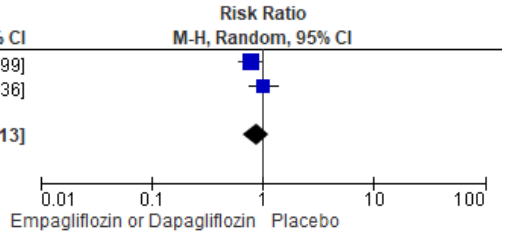
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.61 (P = 0.11)



Patients with no chronic kidney disease in mortality (CV):

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
McMurray 2019	108	1410	139	1406	55.4%	0.77 [0.61, 0.99]
Packer 2020	81	879	79	867	44.6%	1.01 [0.75, 1.36]
Total (95% CI)		**2289**		**2273**	**100.0%**	**0.87 [0.67, 1.13]**
Total events	189		218			

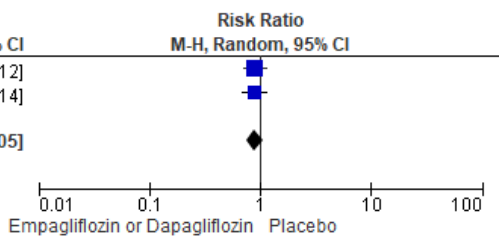
Heterogeneity: Tau² = 0.02; Chi² = 1.88, df = 1 (P = 0.17); I² = 47%
Test for overall effect: Z = 1.03 (P = 0.30)



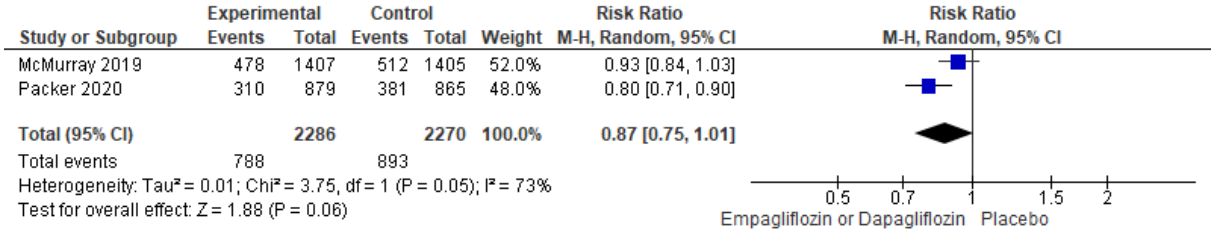
Patients with chronic kidney disease in mortality (CV):

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
McMurray 2019	119	962	134	964	53.2%	0.89 [0.71, 1.12]
Packer 2020	106	981	121	997	46.8%	0.89 [0.70, 1.14]
Total (95% CI)		**1943**		**1961**	**100.0%**	**0.89 [0.75, 1.05]**
Total events	225		255			

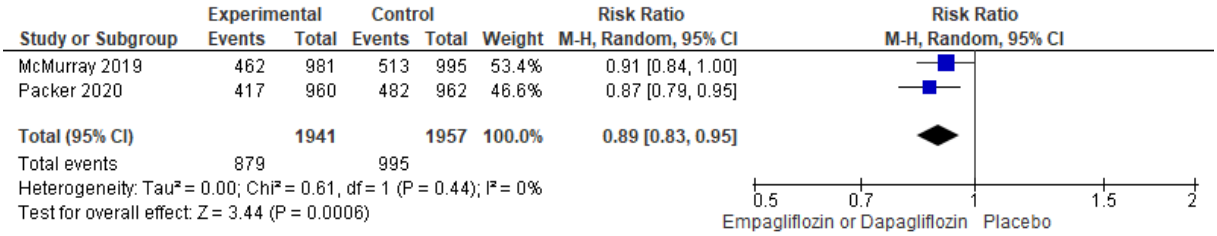
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 1.36 (P = 0.17)



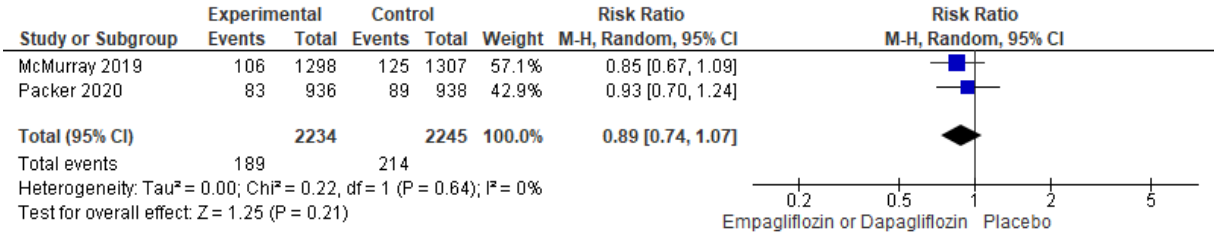
Patients with no chronic kidney disease in serious adverse events:



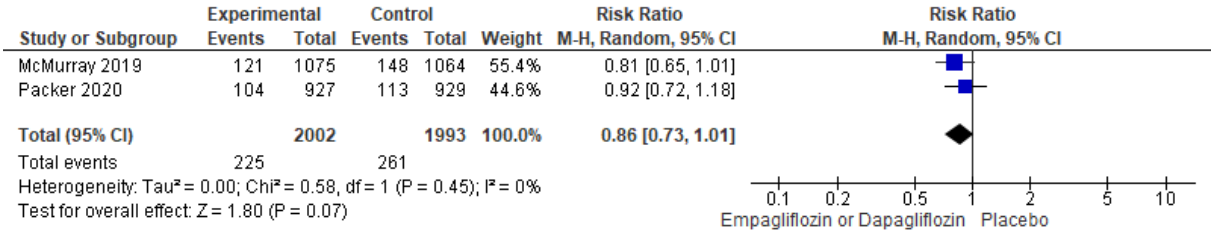
Patients with chronic kidney disease in serious adverse events:



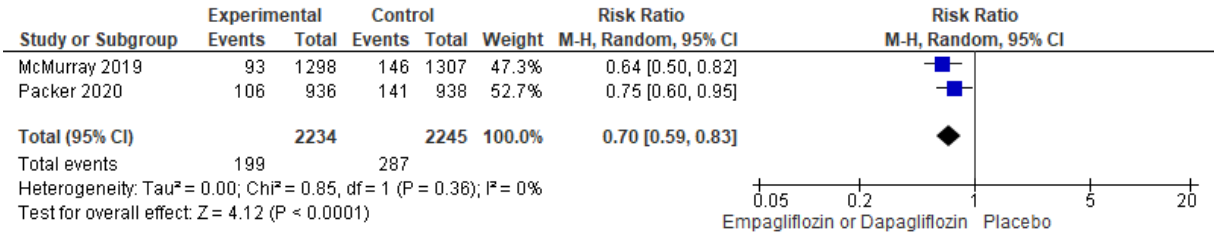
Patients with no diabetes in mortality (CV):



Patients with diabetes in mortality (CV):



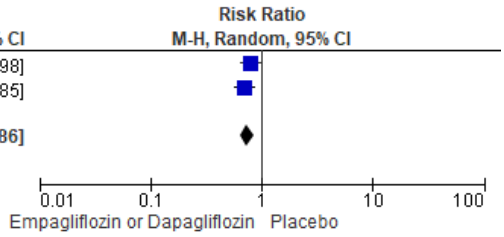
Patients with no diabetes in hospitalization (heart failure):



Patients with diabetes in hospitalization (heart failure):

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
McMurray 2019	138	1075	172	1064	47.1%	0.79 [0.65, 0.98]
Packer 2020	140	927	201	929	52.9%	0.70 [0.57, 0.85]
Total (95% CI)		**2002**		**1993**	**100.0%**	**0.74 [0.64, 0.86]**
Total events	278		373			

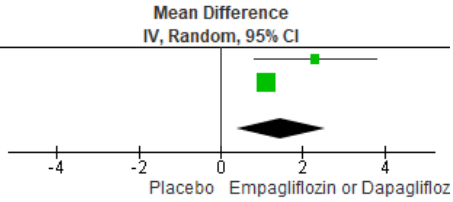
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 4.12 (P < 0.0001)



Patients with no diabetes in quality of life:

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
McMurray 2019	5.4	20.2	1298	3.1	18.4	1307	30.1%	2.30 [0.82, 3.78]
Packer 2020	5.43	0.62	936	4.33	0.63	938	69.9%	1.10 [1.04, 1.16]
Total (95% CI)			**2234**			**2245**	**100.0%**	**1.46 [0.38, 2.54]**

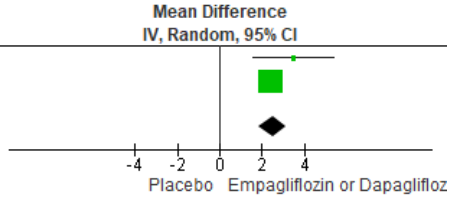
Heterogeneity: Tau² = 0.43; Chi² = 2.51, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 2.65 (P = 0.008)



Patients with diabetes in quality of life:

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
McMurray 2019	7	21.7	1075	3.5	23.27	1064	10.2%	3.50 [1.59, 5.41]
Packer 2020	6.58	0.63	397	4.17	0.64	457	89.8%	2.41 [2.32, 2.50]
Total (95% CI)			**1472**			**1521**	**100.0%**	**2.52 [1.87, 3.17]**

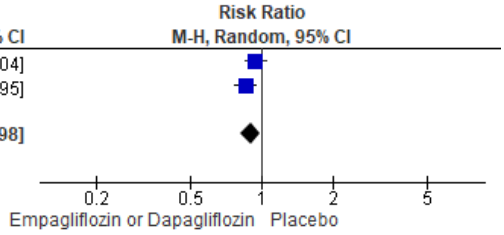
Heterogeneity: Tau² = 0.12; Chi² = 1.25, df = 1 (P = 0.26); I² = 20%
Test for overall effect: Z = 7.63 (P < 0.00001)



Patients with no diabetes in serious adverse events:

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
McMurray 2019	448	1295	481	1305	50.2%	0.94 [0.85, 1.04]
Packer 2020	375	936	439	937	49.8%	0.86 [0.77, 0.95]
Total (95% CI)		**2231**		**2242**	**100.0%**	**0.90 [0.82, 0.98]**
Total events	823		920			

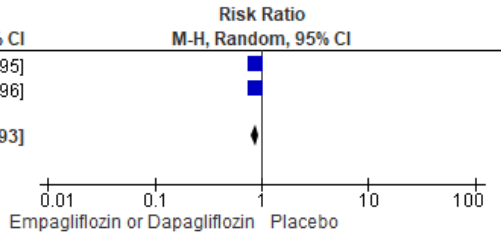
Heterogeneity: Tau² = 0.00; Chi² = 1.56, df = 1 (P = 0.21); I² = 36%
Test for overall effect: Z = 2.35 (P = 0.02)



Patients with diabetes in serious adverse events:

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
McMurray 2019	447	1073	513	1063	52.4%	0.86 [0.79, 0.95]
Packer 2020	397	927	457	926	47.6%	0.87 [0.79, 0.96]
Total (95% CI)		**2000**		**1989**	**100.0%**	**0.87 [0.81, 0.93]**
Total events	844		970			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 4.15 (P < 0.0001)



4 Behandlung bei asymptomatischer linksventrikulärer Dysfunktion

4.1 PICO-Frage

- Fragestellung: medikamentöse Therapieoptionen bei asymptomatischer ventrikulärer Dysfunktion
- Population: asymptomatische Patient*innen mit reduzierter LVEF
- Intervention: medikamentöse
- Kontrolle: Placebo, andere Medikamente, nicht-medikamentöse Optionen
- Outcome: Mortalität, Hospitalisierungen, Lebensqualität, Sicherheit
- Studientyp: aggregierte Evidenz, RCT
- Sprache: deutsch, englisch
- Zeitraum: ohne Begrenzung

4.2 Recherchestrategien

4.2.1 Medline via Pubmed (www.pubmed.gov) (01.06 2023)

Nr.	Suchfrage	Anzahl
#7	**Search: (#3 AND #6) NOT #5**	**246**
#6	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR "clinical trials as topic" [MeSH Terms:noexp] OR randomly [tiab] OR trial [ti]	1,539,551
#5	**Search: #3 AND #4**	**73**
#4	Search: (systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation study[pt] OR validation study[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])	653,804
#3	Search: #1 AND #2	2,576
#2	Search: "systolic dysfunction"[tiab] OR "LV dysfunction"[tiab] OR "left ventricular dysfunction"[tiab] OR „NYHA I"[tiab] OR „NYHA class I"[tiab]	26,971
#1	Search: asymptomatic*[tiab] OR subclinical*[tiab]	238,784

