Prognostic Impact of Diabetes on Long-term Survival Outcomes in Patients With Heart Failure: A Meta-analysis

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OBJECTIVE

Several studies have explored the impact of diabetes on mortality in patients with heart failure (HF). However, the extent to which diabetes may confer risk of mortality and hospitalization in this patient population remains imperfectly known. Here we examine the independent prognostic impact of diabetes on the long-term risk of mortality and hospitalization in patients with HF.

RESEARCH DESIGN AND METHODS

PubMed, Scopus, and Web of Science from January 1990 to October 2016 were the data sources used. We included large (*n* ≥1,000) observational registries and randomized controlled trials with a follow-up duration of at least 1 year. Eligible studies were selected according to predefined keywords and clinical outcomes. Data from selected studies were extracted, and meta-analysis was performed using random-effects modeling.

RESULTS

A total of 31 registries and 12 clinical trials with 381,725 patients with acute and chronic HF and 102,036 all-cause deaths over a median follow-up of 3 years were included in the final analysis. Diabetes was associated with a higher risk of all-cause death (random-effects hazard ratio [HR] 1.28 [95% CI 1.21, 1.35]), cardiovascular death (1.34 [1.20, 1.49]), hospitalization (1.35 [1.20, 1.50]), and the combined end point of all-cause death or hospitalization (1.41 [1.29, 1.53]). The impact of diabetes on mortality and hospitalization was greater in patients with chronic HF than in those with acute HF. Limitations included high heterogeneity and varying degrees of confounder adjustment across individual studies.

CONCLUSIONS

This updated meta-analysis shows that the presence of diabetes per se adversely affects long-term survival and risk of hospitalization in patients with acute and chronic HF.

Heart failure (HF) is a progressive clinical syndrome with a major health and socioeconomic impact. The prevalence of HF is high among persons aged 70 years or older (≥10%) and is projected to increase rapidly in the general population worldwide, mainly because of better life expectancy (1). Although some progress has been made in improving survival in hospitalized patients with HF, the rates of hospital readmissions are rising dramatically, especially in the elderly (1).

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Diabetes is very common among patients with HF (occurring in up to 30–40% of these patients) (2). To date, the burden of morbidity and mortality associated with HF and diabetes represents a major challenge for the sustainability of health care systems. In this context, the 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of HF highlighted the clinical importance of establishing a multidisciplinary team–based approach for the management of diabetes among patients with acute or chronic HF (3).

Currently, there is intense debate about the prognostic value of diabetes per se on the long-term risk of mortality and hospitalization in patients with HF. The prognostic impact of diabetes on long-term survival and risk of hospitalization in patients with acute or chronic HF has been investigated in several observational registries and randomized controlled trials (RCTs). However, as will be discussed in more detail below, while the prognostic impact of diabetes on all-cause death and other relevant clinical outcomes was consistent in most RCTs and registries of patients with chronic HF, more conflicting results have been reported in studies performed in patients with acute HF.

We herein report the results obtained by a comprehensive systematic review and meta-analysis of large observational registries and RCTs (totaling nearly 380,000 patients with HF) to gauge precisely the nature and magnitude of the association between diabetes and the risk of long-term mortality and hospitalization in patients with HF.

RESEARCH DESIGN AND METHODS

Registration of Review Protocol

The protocol for this systematic review was registered in advance with PROSPERO (International Prospective Register of Systematic Reviews, no. CRD42016052165).

Data Sources and Searches

Observational registries and RCTs reporting the incidence rates of all-cause death, cardiovascular death, or hospitalization from any cause in patients diagnosed with HF were included in this meta-analysis. Only large studies with a sample size of at least 1,000 patients and with a follow-up duration of at least 1 year were included. Study patients were of either sex with no restrictions in terms of ethnicity, HF etiology, or comorbid conditions. Diagnosis of HF was based on clinical, biochemical, and/or instrumental evidence according to standardized criteria. Diagnosis of diabetes was based on a prior history of the disease (self-reported or physician diagnosis) as well as the use of hypoglycemic medications, and in some cases, it was also based on a fasting plasma glucose level $\geq$7.0 mmol/L or a hemoglobin A_{1c} (HbA_{1c}) level $\geq$6.5% ($\geq$48 mmol/mol).

Exclusion criteria of this meta-analysis were as follows: *1*) reviews, editorials, abstracts, case reports, practice guidelines, and cross-sectional studies; *2*) studies (observational registries or RCTs) of patients with HF with a sample size of $<$1,000 individuals or with a follow-up duration $<$1 year; and *3*) studies that did not report any hazard ratio (HR) and 95% CI for the outcomes of interest.

