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REVIEW

Diabetes mellitus and risk of new-onset and recurrent heart failure: a systematic review and meta-analysis

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Abstract

Despite mounting evidence of the positive relationship between diabetes mellitus (DM) and heart failure (HF), the entire context of the magnitude of risk for HF in relation to DM remains insufficiently understood. The principal reason is because new-onset HF (HF occurring in participants without a history of HF) and recurrent HF (HF re-occurring in patients with a history of HF) are not discriminated. This meta-analysis aims to comprehensively and separately assess the risk of new-onset and recurrent HF depending on the presence or absence of DM. We systematically searched cohort studies that examined the relationship between DM and new-onset or recurrent HF using EMBASE and MEDLINE (from 1 Jan 1950 to 28 Jul 2019). The risk ratio (RR) for HF in individuals with DM compared with those without DM was pooled with a random-effects model. Seventy-four and 38 eligible studies presented data on RRs for new-onset and recurrent HF, respectively. For new-onset HF, the pooled RR [95% confidence interval (CI)] of 69 studies that examined HF as a whole [i.e. combining HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF)] was 2.14 (1.96–2.34). The large between-study heterogeneity (I^2 = 99.7%, $P < 0.001$) was significantly explained by mean age [pooled RR (95% CI) 2.60 (2.38–2.84) for mean age < 60 years vs. pooled RR (95% CI) 1.95 (1.79–2.13) for mean age ≥ 60 years] ($P < 0.001$). Pooled RRs (95% CI) of seven and eight studies, respectively, that separately examined HFpEF and HFrEF risk were 2.22 (2.02–2.43) for HFpEF and 2.73 (2.71–2.75) for HFrEF. The risk magnitudes between HFpEF and HFrEF were not significantly different in studies that examined both HFpEF and HFrEF risks (P = 0.86). For recurrent HF, pooled RR (95% CI) of the 38 studies was 1.39 (1.33–1.45). The large between-study heterogeneity (I^2 = 80.1%, $P < 0.001$) was significantly explained by the proportion of men [pooled RR (95% CI) 1.53 (1.40–1.68) for < 65% men vs. 1.32 (1.25–1.39) for ≥65% men (P = 0.01)] or the large pooled RR for studies of only participants with HFpEF [pooled RR (95% CI), 1.73 (1.32–2.26) (P = 0.002)]. Results indicate that DM is a significant risk factor for both new-onset and recurrent HF. It is suggested that the risk magnitude is large for new-onset HF especially in young populations and for recurrent HF especially in women or individuals with HFpEF. DM is associated with future HFpEF and HFrEF to the same extent.

Keywords Diabetes mellitus; New-onset heart failure; Recurrent heart failure; Cohort study; Meta-analysis

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Introduction

Heart failure (HF) is a major clinical and public health problem with high prevalence,[1] incurring extraordinary health care expenditures[2] and negatively influencing activities of daily living.[3] Many epidemiological studies have indicated that diabetes mellitus (DM) increases the risk of HF. For example, a recent large cohort study showed a higher risk of hospitalization for HF among patients with than without type 2 DM even if their cardiovascular risk factors were within target ranges.[4]

Because recent trials suggested that HF is preventable by specific pharmacological treatment (sodium glucose co-transporter-2 inhibitor)[5] and intensified multifactorial interventions,[6] HF has received appropriate attention[7] as one of the most common cardiovascular complications of DM.[8] Estimating the magnitude of HF risk among persons with

DM is essential for assessing the importance of HF as a diabetes-related complication and deciding whether prevention of HF should be given priority among diabetes-related complications. However, the entire context of the magnitude of risk for HF in relation to DM remains insufficiently understood. Particularly, new-onset HF (HF occurring without a history of HF) and recurrent HF (HF re-occurring with a history of HF) are not discriminated. The issues regarding risk of new-onset and recurrent HF should be discussed separately considering differences in patients' characteristics, therapy goals, and treatments to achieve goals specific to those at high risk for HF but without symptoms of HF compared with those with prior symptoms of HF.[9] In addition, although we should emphasize that it is impossible to compare new-onset and recurrent HF when the criteria differ between the two conditions, the risk imparted by DM is hypothesized to be quite different between new-onset and recurrent HF considering the burden of hospitalization after an HF diagnosis even though the cause of such hospitalizations is not necessarily due to HF.[10] Based on this hypothesis, results of many previous cohort studies that combined new-onset and recurrent HF as the HF outcome would lead to inaccurate conclusions because these studies failed to consider an interaction effect of DM status and a past history of HF even if risk indicators were adjusted for a history of HF.

Previous meta-analyses of cohort studies that examined the risk of new-onset HF in relation to DM[2,11] included studies on an unselected community population but not on a population selected according to specific characteristics and conditions (e.g. hypertension and renal diseases) that clinicians usually see in a real-world clinical setting. A recent meta-analysis that estimated the risk of new-onset HF failed to exclude studies in which participants with and without a history of HF were combined.[12] Another meta-analysis of cohort studies limited to patients with a history of HF indicated that DM adversely affected all-cause death and hospitalization.[13] However, the causes of death or reasons for hospitalization were not specified. This meta-analysis aims to comprehensively assess the risk of new-onset and recurrent HF depending on the presence or absence DM.

Methods

We followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for conducting meta-analyses of observational studies.[14] The protocol for this meta-analysis was registered in advance with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42019117390).

Search strategy

We used MEDLINE and EMBASE (from 1 Jan 1950 to 28 Jul 2019) as electronic databases for systematic literature searches. Keywords are presented in Appendix 1. Inclusion criteria were (i) cohort study; (ii) DM status of all participants was ascertained before the follow-up period; (iii) at least 6 months of follow-up; (iv) exposure is having DM at baseline; (v) referent is not having DM at baseline; (vi) outcome is new-onset or recurrent HF (see Study outcome); and (vii) the risk indicators [i.e. hazards ratio (HR) or odds ratio (OR)] for HF in relation to DM were described or the risk ratio (RR) could be calculated. Studies that classified new-onset HF into HF with preserved ejection fraction (EF) (HFpEF) and HF with reduced EF (HFrEF) were also considered. Remarks related to (i) to (v) are in Appendix 2.

We examined the reference lists of publications that met our inclusion criteria to identify additional studies that might be suitable for our purpose. We considered articles published in any language. When there were unclear issues within a study, we contacted the authors for clarification before deciding whether the study met these inclusion criteria. If two or more articles existed for one cohort study, priority for choosing one of these articles was given as follows: (i) direct presentation of data on the HR or the OR and its corresponding 95% confidence interval (CI), (ii) long-term follow-up study, and (iii) inclusion of a large number of participants.

Study outcome

As previously mentioned, we considered only studies that separated new-onset from recurrent HF as the study outcome. We defined new-onset HF as HF occurring in participants without a history of HF. When the outcome was incident new-onset HF, included studies had to exclude participants with a history of HF or with current HF. If it was unclear whether such participants were actually excluded, we did not exclude the study if there was no evidence that participants who had history of HF or currently had HF were obviously included. Conversely, even if a study author stated that participants having HF at baseline were excluded, we excluded that study wherein participants were obviously included who had HF of class $\geq$ II in the New York Heart Association (NYHA) classification or a history of HF of class $\geq$ II in the Killip classification. We defined recurrent HF as that which re-occurred in patients with a history of HF although a widely accepted definition does not exist. Thus, when an outcome is recurrent HF, we included only studies that clarified that all participants had already been diagnosed as having HF regardless of the NYHA or Killip classification status.

The endpoints for new-onset HF were hospitalization due to HF or a doctor's diagnosis of HF and for recurrent HF were hospitalization due to previously diagnosed HF or worsening of existing HF. The HF had to be an independent outcome. Studies that combined endpoints from HF and those from other causes (e.g. all-cause hospitalizations and

cardiovascular events) were excluded. In addition, the endpoints had to include both fatal and non-fatal events. Studies that included only HF mortality as the endpoint were excluded.

Data extraction

Two authors (S. K. and H. So.) independently extracted the data. Discrepancies were solved by a third author (K. K.). In addition to the risk indicator and its corresponding 95% CI, we extracted the following data: first author, year, study design, cohort name or affiliation, specificity of study population such as underlying diseases, mean age, percentage of men, number of participants and cases, follow-up duration, percentage of lost to follow-up, risk indicator, methods for ascertaining DM and HF, endpoint corresponding to the study outcome, and confounding factors. When the study outcome was recurrent HF, we added data on the characteristic of the EF (i.e. reduced/preserved/non-specified).

If the risk indicator was expressed as HR or OR and its corresponding 95% CI was not directly provided, we calculated the RR and standard error (SE) of the natural logarithm (log) of RR using the formula: $\mathrm{RR} = \frac{C_1/N_1}{C_0/N_0}$, $\mathrm{SE}(\log\mathrm{RR}) = \sqrt{1/C_0 + 1/C_1 - 1/N_0 - 1/N_1}$, where '1' and '0' are having DM and not having DM at baseline, respectively, and '*C*' and '*N*' are the number of cases and total number of participants, respectively. These risk indicators were standardized into RR. The HR was considered to be the same as the RR. The OR was transformed into the RR using the formula[15]: $\mathrm{RR} = \frac{\mathrm{OR}}{[(1 - P_0) + P_0 \times \mathrm{OR}]}$, $\mathrm{SE}(\log\mathrm{RR}) = \sqrt{\mathrm{SE}^2(\log\mathrm{OR}) \times (\log\mathrm{RR}/\log\mathrm{OR})}$, where P_0 is the incident rate of study endpoints in the referent group. Other remarks with regard to Data Extraction are shown in Appendix 3.

To assess study quality, we adapted the Newcastle-Ottawa Scale (NOS) for this meta-analysis. The NOS consists of the following three broad perspectives: selection of study groups (Selection), comparability of groups (Comparability), and ascertainment of the outcome of interest (Outcome). With regard to Comparability, we selected age and coronary heart disease (CHD) as the most important confounders[16] because HF[17] and DM[18] are typical age-related diseases. Compared with individuals without DM, those with DM have a higher prevalence of CHD,[19] and CHD presents the largest attributable risk for HF among potential risk factors.[1] As to outcome, we used the median of the follow-up duration in the included studies as a cut-off value for a sufficient follow-up duration. Remarks on the criteria for NOS are provided in Appendix 4.

Data synthesis

We separately produced a dataset for estimating the risk of new-onset and recurrent HF in relation to DM. The RR in each study was pooled with a random-effects model if between-study heterogeneity for the magnitude of risk assessed by I^2 was statistically significant.[20] Otherwise, a fixed-effects model was chosen. The analysis was stratified by each of the pre-specified study characteristics [i.e. follow-up duration, mean age, proportion of men, characteristics of risk adjustment, endpoints, and pre-existing diseases (for new-onset and recurrent HF) and characteristic of baseline EF status (for recurrent HF)]. With regard to mean age and proportion of men (%), cut-off values were determined in 5 year and 5% increments, which were close to the median in included studies so that the number of data belonging to the upper and lower values of the cut-off were as similar as possible. In general, the cut-off value was close to the median value of the included studies. Based on the stratified analyses, meta-regression analyses were added to explore the origin of heterogeneity. If a characteristic significantly explained the heterogeneity, that characteristic could be suggested to significantly affect the risk magnitude. Meta-regression was also performed to compare the risk magnitude between HFpEF and HFrEF with adjustment for each included study.

Publication bias was assessed by two formal tests, Begg's rank correlation test[21] and Egger's regression asymmetry test.[22] If publication bias was statistically detected, we adjusted the pooled RR for publication bias using the trim-and-fill method.[23] This method includes (i) the assumption that the funnel plot is symmetrical if there is no publication bias, (ii) detection of hypothetically unpublished data causing the funnel plot to be asymmetrical, and (iii) recalculation of the pooled RR after filling these data as if they had actually existed. Two-sided $P < 0.05$ was considered statistically significant. All analyses were based on statistical software STATA version 14 (STATA Corp., College Station, TX, USA).

