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 expenditures2 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 attention7 as one of the most common cardiovascular complications of DM.8 Estimating the magnitude of HF risk among persons with

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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. 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. 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 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. Another meta-analysis of cohort studies limited to patients with a history of HF indicated that DM adversely affected all-cause death and hospitalization. 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. 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) (HFrEF) 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 ≥ II in the New York Heart Association (NYHA) classification or a history of HF of class ≥ 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: RR = \( \frac{C_1/N_1}{C_2/N_2} \), SE (logRR) = \( \sqrt{\frac{1}{C_0} + \frac{1}{C_1} - \frac{1}{N_0} - \frac{1}{N_1}} \), 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: OR \( \rightarrow \) RR = \( \frac{C_1}{N_1} \times \frac{C_2}{N_2} \), SE (logOR) = \( \sqrt{\frac{SE^2(\log OR) + (\log RR/\log OR)}{P_0} \times \log RR} \), 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 because HF and DM are typical age-related diseases. Compared with individuals without DM, those with DM have a higher prevalence of CHD, and CHD presents the largest attributable risk for HF among potential risk factors. 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. 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 HFrEF and HFrEF with adjustment for each included study.

Publication bias was assessed by two formal tests, Begg’s rank correlation test and Egger’s regression asymmetry test. If publication bias was statistically detected, we adjusted the pooled RR for publication bias using the trim-and-fill method. 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 filing 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; in another, the 95% CI of the RR to calculate its corresponding standard error (SE) was not presented, 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 | Cohort name/affiliation | Population | % men | Age | n | Cases | Dur years | % LOF | Risk | DM | HF | Endpoint |
|--------------|--------|-------------------------|------------|-------|-----|---|------|-----------|-------|------|----|----|----------|
| Chen (2019)^97 | C | MAX General patients | 7 | 40.0 | 2.4 \times 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 |
| Magnussen (2019)^99 | C | BiomarCaRE General | 48 | 49.5 | 78 657 | 5170 | 12.7 | ? | HR | S | R | S/R | Dx |
| Winell (2019)^98 | C | Finnish NHRD and CDR General | — | — | 3.0 \times 10^6 | 3.0 \times 10^5 | 17 | 0 | RR | R | R | Dx |
| Chen (2018)^92 | 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 | Hosp |
| Lamblin (2018)^91 | C | CORONOR CHD | 78 | 66.0 | 3785 | 211 | 5 | 2 | HR | M | M | Hosp |
| LaMonte (2018)^42 | C | WHI Post-menopausal | 0 | 63 | 1.4 \times 10^5 | 2516 | 8.0 | ? | RR | S | S | Hosp |
| Larson (2018)^98 | 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 \times 10^6 | 1.2 \times 10^5 | 10 | 0 | RR | R | R | Hosp |
| Rosengren (2018)^95 | C | NDR, Sweden General | 55 | 62 | 1.6 \times 10^6 | 6.9 \times 10^4 | 5.6 | 1-5 | HR | R | R | Hosp |
| Wandel (2018)^96 | C | PHC in Stockholm AF | 55 | 74 | 9424 | 2259 | 5.4 | 0 | HR | R | R | Dx |
| Wellings (2018)^37 | C | MIDAS CHD | 35 | 63 | 1.1 \times 10^5 | — | 5.0 | 0 | HR | R | R | Hosp |
| Agarwal (2017)^26 | C | HCUP General patients | 42 | 50.2 | 1.7 \times 10^7 | 2.0 \times 10^5 | 5.0 | 0 | RR | R | R | Hosp |
| Ballotari (2017)^44 | C | REDR General | 49 | 50 | 3.6 \times 10^5 | 2321 | 3.0 | 0 | RR | R | R | Hosp |
| Chatterjee (2017)^29 | T | WHS AF | 0 | 69 | 1495 | 187 | 20.6 | 0 | HR | S | S | Dx |
| Jacobs (2017)^97 | C | HOMAGE General/high risk patients | 49 | 74.5 | 10 236 | 470 | 3.5 | 0 | HR | ? | M | Hosp |
| Kim (2017)^40 | C | Explorys Platform General patients | 46 | — | 4.5 \times 10^7 | 9.9 \times 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 | R | M | Dx |
| Policardo (2017)^44 | C | Tuscany Regional Health Care System General | — | — | — | 2.6 \times 10^4 | 5.0 | 0 | RR | 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 |
| Goldharp (2016)^5 | 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 | 53 | 62 | 6742 | 257 | 11.2 | ? | HR | M | M | Dx |
| Chahal (2015)^97 | C | MESA General | 47 | 62 | 6814 | 176 | 7.1 | ? | HR | S | M | Dx |
| Donneguy (2015)^48 | T | CaD trial Post-menopausal | 0 | 63 | 35 983 | 744 | 7.1 | 0 | RR | ? | S | Hosp |
| Qin (2015)^99 | C | UHCMC Breast cancer | 0 | 53 | 1153 | 120 | 7.6 | 29 | RR | R | R | Dx |
| Shah (2015)^20 | C | CALIBER General | 49 | 47 | 1.9 \times 10^6 | 1.4 \times 10^4 | 5.5 | ? | HR | R | R | Dx |
| Miao (2014)^47 | 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 | 50 | 50 | 8569 | 374 | 11.5 | ? | HR | M | M | Dx |
| Ho (2013)^53 | C | The 2nd FHS General | 46 | 50.0 | 1.2 \times 10^4 | 512 | 7.7 | 0 | HR | M | M | Hosp |
| Hung (2013)^100 | C | NHMD CHD | 70 | 63.7 | 15 464 | 1024 | 1 | 13 | OR | R | R | Dx |
| Potpara (2013)^34 | C | Belgrade Atrial Fibrillation Study AH | 63 | 52 | 842 | 83 | 11.2 | 0 | HR | ? | M | M | Dx |