Included and excluded studies were collected following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (4). Additionally, because most of the included studies were observational in design, we followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for the meta-analysis of observational studies (5).

Data Extraction and Quality Assessment

Relevant studies were identified by systematically searching PubMed, Scopus, and Web of Science from 1 January 1990 to 31 October 2016 (date last searched) using the free-text terms "heart failure" (OR "chronic HF" OR "acute HF") AND "diabetes" AND "mortality," "all-cause death," "cardiovascular death," "hospitalization," or "prognosis." Two authors (M.D. and A.M.) independently examined all titles and abstracts and obtained full texts of potentially relevant articles. Working independently and in duplicate, we read the articles and determined whether they met inclusion criteria. Discrepancies were resolved by consensus, referring back to the original article, in consultation with a third author (G.T.). For all studies, we extracted detailed information on study design, study size, source of data, population characteristics, duration of follow-up, outcomes of interest (with reported HRs and 95% CIs), and list of matching and confounding factors. Additionally, in the case of multiple publications, we included the most up-to-date or comprehensive information.

Two authors (M.D. and A.M.) assessed the risk of bias independently. For observational studies, the quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS), as recommended by The Cochrane Collaboration (6). This scale uses a star system (with a maximum of nine stars) to evaluate a study in three domains: selection of participants, comparability of study groups, and the ascertainment of outcomes of interest. We judged studies that received a score of nine stars to be at low risk of bias, studies that scored seven or eight stars to be at medium risk, and those that scored six or less to be at high risk. Any discrepancies were addressed by a joint revaluation of the original article with a third author (G.T.). Similarly, for the RCTs, we used The Cochrane Collaboration's tool for assessing the risk of bias (7). This tool evaluates seven possible sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. For each individual domain, we classified studies into low, unclear, and high risk of bias.

Data Synthesis and Analysis

Based on data from the eligible studies, the primary outcomes of the meta-analysis were all-cause death, cardiovascular death, and hospitalization in patients with coexistent HF and diabetes, in comparison with their counterparts without diabetes. The secondary outcome of the meta-analysis was the combined end point of all-cause death or hospitalization.

We separately calculated pooled HRs for observational registries and RCTs with the respective 95% CIs. Then, we pooled the two types of study to obtain a combined, overall HR estimate. In the case of studies reporting HRs with varying degrees of adjustment, we always used the fully adjusted HR estimate. Visual inspection of the forest plots was used to investigate the possibility of statistical heterogeneity. Statistical heterogeneity was assessed by the I^2 statistic, which provides an estimate of the percentage of variability across studies that is due to heterogeneity rather than chance alone. According to Higgins and Thompson (8), a rough guide to interpretation is as follows: I^2 values of approximately 25% represent low heterogeneity, approximately 50% represent medium heterogeneity,

and approximately 75% represent high heterogeneity.

The results of studies were pooled, and an overall estimate of effect size was calculated using a random-effects method, as the heterogeneity among studies was highly significant. Publication bias was evaluated using the funnel plot and Egger regression test (9).

The primary analysis of this meta-analysis explored the impact of diabetes on the risk of all-cause death, cardiovascular death, or hospitalization, separately. Given the expected heterogeneity of the eligible studies, sensitivity analyses were also carried out to relate these clinical outcomes with the individual study design characteristics. In particular, based on data from the eligible studies, the independent prognostic impact of diabetes on primary study outcomes was assessed by stratifying the studies according to the type of HF population included (acute HF vs. chronic HF), the study design (RCTs vs. registries), the study country (Europe vs. North America vs. Asia Pacific), the baseline left ventricular ejection fraction (LVEF) (≤35% vs. >35%), whether the studies had eight or nine stars on the NOS scale (i.e., the "high-quality" studies), and whether the studies had full adjustment for covariates. Additionally, we tested for possibly excessive influence of individual studies using a meta-analysis influence test that eliminated each of the included studies at a time. All statistical tests were two sided and used a significance level of $P < 0.05$. We used Stata version 14.0 (StataCorp, College Station, Texas) for all statistical analyses.

RESULTS

Based on the titles and abstracts of 9,418 citations, we identified 65 potentially relevant studies (10–74). Of these, we excluded 22 studies for reasons summarized in Supplementary Fig. 1. Thus, 43 studies (31 observational registries and 12 RCTs) were eligible for inclusion in the meta-analysis and were assessed for quality (Supplementary Tables 1 and 2) (29,31–60,62–73).