4.2.2 Datenbanken der Cochrane Library (01.06.2023)

Nr.	Suchfrage	Anzahl
#4	**#1 AND #2 NOT (Conference proceeding):pt in Trials**	**193**
#3	**#1 AND #2 NOT (Conference proceeding):pt in Cochrane Reviews, Cochrane Protocols**	**0**
#2	"systolic dysfunction":ti,ab OR "LV dysfunction":ti,ab OR "left ventricular dysfunction":ti,ab OR "NYHA I":ti,ab OR "NYHA class I":ti,ab	3282
#1	asymptomatic*:ti,ab OR subclinical*:ti,ab	16590

4.2.3 Epistemonikos (01.06.2023)

Nr.	Suchfrage	Anzahl
#1	(title:(asymptomatic* OR subclinical*) OR abstract:(asymptomatic* OR subclinical*)) AND (title:("systolic dysfunction" OR "LV dysfunction" OR "left ventricular dysfunction" OR "NYHA I" OR "NYHA class I") OR abstract:("systolic dysfunction" OR "LV dysfunction" OR "left ventricular dysfunction" OR "NYHA I" OR "NYHA class I")) **Filter**: • Publication type: Primary Study • Studies design: RCT	**8**
#1	(title:(asymptomatic* OR subclinical*) OR abstract:(asymptomatic* OR subclinical*)) AND (title:("systolic dysfunction" OR "LV dysfunction" OR "left ventricular dysfunction" OR "NYHA I" OR "NYHA class I") OR abstract:("systolic dysfunction" OR "LV dysfunction" OR "left ventricular dysfunction" OR "NYHA I" OR "NYHA class I")) **Filter**: • Publication type: Systematic Reviews	**49**

4.2.4 Übersicht der eingeschlossenen Treffer

	Medline	Cochrane	Epistemonikos	Summe
Aggregierte Evidenz	73	0	49	**122**
RCT	246	193	8	**447**
GESAMT				**569**

Anzahl der ausgeschlossenen Publikationen nach Ausschlussgrund:

A1 (Dubletten): 165

A2 (nicht englisch/deutsch): 25

A3 (Conference Abstracts): 2

Eingeschlossene Treffer insgesamt nach Ausschlüssen: 377

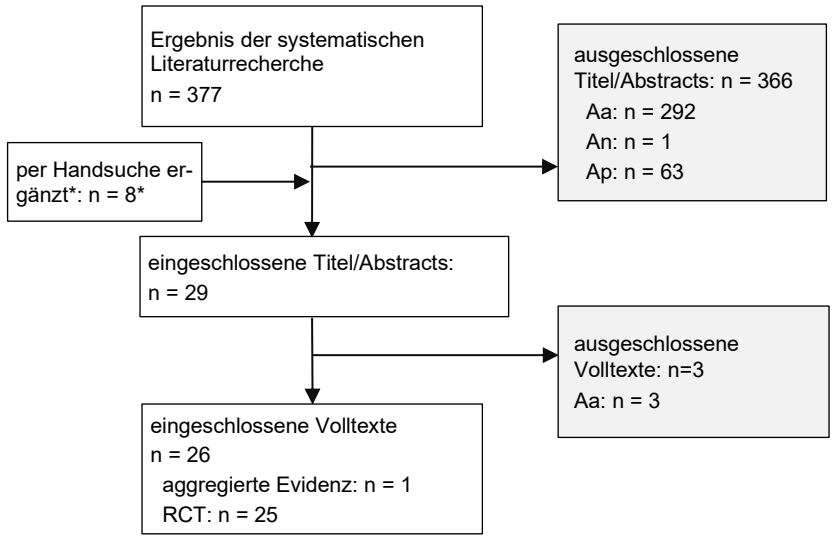
4.3 Screening

4.3.1 Kriterien für den Ein- und Ausschluss

Einschluss	E	Einschluss: Fragestellung passend, Studientyp passend
Ausschluss	Aa	thematisch nicht passend: andere Erkrankung/ Fragestellung/Thema
	An	Anzahl Teilnehmer <50
	Ap	Studientyp nicht passend
	Ad	Doppelpublikation oder nicht erhältlich
	As	Sprache nicht deutsch oder englisch
	Az	falscher Zeitraum (z. B. Suchzeitraum zu weit zurückliegend)
	Aw	zurückgezogen oder Update vorhanden
	Aq	schwache methodische Qualität

Treffen für eine gefundene Leitlinie mehrere Ausschlusskriterien zu, so wird das jeweils erste Kriterium in der Liste bzw. das am zutreffendste Kriterium für die Begründung des Ausschlusses angegeben.

4.3.2 Flowchart



*Da die aLVD-Population nur eine Subgruppe darstellt, die in Titel und Abstract nicht zwingend benannt ist, wurde zusätzlich in Referenzlisten von Übersichtsarbeiten und themenspezifischen internationalen Leitlinien nach weiteren relevanten Primärstudien gesucht. Auf diese Weise wurden 8 weitere Studien bzw. Reports identifiziert.

