Supplementary Information

Drugs and Aging

The Prevalence of Adverse Drug Reactions and Adverse Drug Events from Heart Failure Medications in Frail Older Adults: A Systematic Review

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Table S1 Search strategy

ADRs or ADEs; AND	**Heart Failure; AND**	**Elderly; AND**	**Frailty**
adverse drug reaction* OR adverse drug event* OR adverse effect* OR adrs OR adverse drug effect* OR adverse reaction* OR adverse event* OR adverse outcome* OR complication* OR harm* OR side effect* OR undesirable effect* OR treatment emergent OR tolerability OR toxicity OR safe OR safety OR adverse drug reaction reporting systems OR drug hypersensitivity OR drug monitoring OR drug toxicity OR adverse outcome OR undesirable event* OR unexpected effect* OR unexpected event* OR abnormalities, drug induced OR long term adverse effects	heart failure OR cardiac failure OR congestive heart failure OR heart decompensation OR cardiac decompensation	Aged OR elderly OR Aging OR older adult* OR older people	Frailty OR Frail Elderly OR frail*

Table S2 PRESS validation checklist

TABLE 10: PRESS GUIDELINE ASSESSMENT FORM
***PRESS Guideline* — Search Submission & Peer Review Assessment**

SEARCH SUBMISSION:

Searcher: Mai Duong

Email: mai.duong@sydney.edu.au

Date submitted: Wednesday May 12, 2021 **Date requested by**: Friday May 14, 2021

Systematic Review Title:

The prevalence of adverse drug reactions or adverse drug events with heart failure management in frail older adults: a systematic review and meta-analysis.

This search strategy is...

X	My PRIMARY (core) database strategy — First time submitting a strategy for search question and database
	My PRIMARY (core) strategy — Follow-up review NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions
	SECONDARY search strategy— First time submitting a strategy for search question and database
	SECONDARY search strategy — NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions

Database

CENTRAL, MEDLINE, Embase, Ageline, CINAHL, International Pharmaceutical Abstracts, PsychInfo, and Scopus

Interface

Ovid, EBSCO, Elsevier

Research Question

What is the extent of adverse drug reactions (ADRs) or adverse drug events (ADEs) in frail older adults related to their heart failure (HF) treatment?

(i) What is the prevalence, type and severity of ADRs or ADEs with HF treatment in frail older adults compared to non-frail older adults?

PICO Format

PICOS: Population (frail older adults), Intervention (heart failure medication treatment), Comparator (non-frail older adults), Outcome (ADRs or ADEs), Study Design (systematic review and meta-analysis)

P I C O S Inclusion Criteria

(List criteria such as age groups, study designs, etc., to be included) [optional]

Include randomised controlled trials (RCTs); controlled before-and-after trials; interrupted time series; or meta-analysis; or observational studies (cohort, case-control or cross sectional studies). Studies measuring ADR or ADE with definitions and/or causality assessment criteria; or studies focused on ADRs or ADEs secondary to a specific medication or pharmacological class; or specific ADR or ADE.

Population:
(i) Include only people aged 65 years or older or must separately report outcomes for people aged 65 years or older;
( ) Include people with a primary diagnosis of HF, with disease severity based on the New York Association (NYHA) classification and included persons with mild to severe functional limitations (NYHA grade II-IV). Studies may include people treated for HF in various settings (e.g. hospitalised with HF, receiving care in a nursing home or living independently in the community);
(i) Include studies reporting ADRs or ADEs with definition and/or causality assessment criteria;
(ii) Include only people described as being frail or must separately report outcomes for people described as frail, with a frailty measurement using objective criteria. The term 'frail' must be justified using systematically defined criteria (e.g. the Cardiovascular Health Study Criteria (Fried 2001), Frailty Index score (Mitnitski 2004), CSHA Clinical Frailty Score (Rockwood 2005), frailty phenotype, difficulty performing specified tasks, require assisted living arrangements (e.g. nursing home resident), or other measures of vulnerability).

Exclusion Criteria

(List criteria such as study designs, date limits, etc., to be excluded) [optional]

Exclude qualitative studies, self-reports, case reports, case series, expert opinion or reviews. Exclude trials of pharmacotherapy with cardiovascular agents for indications other than heart failure (e.g., hypertension, angina, atrial fibrillation, stroke, previous myocardial infarction, liver failure, heart rate control, chronic kidney disease).