Results

Literature Searches

Appendices 5 and 6 are flow charts describing the procedures for selecting studies that examined new-onset HF and recurrent HF, respectively. Among studies kept for further review after excluding studies at the title and abstract level, it was impossible to judge whether three of these studies were eligible. In one of these, it was unclear whether the reason for re-hospitalization was HF[24]; in another, the 95% CI of the RR to calculate its corresponding standard error (SE) was not presented[25]; and in the third, the RR could not be calculated because of incorrect data on DM status (i.e. DM/impaired

Table 1 Characteristics of studies that examined the risk of new-onset heart failure in relation to diabetes mellitus

Study source	Design[a]	Cohort name/ affiliation	Population	% men	Age	*n*	Cases	Dur years[b]	% LOF	Risk	Methods[c] DM	Methods[c] HF	Endpoint
Chen (2019)[87]	C	MAX	General patients	7	40.0	2.4×10^5	1318	1.8	?	RR	R	R	Hosp
Fogarassy (2019)[86]	C	Hungarian NCR	Breast cancer	1	58.1	8068	N/A	5.9	0	OR	R	R	Dx
Magnusssen (2019)[89]	C	BiomarCaRE	General	48	49.5	78 657	5170	12.7	?	HR	S	S/R	Dx
Winell (2019)[88]	C	Finnish NHDR and CDR	General	—	—	3.0×10^6	3.0×10^5	17	0	RR	R	R	Dx
Chen (2018)[32]	C	NHI in Taiwan	General	53	60.4	68 582	8420	7.9	0	HR	R	R	Hosp
Eggimann (2018)[33]	C	BEAT-AF	AF	30	68	951	60	3.9	?	HR	S	M	Hosp
Gong (2018)[34]	C	SCREEN-HF	Patients at high risk of HF	55	69	3847	162	5.6	22	HR	S	M	Dx
Lamblin (2018)[91]	C	CORONOR	CHD[d]	78	66.0	3785	211	5	2	HR	M	M	Hosp
LaMonte (2018)[42]	C	WHI	Post-menopausal	0	63	1.4×10^5	2516	8.0	?	RR	S	S	Hosp
Larsson (2018)[94]	C	The 2 cohorts in Sweden	General	53	59.9	71 236	4246	17	?	HR	R	R	Hosp
McAllister (2018)[90]	C	Scottish DM Register	General	47	53.2	3.2×10^6	1.2×10^5	10	0	RR	R	R	Hosp
Rosengren (2018)[35]	C	NDR, Sweden	General	55	62	1.6×10^6	6.9×10^4	5.6	1–5	HR	R	R	Hosp
Wandell (2018)[36]	C	PHC in Stockholm	AF	55	74	9424	2259	5.4	0	HR	R	R	Dx
Wellings (2018)[37]	C	MIDAS	CHD[d]	35	63	1.1×10^5	—	5.0	0	HR	R	R	Hosp
Agarwal (2017)[27]	C	HCUP	General patients	42	50.2	1.7×10^7	2.0×10^5	5.0	0	HR	R	R	Hosp
Ballotari (2017)[38]	C	REDR	General	49	50	3.6×10^5	2321	3.0	0	RR	R	R	Hosp
Chatterjee (2017)[39]	T	WHS	AF	0	69	1495	187	20.6	0	HR	S	S	Dx
He (2017)[41]	C	CRIC	RD[d]	55	58	3557	432	6.3	?	HR	S/M	S	Dx
Jacobs (2017)[97]	C	HOMAGE	General/high risk patients	49	74.5	10 236	470	3.5	0	HR	?	R/M	Hosp
Kim (2017)[40]	C	Explorys Platform	General patients	46	—	4.5×10^7	9.9×10^4	10.0	0	OR	M	M	Dx
Pandey (2017)[43]	C	ORBIT-AF	AF	56	74	6545	236	2.0	4	RR	R	M	Dx
Policardo (2017)[44]	C	Tuscany Regional Health Care System	General	—	—	—	2.6×10^4	5.0	0	HR	R	R	Hosp
Zhang (2017)[31]	C	Montefiore Medical Center	Diastolic dysfunction	37	68	7878	833	5.5	?	HR	R	R	Dx
Eaton (2016)[28]	C	WHI	Post-menopausal	0	64	42 170	1952	13.2	?	HR	S	S	Hosp
Goldhar (2016)[45]	C	Ontario Cancer Registry	Breast cancer	0	52	19 074	—	5.9	?	HR	R	R	Dx
Ho (2016)[29]	C	FHS/ PREVEND/ CHS	General	46	60.1	22 142	1745	12.2	0	HR	R	R	Dx
Sahle (2016)[46]	T	ANBP-2	HT	59	84	6083	373	10.8	?	HR	M	M	Dx
Silverman (2016)[30]	C	MESA	General[e]	53	62	6742	257	11.2	?	HR	M	M	Dx
Chahal (2015)[47]	C	MESA	General[e]	47	62	6814	176	7.1	?	HR	S	M	Dx
Donneyong (2015)[48]	T	CaD trial	Post-menopausal	0	63	35 983	744	7.1	0	RR	?	S	Hosp
Qin (2015)[49]	C	UHCMC	Breast cancer	0	53	1153	120	7.6	29	RR	R	R	Dx
Shah (2015)[50]	C	CALIBER	General[e]	49	47	1.9×10^6	1.4×10^4	5.5	?	HR	R	R	Dx
Miao (2014)[96]	C	MIMIC II	ICU patients	—	58.4	3048	555	1	0	HR	M	R	Dx
Wong (2014)[51]	C	UPMC	suspected HD	59	55	1176	46	1.3	?	RR	M	M	Dx
Brouwers (2013)[52]	C	PREVEND	RD[d]	50	50	8569	374	11.5	?	HR	M	M	Dx
Ho (2013)[53]	C	The 2nd FHS	General	46	60.0	12 631[f]	512	7.7	0	HR	M	M	Hosp
Hung (2013)[100]	C	NHMD	CHD[d]	70	63.7	15 464	1024	1	13	OR	R	R	Dx
Potpara (2013)[54]	C	Belgrade Atrial Fibrillation Study	AH	63	52	842	83	11.2	30	HR	?	M	Dx
Qureshi (2013)[55]	C	Henry Ford Health System	LT	52	53	970	98	5.3	0	RR	M	M	Dx
Agarwal (2012)[56]	C	ARIC	General	45	54	13 555	1487	15.5	?	HR	S/M	M	Hosp

(*Continues*)

Table 1 (continued)

Study source	Design[a]	Cohort name/ affiliation	Population	% men	Age	*n*	Cases	Dur years[b]	% LOF	Methods[c]			Endpoint
										Risk	DM	HF	
Nakajima (2012)[57]	C	J-ACCESS	RD[d]	64	66	2395	64	3.0	?	RR	M	M	Hosp
Sato (2012)[98]	C	Okayama RCH	CHD[d]	73	68.8	197	23	1	0	RR	M	S/M	Hosp
Shafazand (2011)[99]	C	Swedish NHDR	CHD[d]	64	68.9	1.8×10^5	43 034	3	0	HR	R	R	Hosp
Roy (2011)[58]	C	CHS	General	42	73	5464	1134	13.0	?	HR	M	S	Dx
de Simone (2010)[59]	C	SHS phase I	General	64	56	2740	291	11.9	?	RR	M	M	Dx
Goyal (2010)[60]	C	One Million Person-Year Follow-up Study	General	47	38	3.6×10^5	4001	2.9	?	HR	R	R	Dx
Smith (2010)[61]	C	MDCS	General	41	58	5135	112	13.8	1	HR	S/M	R	Dx
van Melle (2010)[62]	C	Heart and Soul Study	CHD[d]	82	67	839	77	4.1	0	HR	S	S	Hosp
Bibbins-Domingo (2009)[63]	C	CARDIA	General	44	24	2637	26	20.0	28	HR	M	M	Hosp
Kenchaiah (2009)[64]	C	PHS	Physicians	100	53	21 094	1109	20.5	?	RR	S	S	Dx
Leung (2009)[65]	C	Saskatchewan Health beneficiaries	General	51	63	5.6×10^5	2293	1.1	?	RR	R	R	Dx
Lewis (2009)[66]	T	PEACE	CAD	82	64	8211	268	4.8	1	HR	R	R	Hosp
Ruigomez (2009)[67]	C	GPRD in 1996, UK	General	47	64	9057	386	3.6	0	HR	R	M	Dx
Nafaji (2008)[92]	C	Perth MONICA Register	CHD[d]	15	54.5	3109	406	14.4	0	HR	M	R	Dx
Aksnes (2007)[68]	T	VALUE	HT	58	66	15 245	754	4.2	?	HR	R	M	Hosp
Fukuda (2007)[69]	C	Cardiovascular Institute Hospital	AF	77	64	248	16	4.1	?	HR	R	M	Hosp
Held (2007)[70]	T	ONTARGGET/TRANSCEND	CHD[d]	70	67	30 798	668	2.4	2	RR	M	M	Hosp
Ito (2007)[71]	C	Nagoya City Higashi Municipal Hospital	RD[d]	64	57	100	6	4.7	?	HR	M	M	Hosp
Ingelsson (2005)[72]	C	ULSAM	General	100	50	2321	259	28.8	?	HR	M	R	Dx
Lentine (2005)[73]	C	USRDS	RD[d]	-	47	27 011	-	3.0	?	HR	R	R	Dx
Bibbins-Domingo (2004)[74]	T	HERS	CHD[d]	0	67	2391	237	6.3	?	HR	S	M	Hosp
Nichols (2004)[75]	C	KPNW	General	48	63	17 076	1693	4.7	?	HR	R	R	Dx
Wylie (2004)[76]	T	OPUS-TIMI 16	CHD[d]	—	60.5	4681	254	0.8	?	OR	?	M	Dx
Lewis (2003)[77]	T	CARE	CHD[d]	87	58	3860	243	5.0	?	HR	?	M	Hosp
Rigatto (2002)[78]	C	University of Manitoba	RD[d]	62	38	638	63	8.9	?	RR	M	M	Dx
Williams (2002)[93]	C	YHAP	General	42	74.3	2176	N/A	14	13	HR	S	M	Dx
Abramson (2001)[95]	T	SHEP	HT	57	71.6	4538	156	4.5	?	HR	S	M	Dx
He (2001)[79]	C	HHANES-I	General	41	50	13 643	1382	19.0	4	HR	S	R	Hosp
Johansson (2001)[80]	C	GPRD in 2000, UK	General	52	72	5000	938	1.0	0	RR	R	M	Dx
Wilhelmsen (2001)[81]	C	MPPS	General	100	52	7495	937	27.0	12	OR	S	R	Hosp
Aronow (1999)[82]	C	Hebrew Hospital	General	32	81	2893	794	3.6	?	HR	M	M	Dx
Chen (1999)[83]	C	New Haven Cohort	General	41	74	1749	173	7.9	13	HR	S	M	Hosp
Kannel (1999)[84]	C	FHS	General	42	63	15 267[f]	486	38.0	0	OR	M	M	Dx
Harnett (1995)[85]	C	Royal Victoria Hospital, Montreal	RD[d]	65	48	299	76	3.4	2	RR	M	M	Dx

Abbreviations: —, no data; ?, unclear; AF, atrial fibrillation; C, cohort; CHD, coronary heart disease; CKD, chronic kidney disease; Dur, duration of follow-up; Dx, diagnosed as HF; HD, heart diseases; HDL-C, high-density lipoprotein cholesterol; HL, hyperlipidaemia; Hosp, hospitalization due to HF; HR, hazards ratio; HT, hypertension; ICU, intensive care unit; LOF, lost to follow-up; M, medical records; N/S, not specified; OR, odds ratio; R, registry; RD, renal diseases, RR, calculated risk ratio (not HR); S, self-report; T, trial; TLV, administration of tolvaptan. Abbreviations of cohort names: ANBP-2, Second Australian National Blood Pressure Study; ARIC, Atherosclerosis Risk in Communities study; BEAT-AF, Basel Atrial Fibrillation Cohort Study; BiomarCaRE, Biomarker for Cardiovascular; CaD, Vitamin D plus calcium; CALIBER, Carbohydrates, Lipids and Biomarkers of Traditional and Emerging Cardiometabolic Risk Factors; CARDIA, Coronary Artery Risk Development in Young Adults Study; CARE, Cholesterol And Recurrent Events; CDR, Causes of Death Register; CHS, Cardiovascular Health Survey; CORONOR, suivi d'une cohorte de patients COROnariens stables en région NORd-pas-de-Calais; CRIC, Chronic Renal Insufficiency Cohort; FHS, Framingham Health Study; GPRD, General Practice Research Database; HCUP, Healthcare Cost and Utilization Project; Health ABC, Health ABC, Health, Aging, and Body Composition Study; HERS, Heart and Estrogen/progestin

Replacement Study; HOMAGE, Heart 'omics' in AGEing study; J-ACCESS, Japanese-Assessment of Cardiac Event and Survival Study; KPNW, Kaiser Permanente Northwest region; MAX, Medicaid Analytic eXtract; MDCS, Malmö Diet and Cancer Study; MESA, Multi-Ethnic Study of Atherosclerosis; MIMIC II, Multi-parameter Intelligent Monitoring in Intensive Care; MONICA, MONItoring trends and determinants in CArdiovascular disease; MPPS, Multifactor Primary Prevention Study; MIDAS, Myocardial Infarction Data Acquisition System; NCR, National Cancer Registry; NDR, National Diabetes Register; NHDR, National Hospital Discharge Register (HDR); NHI, National Health Insurance; NHMD, National Hospital Morbidity Database; NHANES I, First National Health and Nutrition Examination Survey; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; OPUS-TIMI, Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes; ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; PEACE, Prevention of Events with Angiotensin-Converting Enzyme inhibition study; PHC, primary health care centres; PHS, Physicians' Health Study; PREVEND, Prevention of Renal and Vascular Endstage Disease; RCH, Red Cross Hospital; REDR, Reggio Emilia Diabetes Register; SCREEN-HF, Screening Evaluation of the Evolution of New Heart Failure; SHS, Strong Heart Study; SHEP, Systolic Hypertension in the Elderly Program Risk.
Assessment in Europe; TRANSCEND, Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease; UHCMC, University Hospital Case Medical Center; ULSAM, Uppsala Longitudinal Study of Adult Men cohort; UPMC, University of Pittsburgh Medical Center; USRDS, US Renal Data System; VALUE, Valsartan Antihypertensive Long-term Use Evaluation study; WHI, Women's Health Initiative; WHS, Women's Health Study; YHAP, Yale Health and Aging Project.
[a]Meaning that the study was originally designed as a trial but was then treated as a cohort study.
[b]Mean or median follow-up duration is indicated.
[c]Methods for confirmation of DM and HF.
[d]In RD, albuminuria, dialysis, CKD, and receiving kidney transplantation are combined as RD. In CHD, angina, myocardial infarction, and cardiovascular diseases are combined as CHD.
[e]Participants with history of coronary heart diseases were excluded at baseline.
[f]Person-examination based.

glucose tolerance/normal glucose tolerance).[26] We contacted the authors of these studies to clarify these points but received no response. Thus, we did not include those studies in our analysis. Finally, there were 74 studies[27–100] and 38 studies[85,101–137] in which we could estimate RRs for new-onset and recurrent HF, respectively, in relation to DM. One study[85] examined both new-onset and recurrent HF risk.