4.4 Evidenztabelle

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Dries DL, Exner DV, Domanski MJ, et al. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. Journal of the American College of Cardiology 2000; 35(3):681–9. DOI: 10.1016/s0735-1097(99)00608-7. http://www.ncbi.nlm.nih.gov/pubmed/10716471.	Prognose	RCT-Subanalyse SOLVD-P; n=3673 Fragestellung: CKD als Risikofaktor bei aLVD P: aLVD, 80% MI I: Enalapril C: placebo O: divers	creatinine clearance <60% n=757 ≥60% n=2916 all-cause mortality: 22.1% vs. 13.6%; RR 1.41 (1.15–1.74) pump-failure death 7.5% vs. 3.7%; RR 1.68 (1.16–2.44) composite death or HF-hospitalization 30.7% vs. 20.4%, RR 1.33 (1.12–1.59)	siehe SOLVD-P	retrospektive Analyse außerhalb des randomiserten Designs; hypothesengenierend,
Dries DL, Strong MH, Cooper RS, et al. Efficacy of angiotensin-converting enzyme inhibition in reducing progression from asymptomatic left ventricular dysfunction to symptomatic heart failure in black and white patients. Journal of the American College of Cardiology 2002; 40(2):311–7. DOI: 10.1016/s0735-1097(02)01943-5. http://www.ncbi.nlm.nih.gov/pubmed/12106937.	Prognose	RCT-Subanalyse SOLVD-P; n=4054 Fragestellung: Effektivität nach eth. Abstammung bei aLVD P: aLVD, 80% MI I: Enalapril C: placebo O: divers	development of symptomatic HF black vs. white RR 1.81 (95% CI 1.51, 2.17) "despite adjustment for available measures of disease severity"	siehe SOLVD-P	Post-hoc-Analyse außerhalb des randomiserten Designs; hypothesengenierend
Böhm M, Pogue J, Kindermann I, et al. Effect of comorbidities on outcomes and angiotensin converting enzyme inhibitor effects in patients with predominantly left ventricular dysfunction and heart failure. Eur J Heart Fail 2014; 16(3):325–33. DOI: 10.1002/ejhf.23. http://www.ncbi.nlm.nih.gov/pubmed/24464788.	Prognose	RCT-Subanalyse SOLVD-P; n=4228 Fragestellung: Komorbidität als Risikofaktor bei aLVD P: aLVD, 80% MI I: Enalapril C: placebo O: divers	(nur SOLVD-P, nur aLVD) keine Komorbidität: 17.4% 1 Komorbidität: 36.5% 2: 29,3% 3: 12,9% Gesamtmortalität Hypertension: HR 1.32 (1.12–1.54) Diabetes mellitus: HR 1.55 (1.28–1.88) COPD: HR 1.73 (1.30–2.31) Schlaganfall: HR 2.05 (1.58–2.65) Angina pectoris: HR 1.00 (0.86–1.17) eGFR<60 (mL/min): HR 1.61 (1.37–1.89)	siehe SOLVD-P	retrospektive Analyse außerhalb des randomiserten Designs; hypothesengenierend,

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Echouffo-Tcheugui JB, Erqou S, Butler J, et al. Assessing the Risk of Progression From Asymptomatic Left Ventricular Dysfunction to Overt Heart Failure: A Systematic Overview and Meta-Analysis. JACC Heart Fail 2016; 4(4):237–48. DOI: 10.1016/j.jchf.2015.09.015. http://www.ncbi.nlm.nih.gov/pubmed/26682794.	Prognose	prognost. SR mit MA, epidem. Studien u. a. Suchzeitraum: 201503 P: asympt. LV syst./diastol. Dysfunction (ALVSD, ALVDD) I: n.a. C: keine aLVD O: Progression zu sympt. HF Evidenzbasis: 11 Studien (2 retrosp. Kohorten, 8 Kohorten, 1 RCT=SOLVD-P), n=253369 RoB: fair to good; - low risk for bias of participation or study attrition - different quality for definition of LV function and confounding adjustment	median follow-up: 7,9 y Studienpopution: 7x general, 2x diastrol. Dysfunction, 1x Diabetes, 1x Hypertension, 1x KHK, 1x NYHA I (SOLVF-P) Prevalence aLD (6 Kohorten, n=22500) range 1,7-9,9 % overall 4,69 (7,09) absolute risks of progression: ALVSD: 8.4 per 100 person-years (95% CI: 4.0 ;12.8) (7 Studien, n= 4800) ALVDD: 2.8 per 100 person-years (95% CI: 1.9 to 3.7) (4 Studien, n=700) control: 1.04 per 100 person-years (95% CI: 0.0 to 2.2) (4 Studien, n=6000) max. adj. RR ALVSD 4.6 (95% CI: 2.2 to 9.8) (6 Studien, n=20500) ALVDD 1.7 (95% CI: 1.3 to 2.2) (5 Studien, n=7500)	AMSTAR2: critically low/akzeptabel 2/7 kritische Items nicht erfüllt: - kein Protokoll - keine Liste der ausgeschlossenen Studien	(in Anlehnung an GRADE): niedrig Ausgangsniveau: niedrig (Kohorten) 1) Verzerrungsrisiko +/-0 2) Präzision +/-0 3) Direktheit +/-0 4) Konsistenz +/- 0 5) publication bias: kein Hinweis
Rørth R, Jhund PS, Mogensen UM, et al. Risk of Incident Heart Failure in Patients With Diabetes and Asymptomatic Left Ventricular Systolic Dysfunction. Diabetes Care 2018; 41(6):1285–91. DOI: 10.2337/dc17-2583. http://www.ncbi.nlm.nih.gov/pubmed/29626073.	Prognose	RCT-Subanalyse SOLVD-P; n=4228 Fragestellung: Diabetes als Risikofaktor bei aLVD P: aLVD, 80% MI I: Enalapril C: placebo O: symptomatische HF	647 von 4,223 (15%) Diabetes zu Studienbeginn älter, höherer BMI, höherer Blutdruck, höhere Herzfrequenz symptomatische HF nach 6 Monaten without DM 861/3,576 (24%) with DM 214/647 (33%) unadjusted analyses HF onset RR 1.53 [95% CI 1.32-1.78) HF hospitalization RR 2.04 [1.65-2.52]; composite onset HF or cv death RR 1.48 [1.30-1.69]	siehe SOLVD-P	retrospektive Analyse außerhalb des randomiserten Designs; hypothesengenierend,