| Qureshi (2013)^55 | C | Henry Ford Health System LT | 52 | 53 | 970 | 98 | 5.3 | 0 | RR | M | M | Dx |
| Agarwal (2012)^96 | C | ANIC General | 45 | 54 | 13 555 | 1487 | 15.5 | ? | HR | S | M | M | Hosp |
| Study source     | Design | Cohort name/affiliation | Population | % men | Age | n | Cases | Dur years\(^b\) | % LOF | Risk | DM | HD | HF | Endpoint |
|------------------|--------|-------------------------|------------|-------|-----|---|------|----------------|------|------|---|---|---|----------|
| Nakajima (2012)  | C      | J-ACCESS RD\(^d\)       | 64         | 66    | 2395| 64 | 3.00 | ?               | RR   | M    | M  | M  | M  | Hosp     |
| Sato (2012)      | C      | Okayama RCH CHD\(^d\)   | 73         | 68.8  | 197 | 23 | 1.0  | 0               | RR   | M    | S/M| Hosp |
| Shafazand (2011) | C      | Swedish NHDR CHD\(^d\)  | 64         | 68.9  | 1.8 × 10\(^3\) | 43,034 | 3.0 | 0    | HR   | R    | R  | R  | M  | Hosp |
| Roy (2011)       | C      | CHS General             | 42         | 73    | 5464| 1134| 13.0 | ?               | HR   | M    | S  | S  | Dx |         |
| de Simone (2010) | C      | SHS phase I General     | 64         | 56    | 2740| 291 | 11.9 | ?               | RR   | M    | M  | M  | Dx |         |
| Goyal (2010)     | C      | One Million Person-Year Follow-up Study | 47 | 38 | 3.6 × 10\(^5\) | 4,001 | 2.9 | ?   | RR   | R    | R  | Dx |
| Smith (2010)     | C      | MDCS General            | 41         | 58    | 5,135| 112 | 13.8 | 1    | HR   | S/M | R  | Dx |
| van Melle (2010) | C      | Heart and Soul Study CHD | 82       | 67    | 839 | 77  | 4.1  | 0    | HR   | S   | S  | Hos |         |
| Bibbins-Domingo (2009) | C | CARDIA General       | 44         | 24    | 2,637| 26  | 20.0 | 28   | HR   | R   | M  | M  | Hosp |
| Kenchaiah (2009) | C      | PHS Physicians         | 100        | 53    | 21,094| 1,109| 20.5 | ?    | RR   | S   | S  | Dx |         |
| Leung (2009)     | C      | Saskatchewan Health beneficiaries General | 51 | 63 | 5.6 × 10\(^5\) | 2,293 | 1.1 | ?   | RR   | R    | R  | Dx |
| Lewis (2009)     | T      | PEACE CAD              | 82         | 64    | 8,211| 268 | 4.8  | 1    | HR   | R   | R  | Hosp |
| Ruigomez (2009)  | C      | GPRD in 1996, UK General | 47       | 64    | 9,057| 386 | 3.6  | 0    | HR   | R   | M  | Dx |
| Nafaji (2008)    | C      | Perth MONICA Register CHD\(^d\) | 15       | 54.5  | 3,109| 406 | 14.4 | 0    | HR   | M   | R  | Dx |
| Akens (2007)     | T      | VALUE HT               | 58         | 66    | 15,245| 754 | 4.2  | ?    | RR   | M   | M  | Hosp |
| Fukuda (2007)    | T      | Cardiovascular Institute Hospital AF | 77 | 64 | 2,484 | 16 | 4.1  | ?   | RR   | R   | M  | Hosp |
| Held (2007)      | T      | ONTARGET/TRANSCEND CHD\(^d\) | 70       | 67    | 30,798| 668 | 2.4  | 2    | RR   | M   | M  | Hosp |
| Ito (2007)       | T      | Nagoya City Higashi Municipal Hospital RD\(^d\) | 64 | 57 | 100 | 6 | 4.7 | ? | RR   | M   | M  | Hosp |
| Ingelsson (2005) | C      | ULSAM General          | 100        | 50    | 2,321| 259 | 28.8 | ?    | HR   | M   | R  | Dx |
| Lentine (2005)   | C      | USRDS RD\(^d\)         | 47         | 27,011| -   | 3.0 | ?    | HR   | R   | R  | Dx |
| Bibbins-Domingo (2004) | T | HERS CHD\(^d\)       | 0         | 67    | 2,391| 237 | 6.3  | ?    | HR   | S   | M  | Hosp |
| Nichols (2004)   | C      | KPNW General           | 48         | 63    | 17,076| 1,693| 4.7  | ?    | HR   | R   | R  | Dx |
| Wylie (2004)     | T      | OPUS-TIMI 16 CHD\(^d\) | 60.5      | 4681  | 254 | 0.8 | ?    | OR   | ?   | M  | Dx |
| Lewis (2003)     | T      | CARE CHD\(^d\)         | 87         | 58    | 3,860| 243 | 5.0  | ?    | HR   | ?   | M  | Hosp |
| Rigatto (2002)   | C      | University of Manitoba RD\(^d\) | 62 | 38 | 638 | 63 | 8.9 | ? | RR   | M   | M  | Dx |
| Williams (2002)  | C      | YHAP General           | 42         | 74.3  | 2,176| N/A | 14.3 | 13   | HR   | S   | M  | Dx |
| Abramson (2001)  | T      | SHEP HT                | 57         | 71.6  | 4,538| 156 | 4.5  | ?    | HR   | S   | M  | Dx |
| He (2001)        | C      | HHANES-I General       | 41         | 50    | 13,643| 1,382| 19.0 | 4    | HR   | S   | R  | Hosp |
| Johansson (2001) | C      | GPRD in 2000, UK General | 52       | 72    | 5,000| 938 | 1.0  | 0    | RR   | R   | M  | Hosp |
| Wilhelmsen (2001) | C | MPPS General       | 100        | 52    | 7,495| 937 | 27.0 | 12   | OR   | S   | R  | Hosp |
| Aronow (1999)    | C      | Hebrew Hospital General | 32       | 81    | 2,893| 794 | 3.6  | ?    | HR   | M   | M  | Dx |
| Chen (1999)      | C      | New Haven Cohort General | 41 | 74 | 1,749 | 173 | 7.9 | 13   | HR   | S   | M  | Hosp |
| Kannel (1999)    | C      | FHS General            | 42         | 63    | 15,267| 486 | 38.0 | 0    | OR   | M   | M  | Dx |
| Harnett (1999)   | 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...
glucose tolerance/normal glucose tolerance). 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 in which we could estimate RRs for new-onset and recurrent HF, respectively, in relation to DM. One study 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 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 limited DM patients to those with type 2 DM. One differentiated type 1 from type 2 DM. 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 involved studies that were limited the DM patients to type 1 DM.