Was a search filter applied?

Yes x No □

If YES, which one(s) (e.g., Cochrane RCT filter, PubMed Clinical Queries filter)? Provide the source if this is a published filter. *[mandatory if YES to previous question — textbox]*

The search filters for drug interventions, free texts and index terms used to describe ADRs or ADEs were adapted from a Cochrane RCT filter for adverse effects by Golder S et. al. 2019.

Golder, S., Peryer, G. and Loke, Y.K., 2019. Overview: comprehensive and carefully constructed strategies are required when conducting searches for adverse effects data. *Journal of clinical epidemiology*, *113*, pp.36-43.

Other notes or comments you feel would be useful for the peer reviewer? *[optional]*

There are 8 search strategies for review included below. The Scopus strategy includes both the original strategy (1002 results) and followed your truncated recommended strategy (3 results) for comparison.

1. Database: Ovid MEDLINE(R) ALL <1946 to May 10, 2021> Search Strategy:
- -
1 ae.fs. [adverse effects] (1795345)
2 co.fs. [complications] (2031160)
3 de.fs. [drug effects] (3065572)
4 safe.ti,ab. (390361)
5 safety.ti,ab. (549367)
6 undesirable effect*.ti,ab. (3134)
7 treatment emergent.ti,ab. (5485)
8 tolerability.ti,ab. (51701)
9 toxicity.ti,ab. (397618)
10 adrs.ti,ab. (4453)
11 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab. (469244)
12 ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ti,ab. (555986)
13 abnormalities, drug induced/ (14613)
14 adverse drug reaction reporting systems/ (7885)
15 drug hypersensitivity/ (23972)
16 drug monitoring/ (21789)
17 "Drug-Related Side Effects and Adverse Reactions"/ (33494)
18 long term adverse effects/ (665)
19 safety-based drug withdrawals/ (401)
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (7317665)
21 exp heart failure/ (127020)
22 cardiac failure/ (123841)
23 congestive heart failure.ti,ab. (39034)
24 ((heart or cardiac) adj1 (failure* or decompensation or de-compensation)).ti,ab. (187456)
25 21 or 22 or 23 or 24 (224141)
26 Aged/ (3193985)
27 "Aged, 80 and over"/ (958294)
28 Aging/ (234832)
29 elderly.ti,ab. (255685)
30 26 or 27 or 28 or 29 (3450978)
31 Frailty/ (4024)
32 Frail Elderly/ (12394)
33 frail*.ti,ab. (24904)
34 31 or 32 or 33 (29450)
35 20 and 25 and 30 and 34 (292)
36 limit 35 to (abstracts and english language and humans and yr="1960 - Current") (249)
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2. Database: Embase Classic Search Strategy <1947 to 1973>, Embase <1974 to 2021 May 10>:
- -
1 ae.fs. [adverse drug reaction] (1279182)
2 co.fs. [complications] (1762058)
3 complication/ (257660)
4 de.fs. [drug effects] (4641)
5 drug effect/ (777253)
6 safe.ti,ab. (600910)
7 safety.ti,ab. (863531)
8 side-effect*.ti,ab. (405321)
9 undesirable effect*.ti,ab. (4646)
10 treatment emergent.ti,ab. (13119)
11 tolerability.ti,ab. (94657)
12 drug tolerance/ (37525)
13 toxicity.ti,ab. (568321)
14 adrs.ti,ab. (9010)
15 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab. (746854)
16 ((adverse or undesirable or harm*) adj3 (effect* or reaction* or event* or outcome*)).ti,ab. (793990)
17 Adverse drug reaction/ (256528)
18 drug hypersensitivity/ (52416)

19 drug monitoring/ (55747)
20 drug safety/ (449977)
21 drug surveillance program/ (26572)
22 drug toxicity/ (82463)
23 side effect/ (341162)
24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (5961708)
25 exp heart failure/ (557204)
26 cardiac failure/ (252983)
27 congestive heart failure.ti,ab. (58137)
28 ((heart or cardiac) adj1 (failure* or decompensation or de-compensation)).ti,ab. (322544) 29
25 or 26 or 27 or 28 (609709)
30 Aged/ (3225396)
31 elderly.ti,ab. (374141)
32 Aging/ (285761)
33 (older adj1 (adult* or people)).ti,ab. (149062) 34
30 or 31 or 32 or 33 (3515290)
35 Frailty/ (15053)
36 Frail Elderly/ (10791)
37 frail*.ti,ab. (38640)
38 35 or 36 or 37 (44117)
39 24 and 29 and 34 and 38 (742)
40 limit 39 to (abstracts and human and english language and yr="1960 -Current") (683)
****