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Rohde LE, Zimerman A, Vaduganathan M, et al. Associations Between New York Heart Association Classification, Objective Measures, and Long-term Prognosis in Mild Heart Failure: A Secondary Analysis of the PARADIGM-HF Trial. JAMA Cardiol 2023; 8(2):150–8. DOI: 10.1016/j.hrtlng.2021.07.009. http://www.ncbi.nlm.nih.gov/pubmed/36477809.	Prognose	RCT-Subanalyse von PARADIGM-HF n=8326 Fragestellung: Veränderung NYHA-Klassifikation; Zusammenhang NYHA mit nt-proBNP, Assoziation Langzeitprognose P: NYHA ≥II I: C: O: cv death or first HF hospitalization	NYHA I (n=389) NYHA ≥II at 1 y: 228 (58%) NT-proBNP NYHA class I vs II: AUC 0.51 (95% CI, 0.48-0.54) estimated kernel density overlap 93% NYHA class I vs II 79% NYHA I vs III 83% between NYHA II vs III rate of cv events NYHA III vs I, HR 1.84; (95% CI, 1.44-2.37); NYHA III vs II, HR, 1.49; (95% CI, 1.35-1.64). NYHA II vs I, HR, 1.24; (95% CI, 0.97-1.58).	siehe PARADIGM-HF	post-hoc-Analyse außerhalb des randomisierten Designs; hypothesengenierend,
Dries DL, Exner DV, Gersh BJ, et al. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: A retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. Journal of the American College of Cardiology 1998; 32(3):695–703. DOI: 10.1016/s0735-1097(98)00297-6. http://www.ncbi.nlm.nih.gov/pubmed/9741514.	Prognose	RCT-Subanalyse SOLVD-P; Fragestellung: VHF als Risikofaktor bei aSD P: aLVD, 80% MI I: Enalapril C: placebo O: divers	VHF n=419 no VHF n=6098 SOLVD-P: VHF n=168, no VHF n=3855 multivariate analysis (SOLVD-P + SOLVD-T) all-cause mortality RR 1.34 (95% CI 1.12 to 1.62), pump-failure death RR 1.42 (95% CI 1.09 to 1.85) composite death or HF-hospitalization RR 1.26 (95% CI 1.03 to 1.42) arrhythmic death: RR 1.13 (95% CI 0.75 to 1.71)	siehe SOLVD-P	retrospektive Analyse außerhalb des randomiserten Designs; hypothesengenierend,

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Sharpe N, Murphy J, Smith H, et al. Preventive treatment of asymptomatic left ventricular dysfunction following myocardial infarction. Eur Heart J 1990; 11 Suppl B:147–56. DOI: 10.1093/eurheartj/11.suppl_b.147. http://www.ncbi.nlm.nih.gov/pubmed/2142081.	ACE	RCT n =90 P: aLVD 1w after Q wave AMI I: Captopril C1: Frusemid C2: Placebo O: LV volume + function; occurence of HF Reporting-Standards der 1990er; keine detaillierte Beschreibung der Verblindung, nur "double blind"	LVEDVI at 12m captopril: -3,99 (-6,95, -1,03) frusemide: 3,49 (0,14, 6,84) placebo: 7,10 (4,02, 10,18) LVESVI at 12m captopril: -7,56 (-9,98, -5,06) frusemide: 4,78 (1,94, 7,62) placebo: 6,52 (3,90, 9,14) LVEF at 12 m captopril: 7,31 (5,94, 8,68) frusemide: -3,21 (-4,77, -1,65) placebo: -2,31 (-3,75, -0,87) captopril vs. frusemide: difference 10,5% captorpil vs. placebo: difference 9,6% occurrence of clinical HF captopril n= 1/23 (frusemide n=1/26 placebo n=6/22	Selection bias Randomisierung: low Allocation concealment: unclear Performance bias: unclear Detection bias: unclear Attrition bias: high (drop-out) andere Biasursachen: keine	(in Anlehnung an GRADE): sehr niedrig Ausgangsniveau: hoch 1) Verzerrungsrisiko: eher hoch -1 2) Präzision -1 (n) 3) Direktheit -2 (Population vorwiegend Post-MI; Surrogat)

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992; 327(10):669–77. DOI: 10.1056/NEJM199209033271001. http://www.ncbi.nlm.nih.gov/pubmed/1386652.	ACE	RCT SAVE survival and ventricular enlargement trial n=2231 P: AMI, LVEF ≤40 without overt heart failure or symptoms of myocardial ischemia I: Captopril C: Placebo O: survival, ventricular enlargement Follow-up: 42 m Reporting-Standards der 1990er; keine detaillierte Beschreibung der Verblindung, nur "double blind"	Mortality 228/1115 (20 %) vs. 275/1116 (25%) RRR 19% (95 % KI 3; 32); ARR 5% cv death 188/1115 (17%) vs. 234/1116 (21%) RRR 21% (95 % KI, 5; 35); ARR 4% development of severe heart failure 1118/1115 (11%) vs. 179/1116 (16%) RRR 37 % (95% KI 20, 50); ARR 5% HF hospitalization 154/1115 (14%) vs. 192/1116 (17%) RRR 22 % (95% KI 4; 37); ARR 3% recurrent MI 133/1115 (12%) vs. 170/1116 (15%) RRR 25 % (95 % KI 5; 40); ARR 3%	Selection bias Randomisierung: low Allocation concealment: low Performance bias: unclear Detection bias: unclear Attrition bias: low andere Biasursachen: keine	(in Anlehnung an GRADE): hoch Post-MI, sonst moderat Ausgangsniveau: hoch 1) Verzerrungsrisiko: niedrig 2) Präzision +/-0 3) Direktheit -1 (Post-MI)
Rutherford JD, Pfeffer MA, Moyé LA, et al. Effects of captopril on ischemic events after myocardial infarction. Results of the Survival and Ventricular Enlargement trial. SAVE Investigators. Circulation 1994; 90(4):1731–8. DOI: 10.1161/01.cir.90.4.1731. http://www.ncbi.nlm.nih.gov/pubmed/7923656.	ACE	RCT SAVE Substudy Fokus ischämische Events P: AMI, LVEF ≤40 I: Captopril C: Placebo O: recurrent MI and other myocardial ischemic events follow-up: 42 m	recurrent MI 133/1115 (12%) vs. 170/1116 (15%) RRR 25% (95% KI 5; 40%) ARR 3% death after recurrent MI 56/1115 (5%) vs. 80/1116 (7%) RRR 32% (95% KI, 4; 51) ARR 2% Reva 154/1116 (14%) vs. 195/1116 (17%) RRR 24 (95% KI 6; 39) ARR 3% hospitalization for unstable angina: n.s.	siehe Pfeffer 1992	siehe Pfeffer 1992