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 (mean, 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.

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 the outcome was separated into HfPeF and HFrEF.
| Study source | Cohort name/affiliation | Design | Population | EF | % men | Age | n | Cases | Dur | LOF | Risk | DM | HF | Endpoint |
|--------------|------------------------|--------|------------|----|-------|-----|---|-------|-----|-----|------|----|----|----------|
| Kim (2019)   | KorHF                  | C      | N/S        | N/S | 50    | 67  | 3162 | 863  | 1.5 | ?    | HR  | R   | ?        | Hosp     |
| Chen (2018)  | Sun Yat-sen University | C      | N/S        | N/S | 66    | 64.9| 587  | 384  | 7.0 | ?    | RR  | M   | M        | Hosp     |
| Cooper (2018)| HA-ACTION             | T      | N/S        | ↓   | 77    | 59  | 6214 | 243  | 1.0 | ?    | HR  | M   | R        | Hosp     |
| Iorio (2018) | Cardiomet® in Trieste  | T      | N/S        | N/S | 75    | 77  | 2314 | 510  | 2.6 | ?    | HR  | M   | R        | Hosp     |
| Kristensen (2018)| ATMOSPHERE | T     | N/S        | ↓   | 78   | 63  | 7016 | 1324 | 2.7 | 1    | RR  | M   | R        | Hosp     |
| Retwinski (2018)| ESC-HF-LT            | C      | N/S        | N/S | 70    | 65.3| 1080 | 377  | 1.0 | 0    | RR  | M   | S/M      | Hosp     |
| Rorth (2018) | DNPR                   | T      | N/S        | N/S | 74    | 69  | 3385 | 437  | 3.4 | ?    | RR  | S   | R        | Hosp     |
| Sandesara (2018)| TOPCAT               | C      | N/S        | N/S | 66    | 64  | 587  | 384  | 7.0 | ?    | RR  | M   | M        | Hosp     |
| Takimura (2018)| ESC-HF-LT             | C      | N/S        | N/S | 72    | 72  | 9428 | 437  | 3.4 | ?    | RR  | M   | S        | Hosp     |
| Dauriz (2017) | Local Health Department| C      | N/S        | N/S | 45    | 77  | 8816 | 510  | 2.6 | 1    | RR  | M   | R        | Hosp     |
| Farre (2017) | Catasotal              | T      | N/S        | N/S | 78    | 63  | 7016 | 1324 | 2.7 | 1    | RR  | M   | R        | Hosp     |

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

**Methods**

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

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

Methods for confirmation of DM and HF.