Overall, the eligible studies accounted for an aggregate of 381,725 patients with HF (median age 68.9 years; 56% men), including 199,832 patients with acute HF and 181,893 with chronic HF, who were followed for a median period of 3 years (interquartile range 1.5–4.3). The prevalence of diabetes in the whole sample was 26.1% (n = 99,720), including 47,495 (23.8%) patients with acute HF and 52,225 (28.7%) with chronic HF, respectively. The eligible studies were carried out in Europe (Norway, Sweden, Denmark, Belgium, the Netherlands, U.K., Czech Republic, France, Spain, and Italy), North America (U.S. and Canada), Middle East (Saudi Arabia and Israel), and Western Pacific (Australia, Japan, and Singapore).

With regard to the primary study outcomes, the present meta-analysis

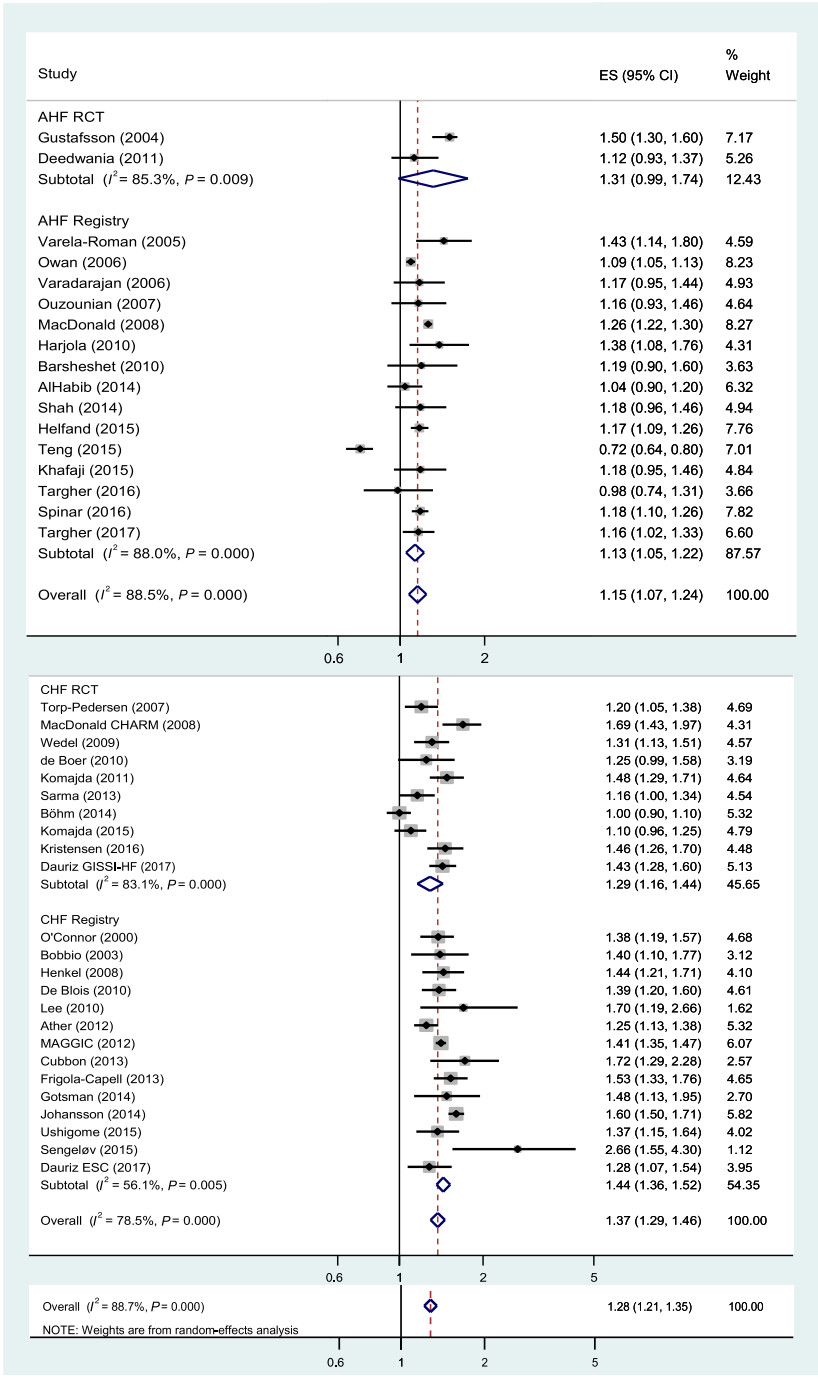

Figure 1—Forest plot and pooled estimates of the effect of diabetes on the risk of all-cause death in 41 eligible studies, stratified by subtype of HF (acute HF [AHF] vs. chronic HF [CHF]) and study design (registries vs. RCTs). CHARM, Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity; ES, effect size; ESC, ESC-HFA Heart Failure Long-Term Registry; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure.