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Konstam MA, Kronenberg MW, Rousseau MF, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. SOLVD (Studies of Left Ventricular Dysfunction) Investigators. Circulation 1993; 88(5 Pt 1):2277–83. DOI: 10.1161/01.cir.88.5.2277. http://www.ncbi.nlm.nih.gov/pubmed/8222122.	ACE	RCT SOLVD-Prevention Substudy Remodeling n=108 (radionuclide ventriculograms) + n=19 (catheterizations) P: LVEF < 35% I: Enalapril C: Placebo O: long-term progression of LV dilatation	change in EDV at 1 year (catheterization) at mean25 months (radionuclide) Radionuclide EDV0 enalapril: decrease (120 +/- 25 to 113 +/- 25 mL/m2 placebo: increase (119 +/- 28 to 124 +/- 33 mL/m2, mean +/- SD) Differences less than described in patients with symptomatic HF "ACE inhibitor treatment slows or reverses LV dilatation in patients with asymptomatic LV systolic dysfunction. Compared with symptomatic patients, asymptomatic patients manifest a slower rate of spontaneous LV dilatation and less reduction in LV volumes by enalapril"	siehe Yusuf 1992 Substudie, Auswahl der Pat. unklar (selection bias)	(in Anlehnung an GRADE): sehr niedrig Ausgangsniveau: hoch 1) Verzerrungsrisiko: eher hoch -1 2) Präzision -1 (n) 3) Direktheit -2 (Population vorwiegend Post-MI; Surrogat)

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Yusuf S, Pitt B, Davis CE, et al. 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. DOI: 10.1056/NEJM199209033271003. http://www.ncbi.nlm.nih.gov/pubmed/1463530.	ACE	RCT SOLVD-Prevention; n=4228 P: LVEF < 35% I: Enalapril C: Placebo O: mortality, cv mortality Follow-up: 37,4m Reporting-Standards der 1990er; keine detaillierte Beschreibung der Verblindung, nur "double blind"	80% mit MI; 33% NYHA II; 67% aLVD mortality 313/2111 (14,8%) vs. 334/2117 (15,8%) RRR 8% (95% KI -8;21) n.s. cv mortality 265/2111 (12,6%) vs. 298/2117 (14,1% RRR 12% (95% KI -3; 26) n.s. Development of CHF 438/2111 (20,7%) vs. 640/2117 (30,2%) RRR 37% (95% KI 28; 44) 1st HF hospitalization 184/2111 (8,7%) vs. 273/2117 (12,9%) RRR 36% (95% KI 22; 46) Subgruppe NYHA I: mortality or hospitalisation: RRR 21% (95% KI 7; 33) mortality or development of HF: RRR 28% (95% KI 18; 37)	Selection bias Randomisierung: unclear Allocation concealment: unclear Performance bias: unclear Detection bias: unclear Attrition bias: low andere Biasursachen: keine	(in Anlehnung an GRADE): moderat Post-MI, sonst niedrig Ausgangsniveau: hoch 1) Verzerrungsrisiko: niedrig (weil gewählte Endpunkte nicht anfällig dafür) 2) Präzision -1 (Einzelendpunkte n.s.) 3) Direktheit -1 (Population vorwiegend Post-MI)
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. DOI: 10.1016/S0140-6736(03)13501-5. http://www.ncbi.nlm.nih.gov/pubmed/12788569.	ACE	RCT SOLVD-Prevention; Langzeit-Follow-up n=4228 P: LVEF < 35% I: Enalapril C: Placebo O: mortality, cv mortality Follow-up: 11,2 y	80% mit MI 33% NYHA II; 67% aLVD all cause death: 1074/2111 vs. 1195/2217 (56,4%) HR 0,86 (0,79; 0,93) cv death: 791/2111 (37,0%) vs. 888/2117 (42,0%) HR 0,84 (0,77; 0,93) Subgruppe NYHA I/aLVD (n=3105) mortality: 780 (50,4%) vs. 865 (55,6%) HR (aus forest plot): ca. 0,85 (95% KI ca. 0,78; 0,96) --> größerer Benefit als mit NYHA II	siehe Yusuf 1992	(in Anlehnung an GRADE): hoch Post-MI, sonst moderat Ausgangsniveau: hoch 1) Verzerrungsrisiko: niedrig (da Endpunkte nicht anfällig dafür) 2) Präzision +/-0 3) Direktheit -1 (Population vorwiegend Post-MI)

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Kober L; Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensinconverting- enzyme inhibitor trandolapril in patients with left ventricular Dysfunction after myokardial Infarction N Engl J Med. 1995;333: 1670–1676.	ACE	RCT TRACE n=1749 P: AMI, LVEF ≤35% I: Trandolapril C: Placebo O: diverse Reporting-Standards der 1990er; keine detaillierte Beschreibung der Verblindung, nur "double blind"	Mortality 304/876 (34,7%) vs. 369/873 (42,3%); RR 0,78 (95% KI 0,67; 0,91) ARR 7,6% cv death 226/876 (25,8%) vs. 288/873 (33,0%) RR 0.75 (95 % KI, 0.63; 0.89) ARR 7,2% Progression to severe HF 125/876 (14%) vs. 171/873 (19,6%) RR 0.71 (95% KI 0.56; 0.89); ARR 5,6% recurrent myocardial infarction (fatal or nonfatal): n.s. aLVD: NYHA class I at baseline 42%/40% mortality Killip class 1 72/363 (19,8%) vs. 96/361 (26,6%) RR 0.70 (0.52–0.96); ARR 6,8%	Selection bias Randomisierung: low Allocation concealment: low Performance bias: unclear Detection bias: low Attrition bias: low (Mortalität) high (andere Endpunkte, wg. hohem drop-out) andere Biasursachen: keine	(in Anlehnung an GRADE): hoch Post-MI, sonst moderat Ausgangsniveau: hoch 1) Verzerrungsrisiko: für Mortalität niedrig 2) Präzision +/-0 3) Direktheit -1 (Population vorwiegend Post-MI)