3. Database: EBM Reviews - Cochrane Central Register of Controlled Trials Search Strategy <April 2021>:
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1 ae.fs. [adverse effects] (130832)
2 co.fs. [complications] (55061)
3 de.fs. [drug effects] (122139)
4 safe.ti,ab. (70565)
5 safety.ti,ab. (233410)
6 undesirable effect*.ti,ab. (393)
7 treatment emergent.ti,ab. (8586)
8 tolerability.ti,ab. (56827)
9 toxicity.ti,ab. (37922)
10 adrs.ti,ab. (668)
11 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab. (173281)
12 ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ti,ab. (182109)
13 abnormalities, drug induced/ (46)
14 adverse drug reaction reporting systems/ (90)
15 drug hypersensitivity/ (456)
16 drug monitoring/ (1842)
17 "Drug-Related Side Effects and Adverse Reactions"/ (1587)
18 long term adverse effects/ (38)
19 safety-based drug withdrawals/ (5)
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (576828)
21 exp heart failure/ (9710)
22 cardiac failure/ (9456)
23 congestive heart failure.ti,ab. (5309)
24 ((heart or cardiac) adj1 (failure* or decompensation or de-compensation)).ti,ab. (29012)
25 21 or 22 or 23 or 24 (30020)
26 Aged/ (213960)
27 "Aged, 80 and over"/ (55094)
28 Aging/ (3712)
29 elderly.ti,ab. (46908)
30 26 or 27 or 28 or 29 (251440)
31 Frailty/ (168)
32 Frail Elderly/ (742)
33 frail*.ti,ab. (3841)
34 31 or 32 or 33 (4022)
35 20 and 25 and 30 and 34 (41)
36 limit 35 to (abstracts and english language and humans and yr="1960 - Current") [Limit not valid; records were

retained] (33)
****

4. Database: International Pharmaceutical Abstracts Search Strategy <1970 to April 2021>:
- -
1 complication*.mp. (12712)
2 co.fs. [complications] (3) 3
safe.ti,ab. (15069)
4 safety.ti,ab. (41356)
5 undesirable effect*.ti,ab. (171)
6 treatment emergent.ti,ab. (1083)
7 tolerability.ti,ab. (8831)
8 toxicity.ti,ab. (24797)
9 adrs.ti,ab. (1427)
10 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab. (46682)
11 ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ti,ab. (51217)
12 hypersensitivity.mp. (2331)
13 (drug adj1 monitoring).mp. (3037)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (121796)
15 heart failure.mp. (7007)
16 cardiac failure.mp. (321)
17 (congestive adj1 heart adj1 failure).mp. (2118)
18 ((heart or cardiac) adj1 (failure* or decompensation or de-compensation)).ti,ab. (6763)
19 15 or 16 or 17 or 18 (7221)
20 Aged.mp. (18831)
21 senior*.mp. (1100)
22 geriatric.mp. (2300)
23 elderly.ti,ab. (9583)
24 Aging.mp. (2966)
25 (older adj1 (adult* or people)).ti,ab. (1937)
26 20 or 21 or 22 or 23 or 24 or 25 (32065)
27 frailty.mp. (148)
28 frail*.ti,ab. (337)
29 (Frail adj1 Elderly).mp. (87)
30 27 or 28 or 29 (337)
31 14 and 19 and 26 and 30 (9)
****