Mean of median follow-up duration is indicated.

Excluding 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
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 ≥ 60 years [pooled RR (95% CI), 1.95 (1.79–2.13)]. Meta-regression analysis indicated that the difference in 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 (I² = 80.1%, P < 0.001) (Figure 3). Results of

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 (I² = 80.1%, P < 0.001) (Figure 3). Results of
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 HFP EF
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 | I² (%) | P value for I² | 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                                         | 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                                       |     |                 |                |        |                |                 |
| ≥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                                         |     |                 |                |        |                |                 |
| ≥50%                                          | 53  | 2.03 (1.76–2.35) | <0.001         | 99.3   | <0.001         | 0.11            |
| <50%                                          | 51  | 2.33 (1.99–2.72) | <0.001         | 99.4   | <0.001         |                 |
| Risk adjustment                               |     |                 |                |        |                |                 |
| Both age and CHD                              | 64  | 1.78 (1.70–1.87) | <0.001         | 91.7   | <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 HF⁴        | 57  | 1.96 (1.73–2.23) | <0.001         | 99.6   | <0.001         | 0.02            |
| Underlying diseases                           |     |                 |                |        |                |                 |
| Non-hospital-based study⁵                     | 67  | 2.30 (2.02–2.62) | <0.001         | 99.6   | <0.001         |                 |
| 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            |
| Others⁶                                       | 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.

*Cohort study that was originally designated as a trial.

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.

Data were not available in two studies.⁴⁰,⁷³

*Including community-based study or specific populations such as post-menopausal, nurses, and physicians.

*Multivariate regression analysis was performed.

*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 | I² (%) | P value for I² | 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                                         | 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                                       |     |                 |                |        |                |                 |
| ≥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)
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 HFrEF 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.9

Given that diastolic dysfunction is the first hallmark of diabetic cardiomyopathy,9 the risk magnitude for HF in individuals with DM would be larger for HFrpEF than for HFrEF. That is because among those with HF, the proportion of HFrpEF 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 HFrpEF and HFrEF. One plausible explanation is that it is difficult to detect the HF in the early stage that is classified as HFrEF, which specifically occurs in patients with DM.

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 HFrpEF. 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 HFrpEF 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 HFrpEF, indicating that HFrpEF 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

| Variable | n | RR (95% CI) | P value for RR | I² (%) | P value for I² | Meta-regression |
|----------|---|-------------|---------------|--------|----------------|----------------|
| Including non-hospitalizations for HF | 45 | 1.40 (1.33–1.46) | <0.001 | 81.5 | <0.001 | 0.52 |
| Special characteristics | | | | | | |
| Non-specified | 36 | 1.33 (1.30–1.35) | <0.001 | 83.2 | <0.001 | 0.9 |
| After CRT and/or LVAD implantation | 8 | 1.41 (1.24–1.61) | <0.001 | 51.9 | 0.04 | 0.88 |
| After AMI | 2 | 1.25 (1.05–1.48) | 0.01 | 67.5 | 0.08 | 0.26 |
| Others | 2 | 1.66 (1.26–2.18) | <0.001 | 0.0 | 0.4 | 0.45 |
| EF status | | | | | | |
| Non-specified | 24 | 1.33 (1.28–1.38) | <0.001 | 59.6 | <0.001 | 0.9 |
| 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.

Cohort study that was originally designated as a trial.

Data based on the subgroup analysis according to age instead of gender were used.

Worsening of HF that did not lead to hospitalization.

Because one study124 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.

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.

Including patients on dialysis (1 study) and who were administered tolvaptan (1 study).

Multivariate regression analysis was performed.
mortality such as angiotensin-converting enzyme inhibitors, beta-blockers, and spironolactone.\textsuperscript{143} In addition, women were less likely to undergo assessment of left ventricular function.\textsuperscript{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,\textsuperscript{144} for which no effective treatment with a high grade of evidence has been identified.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{142} 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

ESC Heart Failure 2020; 7: 2146–2174
DOI: 10.1002/ehf2.12782
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 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 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

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* #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

4. Did the study confirm that the outcome (i.e. recurrent episode of HF) 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