Study characteristics

Characteristics of 74 eligible studies of the risk for incident new-onset HF are shown in *Table* 1. Ten studies[39,46,48,66,68,70,74,76,77,95] involved studies that were originally trials but were subsequently treated as cohort studies. Most included studies did not differentiate type 1 and type 2 DM. Exceptionally, 10 studies[32,38,50–52,56,59,75,88,90] limited DM patients to those with type 2 DM. One differentiated type 1 from type 2 DM.[94] Ranges (median) of mean age and follow-up duration in the participants of included studies were from 24 to 84 years (62 years) and from 0.8 to 38 years (5.6 years), respectively. Median of proportion of men was 49%. As to the endpoint, 44 studies[27–31,34,36,39–41,43,45–47,49–52,54,55,58–61,64,65,67,72,73,75,76,78,80,82,84–86,88,89,92,93,95,96,100] used a diagnosis of HF regardless of whether the incident HF resulted in hospitalization. Appendix 7 shows study confounders that were considered when the relationship between DM and new-onset HF was examined. Most of the included studies (51 studies[27–37,39–41,44–47,50,52,53,58,60–62,66–69,72–74,76–86,91–95,97,99,100]) adjusted the RR for new-onset HF at least for age and CHD. Appendix 8 shows the results of study quality assessments according to the NOS. Mean score [standard deviation (SD)] was 5.4 (1.3) (full marks = 8).

Table 2 shows characteristics of the 38 eligible studies that examined the risk for recurrent HF. In comparing those 38 studies with the 74 studies that examined risk for new-onset HF, the study population was relatively old (median, 67 years; range, from 54 to 79 years), follow-up duration was relatively short (median, 2.0 years; range, from 0.8 to 7.0 years), and the proportion of men was higher (median, 68%) in the 38 studies. Fourteen studies[102,103,105,108,111,120,122–126,128,132,133] were originally designed as trials. All but two included studies[120,123] used hospitalization due to HF as the study endpoint. Only three studies[115,116,136] limited the DM patients to type 2 DM. Half of the included studies [19 studies[85,102,104,106–108,110,112,113,115,118,120,122,124,126,127,132–134] adjusted the RR at least for age and CHD (Appendix 9)]. Assessment of study quality resulted in a mean score (SD) of 5.5 (1.2) (Appendix 10).

Overall analysis of new-onset heart failure risk in relation to diabetes mellitus

Among the 74 studies of the risk for incident new-onset HF, in four,[28–31] the outcome was separated into HFpEF and HFrEF,

Table 2 Characteristics of studies that examined risk of recurrent heart failure in relation to diabetes mellitus

Study source	Cohort name/affiliation	Design[a]	Population	EF	% men	Age	*n*	Cases	Dur[b]	LOF	Risk	Methods[c]		Endpoint
												DM	HF	
Kim (2019)[134]	KorHF	C	N/S	N/S	50	67	3162	863	1.5	?	HR	R	?	Hosp
Chen (2018)[101]	Sun Yat-sen University	C	N/S	N/S	66	64.9	587	384	7.0	?	RR	M	M	Hosp
Cooper (2018)[102]	HA-ACTION	T	N/S	↓	77	59	6214	—	1.0	?	HR	M	R	Hosp
Iorio (2018)[137]	Cardionet® in Trieste	C	N/S	N/S	57	77	2314	510	2.6	?	HR	M	R	Hosp
Kristensen (2018)[103]	ATMOSPHERE	T	N/S	↓	78	63	7016	1324	2.7	1	RR	M	M	Hosp
Retwinski (2018)[136]	ESC-HF-LT	C	N/S	N/S	70	65.3	1080	377	1	0	RR	M	S/M	Hosp
Rorth (2018)[104]	DNPR	C	N/S	N/S	71	54	2.6×10^4	11 234	2.1	0	HR	R	R	Hosp
Sandesara (2018)[105]	TOPCAT	T	N/S	→	49	69	3385	437	3.4	?	RR	S	R	Hosp
Takimura (2018)[135]	Tokyo General Hospital	C	TLV	N/S	58	79	1191	285	1	0	HR	M	M	Hosp
Dauriz (2017)[106]	ESC-HF-LT	C	N/S	N/S	72	72	9428	1030	1.0	32	HR	S	R	Hosp
Farre (2017)[107]	Local Health Department in Catsalut	C	N/S	N/S	45	77	8.8×10^4	7725	1.0	0	OR	R	R	Hosp
Kristensen (2017)[108]	I-PRESERVE	T	N/S	→	40	72	4128	661	3.8	?	HR	R	R	Hosp
Mohamedali (2017)[109]	ACMC	C	LVAD	↓	78	60	288	57	3.1	0	RR	M	?	Hosp
Echouffo-Tcheugui (2016)[110]	NCDR-ICD	C	CRT	↓	67	75	1.8×10^4	4380	3.0	?	RR	M	R	Hosp
Kristensen (2016)[111]	PARADIGM-HF	T	N/S	↓	78	64	8274	1179	2.0	?	RR	M	R	Hosp
Ruigomez (2016)[112]	TWIN	C	N/S	N/S	52	75	3516	633	4.5	0	HR	R	R	Hosp
Kaneko (2015)[113]	Shinken	C	N/S	N/S	70	69	282	55	2.5	?	HR	M	R	Hosp
Takeda (2015)[114]	CUMC	C	LVAD	↓	83	57	293	33	2.0	3	HR	M	M	Hosp
Carrasco-Sanchez (2014)[115]	RICA	C	N/S	N/S	45	78	1082	383	1.0	0	HR	S/M	R	Hosp
Cubbon (2014)[116]	MCRC	C	N/S	↓	74	67	628	44	1.0	0	OR	M	R	Hosp
Paoletti (2014)[117]	Four Italian Centre	C	CRT	↓	75	70	559	143	2.5	0	HR	M	M	Hosp
Sakata (2014)[118]	CHART-2	C	Stage C/D	N/S	68	69	4736	—	3.1	?	HR	M	M	Hosp
Larina (2013)[119]	RSMU	C	N/S	N/S	66	68	248	87	6.5	?	RR	M	M	Hosp
Sarma (2013)[120]	EVEREST	T	N/S	↓	74	66	4131	1495	0.8	?	HR	S	M	Worse
Verbrugge (2012)[121]	Ziekenuis OostLimberg	C	CRT	↓	68	71	172	47	1.5	0	HR	M	M	Hosp
Deedwania (2011)[122]	EPHESUS	T	AMI	↓	69	66	2238	314	1.3	?	HR	R	R	Hosp
Martin (2011)[123]	MADIT-CRT	T	CRT	↓	75	64.6	1817	329	2.0	?	RR	?	M	Worse
Aguilar (2010)[124]	DIG	T	N/S	→	59	67	987	221	3.1	?	HR	S	?	Hosp
Sze (2010)[125]	MRDIT II	T	ICD/CRT	↓	84	—[d]	1218	253	1.7	1	HR	?	M	Hosp
MacDonald (2008a)[126]	CHARM	T	N/S	N/S	68	66	7599	^{5}1135[e]	3.1[f]	0	HR	?	M	Hosp
Macdonald (2008b)[127]	SMR	C	N/S	N/S	47	74	1.2×10^5	7.0×10^4	5.0	0	HR	R	R	Hosp
Ghali (2007)[128]	COMPANION	T	NYHA III/IV	↓	68	66	1519	283	1.3	10	RR	S	M	Hosp
Ruiz-Ruiz (2007)[129]	HCU Lozano Blesa	C	N/S	N/S	53	73	111	54	1.8	0	OR	M	M	Hosp
Formiga (2006)[130]	Hospital Universitari de Bellvitge	C	N/S	N/S	43	79	88	32	0.8	0	RR	M	M	Hosp
Garcia (2005)[131]	Hospital Universitari Germans Trias i Pujol	C	N/S	N/S	27	65.3	362	70	1.0	?	RR	S	R	Hosp
Domanski (2003)[132]	BEST	T	N/S	N/S	78	60	2708	1045	2.0	0	HR	?	?	Hosp
Shindler (1996)[133]	SOLVD	T	N/S	↓	80	61	2569	80	3.4	?	HR	S	S	Hosp
Harnett (1995)[85]	Royal Victoria Hospital, Montreal	C	dialysis	N/S	60	59	133	75	3.0	0	HR	M	M	Hosp

Abbreviations: —, no data; ?, unclear; C, cohort; CRT, cardiac resynchronization therapy; Dur, duration of follow-up; EF, ejection fraction; Hosp, hospitalization due to HF; HR, hazards ratio; ICD, implantable cardioverter–defibrillator; LOF, lost to follow-up; LVAD, left ventricular assist device placement; M, medical records; N/S, not specified; NYHA, New York Heart Association class; OR, odds ratio; R, registry; RR, calculated risk ratio (not HR); S, self-report; T, trial; worse, worsening of HF.

Cohort name abbreviations: ACMC, Advocate Christ Medical Center; ATMOSPHERE, Aliskiren Trial of Minimizing OutcomeS for Patients with Heart Failure; BEST, Beta-blocker Evaluation of Survival Trial; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity programme; CHART-2, Chronic Heart Failure Analysis and Registry in the

Tohoku District-2; COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CUMC, Columbia Presbyterian Medical Center; DIG, Digitalis Investigation Group ancillary study; DNPR, Danish National Patients Registry; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; ESC-HF-LT, European Society of Cardiology Heart Failure Long-Term Registry; EVEREST, Efficacy of Vasopressin Antagonism in Heart Failure Outcome study with Tolvaptan trials; HCU, Hospital Clínico Universitario; HF-ACTION, Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training; I-PRESERVE, Irbesartan in Heart Failure With Preserved Ejection Fraction; KorHF, Korean Heart Failure registry; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy; MCRC, Multidisciplinary Cardiovascular Research Centre; NCRD-ICD, National Cardiovascular Data Registry's Implantable Cardioverter-Defibrillator Registry; PARADIGM-HF, Prospective comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure trial; RICA, Registro de Insuficiencia Cardiaca registry; RSMU, Russian State Medical University; SMR, Scottish Morbidity Record database; SOLVD, Studies of Left Ventricular Dysfunction trials; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial; TWIN, The Health Improvement Network.

[a]Meaning that the study was originally designed as a trial but then was treated as a cohort study.

[b]Mean or median follow-up duration is indicated.

[c]Methods for confirmation of DM and HF.

[d]53.2% of patients were 65 years or older.

[e]Estimated value.

[f]Datum was based on follow-up for all-cause mortality.

and the risk of HF was not examined as a whole. One study[27] only included systolic HF as an endpoint (i.e. diastolic HF was excluded.) The remaining 69 studies estimated DM-related new-onset HF risk as a whole (i.e. regardless of EF status). *Figure* 1 is a forest plot of the RR for new-onset HF in participants with DM compared with those without DM. Of the 69 included studies, 13 studies[32,35,36,38,44,50,60,65,80,84,88–90] presented data on RR by gender; of these, seven studies[32,35,50,87–90] also examined the risk for HF by age. The RR was above 1 in all included studies. The pooled RR (95% CI) was 2.14 (1.96–2.34). Publication bias was statistically detected not by Egger's test (P = 0.45) but by Begg's test (P = 0.02). However, adjusting the pooled RR for publication did not change the result.