5. Database: APA PsycInfo Search Strategy*** <1806 to April Week 4 2021> (post-validation update 18.05.21):
- -
1 exp "Side Effects (Drug)"/ (59848)
2 exp Geriatrics/ (14589)
3 exp Aging/ (82944)
4 exp Older Adulthood/ (9084)
5 exp Geriatric Patients/ (13895)
6 complication*.mp. (35270)
7 safe.ti,ab. (35178)
8 safety.ti,ab. (69507)
9 undesirable effect*.ti,ab. (375)
10 treatment emergent.ti,ab. (1370)
11 tolerability.ti,ab. (7550)
12 toxicity.ti,ab. (9191)
13 adrs.ti,ab. (314)
14 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab. (42990)
15 ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ti,ab. (49914)
16 hypersensitivity.mp. (4769)
17 (drug adj1 monitoring).mp. (1777)
18 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (184728)
19 heart failure.mp. (4454)
20 cardiac failure.mp. (144)
21 (congestive adj1 heart adj1 failure).mp. (959)
22 ((heart or cardiac) adj1 (failure* or decompensation or de-compensation)).ti,ab. (4293)
23 19 or 20 or 21 or 22 (4597)
24 Aged.mp. (620776)

25 senior*.mp. (30626)
26 geriatric.mp. (39958)
27 elderly.ti,ab. (59882)
28 Aging.mp. (114591)
29 (older adj1 (adult* or people)).ti,ab. (67473)
30 24 or 25 or 26 or 27 or 28 or 29 (742406)
31 frailty.mp. (2708)
32 frail*.ti,ab. (5180)
33 (Frail adj1 Elderly).mp. (2591)
34 31 or 32 or 33 (6172)
35 18 and 23 and 30 and 34 (8)
36 limit 35 to (human and english language and abstracts and yr="1960 -Current") (7)
37 1 or 18 (232116)
38 2 or 3 or 4 or 5 or 30 (752758)
39 23 and 34 and 37 and 38 (7)

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****(Use of subject headings and keyword searches applied post-validation to PsychInfo and CINAHL – search strategy was updated May 18, 2021)*

6. EBSCO CINAHL Search***

CINAHL Search Strategy 11.05.21 (post-validation update 18.05.21)

#	Query	Results
S60	S37 AND S44 AND S52 AND S58	85
S59	S37 AND S44 AND S52 AND S58	85
S58	S53 OR S54 OR S55 OR S56 OR S57	17,336
S57	(MH "Frail Elderly")	7,894
S56	(MH "Frailty Syndrome")	2,728
S55	TI frail* OR AB frail*	13,956
S54	TI Frail Elderly OR AB Frail Elderly	2,154
S53	TI Frailty OR AB Frailty	8,610
S52	S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51	1,060,605
S51	(MH "Aged, 80 and Over+")	306,998
S50	(MH "Aged+")	868,914
S49	TI older people OR AB older people	29,655
S48	TI older adult* OR AB older adult*	69,173
S47	TI Aging OR AB Aging	60,990
S46	TI elderly OR AB elderly	94,046
S45	TI Aged OR AB Aged	196,047
S44	S38 OR S39 OR S40 OR S41 OR S42 OR S43	70,616
S43	(MH "Heart Failure+")	44,053
S42	TI cardiac decompensation OR AB cardiac decompensation	173
S41	TI heart decompensation OR AB heart decompensation	171
S40	TI congestive heart failure OR AB congestive heart failure	8,730
S39	TI cardiac failure OR AB cardiac failure	5,533
S38	TI heart failure OR AB heart failure	55,919
S37	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36	707,683
S36	(MH "Substance Withdrawal, Controlled")	989
S35	(MH "Drug Monitoring")	8,073
S34	(MH "Drug Hypersensitivity+")	7,131
S33	(MH "Abnormalities, Drug-Induced")	1,220
S32	(MH "Drug Toxicity+")	17,121
S31	(MH "Medication Side Effects (Saba CCC)")	1
S30	(MH "Treatment Complications, Delayed")	2,330
S29	(MH "Adverse Drug Event+")	30,554
S28	(MH "Adverse Health Care Event+")	69,136
S27	TI long term adverse effects OR AB long term adverse effects	1,010