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
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;360:752–760.	ARB	RCT, n=5477 P: AMI, ≥50 y; HF during the acute phase or a new Q-wave anterior infarction or reinfarction I: Losartan C: Captopril O: all-cause mortality "superior or non-inferior"	(Gesamtpopulation) all-cause mortality at 2,7 y 499 (18%) vs. 447 (16%) RR 1,13 [95% CI 0·99–1·28] sudden cardiac death or resuscitated cardiac arrest 239 (9%) vs. 203 (7%), RR 1,19 (0·98–1·43) fatal or non-fatal reinfarction 384 (14%) vs. 379 (14%), RR 1,03 (0·89–1·18), allcause hospital admission rates 1806 (66%) vs. 1774 (65%), 1,03 (0·97–1·10) Cough 256 (9·3%) vs. 512 (18·7%) p <0,0001 Hypotension 365 (13·3%) vs. 445 (16·3%) p=0,002 aLVD: Killip class 1 (no signs of HF): 1735 (31,7%) gemäß forest plot Killip-Klasse kein Effektmodulator	Selection bias Randomisierung: low Allocation concealment: low Performance bias: low Detection bias: low Attrition bias: low andere Biasursachen: keine	(in Anlehnung an GRADE): niedrig Post-MI, sonst sehr niedrig Ausgangsniveau: hoch 1) Verzerrungsrisiko: niedrig 2) Präzision -1 (n.s.) 3) Direktheit -2 (Population nicht nur aLVD, Post-MI)
Pfeffer MA. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003; 349:1893–1906.	ARB	RCT VALIANT n=14.703 P: AMI I: Valsartan C: Captopril, Valsartan+Captopril O: death from any cause "superior or non-inferior"	median follow-up 24.7 months (Gesamtpopulation) death from any cause (valsartan vs. Kombi vs. Captopril) 979 (19,9%) vs. 941 (19,3%) vs. 958 (19,5%) valsartan vs. captopril HR 1.00 (97,5% KI 0.90; 1.11) Kombi vs. captopril HR 0.98 (97.5 KI 0.89; 1.09; aLVD: Killip class 1 (no signs of HF): 4099 (27,9%) gemäß forest plot Killip-Klasse kein Effektmodulator	Selection bias Randomisierung: low Allocation concealment: low Performance bias: unclear Detection bias: low Attrition bias: low andere Biasursachen: keine	(in Anlehnung an GRADE): niedrig Post-MI, sonst sehr niedrig Ausgangsniveau: hoch 1) Verzerrungsrisiko: niedrig 2) Präzision -1 (n.s.) 3) Direktheit -2 (Population nicht nur aLVD, Post-MI)

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Pfeffer MA et al.; PARADISE-MI Investigators and Committees. Angiotensin Receptor-Neprilysin Inhibition in Acute Myocardial Infarction. N Engl J Med. 2021 Nov 11;385(20):1845-1855. doi: 10.1056/NEJMoa2104508. Erratum in: N Engl J Med. 2021 Dec 30;385(27):2592. PMID: 34758252.	ARNI	RCT PARADISE-MI n=5661 P: AMI I: Sacubitril/Valsartan C: Ramipril O: death from cardiovascular causes or incident heart failure	mediane LVEF ca. 36% 2281 Killip-Klasse 1 Gesamtgruppe: cv Mortalität: n.s. Herzinsuffizienz-Ereignisse: n.s.	nicht bewertet, da nicht empfehlungsbegründend	(in Anlehnung an GRADE): nach MI niedrig sonst sehr niedrig Ausgangsniveau: hoch 1) Verzerrungsrisiko: nicht bewertet 2) Präzision -1 (n.s.) 3) Direktheit -1/2 (Population)
Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet. 2001;357:1385–1390.	BB	RCT CAPRICORN, n=1959 P: AMI (53%); LVEF ≤ 40% I: Carvedilol C: Placebo O: diverse	(Gesamtpopulation) all-cause mortality or hospital admission for cv problems 340 [35%] vs 367 [37%], HR 0·92 [95% CI 0·80–1·07]) all-cause mortality 116/975 [12%] vs 151/984 [15%], HR 0·77 [0·60–0·98] Anteil aLVD: nach Goldberg 2006: 1023/1959 (52%) nach Reed 2015: 54% als Quelle jeweils Dargie 2001 angegeben, dort aber keine Angaben zum Anteil der Pat. mit aLVD	Selection bias Randomisierung: low Allocation concealment: low Performance bias: unclear Detection bias: low Attrition bias: low andere Biasursachen: Sponsor nicht berichtet	(in Anlehnung an GRADE): niedrig Post-MI, sonst sehr niedrig Ausgangsniveau: hoch 1) Verzerrungsrisiko: niedrig 2) Präzision -1 (n.s.) 3) Direktheit -2 (Population nicht nur aLVD, Post-MI)

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Doughty RN, Whalley GA, Walsh HA, et al. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. Circulation. 2004;109:201–206.	BB	RCT, CAPRICORN Substudy n=98 P: AMI (53%); LVEF ≤ 40%; Hypertension I: Carvedilol C: Placebo O: structural and functional changes in the left ventricle	improved LVEF from baseline to follow-up (median: 6 years) (36%–47%) reduced LV end-diastolic dimensions (62 vs 56 mm) reduced end-systolic dimensions (53 vs 42 mm) LVEF increased in 69% keine Infos zu aLVD-Subgruppe	siehe Dargie 2001	(in Anlehnung an GRADE): sehr niedrig Ausgangsniveau: hoch 1) Verzerrungsrisiko: niedrig 2) Präzision -1 (n) 3) Direktheit -2 (Population nicht nur aLVD, Post-M, Surrogatl)
Colucci WS, Kolias TJ, Adams KF, et al. Metoprolol reverses left ventricular remodeling in patients with asymptomatic systolic dysfunction: The REversal of VEntricular Remodeling with Toprol-XL (REVERT) trial. Circulation 2007; 116(1):49–56. DOI: 10.1161/CIRCULATIONAHA.106.666016. http://www.ncbi.nlm.nih.gov/pubmed/17576868.	BB	RCT (REVERT), n=149 P: LVEF <40%, NYHA I I: Metoprolol succinate (200 mg, 50 mg) C: Placebo O: left ventricular remodeling at 12m "Patients previously treated for symptomatic HF were allowed to participate if they met the inclusion and exclusion criteria for the study."	200-mg group end-systolic volume index 14+/-3 mL/m2 decrease (least square mean+/-SE) --> P<0.05 vs. baseline and vs. placebo end-diastolic volume index (14+/-3) --> different vs. baseline (P<0.05) but not vs. placebo LVEF 6+/-1% increase --> P<0.05 vs. baseline and vs. placebo 50-mg group end-systolic/diastolic volume indexes --> different vs. baseline (P<0.05) but not vs. placebo LVEF 4+/-1% increase --> P<0.05 vs. baseline and vs. placebo	Selection bias Randomisierung: unclear Allocation concealment: unclear Performance bias: unclear Detection bias: low Attrition bias: low andere Biasursachen: keine	(in Anlehnung an GRADE): niedrig Ausgangsniveau: hoch 1) Verzerrungsrisiko: niedrig 2) Präzision -1 (n) 3) Direktheit -1 (Surrogat)