Figure 2A is a forest plot of seven studies[28–31,34,42,55] that examined HFpEF and eight studies[28–31,34,42,55,56] that examined HFrEF risk in relation to DM. The RR (95% CI) was 2.22 (2.02–2.43) for HFpEF and 2.73 (2.71–2.75) for HFrEF. After one study with an extremely large study weight was excluded,[56] the pooled RR (95% CI) was 2.22 (1.98–2.49) (*Figure* 2B). In seven studies that classified HF into HFpEF and HFrEF and examined both of these risks, there was not a significant difference in the risk magnitude between HFpEF and HFrEF according to the meta-regression analysis (P = 0.86).

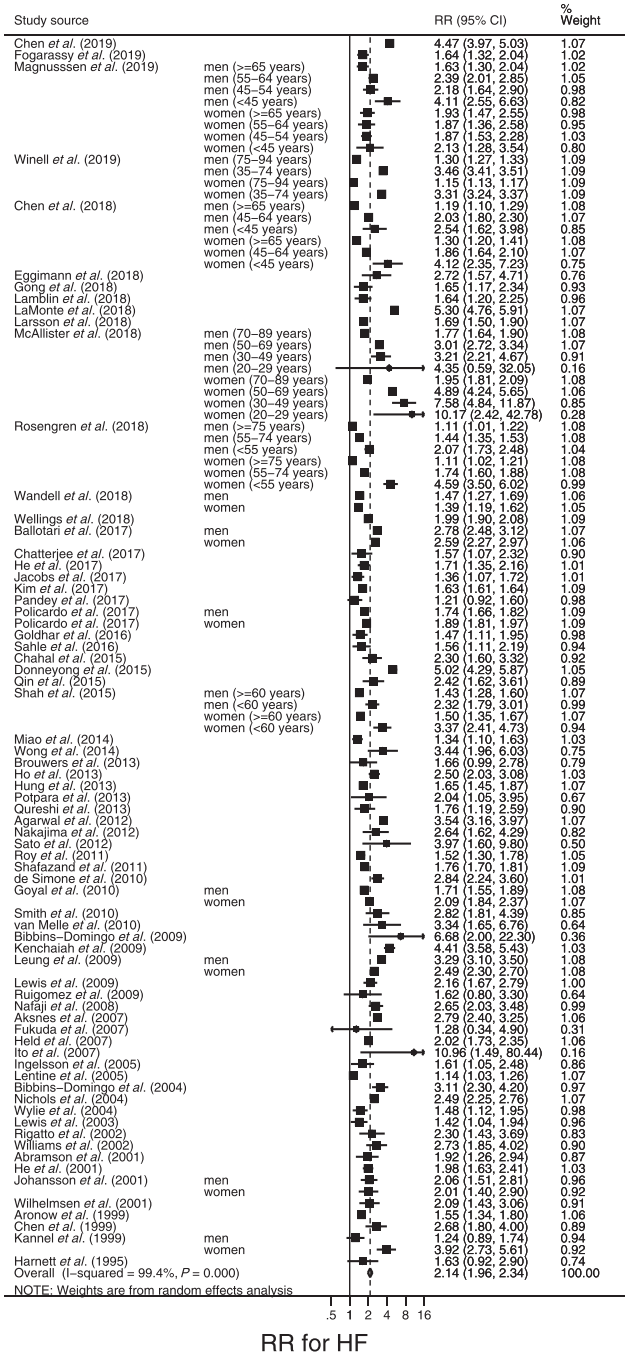
Overall analysis of recurrent heart failure risk in relation to diabetes mellitus

Figure 3 is a forest plot of the RR for recurrent HF in HF patients with DM compared with those without DM. Of the 38 included studies, three studies[124,127,134] examined risk by gender, and two studies[126,137] classified the HF patients by the EF at baseline. The RR was above 1 in all but one study.[103] Statistically significant publication bias was detected not by Begg's test (P = 0.12) but by Egger's test (P = 0.03). Results of the trim-and-fill method[23] of adjusting for publication bias suggested seven hypothetically unpublished studies that caused inflation of RR. After these hypothetical studies were included, the RR was slightly deflated to 1.33 (95% CI, 1.27–1.40).

Sensitivity analysis of new-onset heart failure risk in relation to diabetes mellitus

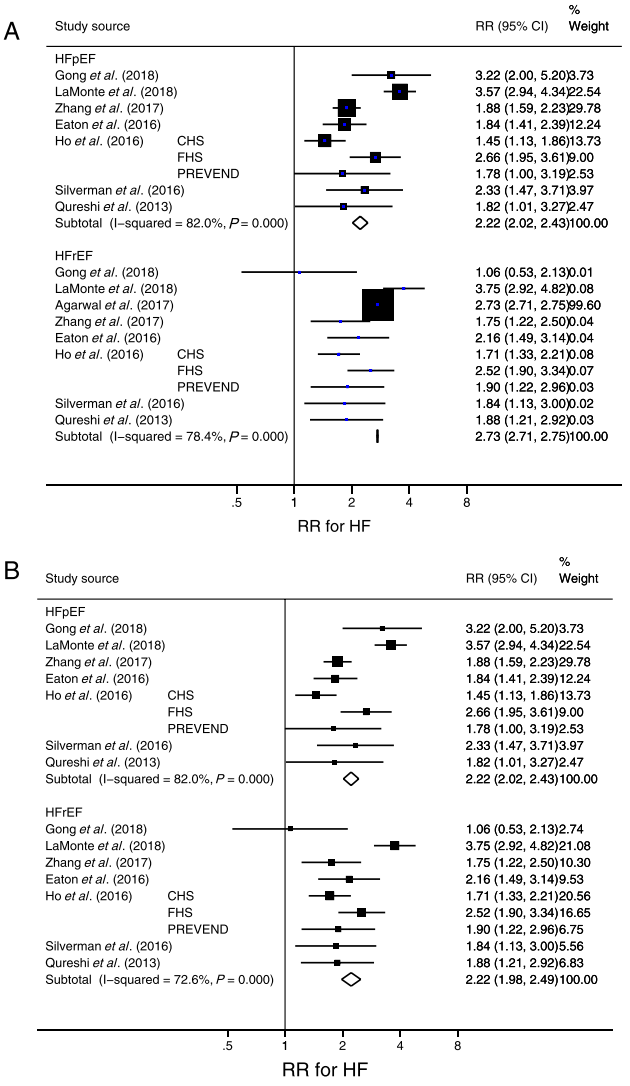
There was large between-study heterogeneity (I^2 = 99.7%, $P < 0.001$) (*Figure* 1). *Table* 3 shows the results of sensitivity analyses wherein the 69 studies shown in *Figure* 1 were stratified according to key study characteristics (*Table* 1). Although a weaker association was observed in limiting the analysis to studies that adjusted the RR for new-onset HF for age and CHD compared with those without those adjustments, the pooled RR was significant regardless of the adjustment [RR (95% CI), 1.78 (1.70–1.87) vs. 2.71 (2.26–3.25)]. In

Figure 1 Forest plot of the risk ratios (RRs) for new-onset heart failure (HF) in participants with diabetes mellitus compared with those without diabetes mellitus. The RRs in each study are indicated by squares. The area of squares is proportional to the study weight (i.e. inverse of square of standard error of the RR). The pooled RR is indicated by a diamond.



studies of a population with a mean age < 60 years, the RR was larger for new-onset HF [pooled RR (95% CI), 2.60 (2.38–2.84)] than in studies with a population having a mean age of ≥60 years [pooled RR (95% CI), 1.95 (1.79–2.13)]. Meta-regression analysis indicated that the difference in

Figure 2 (A) Forest plot of the risk ratio (RR) for new-onset heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) in participants with diabetes mellitus compared with those without diabetes mellitus. (B) The forest plot after excluding one study (Agarwal *et al.*) with an extremely large study weight (i.e. inverse of square of standard error of the RR). The RR in each study is indicated by a square. The area of squares is proportional to the study weight. The pooled RR is indicated by a diamond. Abbreviations: CHS, Cardiovascular Health Survey; FHS, Framingham Health Study; Prevention of Renal and Vascular End-Stage Disease.

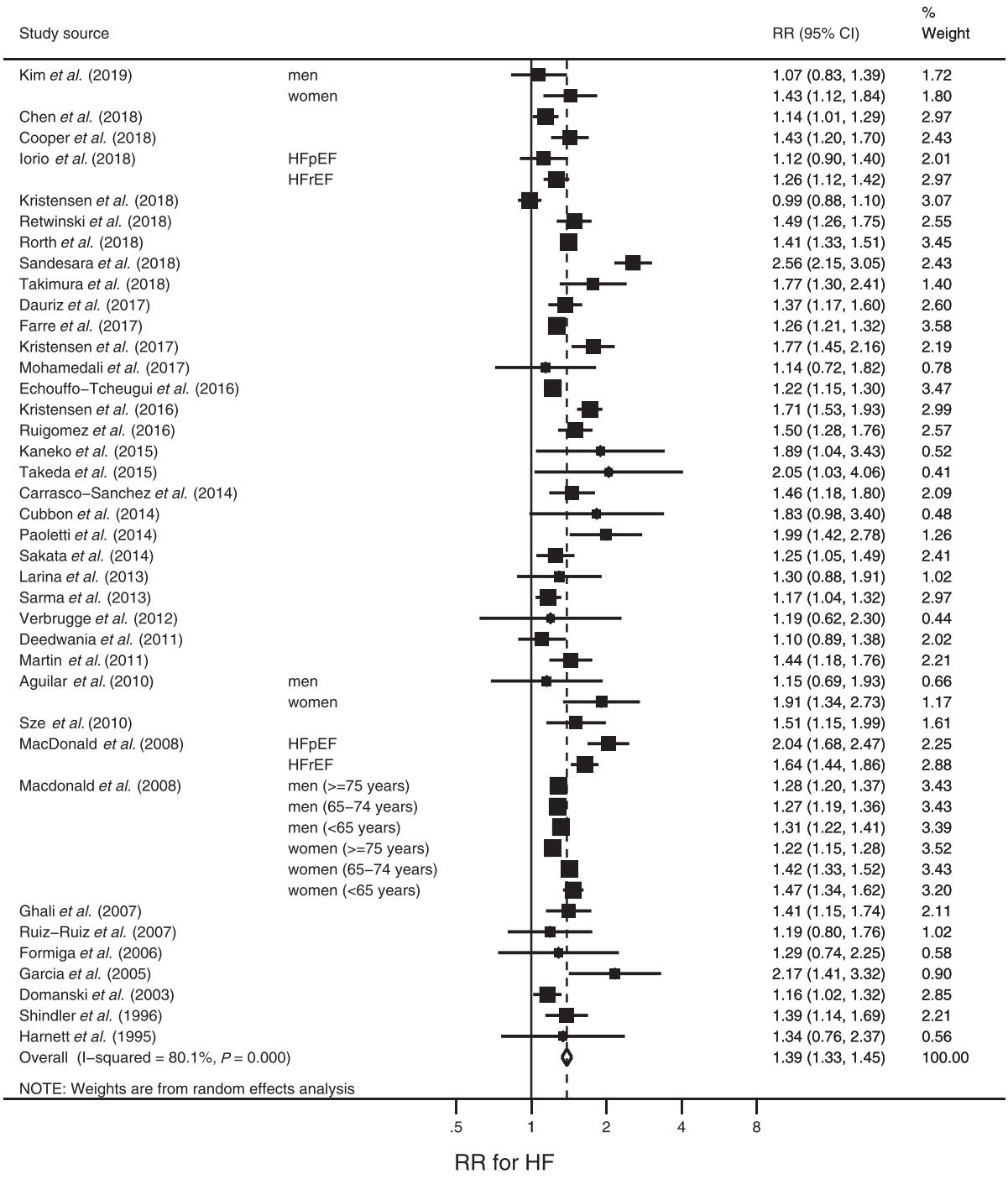


mean age of the study population significantly explained the between-study heterogeneity in the RR ($P < 0.001$).