S26	TI abnormalities, drug induced OR AB abnormalities, drug induced	26
S25	TI unexpected event* OR AB unexpected event*	821
S24	TI unexpected effect* OR AB unexpected effect*	561
S23	TI undesirable event* OR AB undesirable event*	116
S22	TI adverse outcome OR AB adverse outcome	26,879
S21	TI drug toxicity OR AB drug toxicity	2,673
S20	TI drug monitoring OR AB drug monitoring	3,994
S19	TI drug hypersensitivity OR AB drug hypersensitivity	534
S18	TI adverse drug reaction reporting systems OR AB adverse drug reaction reporting systems	44
S17	TI safety OR AB safety	191,313
S16	TI safe OR AB safe	104,894
S15	TI toxicity OR AB toxicity	45,064
S14	TI tolerability OR AB tolerability	13,859
S13	TI treatment emergent OR AB treatment emergent	2,277
S12	TI undesirable effect* OR AB undesirable effect*	903
S11	TI side effect* OR AB side effect*	47,054
S10	TI harm* OR AB harm*	58,479
S9	TI complication* OR AB complication*	202,940
S8	TI adverse outcome* OR AB adverse outcome*	29,644
S7	TI adverse event* OR AB adverse event*	67,876
S6	TI adverse reaction* OR AB adverse reaction*	11,763
S5	TI adverse drug effect* OR AB adverse drug effect*	2,673
S4	TI adrs OR AB adrs	1,853
S3	TI adverse effect* OR AB adverse effect*	43,275
S2	TI adverse drug event* OR AB adverse drug event*	4,751
S1	TI adverse drug reaction* OR AB adverse drug reaction*	5,105

****(Use of subject headings and keyword searches applied post-validation to PsychInfo and CINAHL – search strategy was updated May 18, 2021)*

7. EBSCO Ageline Search 11.05.21

#	Query	Results
S41	S22 AND S28 AND S36 AND S40	15
S40	S37 OR S38 OR S39	6,329
S39	frail*	6,329
S38	Frail Elderly	4,250
S37	Frailty	2,443
S36	S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35	161,951
S35	older people	129,446
S34	older adult*	134,359
S33	geriatric*	38,829
S32	senior*	9,336
S31	Aging	75,697
S30	elderly	131,510
S29	Aged	138,398
S28	S23 OR S24 OR S25 OR S26 OR S27	1,266
S27	cardiac decompensation	3
S26	heart decompensation	4
S25	congestive heart failure	970
S24	cardiac failure	697
S23	heart failure	1,253
S22	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	12,291
S21	long term adverse effects	13
S20	unexpected event*	22
S19	undesirable event*	21
S18	drug toxicity	45
S17	drug monitoring	89
S16	drug hypersensitivity	1
S15	safety	4,983
S14	safe	1,899
S13	treatment emergent	21
S12	undesirable effect*	26
S11	side effect*	1,514
S10	harm*	1,806
S9	complication*	1,532
S8	adverse outcome*	691
S7	adverse event*	818
S6	adverse reaction*	460
S5	adverse drug effect*	120
S4	ADRs	61
S3	adverse effect*	863
S2	adverse drug event*	356
S1	"adverse drug reaction*"	384

8. Elsevier Scopus Search
(Original)

1. ADRs and ADEs

Drug intervention filters - (adapted from Golder 2019)
(adverse AND drug AND reaction*) OR (adverse AND drug AND event*) OR (adverse AND effect*) OR adrs OR (adverse AND drug AND effect*) OR (adverse AND reaction*) OR (adverse AND event*) OR (adverse AND outcome*) OR complication* OR harm* OR side-effect* OR (undesirable AND effect*) OR (treatment AND emergent) OR tolerability OR toxicity OR safe OR safety OR (adverse AND drug AND reaction AND reporting AND systems) OR (drug AND hypersensitivity) OR (drug AND monitoring) OR (drug AND toxicity) OR (undesirable AND event*) OR (unexpected AND effect*) OR (unexpected AND event*) OR (abnormalities AND drug AND induced) OR (long AND term AND adverse AND effects)

2. Heart Failure

(heart AND failure) OR (cardiac AND failure) OR (congestive AND heart AND failure) OR (heart AND decompensation) OR (cardiac AND decompensation)

3. Elderly

Aged OR elderly OR Aging OR (older AND adult*) OR (older AND people)

4a. Frailty

Frailty OR (Frail AND Elderly) OR frail*
-1002 document results

(Peer reviewed Truncated recommendations and results)

1. ADRs and ADEs

((adverse OR undesirable OR unexpected) AND (effect* OR event* OR reaction* OR outcome*)) OR ADRS OR "adverse drug reaction reporting system*" OR ((drug* OR treatment) AND (hypersensitive* OR hyper-sensitiv* OR monitoring OR toxicity OR tolerability OR safe* OR abnormalit* OR harm* OR side-effect* OR reaction* OR event* OR effect* OR complication* OR emergent))