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

C2. Specific characteristics (e.g. post-menopausal, specific occupation)
C3. Specific underlying diseases (e.g. coronary heart diseases (CHD), renal diseases, atrial fibrillation)
C4. Study design was originally a trial.
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.
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)                           | None                                                                                                                                       |
| Fogarassy (2019)                      | Age, HT, CHD, stroke, cancer stage, chemotherapies, antihypertensive agents                                                               |
| Magnussen (2019)                      | Age, gender, smoking, BMI, HT, antihypertensive medication, TC                                                                             |
| Winell (2019)                         | (Age), (gender)                                                                                                                                |
| Chen (2018)                           | Age, gender, region, CHD, coronary revascularization, medication                                                                            |
| Eggimann (2018)                       | Age, BMI, valve surgery, arrhythmia intervention, QTc, BNP                                                                                   |
| Gong (2018)                           | Age, smoking, BMI, MI, OSA, NT-proBNP, Hb, calcium channel blocker                                                                            |
| McAllister (2018)                     | (Age), (gender)                                                                                                                                |
| Lamblin (2018)                        | Age, BMI, HT, multi-vessel CAD, angina, AF, (CHD)                                                                                             |
| LaMonte (2018)                        | (Gender)                                                                                                                                     |
| Larsson (2018)                        | Age, gender, BMI, education, (CHD), FH of MI, smoking, PA, HT, HL, alcohol, DASH diet score                                                  |
| Magnus (2018)                         | Age, (gender), income, education, marital status, duration of DM, stroke, CHD, AF, renal dialysis or transplantation                           |
| Winell (2018)                         | Age, gender, obesity, socio-demography, HT, valvular disease, cardiomyopathy, COPD, OSA                                                       |
| Chen (2018)                           | Age, gender, race, insurance, HT, (CHD), liver disease, CKD, dyslipidaemia                                                                  |
| Eggimann (2018)                       | Age, gender, race, HT, CAD, AF, income, ventricular premature complexes                                                                     |
| Goyal (2018)                          | (Gender)                                                                                                                                     |
| McAllister (2018)                     | None                                                                                                                                        |
| Lamblin (2018)                        | Age, (gender), race, assignment, smoking, PA, alcohol, BMI, SBP, HL, history of MI, CKD, (AF), medication                                     |
| Rosengren (2018)                      | Age, (gender), income, education, (CHD), FH of MI, smoking, PA, HT, HL, alcohol, DASH diet score                                               |
| Winell (2018)                         | Age, gender, BMI, education, (CHD), FH of MI, smoking, PA, HT, HL, alcohol, DASH diet score                                                  |
| Chen (2017)                           | Age, gender, smoking, obesity, HT, DM, dyslipidaemia, CHD                                                                                     |
| Ballotari (2017)                      | None                                                                                                                                        |
| Chahal (2017)                         | Age, gender, smoking, BMI, SBP, HR, Cre, LVH, (CVD)                                                                                           |
| Goldhar (2016)                        | Age, gender, smoking, alcohol, BMI, HT, MI, LVH, LBBB (left bundle branch block)                                                            |
| Ho (2016)                             | Age, gender, smoking, BMI, HT, MI, LVH, LBBB (left bundle branch block)                                                                     |
| Sahle (2016)                          | Age, gender, smoking, BMI, BP, CVD, eGFR, HDL                                                                                                 |
| Silverman (2016)                      | Men: age, gender, race, HR, 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, HR, HT, smoking, HDL, eGFR, IL-6, coronary artery calcium score, MI during follow-up, proBNP, troponin T, LV mass index |
| Zhang (2017)                          | 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)                          | Age, education, income, smoking, HT, AF, CHD, chronic lung disease, PA, medication, alcohol, other morbidities, anaemia                            |
| Goldhar (2016)                        | Age, gender, smoking, alcohol, BMI, HT, MI, LVH, LBBB (left bundle branch block)                                                            |
| Ho (2016)                             | Age, gender, smoking, alcohol, BMI, HT, MI, LVH, LBBB (left bundle branch block)                                                            |
| Sahle (2016)                          | Age, gender, smoking, BMI, BP, CVD, eGFR, HDL                                                                                                 |
| Silverman (2016)                      | Men: age, gender, race, HR, 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, HR, HT, smoking, HDL, eGFR, IL-6, coronary artery calcium score, MI during follow-up, proBNP, troponin T, LV mass index |
| Chahal (2017)                         | Age, gender, smoking, BMI, SBP, HR, Cre, LVH, (CVD)                                                                                           |
| Donneyong (2015)                      | None                                                                                                                                        |
| Qin (2015)                            | None                                                                                                                                        |
| Shah (2015)                           | Age, gender, smoking, deprivation, BMI, SBP, HDL, TC, statin, (CHD), antihypertensive drugs                                                   |
| Miao (2014)                           | Age, obesity, arrhythmias, PVD, pulmonary disease, pulmonary vascular disease, HT, hypothyroidism, CKD, LD, AIDS, weight loss, electrolyte disorders |
| Wong (2014)                           | None                                                                                                                                        |
| Brouwers (2013)                       | Age, gender, obesity, HT, MI, smoking, AF, HL, Cre, cystatin C, UA, CRP, NT-proBNP, hs-TnT                                                |
| Ho (2013)                             | Age, gender, HT, BMI, HR, MI, CHD, smoking, valvular disease, HDL, AF, LVH, LBBB                                                               |
| Hung (2013)                           | (CHD), age, gender                                                                                                                              |
| Potpara (2013)                        | Age, gender, medication                                                                                                                        |
| Qureshi (2013)                        | None                                                                                                                                        |
| Agarwal (2012)                        | Age, gender, race                                                                                                                             |
| Nakajima (2012)                       | None                                                                                                                                        |
| Sato (2012)                           | None                                                                                                                                        |
| Shafazand (2011)                      | (CHD), smoking, HT, MVD                                                                                                                         |
| Roy (2011)                            | (CHD), age, gender, stroke, AF, valvular disease                                                                                               |
| de Simone (2010)                      | Multiple (65 characteristics)                                                                                                                  |
| Goyal (2010)                          | None                                                                                                                                        |
| Smith (2010)                          | Age, gender, CHD, AF, valvular diseases                                                                                                         |