Stratified analyses of recurrent heart failure risk in relation to diabetes mellitus

Similar to new-onset HF risk, there was large between-study heterogeneity (I^2 = 80.1%, $P < 0.001$) (*Figure* 3). Results of

Figure 3 Forest plot of the risk ratios (RRs) for recurrent heart failure (HF) in HF patients with diabetes mellitus compared with those without diabetes mellitus. The RR in each study is indicated by a square. The area of squares is proportional to the study weight (i.e. inverse of square of standard error of the RR). The pooled RR is indicated by a diamond. Abbreviations: pEF, preserved ejection fraction; rEF, reduced ejection fraction.



sensitivity analyses of recurrent HF risk in which the 38 included studies were stratified according to key study characteristics (*Table* 2) are presented in *Table* 4. A relatively large association was observed when analysing only studies with proportions of men < 65% [pooled RR (95% CI), 1.53 (1.40–1.68)] compared with studies having ≥65% men [pooled RR (95% CI), 1.32 (1.25–1.39)]. The effect of the proportion of men on between-study heterogeneity in the RR for recurrent HF was statistically significant (P = 0.01). Studies limiting participants to those having HF with HFpEF

Table 3 Stratified analysis of risk ratio for new-onset heart failure in relation to diabetes mellitus using pre-specified study characteristics

Variable	*n*	RR (95% CI)	*P* value for RR	I^2 (%)	*P* value for I^2	Meta-regression
Total	106	2.14 (1.96–2.34)	<0.001	99.7	<0.001	
Follow-up period						
≥6 years	56	2.40 (2.14–2.68)	<0.001	97.0	<0.001	
<6 years	50	1.94 (1.69–2.23)	<0.001	99.6	<0.001	0.01
Study design						
Trial[a]	10	2.15 (1.62–2.86)	<0.001	93.0	<0.001	
Non-trial	96	2.14 (1.95–2.35)	<0.001	99.5	<0.001	0.92
Mean age[a]						
≥60 years	64	1.95 (1.79–2.13)	<0.001	98.2	<0.001	
<60 years	52	2.60 (2.38–2.84)	<0.001	96.5	<0.001	0.001
% men[c]						
≥50%	53	2.03 (1.76–2.35)	<0.001	99.3	<0.001	
<50%	51	2.33 (1.99–2.72)	<0.001	99.4	<0.001	0.11
Risk adjustment						
Both age and CHD	64	1.78 (1.70–1.87)	<0.001	91.7	<0.001	
Failure in adjustment for age and/or CHD	42	2.71 (2.26–3.25)	<0.001	99.7	<0.001	<0.001
Endpoint						
Only hospitalization due to HF	49	2.34 (2.11–2.60)	<0.001	97.5	<0.001	
Including non-hospitalizations for HF[d]	57	1.96 (1.73–2.23)	<0.001	99.6	<0.001	0.02
Underlying diseases						
Non-hospital-based study[e]	67	2.30 (2.02–2.62)	<0.001	99.6	<0.001	—[f]
RD	7	1.99 (1.36–2.93)	<0.001	80.8	<0.001	0.23
AF	7	1.45 (1.32–1.59)	<0.001	26.8	0.22	0.045
CHD	12	1.94 (1.77–2.12)	<0.001	79.9	<0.001	0.41
breast cancer	3	1.69 (1.44–1.97)	<0.001	50.8	0.13	0.32
HT	3	2.08 (1.40–3.11)	<0.001	81.7	0.004	0.70
Others[g]	7	1.99 (1.32–3.00)	0.001	98.0	<0.001	0.40

Abbreviations: AF; atrial fibrillation; CHD, coronary heart disease; HT, hypertension; RD, renal disease.
[a]Cohort study that was originally designated as a trial.
[b]Total number of data was different from the other stratified analyses because in this stratified analysis, priority for data extraction was given to data based on subgroup analysis according to age instead of gender if a study provided data on subgroup analysis based on both age and gender. In the other stratified analyses, priority for data extraction was given to data based on the subgroup analysis based on gender.
[c]Data were not available in two studies.[40,73]
[d]Incident HF that did not lead to hospitalization.
[e]Including community-based study or specific populations such as post-menopausal, nurses, and physicians.
[f]Multivariate regression analysis was performed.
[g]Including non-specified diseases (i.e. hospital-based study), preclinical cardiac dysfunction, after liver transplantation, patients at high risk of vascular diseases, and suspected heart diseases.

Table 4 Stratified analysis of risk ratio for recurrent heart failure in relation to diabetes mellitus using pre-specified study characteristics

Variable	*n*	RR (95% CI)	*P* value for RR	I^2 (%)	*P* value for I^2	Meta-regression
Total	47	1.39 (1.33–1.45)	<0.001	80.1	<0.001	
Follow-up period						
≥2 years	30	1.41 (1.32–1.49)	<0.001	85.6	<0.001	
<2 years	17	1.34 (1.26–1.43)	<0.001	64.5	0.04	0.65
Study design						
Trial[a]	14	1.47 (1.28–1.70)	<0.001	91.0	<0.001	
Non-trial	33	1.33 (1.28–1.38)	<0.001	56.9	<0.001	0.23
Mean age[b]						
≥65 years	33	1.41 (1.34–1.49)	<0.001	79.6	<0.001	
<65 years	14	1.34 (1.23–1.47)	<0.001	82.0	<0.001	0.41
Men						
≥65%	30	1.32 (1.25–1.39)	<0.001	72.0	<0.001	
<65%	17	1.53 (1.40–1.68)	<0.001	87.0	<0.001	0.01
Risk adjustment						
Both age and CHD	27	1.36 (1.30–1.41)	<0.001	73.2	<0.001	
Failure in adjustment for age and/or CHD	20	1.46 (1.28–1.67)	<0.001	85.4	<0.001	0.36
Endpoint						
Only hospitalization due to HF	2	1.24 (1.12–1.37)	<0.001	67.5	0.08	

(*Continues*)

Table 4 (continued)

Variable	*n*	RR (95% CI)	*P* value for RR	I^2 (%)	*P* value for I^2	Meta-regression
Including non-hospitalizations for HF[c]	45	1.40 (1.33–1.46)	<0.001	80.5	<0.001	0.52
Special characteristics						
Non-specified	36	1.33 (1.30–1.35)	<0.001	83.2	<0.001	[g]
After CRT and/or LVAD implantation	8[d]	1.41 (1.24–1.61)	<0.001	51.9	0.04	0.88
After AMI[e]	2[d]	1.25 (1.05–1.48)	0.01	67.5	0.08	0.26
Others[f]	2	1.66 (1.26–2.18)	<0.001	0.0	0.40	0.45
EF status						
Non-specified	24	1.33 (1.28–1.38)	<0.001	59.6	<0.001	—[g]
Reduced EF	17	1.37 (1.24–1.50)	<0.001	80.4	<0.001	0.82
Preserved EF	6	1.72 (1.32–2.26)	<0.001	86.7	<0.001	0.02

Abbreviations: AMI, acute myocardial infarction; CHD, coronary heart disease; CRT, cardiac resynchronization therapy; EF, ejection fraction; LVAD, left ventricular assist device.
[a]Cohort study that was originally designated as a trial.
[b]In one study,[124] data based on the subgroup analysis according to age instead of gender were used.
[c]Worsening of HF that did not lead to hospitalization.
[d]Because one study[125] was included in the two categories indicated as #, total number of data (n = 47) in this stratified analysis was different from that in the overall analysis.
[e]Number of data and RRs are not consistent with those in the text because a sub-cohort study wherein the cohort was limited to patients having underlying diseases indicated as was excluded from this stratified analysis if the original cohort study existed.
[f]Including patients on dialysis (1 study) and who were administered tolvaptan (1 study).
[g]Multivariate regression analysis was performed.

showed a larger RR [pooled RR (95% CI), 1.73 (1.32–2.26)] than did studies of only those having HF with HFrEF [pooled RR (95% CI), 1.37 (1.24–1.50)] or when the EF was not specified among HF patients [pooled RR, 1.33 (1.28–1.38)]. Limiting patients to those with HFpEF significantly explained study heterogeneity in the RR for recurrent HF (P = 0.002). Analysis of only studies that adjusted the RR for age and CHD showed that the RR for recurrent HF remained significant [pooled RR, 1.36 (1.30–1.41)].

Discussion

This meta-analysis is the first to separately assess the risk of new-onset and recurrent HF in individuals with DM. Current results confirm that DM is a significant risk factor for both new-onset and recurrent HF. The explanation for these results is that impaired insulin signalling is associated with early changes in the heart such as cardiac stiffness, hypertrophy, and fibrosis.[138]

Given that diastolic dysfunction is the first hallmark of diabetic cardiomyopathy,[139] the risk magnitude for HF in individuals with DM would be larger for HFpEF than for HFrEF. That is because among those with HF, the proportion of HFpEF was greater than that of HFrEF in individuals with than without DM. However, the current meta-analysis revealed no difference in the magnitude of risk between HFpEF and HFrEF. One plausible explanation is that it is difficult to detect the HF in the early stage that is classified as HFpEF, which specifically occurs in patients with DM.[140]

The stratified analysis by the study population's mean age suggested that the risk magnitude of new-onset HF in relation to DM was especially large in relatively young study populations (i.e. in the current meta-analysis, ≤60 years). Thus, individuals with DM had a high risk of incident HF even if relatively young. A possible explanation is that the relative contribution of DM to HF is larger in the young than in the elderly, as the younger population has not yet experienced the health burdens of aging or age-associated conditions such as CHD, which might overwhelm the contribution of DM to HF. However, a further plausible explanation should be sought.

According to the results of the meta-regression analysis wherein the baseline EF status was an explanatory variable, it is suggested that the impact of DM on the risk of recurrent HF is relatively large in HF patients with HFpEF. It is possible that individuals with DM had an especially poor prognosis as compared with those without DM in terms of recurrent HF when the EF is preserved. This possibility is supported by the RELAX (PhosphodiesteRasE-5 Inhibition to Improve CLinical Status and EXercise Capacity) study reporting that impaired exercise capacity, increased left ventricular hypertrophy, high prevalence of co-morbidities, and increased biomarkers of fibrosis, oxidative stress, inflammation, and vasoconstrictions in HFpEF patients with DM could contribute to adverse outcomes.[141] Differences in these cardiovascular phenotypes between patients with and without DM were notable among HF cases, in particular HFpEF, indicating that HFpEF is a heterogeneous syndrome.[142]

Results of the stratified analysis according to the proportion of men (65%) suggested that the impact of DM on the risk of recurrent HF was stronger in women than in men. This could be explained by deficiencies in managing HF rather than susceptibility of women with DM to recurrent HF. The Euro Heart Survey on Heart Failure indicated that, compared with men, women were less often treated with drugs proven to reduce

mortality such as angiotensin-converting enzyme inhibitors, beta-blockers, and spironolactone.[143] In addition, women were less likely to undergo assessment of left ventricular function.[143] Another explanation is that, in comparison with men, women have less potential to benefit from management of HF rather than to suffer from deficiencies in management, because women have a higher proportion of HFpEF,[144] for which no effective treatment with a high grade of evidence has been identified.[145]

Several limitations should be addressed. First, the follow-up period varied among studies, which could affect study results. Second, a meta-analysis of observational studies generally elicits a low grade of evidence. Furthermore, according to the method for assessing the quality of evidence,[146] our findings of large between-study heterogeneity and statistically significant publication bias might have further downgraded the quality of evidence. However, regarding the suspected publication bias, the RR that was deflated by the adjustment for publication bias was modest. It is unlikely that we need to change the general conclusions. Third, in most studies, type 2 DM was not differentiated from type 1 DM, although most patients with DM have type 2 and many features of cardiac phenotypes are shared by type 1 and type 2 DM.[147] In addition, we could not perform sensitivity analyses based on characteristics of patients with DM at baseline such as duration of DM, haemoglobin A1c, and hypoglycaemic medications including insulin use as most studies lacked these data. These characteristics could substantially affect the results. Fourth, hospitalization has a narrower range of endpoints involved in HF outcomes than a doctor's diagnosis or self-report of HF that did or did not lead to hospitalization due to HF. The characteristics of endpoints could modify the impact of DM on the risk of HF given that the HF cases with DM were more likely to have experienced hospitalization than those without DM.[141] Lastly, as is inherent to the nature of study-level meta-analyses, degrees of confounder adjustments across the included studies varied, which hampers a comprehensive assessment of the impact of a risk factor (i.e. DM in this meta-analysis) on the outcome (i.e. new-onset and recurrent HF in this meta-analysis).

Conclusions

The present results indicate that DM is a significant risk factor for both new-onset and recurrent HF. It is suggested that the risk magnitude is large for new-onset HF especially in young populations and for recurrent HF especially in women or those with HFpEF. These findings help to specify the populations that should be the focus of preventive strategies for DM-related HF. It is also indicated that DM is associated with future HFpEF and HFrEF to the same extent, which could possibly be explained by a current finding that HF in the early stage in patients with DM is difficult to detect.

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Conflict of interest

None declared.

Author Contributions

All authors conceived and designed the research; S.K., K.F., C. H., T.S., and M.I. acquired the data; S.K., K.K., and H.So. analysed the data; S.K. drafted the manuscript; and S.K., T. Y., K.K., K.W., H.Sh., T.I., and H.So. interpreted the results and made critical revision of the manuscript for important intellectual content. All authors approved the submission of the final manuscript.