comprised a total of 102,036 all-cause deaths (*n* = 41 studies available), 9,620 cardiovascular deaths (*n* = 11 studies), and 7,276 hospitalizations for any reason but mostly for HF (*n* = 9 studies).

Risk of All-Cause Death

The forest plot shown in Fig. 1 includes a total of 41 studies (12 RCTs [31,41,44,46,50,53,56,60,62,65–67] and 29 observational registries [28,29,32–39,42,43,45,48,49,51,52,54,55,57–59,63,64,68–71,73]) and provides the distribution of studies by estimate of the association between diabetes and the risk of all-cause death in 371,663 patients with HF (26.4% with diabetes), stratified by both HF subtype and study design.

Overall, as shown in the figure, patients with coexistent diabetes and HF showed a 28% increased risk of all-cause death (random-effects HR 1.28 [95% CI 1.21, 1.35]; I^2 = 88.7%) compared with those without diabetes. When this comparison was stratified by HF subtype, presence of diabetes was associated with an increased risk of all-cause death both in patients with chronic HF (24 studies; *n* = 176,651 of whom 29.0% had diabetes; 38,926 total deaths) and in those with acute HF (17 studies; *n* = 195,012 of whom 24.1% had diabetes; 63,110 total deaths): random-effects HR 1.37 (95% CI 1.29, 1.46); I^2 = 78.5% and 1.15 (95% CI 1.07, 1.24); I^2 = 88.5%, respectively. As also shown in Fig. 1, similar results were found when the comparison of risk of all-cause death between patients with and without diabetes was further stratified by study design, except for a borderline significance for RCTs (*n* = 2 studies; random-effects HR 1.31 [95% CI 0.99, 1.74]) performed in patients with acute HF.

The Egger regression test did not show statistically significant asymmetry of the funnel plot, thus suggesting that publication bias was unlikely (Supplementary Fig. 2*A*).

Of note, as shown in Supplementary Table 3, we also obtained similar results by stratifying the included studies according to either study country or baseline LVEF (≤35% vs. >35%) or by limiting the analyses to "high-quality" observational registries (i.e., NOS score ≥7, as specified in Supplementary Table 4). Moreover, eliminating each of the included studies from the analysis had no effect on the overall risk of all-cause death (data not shown). Finally, the simultaneous exclusion of the studies by Teng et al. (70) and by Sengeløv et al. (68) did not change the risk estimates of all-cause death either in the overall cohort (random-effects HR 1.29 [95% CI 1.23, 1.35]) or in the subgroups of patients with chronic HF (random-effects HR 1.36 [95% CI 1.29, 1.45]) or those with acute HF (random-effects HR 1.20 [95% CI 1.13, 1.26]).

Risk of Cardiovascular Death

The risk of cardiovascular death carried by diabetes comorbid with HF is summarized in Fig. 2 as the pooled estimate from 11 studies carried out in patients with chronic HF (five RCTs [46,53,62,66,67] and five registries [40,48,54,64,73]; *n* = 83,989; 27.7% with diabetes) and in those with acute HF (one RCT [31]; *n* = 2,238; 50% with diabetes): overall random-effects HR 1.34 (95% CI 1.20, 1.49); I^2 = 77.1%. The exclusion of the single RCT study of patients with acute HF (31) did not change the pooled risk estimate (random-effects HR 1.36 [95% CI 1.21, 1.53]). Similar results were also found when the comparison of risk of cardiovascular death between patients with chronic HF with and without diabetes was stratified by study design: random-effects HR 1.42 (95% CI 1.23, 1.65) for registries and random-effects HR 1.32 (95% CI 1.11, 1.56) for RCTs (Fig. 2).

Risk of bias analyses reported nonsignificant results (Supplementary Fig. 2*B*).

Risk of Hospitalization

Figure 3 shows the impact of diabetes per se on the risk of hospitalization in nine studies (five RCTs [31,46,53,66,67] and four registries [36,37,39,64]; *n* = 46,283; 36.9% with diabetes) that reported data suitable for the pooled analysis.