2. Heart Failure

((heart OR cardiac) AND (failure OR decompensation))

3. Elderly

Elderly OR Age* OR (older AND (adult* OR people OR person*)) (*392*

document results retrieved)

0. Frailty

Frailty OR (Frail AND Elderly) OR frail*

(*3 document results retrieved)*

PEER REVIEW ASSESSMENT: THIS SECTION TO BE FILLED IN BY THE REVIEWER

	Email:	Date completed:
Dr Yulia Ulyannikova	yulia.ulyannikova@sydney.edu.au	14 May 2021

1. TRANSLATION			
	A. No revisions	☐	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If "B" or "C," please provide an explanation or example:

2. BOOLEAN AND PROXIMITY OPERATORS			
	A. No revisions	☐	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If "B" or "C," please provide an explanation or example:

If "B" or "C," please provide an explanation or example:

3. SUBJECT HEADINGS			
	A. No revisions	☐	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

PsycInfo is a database with a thesaurus. Currently the search includes no subject headings.

CINAHL is a database with a thesaurus, currently the search includes no subject headings

4. TEXT WORD SEARCHING			
	A. No revisions	☐	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If "B" or "C," please provide an explanation or example:

5. SPELLING, SYNTAX, AND LINE NUMBERS			
	A. No revisions	☐	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If "B" or "C," please provide an explanation or example:

6. LIMITS AND FILTERS			
	A. No revisions	☐	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If "B" or "C," please provide an explanation or example:

7. OVERALL EVALUATION (Note: If one or more "revision required" is noted above, the response below must be "revisions required".)			
	A. No revisions	☐	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If "B" or "C," please provide an explanation or example:

Add subject heading search to PsycInfo and CINAHL search strategies. Use keyword searches with subject headings.

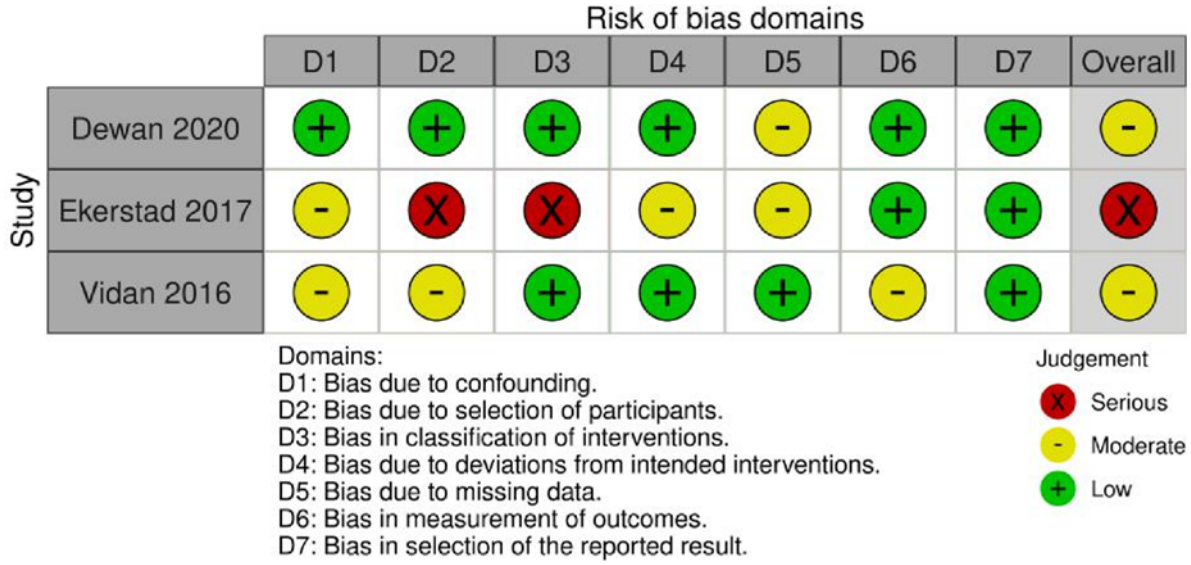
****(Use of subject headings and keyword searches applied post-validation to PsychInfo and CINAHL – search strategy was updated May 18, 2021)*

Table S3 Eligible guideline directed heart failure specific medications in search strategy