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Appendix 1: Study keywords used for electronic literature searches

S1 (retrospective OR retrospectively OR longitudinal OR prospective OR prospectively OR cohort OR followup OR follow-up OR "follow up" OR period OR observation OR observational OR concurrent) AND (study OR studies)
S2 "odds ratio" OR "OR" OR "RR" OR "relative risk[*1]" OR "hazard ratio[*1]" OR ((incident OR incidence) AND rate[*1]) OR person-years OR "person years" OR "risk ratio[*1]"
S3 ti((failure OR insufficiency OR decompensation OR incompetence) AND (heart OR cardiac OR myocardial) OR "congestive failure" OR (diabetic AND (heart OR myocardial OR cardiomyopath[*3])))
S4 (MJEMB ("heart failure") OR MJEMB ("congestive heart failure")) OR (MJMESH ("Heart Failure")) OR (MJMESH ("Diabetes Complications") AND MESH ("Heart Failure"))
S5 S4 OR S3

S6 (glycemia OR hyperglucemia OR hyperglycaemia OR hyperglycemia OR glycaemia OR glucose OR diabet[*2]) AND ti (predict[*3] OR risk OR (associated AND factors) OR incident OR incidence OR determinant[*1] OR profile[*1])
S7 ab (glycemia OR hyperglucemia OR hyperglycaemia OR hyperglycemia OR glycaemia OR glucose OR diabet[*2])
S8 (S6 OR S7) AND S5
S9 NOT (RTYPE("Conference Abstract" OR "Conference Paper" OR "Letter" OR "Editorial" OR "Case Reports" OR "Note" OR "Short Survey" OR "Comment" OR "Review"))
S10 S1 AND S2 AND S8 AND S9

MESH: thesaurus terms of MEDLINE
EMB: thesaurus terms of EMBASE
MJ: major thesaurus terms
RTYPE: publication type

'ti' and 'ab' indicate that the descriptor terms in parentheses exist in the title and abstract, respectively.

Asterisk (*) and its subsequent number in each bracket indicate allowing inflections within the number of characters.

Appendix 2: Study inclusion criteria

1) Cohort study

We also considered a study that was originally designed as a trial such as a randomized controlled trial but then was treated as a cohort study.

2) Diabetes status [i.e. whether a participant had diabetes mellitus (DM) or not] of all participants was ascertained before the follow-up period.

Even if the type of design was a cohort study, a study that concurrently examined whether the participants developed DM and whether they developed HF was excluded.

3) At least 6 months of follow-up

The interest of this study is the chronic effect of DM. Therefore, studies whose outcome was incident early-onset HF (e.g. HF occurring during hospitalization due to coronary heart disease) were excluded.

4) Exposure is having DM at baseline.

Every participant in the risk group had to have DM at baseline. For example, studies were excluded in which the risk group, that is, participants with impaired fasting glucose/impaired glucose tolerance (IFG/IGT), were combined with those with DM.

5) Referent is not having DM at baseline.

Studies had to include only participants who did not have DM at baseline. For example, studies were excluded that only included individuals with normal glucose tolerance (i.e. excluded those with IFG/IGT).

Appendix 3: Remarks on data extraction in this meta-analysis

If two or more risk indicators with different degrees of adjustments for confounding factors were provided within one study, we extracted the most fully adjusted risk indicators in the individual study. If both overall and subgroup analyses (e.g. age, gender, and age and gender) were performed in an individual study, the most finely stratified data (i.e. age and gender in the above example) were extracted. If the risk indicators were provided for each subgroup into which the participants were classified by either gender or age, priority for the overall analysis was given to the data based on the subgroup analysis by gender. In this case, data based on the subgroup analysis by age, instead of those by gender, were used in subsequent stratified analyses.

When a study included participants with type 2 diabetes mellitus (DM) but excluded those with type 1 DM, we simply pooled the data on the risk for HF in individuals with type 2 DM with the data on the risk for HF in studies which type 1 and type 2 DM were combined because type 2 DM accounts for almost all individuals with DM. One study[94] provided data on the risk for HF in individuals with type 1 DM and type 2 DM separately but did not provide data on the risk for HF wherein type 1 and type 2 DM were combined. In this case, we chose the data on type 2 DM.

Appendix 4: Study quality assessment using the Newcastle-Ottawa Quality Assessment Scale adapted for this meta-analysis

< For studies that examined the risk of new-onset heart failure (HF) in relation to diabetes mellitus (DM) >

S: Selection
S1. Representative of the cohort

a) Non-selected study population except for age and gender* #1

b) Specific characteristics (e.g. post-menopausal, specific occupation)
c) Specific underlying diseases (e.g. coronary heart diseases (CHD), renal diseases, atrial fibrillation)
d) Study design was originally a trial.
e) Non-selected patients

S2. Relationship between the analysis sample and the full cohort?

a) Equal*
b) Analysis sample was a random sample of the full cohort
c) The non-exposed cohort (i.e. individuals without DM) was selected for the exposed cohort (i.e. individuals with DM) (e.g. propensity-matched cohort)

S3. Confirmation of exposure (i.e. whether participants had DM at baseline)

a) Medical records* [#2]
b) Registry* (e.g. accessing study-specific database, using the code of the International Statistical Classification of Diseases)
c) Self-report/questionnaire
d) Unclear

S4. Did the study confirm that the outcome (i.e. incident heart failure) was not present at the beginning of the study? [#3]

a) Yes*
b) Unclear

C: Comparability
C1. Did the study control for the most important factors (i.e. age and CHD)?

a) Yes*
b) No

O: Outcome
O1. Ascertainment of outcome

a) Medical records (i.e. doctor's diagnosis)
b) Registry* (e.g. accessing study-specific database, investigators' reviews using the code of the International Statistical Classification of Diseases)
c) Self-report/questionnaire
d) Unclear

O2. Duration of follow-up

a) ≥6 years *
b) < 6 years

O3. Adequacy of follow-up of cohorts

a) Complete follow-up (i.e. lost to follow-up rate was zero)*
b) Not complete follow-up, but appropriate reasons for the lost to follow-up were described*
c) Neither complete follow-up nor description of appropriate reasons for the lost to follow-up
d) Follow-up rate was unclear

< For studies that examined the risk of recurrent HF in relation to DM >

S: Selection

1. Representative of the cohort

a) Typical patients with HF*
b) Typical patients with HF, but limited to patients within specific range of ejection fraction*
c) Specific characteristics (e.g. receiving cardiac resynchronization therapy or left ventricular assist device placement)
d) Specific underlying diseases (e.g. CHD)
e) Study design was originally a trial

2. Relationship between the analysis sample and the full cohort?

a) Equal*
b) Not equal

3. Confirmation of exposure (i.e. whether patients had DM at baseline)

a) Medical records* [#3]
b) Registry* (e.g. accessing study-specific database, using the code of the International Statistical Classification of Diseases)
c) Self-report/questionnaire
d) Unclear

4. Did the study confirm that the outcome (i.e. recurrent episode of HF) was not present at the beginning of the study? [#4]

C: Comparability

1. Did study control for the most important factors (i.e. age and CHD)?

a) Yes
b) No

O: Outcome

1. Ascertainment of outcome

a) Medical records (i.e. doctor's diagnosis)
b) Registry* (e.g. accessing study-specific database, investigators' reviews using the code of the International Statistical Classification of Diseases)
c) Self-report/questionnaire
d) Unclear

2. Duration of follow-up

a) ≥2.1 years*
b) ≤2 years

3. Adequacy of follow-up of cohorts

a) Complete follow-up (i.e. lost to follow-up rate was zero)*
b) Not complete follow-up, but appropriate reasons for the lost to follow-up were described*
c) Neither complete follow-up nor description of appropriate reasons for the lost to follow-up
d) Follow-up rate was unclear

NOS scale consists of 7 criteria that are classified into the following 3 broad perspectives: S (Selection), C (Comparability), and O (Outcome). One star (*) corresponds to one point. Full score is 8.

[#1] Including population that excluded participants with CHD at baseline.

[#2] Including direct measurement of blood glucose levels by the study.

[#3] Including direct measurement of blood glucose levels by the study.

[#4] In meta-analysis of risk of recurrent HF, this criterion is not applicable. All studies were given one point.

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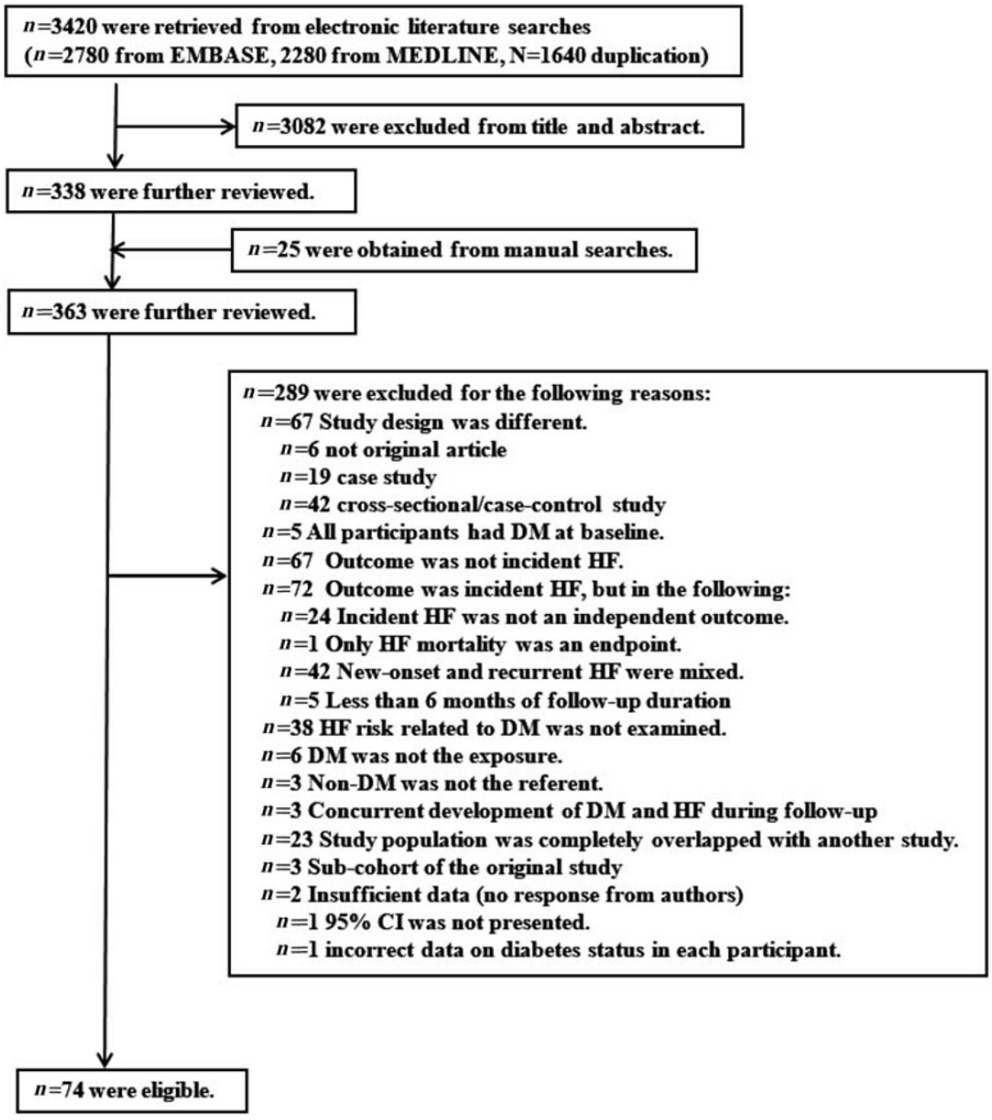
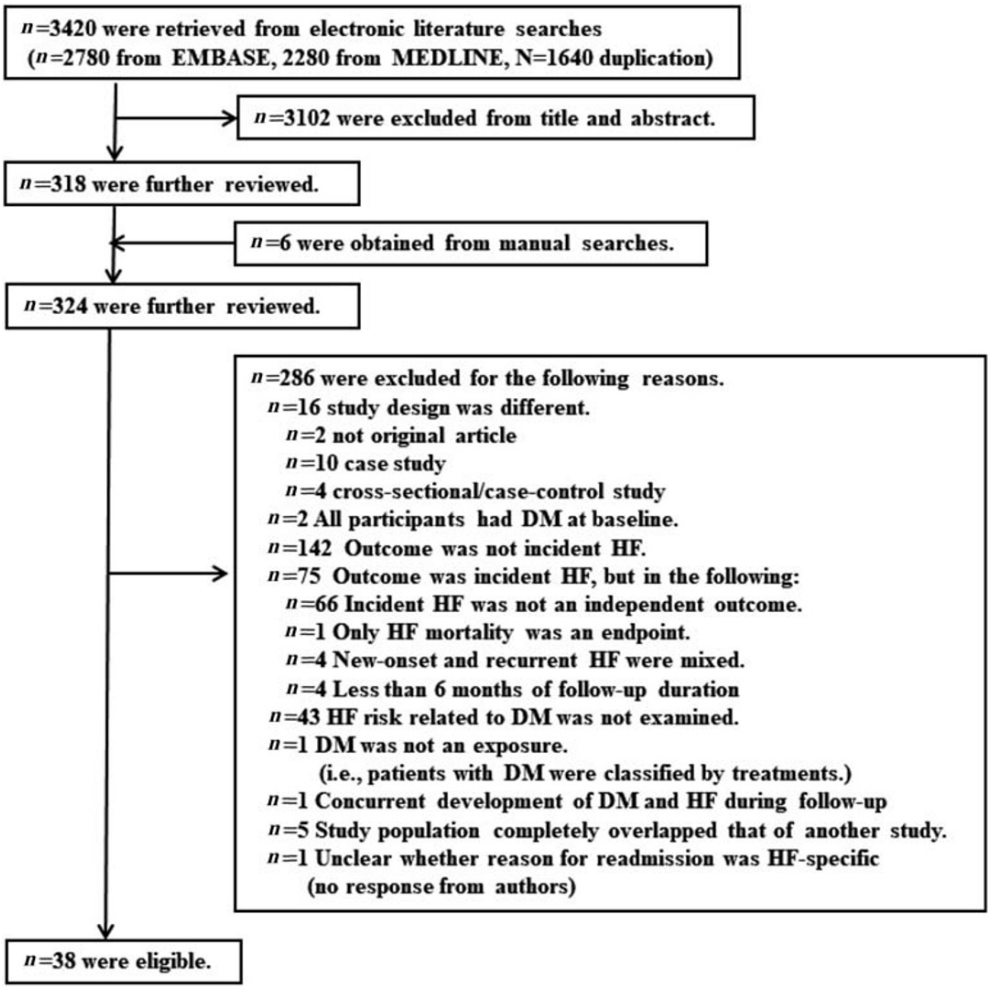
Appendix 5: Flow chart describing procedures for selection of studies that examined the risk of incident new-onset heart failure (HF) in relation to diabetes mellitus (DM)