Patients with coexistent HF and diabetes had a significantly higher risk of hospitalization compared with those without diabetes (overall random-effects HR 1.35 [95% CI 1.20, 1.50]; I^2 = 76.9%). Further analyses performed by stratifying for HF subtype showed that the coexistence of diabetes was associated with an increased risk of hospitalization in patients with chronic HF who were enrolled both in RCTs (random-effects HR 1.55 [95% CI 1.27, 1.82]; I^2 = 84.8%) and in registries (random-effects HR 1.32 [95% CI 1.18, 1.46]; I^2 = 0%). Conversely, such association did not reach statistical significance in patients with acute HF (random-effects HR 1.15 [95% CI 0.96, 1.37]).

Also shown in Fig. 3, when the analysis was restricted only to the seven studies

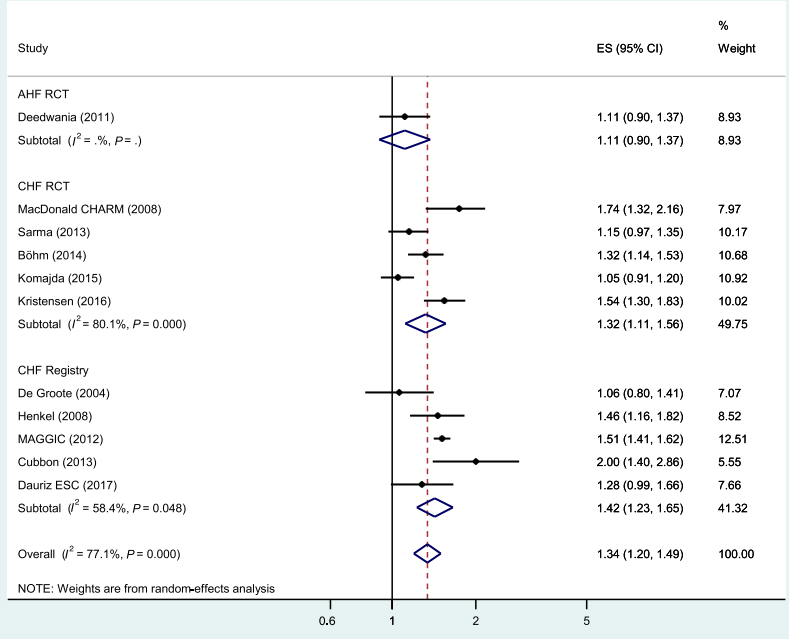

Figure 2—Forest plot and pooled estimates of the effect of diabetes on the risk of cardiovascular death in 11 eligible studies, stratified by subtype of HF (acute HF [AHF] vs. chronic HF [CHF]) and study design (registries vs. RCTs). CHARM, Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity; ES, effect size; ESC, ESC-HFA Heart Failure Long-Term Registry.