(Continues)
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; HR, 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-proADM, 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.

| Study source | Confounders |
|--------------|-------------|
| van Melle (2010) | Age, gender, race, smoking, BMI, PA, LDL, SBP, MI during follow-up, LVEF, wall motion abnormality, diastolic dysfunction, CRP, medication (CHD) |
| Bibbins-Domingo (2009) | None |
| Kennaiah (2009) | Age, gender |
| Lewis (2009) | Age, BMI, MI, bypass surgery, HT, angina, GFR, LVEF, medication (CHD) |
| Ruigomez (2009) | Age, gender, AF, alcohol, smoking, BMI, HT, hyperlipidaemia, venous thromboembolism, CHD, cardiac diseases, COPD |
| Nafaji (2008) | Age, gender, smoking, HT, ECG, CARP, streptokinase or rTPA |
| Bibbins-Domingo (2004) | None |
| Nichols (2004) | Age, CHD, BNP, ECG, HR |
| Wylie (2004) | Age, PA, HT, previous MI, LVEF |
| Lewis (2003) | Age, DBP, CHD, systolic dysfunction, Hb, albumin, LV mass |
| Rigatto (2002) | None |
| Williams (2002) | Age, gender, HT, MI, PP, depression, functional limitations |
| Abramson (2001) | Age, gender, smoking, MI, angina, SBP, DBP, TC, HLD, ECG, trial group, ADL |
| He (2001) | Age, gender, race, CHD |
| Johansson (2001) | Age, smoking, BMI, hyperlipidaemia, prior dyspnea irrelevant to HT, prior co-morbidity (inc. CHD) |
| Wilhelmsen (2001) | Age, gender, smoking, alcohol, coffee, BMI, HT, (CHD) |
| Aronow (1999) | Age, gender, race, HT, (CHD) |
| Chen (1999) | Age, gender, PP, BMI, MI during follow-up |
| Kannel (1999) | Age, gender, SBP, LVH, heart rate, (CHD), valve disease |
| Harnett (1995) | Age, DBP, CHD, systolic dysfunction, Hb, albumin, LV mass |