Abbreviation: CI, confidence interval

Appendix 6: Flow chart describing procedures for selection of studies that examined risk of recurrent heart failure (HF) in relation to diabetes mellitus (DM)



Appendix 7: Study confounders considered when the relationship between diabetes mellitus and new-onset heart failure was examined

Study source	Confounders
Chen (2019)[87]	None
Fogarassy (2019)[86]	Age, HT, CHD, stroke, cancer stage, chemotherapies, antihypertensive agents
Magnusssen (2019)[89]	Age, gender, smoking, BMI, HT, antihypertensive medication, TC
Winell (2019)[88]	(Age), (gender)
Chen (2018)[32]	Age, gender, region, CHD, coronary revascularization, medication
Eggimann (2018)[33]	Age, BMI, valve surgery, arrhythmia intervention, QTc, BNP
Gong (2018)[34]	Age, smoking, BMI, MI, OSA, NT-proBNP, Hb, calcium channel blocker
McAllister (2018)[90]	(Age), (gender)
Lamblin (2018)[91]	Age, BMI, HT, multi-vessel CAD, angina, AF, (CHD)
LaMonte (2018)[42]	(Gender)
Larsson (2018)[94]	Age, gender, BMI, education, (CHD), FH of MI, smoking, PA, HT, HL, alcohol, DASH diet score
Rosengren (2018)[35]	Age, (gender), income, education, marital status, duration of DM, stroke, CHD, AF, renal dialysis or transplantation
Wandell (2018)[36]	Age, (gender), obesity, socio-demography, HT, valvular disease, cardiomyopathy, COPD, OSA
Wellings (2018)[37]	Age, gender, race, insurance, HT, (CHD), liver disease, CKD, dyslipidaemia
Agarwal (2017)[27]	Age, gender, race, HT, CAD, AF, income, ventricular premature complexes
Ballotari (2017)[38]	None
Chatterjee (2017)[39]	Age, (gender), race, assignment, smoking, PA, alcohol, BMI, SBP, HL, history of MI, CKD, (AF), medication
He (2017)[41]	Age, gender, education, WC, SBP, cystatin C, urine albumin, CVD
Jacobs (2017)[97]	Age, gender, BMI, smoking, CAD, HT, SBP, HR, Cre, antihypertensive agents
Kim (2017)[40]	Age, gender, smoking, obesity, HT, DM, dyslipidaemia, CHD
Pandey (2017)[43]	None
Policardo (2017)[44]	Age, (gender), Charlson's index, CVD
Zhang (2017)[31]	RD, malignancy, Hb, Na, K, BUN, Cre, baseline EF medication Age, gender, socioeconomic status, race/ethnicity, HT, MI, PVD, cerebrovascular accident, pulmonary disease, RD, malignancy, Hb, Na, K, BUN, Cre, baseline EF medication
Eaton (2016)[28]	Age, education, income, smoking, HT, AF, CHD, chronic lung disease, PA, medication, alcohol, other morbidities, anaemia
Goldhar (2016)[45]	Age, (gender), income, rural status, HT, previous MI, chemotherapy regimens, cancer stage
Ho (2016)[29]	Age, gender, smoking, alcohol, BMI, HT, MI, LVH, LBBB (left bundle branch block)
Sahle (2016)[46]	Age, gender, smoking, BMI, BP, CVD, eGFR, HDL
Silverman (2016)[30]	Men: age, gender, race, HrR, HT, BMI, TC, HDL, eGFR, IL-6, coronary artery calcium score, MI during follow-up, proBNP, Troponin T, LV mass index; women: age, gender, race, HrR, HT, smoking, HDL, eGFR, IL-6, coronary artery calcium score, MI during follow-up, proBNP, troponin T, LV mass index
Chahal (2015)[47]	Age, gender, smoking, BMI, SBP, HrR, Cre, LVH, (CVD)
Donneyong (2015)[48]	None
Qin (2015)[49]	None
Shah (2015)[50]	Age, gender, smoking, deprivation, BMI, SBP, HDL, TC, statin, (CHD), antihypertensive drugs
Miao (2014)[96]	Age, obesity, arrhythmias, PVD, pulmonary disease, pulmonary vascular disease, HT, hypothyroidism, CKD, LD, AIDS, weight loss, electrolyte disorders
Wong (2014)[51]	None
Brouwers (2013)[52]	Age, gender, obesity, HT, MI, smoking, AF, HL, Cre, cystatine C, UA, CRP, NT-proBNP, hs-TnT
Ho (2013)[53]	Age, gender, HT, BMI, HrR, MI, CHD, smoking, valvular disease, HDL, AF, LVH, LBBB
Hung (2013)[100]	(CHD), age, gender
Potpara (2013)[54]	Age, gender, medication
Qureshi (2013)[55]	None
Agarwal (2012)[56]	Age, gender, race
Nakajima (2012)[57]	None
Sato (2012)[98]	(CHD), smoking, HT, MVD
Shafazand (2011)[99]	(CHD), age, gender, stroke, AF, valvular disease
Roy (2011)[58]	Multiple (65 characteristics)
de Simone (2010)[59]	None
Goyal (2010)[60]	Age, (gender), CHD, AF, valvular diseases
Smith (2010)[61]	Age, gender, BMI, HT, MI, (AF), smoking, MR-proANP, NT-proBNP, MR-proADM, CRP, cystatine C, copeptin

(*Continues*)

Study source	Confounders
van Melle (2010)[62]	Age, gender, race, smoking, BMI, PA, LDL, SBP, MI during follow-up, LVEF, wall motion abnormality, diastolic dysfunction, CRP, medication
Bibbins-Domingo (2009)[63]	(CHD)
Kenchaiah (2009)[64]	None
Leung (2009)[65]	Age, gender
Lewis (2009)[66]	Age, BMI, MI, bypass surgery, HT, angina, GFR, LVEF, medication
Ruigomez (2009)[67]	Age, gender, AF, alcohol, smoking, BMI, HT, hyperlipidaemia, venous thromboembolism, CHD, cardiac diseases, COPD
Nafaji (2008)[92]	Age, gender, smoking, HT, ECG, CARP, streptokinase or rTPA
Aksnes (2007)[68]	Age, LVH, CHD, DM during follow-up
Fukuda (2007)[69]	Age, gender, HT, structural heart disease, persistent AF, %FS, LAD, LVH
Held (2007)[70]	None
Ito (2007)[71]	Anaemia (Hb $<$ 10 g/dL)
Ingelsson (2005)[72]	(Age), (gender), MI, HT, LVH, smoking, BMI
Lentine (2005)[73]	Age, gender, smoking, employment, BMI, cause of ESRD, anaemia, MI, arrhythmia, peripheral artery disease, donors' characteristics, graft function, complications during follow-up
Bibbins-Domingo (2004)[74]	Age, (gender), smoking, SBP, BMI, ECG, CAD grafting, no. of ischaemic origin, Cre
Nichols (2004)[75]	None
Wylie (2004)[76]	Age, CHD, BNP, ECG, HrR
Lewis (2003)[77]	Age, PA, HT, previous MI, LVEF
Rigatto (2002)[78]	Age, SBP, Hb, albumin, cadaveric donor, (CHD)
Williams (2002)[93]	Age, gender, HT, MI, PP, depression, functional limitations
Abramson (2001)[95]	Age, gender, race, smoking, MI, angina, SBP, DBP, TC, HDL, ECG, trial group, ADL
He (2001)[79]	Age, gender, race, CHD
Johansson (2001)[80]	Age, smoking, BMI, hyperlipidaemia, prior dyspnea irrelevant to HT, prior co-morbidity (inc. CHD)
Wilhelmsen (2001)[81]	Age, (gender), smoking, alcohol, coffee, BMI, HT, (CHD)
Aronow (1999)[82]	Age, gender, race, HT, CHD
Chen (1999)[83]	Age, gender, PP, BMI, MI during follow-up
Kannel (1999)[84]	Age, (gender), SBP, LVH, heart rate, (CHD), valve disease
Harnett (1995)[85]	Age, DBP, CHD, systolic dysfunction, Hb, albumin, LV mass

The confounder in parentheses indicates that the risk measure was adjusted for this confounder although the adjustment was not stated.

Abbreviations: ADL, activities of daily living; AF, atrial fibrillation; BMI, body mass index; AIDS, acquired immunodeficiency syndrome; BNP, brain natriuretic peptide; BP, blood pressure; CARP, coronary artery revascularization procedure; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Cre, creatinine; CRP, C-reactive protein; CVA, cerebrovascular accidents; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; FS, fractional shortening; GFR, estimated glomerular filtration rate; Hb, haemoglobin; HDL-C, high-density lipoprotein cholesterol; HL, hyperlipidaemia; HrR, heart rate; hs-TnT, high-sensitivity troponin T; HT, hypertension; IL, interleukin; LAD, left atrial diameter; LBBB, left bundle branch block; LD, liver diseases; LDL-C, low-density lipoprotein cholesterol; LT, liver transplantation; LV mass, left ventricular mass; LVH, left ventricular hypertrophy; MI, myocardial infarction; MR-proANP, mid-regional pro-atrial natriuretic peptide; MR pro-ADM, Mid-regional pro-adrenomedullin; MVD, multi-vessel disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; OSA, obstructive sleep apnoea; PA, physical activity; PP, pulse pressure; PVD, peripheral vascular disease; RD, renal diseases; rTPA, recombinant tissue plasminogen activator; SBP systolic blood pressure; TC, total cholesterol; UAE, urine albumin excretion; WC, waist circumference.