Drug class	Example of medications
angiotensin-converting enzyme inhibitors (ACEIs)	enalapril
angiotensin-2 receptor antagonists/blockers (ARBs)	candesartan
angiotensin receptor neprilysin inhibitor (ARNI)	sacubitril/valsartan
aldosterone/mineralocorticoid receptor antagonists (MRAs)	spironolactone, eplerenone
renin inhibitor	aliskiren
beta-blockers	bisoprolol
renin inhibitor	aliskiren
diuretics	furosemide
calcium channel blockers (CCBs)	verapamil, diltiazem
cardiac glycosides	digoxin
inotropes/adrenergic agonists	dobutamine, dopamine
I_f channel inhibitors	ivabradine
SGLT-2 inhibitors	dapagliflozin, empagliflozin
vasodilators	nitroglycerin, isosorbide dinitrate, hydralazine

Note: The treatments can be administered alone or in combination; in fixed or titrated (up/down) regimens

Figure S1 Risk of bias assessment: ROBINS-I summary for non-randomised intervention studies



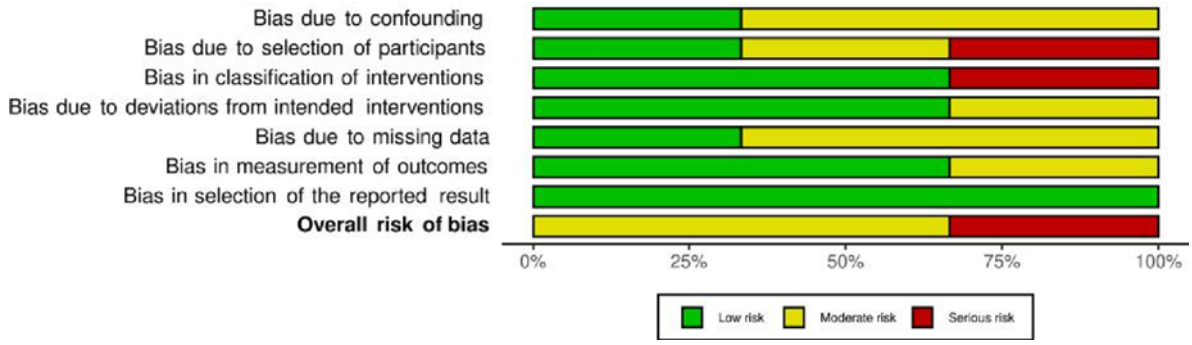


Table S4: GRADE criteria and scoring

Table S4a: GRADE Assessment Criteria

Each of the domains were assessed from "high" quality evidence and given downgrade or upgrade points accordingly.

	Domain	Description	No downgrade given (0) if:	Downgrade given by one level (-1) if:
Factors that can downgrade the quality of evidence include:				
1	**Study design**	Randomised controlled trials (0) and observational studies (-1) were included in this review.	Studies were RCTs.	Studies were observational in design.
2	**Risk of bias/ study limitation**	Study limitations were determined with the Cochrane risk of bias assessment tool ROB-2 for RCTs and ROBINS-I for observational studies.	Studies had "low" overall risk of bias score.	Studies had "moderate" or "high" overall risk of bias score.
3	***Inconsistency**	Inconsistency was based on presence of statistical heterogeneity (I^2) but was not performed in this review's narrative analysis. We did not conduct a meta-analysis. Investigators were unable to determine the differences in underlying treatment effect nor identify a plausible explanation if heterogeneity existed.	Inconsistency was not present.	All outcomes were downgraded since investigators unable to demonstrate if statistical heterogeneity was present.
4	**Indirectness**	Indirectness was evaluated using the PICO format to determine how well the evidence included in the review answered the research question, including: Population: older age, frailty Intervention: HF specific medication Comparator: non-frail older adults Outcome: ADR or ADE	Indirectness was not observed.	Indirectness was present in either population, intervention comparator or outcomes.
5	**Imprecision**	Imprecision was evaluated on optimal information size implication and variation in the effect observed from confidence intervals.	There were narrow confidence intervals around the point estimate, if null effect and appreciable harm or benefit were both not included or if confidence interval excludes point estimate.	No point estimate given, if there were wide confidence intervals around the point estimate, or if confidence intervals do not include the null effect but do include appreciable harm or benefit.
6	***Publication bias**	Publication bias was a systematic under or over estimate of the underlying effect due to the selective publication of studies or availability of their data. We did not perform a meta-analysis so did not assess publication bias because funnel plots were not generated in a narrative synthesis.	Publication bias was not observed.	All outcomes were downgraded because publication bias is strongly suspected in a very small (scarce) number of studies despite absence of a funnel plot.