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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)      | 1  | 0  | 0  | 1  | 1  | 0  | 0  | 0  | 3     |
| Fogarassy (2019) | 0  | 1  | 1  | 1  | 1  | 0  | 1  | 0  | 6     |
| Magnusson (2019) | 1  | 1  | 0  | 1  | 0  | 1  | 1  | 0  | 5     |
| Winell (2019)    | 1  | 1  | 1  | 1  | 0  | 1  | 1  | 1  | 7     |
| Chen (2018)      | 1  | 0  | 1  | 1  | 1  | 1  | 1  | 7  | 7     |
| Eggimann (2018)  | 0  | 1  | 0  | 1  | 1  | 1  | 0  | 0  | 4     |
| Gong (2018)      | 0  | 1  | 0  | 1  | 1  | 1  | 0  | 1  | 5     |
| McAllister (2018)| 1  | 1  | 1  | 1  | 0  | 1  | 1  | 1  | 7     |
| Lamblin (2018)   | 0  | 1  | 0  | 1  | 1  | 0  | 0  | 0  | 5     |
| LaMonte (2018)   | 0  | 1  | 0  | 1  | 1  | 1  | 0  | 1  | 3     |
| Larsson (2018)   | 1  | 1  | 0  | 1  | 1  | 1  | 0  | 1  | 7     |
| Rosengren (2018) | 1  | 0  | 1  | 1  | 1  | 0  | 1  | 6  | 6     |
| Cambell (2018)   | 1  | 1  | 1  | 1  | 1  | 0  | 0  | 1  | 7     |
| Wellings (2018)  | 0  | 1  | 1  | 0  | 1  | 1  | 0  | 1  | 5     |
| Agarwal (2017)   | 0  | 0  | 1  | 1  | 1  | 1  | 0  | 1  | 5     |
| Ballotari (2017) | 1  | 1  | 1  | 0  | 0  | 1  | 0  | 1  | 5     |
| Chatterjee (2017)| 0  | 1  | 0  | 1  | 1  | 1  | 0  | 1  | 5     |
| He (2017)        | 1  | 1  | 1  | 1  | 1  | 0  | 0  | 1  | 6     |
| Jacobs (2017)    | 0  | 1  | 0  | 1  | 1  | 1  | 0  | 1  | 5     |
| Kim (2017)       | 0  | 1  | 1  | 1  | 1  | 1  | 1  | 7  | 7     |
| Paney (2017)     | 0  | 1  | 1  | 1  | 0  | 1  | 1  | 1  | 7     |
| Policardo (2017) | 1  | 1  | 1  | 0  | 1  | 1  | 0  | 1  | 6     |
| Zhang (2017)     | 0  | 1  | 1  | 1  | 1  | 1  | 0  | 0  | 5     |
| Eaton (2016)     | 1  | 1  | 0  | 1  | 1  | 0  | 1  | 0  | 5     |
| Goldhar (2016)   | 0  | 1  | 1  | 1  | 1  | 0  | 0  | 5  | 5     |
| Ho (2016)        | 0  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 7     |
| Sahle (2016)     | 0  | 1  | 1  | 1  | 1  | 1  | 1  | 0  | 6     |
| Silverman (2016) | 1  | 1  | 1  | 0  | 1  | 1  | 1  | 0  | 6     |
| Chahal (2015)    | 1  | 1  | 0  | 0  | 1  | 1  | 1  | 1  | 0     |
| Donnay (2015)    | 0  | 1  | 0  | 1  | 0  | 0  | 1  | 1  | 4     |
| Qin (2015)       | 0  | 1  | 1  | 1  | 0  | 1  | 0  | 1  | 5     |
| Shah (2015)      | 1  | 1  | 1  | 0  | 1  | 1  | 0  | 0  | 5     |
| Miao (2014)      | 0  | 1  | 1  | 1  | 1  | 0  | 1  | 1  | 5     |
| Wong (2014)      | 0  | 1  | 1  | 0  | 0  | 1  | 0  | 0  | 3     |
| Brouwers (2013)  | 0  | 1  | 1  | 1  | 1  | 1  | 0  | 1  | 5     |
| Ho (2013)        | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 8     |
| Hung (2013)      | 0  | 1  | 1  | 1  | 1  | 1  | 0  | 0  | 5     |
| Potpara (2013)   | 0  | 1  | 0  | 1  | 0  | 1  | 1  | 1  | 5     |
| Qureshi (2013)   | 0  | 1  | 0  | 1  | 0  | 1  | 0  | 1  | 4     |
| Agarwal (2012)   | 1  | 1  | 1  | 1  | 0  | 0  | 1  | 0  | 6     |
| Nakajima (2012)  | 0  | 1  | 1  | 1  | 0  | 1  | 0  | 0  | 4     |
| Sato (2012)      | 0  | 1  | 1  | 0  | 0  | 1  | 0  | 1  | 4     |
| Shafazand (2011) | 0  | 1  | 1  | 1  | 1  | 0  | 1  | 0  | 6     |
| Roy (2011)       | 1  | 1  | 1  | 1  | 1  | 0  | 0  | 1  | 6     |
| de Simone (2010) | 1  | 1  | 1  | 0  | 1  | 1  | 0  | 0  | 6     |
| Goyal (2010)     | 1  | 1  | 0  | 1  | 1  | 1  | 0  | 0  | 6     |
| Smith (2010)     | 1  | 1  | 1  | 1  | 1  | 1  | 0  | 1  | 7     |
| van Melle (2010) | 0  | 1  | 0  | 1  | 1  | 0  | 0  | 1  | 4     |
| Bibbins-Domingo (2009) | 1  | 1  | 1  | 0  | 1  | 1  | 7  | 7     |
| Kenchaiah (2009) | 0  | 1  | 0  | 0  | 0  | 0  | 0  | 0  | 2     |
| Leung (2009)     | 1  | 0  | 1  | 1  | 0  | 1  | 0  | 0  | 4     |
| Lewis (2009)     | 0  | 1  | 1  | 1  | 1  | 0  | 0  | 5  | 5     |
| Ruigomez (2009)  | 1  | 1  | 1  | 1  | 1  | 0  | 1  | 7  | 7     |
| Nafaji (2008)    | 0  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 7     |
| Aksnes (2007)    | 0  | 1  | 1  | 0  | 1  | 1  | 0  | 0  | 4     |