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Vantrimpont P, Rouleau JL, Wun CC, et al. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. SAVE Investigators. Journal of the American College of Cardiology 1997; 29(2):229–36. DOI: 10.1016/s0735-1097(96)00489-5. http://www.ncbi.nlm.nih.gov/pubmed/9014971.	BB	RCT (SAVE), n=2231, davon n=789 mit BB retrospektive Analyse P: AMI, aLVD I: ACE + BB C: ACE ohne BB O: diverse at 3,5 y	cv death: 30%, (95% CI 12%; 44%) development of HF: 21% (95% CI 3%; 36%) recurrent MI: 11% (95% CI 13%; 31%) n.s. independent of the use of captopril	nicht bewertet, da retrospektiv, hypothesen-generierend	hypothesengenerierend
Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Lancet. 1997;349: 375–380.	BB	RCT, n=415; davon n=124 aLVD P: CHF, ischämisch I: Carvedilol C: Placebo O: diverse at 12m	Ergebnisse Gesamtpopulation: at 12 m: LVEF vs. placebo +5.3% (2p < 0.0001) end-diastolic dimensions vs. placebo 1.7 mm (2p = 0.06) decrease end-systolic dimensions vs. placebo 3.2 mm (2p = 0.001) decrease treadmill exercise duration, 6 min walk distance, NYHA class, SAS score: no changes at 19 m: episodes of worsening HF 82 vs 75; RR 1.12 [95% CI 0.82-1.53]) death or hospital admission: 104/208 (50%) vs. 131/207 (63%); RR 0.74 [0.57-0.95]) hospitalisation 99/208 vs. 120/207 RR 0.77 (10.59-1.00) all-cause death 20/208 vs. 26/207 RR 0.76 (0.42-1.36)	Selection bias Randomisierung: low Allocation concealment: low Performance bias: unclear Detection bias: low Attrition bias: low andere Biasursachen: keine	(in Anlehnung an GRADE): sehr niedrig Ausgangsniveau: hoch 1) Verzerrungsrisiko: niedrig 2) Präzision -2 (n; zuvor NYHA>I)) 3) Direktheit -1 (Surrogat)

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Exner DV, Dries DL, Waclawiw MA, et al. Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: A post hoc analysis of the Studies of Left Ventricular Dysfunction. Journal of the American College of Cardiology 1999; 33(4):916–23. DOI: 10.1016/s0735-1097(98)00675-5. http://www.ncbi.nlm.nih.gov/pubmed/10091816.	BB	RCT (SOLVD-P), n=4223, davon n=1015 (24%) mit BB retrospektive Analyse P: LVEF <35%;NYHA I + II (33%) I: ACE + BB C: ACE ohne BB O: diverse at 3,5 y	in BB-Gruppe 70% NYHA I (ca. 710) beta-blocker use associated with a significant reduction in the risk of death RR = 0.77 (95% CI 0.63 to 0.94)	nicht bewertet, da retrospektiv, hypothesen-generierend	hypothesengenerierend
Potter E, Stephenson G, Harris J, et al. Screening-guided spironolactone treatment of subclinical left ventricular dysfunction for heart failure prevention in at-risk patients. Eur J Heart Fail 2022; 24(4):620–30. DOI: 10.1002/ejhf.2428. http://www.ncbi.nlm.nih.gov/pubmed/35014128.	MRA	RCT, n=346 P: ≥65 y + hypertension/diabetes/obesity I: echo-guided Spi-ronolacton treatment* C: Standard O: incident HF at 24 m * Spironolactone started if subclinical LVD (global longitudinal strain [GLS] ≤16%) or diastolic abnormalities (at least one of E/e' >15, E/e' >10 with left atrial enlargement [LAE] or impaired relaxation [E/A < 0.8, IR], LAE with IR), or borderline GLS (17%) with IR or borderline GLS with LAE	Spironolacton bei 161 Pat. gestartet, da im Echo subclinical LVD n.s. trial stopped: 55% spironolactone discon-tinuation due to decline in renal function	nicht bewertet, da nicht empfehlungsbegründend	(in Anlehnung an GRADE): sehr niedrig Ausgangsniveau: hoch 1) Verzerrungsrisiko: nicht bewertet 2) Präzision -1 (n.s.) 3) Direktheit -2 (Population, kein direkter Placebo-Vergleich)

Referenz	Thema	Studiencharakteristika	Studienergebnisse	Methodische Qualität	Aussagesicherheit
Nesti L, Pugliese NR, Sciuto P, et al. Effect of empagliflozin on left ventricular contractility and peak oxygen uptake in subjects with type 2 diabetes without heart disease: Results of the EMPA-HEART trial. Cardiovasc Diabetol 2022; 21(1):181. DOI: 10.1136/heartjnl-2019-316215. http://www.ncbi.nlm.nih.gov/pubmed/36096863.	SGLT2-I	RCT (n=44) P: type 2 diabetes (T2D) without heart disease I: Empagliflozin C: Sitagliptin O: myocardial contractility (left ventricle global longitudinal strain, LV-GLS) and/or cardiopulmonary fitness (peak oxygen uptake, VO2peak) at 6 m	Anteil der Pat. mit aLVD ("subclinical dysfunction") unklar, da erst post-hoc über median definiert Subgruppenanalyse baseline LV-GLS below median: + 2.05% (+ 1.14/+ 2.96)	nicht bewertet, da nicht empfehlungsbegründend	Aussagesicherheit der Evidenz (in Anlehnung an GRADE): sehr niedrig Ausgangsniveau: hoch 1) Verzerrungsrisiko: nicht bewertet 2) Präzision -1 (n; klinische Relevanz des Effektes unklar) 3) Direktheit -2 (Population, Surrogatparameter)