Factors that can upgrade the quality of evidence by one level:

- if dose-response gradient or relationship was observed in frail compared to non-frail participants,
- if demonstrated large or very large effects,
- if all plausible residual confounders would reduce a demonstrated effect or suggest a spurious effect if no effect was observed.

**NA* – not applicable since no meta-analysis and subgroup analysis was performed.

Table S4b: Definition of grades of evidence [21]

Score	Rationale for scoring overall quality of evidence
High	further research is very unlikely to change the confidence in the estimate of effect.
Moderate	further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.
Low	further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	any estimate of effect is very uncertain.

Table S4c. GRADE Scoring

Outcome	Study Design	Risk of Bias	*Inconsistency	Indirectness	Imprecision	*Publication bias	Overall Score
Renin angiotensin system inhibitors (Dewan et a!. 2020)							
Mortality	**-1**	**-1**	**NA**	**0**	**0**	**NA**	**Low**
Hospitalisation	**-1**	**-1**	**NA**	**0**	**0**	**NA**	**Low**
ACEI/ARB (Vidan et a!. 2016)							
Mortality	**-1**	**-1**	**NA**	**0**	**0**	**NA**	**Very Low**
Digoxin (Ekerstad et a!. 2017)							
Falls	**-1**	**-1**	**NA**	**-1**	**-1**	**NA**	**Very Low**
Tiredness	**-1**	**-1**	**NA**	**-1**	**-1**	**NA**	**Very Low**
Nausea	**-1**	**-1**	**NA**	**-1**	**-1**	**NA**	**Very Low**
Hospital readmission	**-1**	**-1**	**NA**	**-1**	**-1**	**NA**	**Very Low**
No data was available to assess the following clinical outcomes							
Fractures due to falls, worsening renal function, dyspnea, dizziness, syncope, hyper/hypo-kalaemia, cognitive function, oedema, infections, gynecomastia, quality of life, glucose levels, arrythmias	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**

**NA* – not applicable since no meta-analysis and subgroup analysis were performed and downgraded by one level.

Table S5 Subgroup of included participants from a secondary analysis of two randomised controlled trials. (Dewan et al. 2020)[25]

	PARADIGM-HF[26]	ATMOSPHERE[27]	Dewan -Frailty analysis of PARADIGM-HF and ATMOSPHERE	Dewan- Frailty Subgroup >75 (n, %)
Total population (n)	8399	7016	15415	2544
Intervention	sacubitril/valsartan (ARNI) (n=4187)	aliskiren + enalapril (n=2340) aliskiren (n=2340)	Sub-analysis of frailty	Subgroup analysis by age
Comparator	enalapril (n=4212)	enalapril (n=2336)	Non frail FI <0.210 Frail Subgroups: FI 0.211–0.310; FI >0.311	Non frail FI <0.210 (n=474) Frail Subgroups: FI 0.211–0.310; (n=795) FI >0.311 (n=829)
Frailty	No	No	Yes-frailty data available for n=13265/15415	Yes-frailty data available for n=2098/2544
Run-in phase prior to randomization (median, IQR days)	2-part single blind enalapril (15, 14-21) sacubitril/valsartan (29, 26-35)	2-part single blind enalapril (28, 16-39) enalapril + aliskiren (18, 14-24)	NA	NA
Proportion (n,%) of patients with reported adverse events and discontinued run-in phase	enalapril 591/1102, 5.6% sacubitril/valsartan 547/977, 5.8%	enalapril 370/1047, 3.5% aliskiren + enalapril 428/724, 5.9%	NA	NA

Note: The authors calculated frailty from cumulative deficits in a 42-item frailty index (FI) in participants in the PARADIGM-HF and ATMOSPHERE trials. Excluded from analysis were patients with ≥20% missing variables. Participants with FI<0.210 were considered non-frail/robust, and patients with FI>0.210 were considered frail, and further divided into groups by increments of 0.100 (0.211-0.310 or >0.311).[25]
NA: Not provided by authors