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

| Study source | Confounders                                                                                                                                                                                                 |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kim (2019)   | Age, (gender), BMI, SBP, HR, HT, CHD, Hb, Na, Cre, NT-proBNP, LVEF, medications                                                                                                                                  |
| Chen (2018)  | None                                                                                                                                                                                                      |
| Cooper (2018)| Age, gender, race, BMI, SBP, HrR, NYHA, CHD, AF, PVD, COPD, CKD, ACE-I, ARB, diuretics                                                                                                                     |
| Kristensen (2018) | Age, gender                                                                                                                                 |
| Retwinski (2018) | None                                                                                                                                               |
| Rorth (2018) | Age, gender, education, IHD, AF, CKD, COPD, HT, stroke, cancer, medications                                                                    |
| Sandesara (2018) | None                                                                                                                                               |
| Takimura (2018) | Age, duration after previous HF, Hb, UA, LVEF, LAVI                                                                                            |
| Dauriz (2017) | Age, gender, smoking, BMI, SBP, eGFR, LVEF, IHD, HT, statin, stroke, COPD, Hb                                                                       |
| Farre (2017) | 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) | Age, gender, recent HF, LVEF, HrR, eGFR, NT-proBNP, neutrophils, COPD, MI, ischaemic origin                                                      |
| Mohamedali (2017) | None                                                                                                                                               |
| Echouffo-Tcheugui (2016) | 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) | None                                                                                                                                               |
| Ruizgomez (2016) | Age, gender, smoking, alcohol, BMI, residence, IHD, stroke, HT, AF, hyperlipidaemia, COPD, asthma, RD, visiting hospital in the previous year |
| Kaneko (2015) | Age, IHD, DBP, HrR, diuretics                                                                                                                                                                             |
| Takeda (2015) | Age, NYHA, GFR, Na, BMI, anaemia, PVD, beta-blocker, ACE-Is, ARBs                                                                               |
| Carrasco-Sanchez (2014) | Pulmonary congestion, previous HF, diuretics                                                                                                     |
| Cubbon (2014) | None                                                                                                                                               |
| Paoletti (2014) | Age, gender, smoking, BMI, SBP, HT, dyslipidaemia, LVEF, HrR, Hb, Cre, BNP, medications                                                            |
| Sakata (2014) | None                                                                                                                                               |
| Lin (2013)   | Age, gender, smoking, BMI, SBP, EF, Na, BUN, QRS duration, BNP/NT-proBNP, AF, HT, CKD, stroke, medications                                           |
| Sarma (2013) | Obesity, HT, COPD, CKD, NYHA, right ventricular function, ischaemic aetiology of HF Propensity-matched for age, gender, smoking, BMI, SBP, DBP, HrR, others (multiple) (previous diseases, laboratory data, medications) |
| Verbrugge (2012) | (Continues)                                                                                                                                 |
| Deedwania (2011) | (Continues)                                                                                                                                 |

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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; HR, 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        | Confounders                                                                 |
|---------------------|-----------------------------------------------------------------------------|
| Martin (2011)       | None                                                                        |
| Aguilar (2010)      | Age, gender, obesity, ischaemic origin, NYHA                                |
| Sze (2010)          | Gender, NYHA, AF, wide QRS, HR, one of renal function indicators, beta-blocker, diuretics |
| MacDonald (2008)    | 32 covariates (including age, gender, smoking, SBP, DBP, NYHA, LVEF, HR, IHD, stroke, AT, pacemaker, various medications) |
| MacDonald (2008)    | Age, (gender), co-morbidities (including CHD)                                |
| Ghali (2007)        | None                                                                        |
| Ruiz-Ruiz (2007)    | None                                                                        |
| Formiga (2006)      | Age, gender, SBP, PIP                                                        |
| Garcia (2005)       | None                                                                        |
| Domanski (2003)     | Age, gender, BMI, race, Cre, SBP, aetiology of HF, cholesterol, diuretics, vasodilators |
| Shindler (1996)     | Age, gender, race, EF, aetiology of left ventricular dysfunction, NYHA       |
| Harnett (1995)      | 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.
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| Study source | S1 | S2 | S3 | S4 | C1 | O1 | O2 | O3 | Score |
|--------------|----|----|----|----|----|----|----|----|-------|
| Carrasco-Sanchez (2014) | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 7 |
| Cubbon (2014) | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 6 |
| Paoletti (2014) | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 6 |
| Sakata (2014) | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 6 |
| Larina (2013) | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 6 |
| Sarma (2013) | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 4 |
| Verbrugge (2012) | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 5 |
| Deedwania (2011) | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 4 |
| Martin (2011) | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 3 |
| Aguilar (2010) | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 4 |
| Sze (2010) | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 4 |
| MacDonald (2008) | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 4 |
| Macdonald (2008) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Ghali (2007) | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 4 |
| Ruiz-Ruiz (2007) | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 6 |
| Formiga (2006) | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| Garcia (2005) | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 4 |
| Domanski (2003) | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 4 |
| Shindler (1996) | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 4 |
| Harnett (1995) | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 6 |

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