Appendix 8: Results of assessing quality of studies that examined the risk of new-onset heart failure in relation to diabetes mellitus based on the adapted Newcastle-Ottawa Scale (NOS). The criterion corresponding to each combination of a capital letter and a number is indicated in Appendix 4

Study source	S1	S2	S3	S4	C1	O1	O2	O3	Score
Chen (2019)[87]	0	0	1	1	0	1	0	0	3
Fogarassy (2019)[86]	0	1	1	1	1	1	0	1	6
Magnusssen (2019)[89]	1	1	0	1	0	1	1	0	5
Winell (2019)[88]	1	1	1	1	0	1	1	1	7
Chen (2018)[32]	1	0	1	1	1	1	1	1	7
Eggimann (2018)[33]	0	1	0	1	1	1	0	0	4
Gong (2018)[34]	0	1	0	1	1	1	0	1	5
McAllister (2018)[90]	1	1	1	1	0	1	1	1	7
Lamblin (2018)[91]	0	1	1	1	1	1	0	0	5
LaMonte (2018)[42]	0	1	0	1	0	0	1	0	3
Larsson (2018)[94]	1	1	1	1	1	1	1	0	7
Rosengren (2018)[35]	1	0	1	1	1	1	0	1	6
Wandell (2018)[36]	1	1	1	1	1	1	0	1	7
Wellings (2018)[37]	0	1	1	0	1	1	0	1	5
Agarwal (2017)[27]	0	0	1	1	1	1	0	1	5
Ballotari (2017)[38]	1	1	1	0	0	1	0	1	5
Chatterjee (2017)[39]	0	1	0	1	1	0	1	1	5
He (2017)[41]	1	1	1	1	1	0	1	0	6
Jacobs (2017)[97]	0	1	0	1	1	1	0	1	5
Kim (2017)[40]	0	1	1	1	1	1	1	1	7
Pandey (2017)[43]	0	1	1	1	0	1	0	1	5
Policardo (2017)[44]	1	1	1	0	1	1	0	1	6
Zhang (2017)[31]	0	1	1	1	1	1	0	0	5
Eaton (2016)[28]	1	1	0	1	1	0	1	0	5
Goldhar (2016)[45]	0	1	1	1	1	1	0	0	5
Ho (2016)[29]	0	1	1	1	1	1	1	1	7
Sahle (2016)[46]	0	1	1	1	1	1	1	0	6
Silverman (2016)[30]	1	1	1	0	1	1	1	0	6
Chahal (2015)[47]	1	1	0	0	1	1	1	0	5
Donneyong (2015)[48]	0	1	0	1	0	0	1	1	4
Qin (2015)[49]	0	1	1	1	0	1	1	0	5
Shah (2015)[50]	1	1	1	0	1	1	0	0	5
Miao (2014)[96]	0	1	1	1	0	1	0	1	5
Wong (2014)[51]	0	1	1	0	0	1	0	0	3
Brouwers (2013)[52]	0	1	1	1	1	1	1	0	6
Ho (2013)[53]	1	1	1	1	1	1	1	1	8
Hung (2013)[100]	0	1	1	1	1	1	0	0	5
Potpara (2013)[54]	0	1	0	1	0	1	1	1	5
Qureshi (2013)[55]	0	1	1	0	0	1	0	1	4
Agarwal (2012)[56]	1	1	1	1	0	1	1	0	6
Nakajima (2012)[57]	0	1	1	1	0	1	0	0	4
Sato (2012)[98]	0	1	1	0	0	1	0	1	4
Shafazand (2011)[99]	0	1	1	1	1	1	0	1	6
Roy (2011)[58]	1	1	1	1	1	0	1	0	6
de Simone (2010)[59]	1	1	1	1	0	1	1	0	6
Goyal (2010)[60]	1	1	1	1	1	1	0	0	6
Smith (2010)[61]	1	1	1	1	1	1	1	0	7
van Melle (2010)[62]	0	1	0	1	1	0	0	1	4
Bibbins-Domingo (2009)[63]	1	1	1	1	0	1	1	1	7
Kenchaiah (2009)[64]	0	1	0	0	0	0	1	0	2
Leung (2009)[65]	1	0	1	1	0	1	0	0	4
Lewis (2009)[66]	0	1	1	1	1	1	0	0	5
Ruigomez (2009)[67]	1	1	1	1	1	1	0	1	7
Nafaji (2008)[92]	0	1	1	1	1	1	1	1	7
Aksnes (2007)[68]	0	1	1	0	1	1	0	0	4

(*Continues*)

Study source	S1	S2	S3	S4	C1	O1	O2	O3	Score
Fukuda (2007)[69]	0	1	1	1	1	1	0	0	5
Held (2007)[70]	0	1	1	0	0	1	0	0	3
Ito (2007)[71]	0	1	1	1	0	1	0	0	4
Ingelsson (2005)[72]	1	1	1	1	1	1	1	0	7
Lentine (2005)[73]	0	1	1	1	1	1	0	0	5
Bibbins-Domingo (2004)[74]	0	1	0	1	1	1	1	0	5
Nichols (2004)[75]	1	0	1	1	0	1	0	0	4
Wylie (2004)[76]	0	1	0	1	1	1	0	0	4
Lewis (2003)[77]	0	1	0	1	1	1	0	0	4
Rigatto (2002)[78]	0	1	1	1	1	1	1	0	6
Williams (2002)[93]	1	1	0	1	1	1	1	1	7
Abramson (2001)[95]	0	1	0	1	1	1	0	0	4
He (2001)[79]	1	1	0	1	1	1	1	1	7
Johansson (2001)[80]	1	0	1	1	1	1	0	1	6
Wilhelmsen (2001)[81]	1	1	0	1	1	1	1	0	6
Aronow (1999)[82]	1	1	1	1	1	1	0	0	6
Chen (1999)[83]	1	1	0	1	1	1	1	0	6
Kannel (1999)[84]	1	1	1	1	1	1	1	1	8
Harnett (1995)[85]	0	1	1	1	1	1	0	1	6

Appendix 9: Study confounders considered when the relationship between diabetes mellitus and recurrent heart failure was examined

Study source	Confounders
Kim (2019)[134]	Age, (gender), BMI, SBP, HR, HT, CHD, Hb, Na, Cre, NT-proBNP, LVEF, medications
Chen (2018)[101]	None
Cooper (2018)[102]	Age, gender, race, BMI, SBP, HrR, NYHA, CHD, AF, PVD, COPD, CKD, ACE-I, ARB, diuretics
Iorio (2018)[137]	Age, gender
Kristensen (2018)[103]	None
Retwinski (2018)[136]	None
Rorth (2018)[104]	Age, gender, education, IHD, AF, CKD, COPD, HT, stroke, cancer, medications
Sandesara (2018)[105]	None
Takimura (2018)[135]	Age, duration after previous HF, Hb, UA, LVEF, LAVI
Dauriz (2017)[106]	Age, gender, smoking, BMI, SBP, eGFR, LVEF, IHD, HT, statin, stroke, COPD, Hb
Farre (2017)[107]	Age, gender, recent HF, anaemia, valvular disease, IHD, CKD, dialysis, AF, cardiac conduction disorders, cancer, stroke, dementia, cirrhosis number of hospitalization, visits to emergency department
Kristensen (2017)[108]	Age, gender, recent HF, LVEF, HrR, eGFR, NT-proBNP, neutrophils, COPD, MI, ischaemic origin
Mohamedali (2017)[109]	None
Echouffo-Tcheugui (2016)[110]	Age, gender, race, LVEF, NYHA, AF, ischaemic cardiomyopathy, ECG (LBBB, wide QRS), cardiac conduction disorders, HF duration, Cre, history of syncope, FH of sudden death, CHD, ventricular tachycardia medications
Kristensen (2016)[111]	None
Ruigomez (2016)[112]	Age, gender, smoking, alcohol, BMI, residence, IHD, stroke, HT, AF, hyperlipidaemia, COPD, asthma, RD, visiting hospital in the previous year
Kaneko (2015)[113]	Age, IHD, DBP, HrR, diuretics
Takeda (2015)[114]	None
Carrasco-Sanchez (2014)[115]	Age, NYHA, GFR, Na, BMI, anaemia, PVD, beta-blocker, ACE-Is, ARBs
Cubbon (2014)[116]	Pulmonary congestion, previous HF, diuretics
Paoletti (2014)[117]	None
Sakata (2014)[118]	Age, gender, smoking, BMI, SBP, HT, dyslipidaemia, LVEF, HrR, Hb, Cre, BNP, medications
Larina (2013)[119]	None
Sarma (2013)[120]	Age, gender, smoking, BMI, SBP, EF, Na, BUN, QRS duration, BNP/NT-proBNP, AF, HT, CKD, stroke, medications
Verbrugge (2012)[121]	Obesity, HT, COPD, CKD, NYHA, right ventricular function, ischaemic aetiology of HF
Deedwania (2011)[122]	Propensity-matched for age, gender, smoking, BMI, SBP, DBP, HrR, others (multiple) (previous diseases, laboratory data, medications)

(*Continues*)

Study source	Confounders
Martin (2011)[123]	None
Aguilar (2010)[124]	Age, gender, obesity, ischaemic origin, NYHA
Sze (2010)[125]	Gender, NYHA, AF, wide QRS, HrR, one of renal function indicators, beta-blocker, diuretics
MacDonald (2008)[126]	32 covariates (including age, gender, smoking, SBP, DBP, NYHA, LVEF, HrR, IHD, stroke, AT, pacemaker, various medications)
Macdonald (2008)[127]	Age, (gender), co-morbidities (including CHD)
Ghali (2007)[128]	None
Ruiz-Ruiz (2007)[129]	None
Formiga (2006)[130]	Age, gender, SBP, PIP
Garcia (2005)[131]	None
Domanski (2003)[132]	Age, gender, BMI, race, Cre, SBP, aetiology of HF, cholesterol, diuretics, vasodilators
Shindler (1996)[133]	Age, gender, race, EF, aetiology of left ventricular dysfunction, NYHA
Harnett (1995)[85]	Age, IHD, EF, Hb, albumin, DBP, LV mass

The confounder in parentheses indicates that the risk measure was adjusted for this confounder although the adjustment was not stated.

Abbreviations: ACE-Is, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; AMI, acute myocardial infarction; ARBs, angiotensin receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Cre, creatinine; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; FH, family history; Hb, haemoglobin; HL, hyperlipidaemia; HrR, heart rate; hs-TnT, high-sensitivity troponin T; HT, hypertension; ICD, implantable cardioverter–defibrillator; LAVI, left atrial volume index; LBBB, left bundle branch block; LVAD, left ventricular assist device placement, LV mass, left ventricular mass; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association classification; PIP, procollagen type 1; PVD, peripheral vascular disease; RD, renal diseases; SBP systolic blood pressure; TC, total cholesterol; UA, uric acid; VT, ventricular tachycardia.

Appendix 10: Results of assessing quality of studies that examined the risk of recurrent heart failure in relation to diabetes mellitus based on the adapted Newcastle-Ottawa Scale (NOS). The criterion corresponding to each combination of a capital letter and a number is indicated in Appendix 4

Study source	S1	S2	S3	S4	C1	O1	O2	O3	Score
Kim (2019)[134]	1	1	1	1	1	0	0	0	5
Chen (2018)[101]	1	1	1	1	0	1	1	0	6
Cooper (2018)[102]	0	1	1	1	1	1	0	0	5
Iorio (2018)[137]	1	1	1	1	0	1	1	0	6
Kristensen (2018)[103]	0	1	1	1	0	1	1	1	6
Retwinski (2018)[136]	1	1	1	1	0	1	0	1	6
Rorth (2018)[104]	1	1	1	1	1	1	1	1	8
Sandesara (2018)[105]	0	1	0	1	0	1	1	0	4
Takimura (2018)[135]	0	1	1	1	0	1	0	1	5
Dauriz (2017)[106]	1	1	0	1	1	1	0	0	5
Farre (2017)[107]	1	1	1	1	1	1	0	1	7
Kristensen (2017)[108]	0	1	1	1	1	1	1	0	6
Mohamedali (2017)[109]	0	1	1	1	0	0	1	1	5
Echouffo-Tcheugui (2016)[110]	0	1	1	1	1	1	1	0	6
Kristensen (2016)[111]	0	1	1	1	0	1	1	0	5
Ruigomez (2016)[112]	1	1	1	1	1	1	1	1	8
Kaneko (2015)[113]	1	1	1	1	1	1	1	0	7
Takeda (2015)[114]	0	1	1	1	0	1	1	1	6

(*Continues*)

Study source	S1	S2	S3	S4	C1	O1	O2	O3	Score
Carrasco-Sanchez (2014)[115]	1	1	1	1	1	1	0	1	7
Cubbon (2014)[116]	1	1	1	1	0	1	0	1	6
Paoletti (2014)[117]	0	1	1	1	0	1	1	1	6
Sakata (2014)[118]	0	1	1	1	1	1	1	0	6
Larina (2013)[119]	1	1	1	1	0	1	1	0	6
Sarma (2013)[120]	0	1	0	1	1	1	0	0	4
Verbrugge (2012)[121]	0	1	1	1	0	1	0	1	5
Deedwania (2011)[122]	0	0	1	1	1	1	0	0	4
Martin (2011)[123]	0	1	0	1	0	1	0	0	3
Aguilar (2010)[124]	0	1	0	1	1	0	1	0	4
Sze (2010)[125]	0	1	0	1	0	1	0	1	4
MacDonald (2008)[126]	0	1	0	1	1	1	1	1	6
Macdonald (2008)[127]	1	1	1	1	1	1	1	1	8
Ghali (2007)[128]	0	1	0	1	0	1	0	1	4
Ruiz-Ruiz (2007)[129]	1	1	1	1	0	1	0	1	6
Formiga (2006)[130]	1	1	1	1	0	1	0	1	6
Garcia (2005)[131]	1	1	0	1	0	1	0	0	4
Domanski (2003)[132]	0	1	0	1	1	0	1	1	5
Shindler (1996)[133]	0	1	0	1	1	0	1	0	4
Harnett (1995)[85]	0	1	1	1	1	1	0	1	6

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