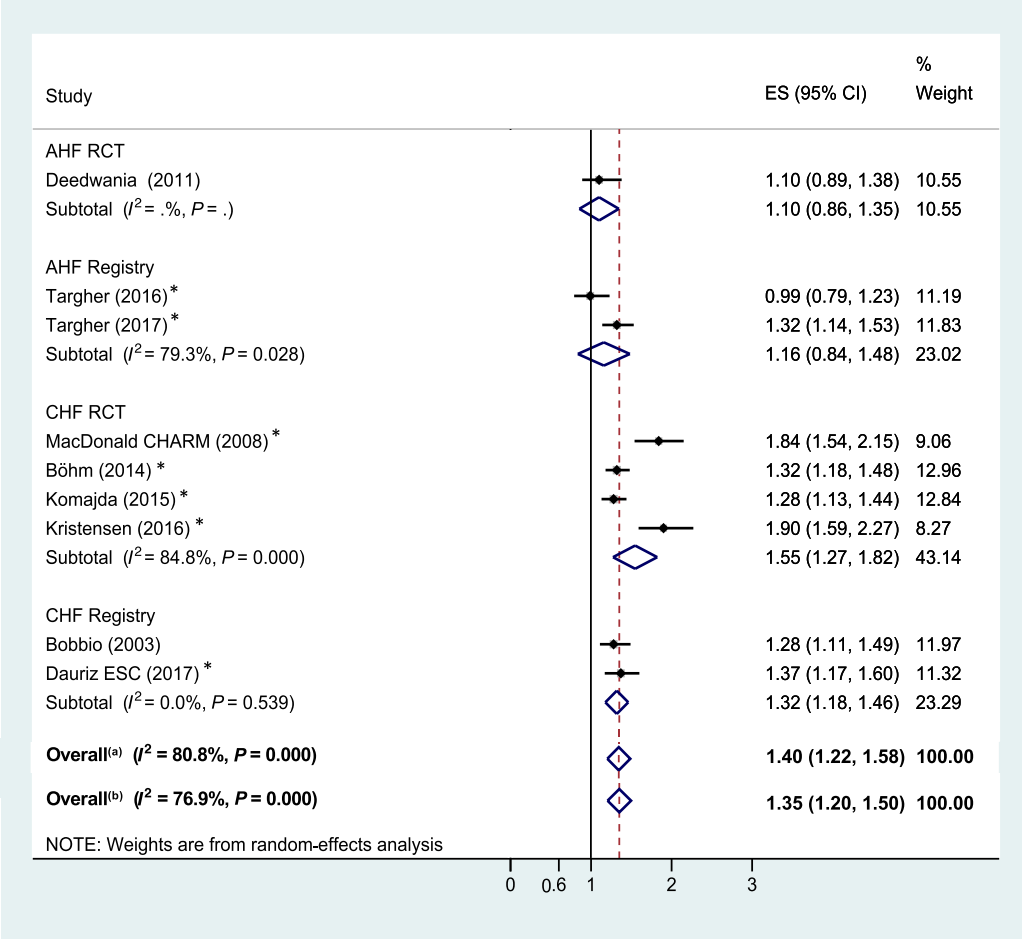

Figure 3—Forest plot and pooled estimates (marked with letter "b") of the effect of diabetes on the risk of hospitalization in nine eligible studies, stratified by subtype of HF (acute HF [AHF] vs. chronic HF [CHF]) and study design (registries vs. RCTs). At the bottom of the forest plot are also reported the pooled estimates (marked with letter "a") of the prognostic effect of diabetes on the risk of hospitalization when the analysis was restricted only to the seven studies (marked with an asterisk) that examined the risk of hospitalization for HF. CHARM, Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity; ES, effect size; ESC, ESC-HFA Heart Failure Long-Term Registry.

(i.e., four RCTs [46,53,66,67] and three registries [36,37,64]) that examined the risk of hospitalization for HF, patients with coexistent HF and diabetes had a significantly higher risk of hospitalization compared with those without diabetes (overall random-effects HR 1.40 [95% CI 1.22, 1.58]; I^2 = 80.8%).

Risk of bias analyses reported no significant results (Supplementary Fig. 2*C*).

As reported in Supplementary Table 3, we also obtained similar results with regard to the risk of cardiovascular death or hospitalization by stratifying the included studies according to either study country or baseline LVEF (≤35% vs. >35%) or by limiting the analyses to "high-quality" studies. Finally, eliminating each of the included studies from the analysis had no effect on the overall risk of cardiovascular death or hospitalization (data not shown).

Risk of the Combined End Point

Figure 4 shows the impact of diabetes per se on risk of the combined end point of all-cause death or hospitalization. Nine studies (six RCTs [46,53,56,60,65,67] and three registries [39,47,58]; *n* = 44,680; 32.8% with diabetes), involving only patients with chronic HF, reported data suitable for the pooled analysis.

Patients with coexistent diabetes and chronic HF had a higher risk of the combined end point compared with those without diabetes (overall random-effects HR 1.41 [95% CI 1.29, 1.53]; I^2 = 78.2%). Similar findings were observed when the statistical analysis was restricted to RCTs (random-effects HR 1.48 [95% CI 1.31, 1.66]; I^2 = 84.6%) or registries (random-effects HR 1.28 [95% CI 1.19, 1.38]; I^2 = 0%), respectively.

As also shown in Fig. 4, when the analysis was restricted to the four eligible studies (i.e., three RCTs [46,53,67] and one observational registry [47]) that examined the combined end point of all-cause death or hospitalization for HF, patients with coexistent diabetes and chronic HF had a higher risk of the combined end point than those without diabetes (overall random-effects HR 1.54 [95% CI 1.28, 1.79]; I^2 = 84.6%).

CONCLUSIONS

This is the most updated and largest systematic review and meta-analysis aimed at examining the independent prognostic impact of diabetes on the long-term risk of mortality and hospitalization in patients with acute and chronic HF.

The main and novel findings of this meta-analysis are as follows: *1*) the presence of diabetes was common among patients with HF (occurring in nearly one-quarter of these patients); *2*) the presence of diabetes was associated with an approximately

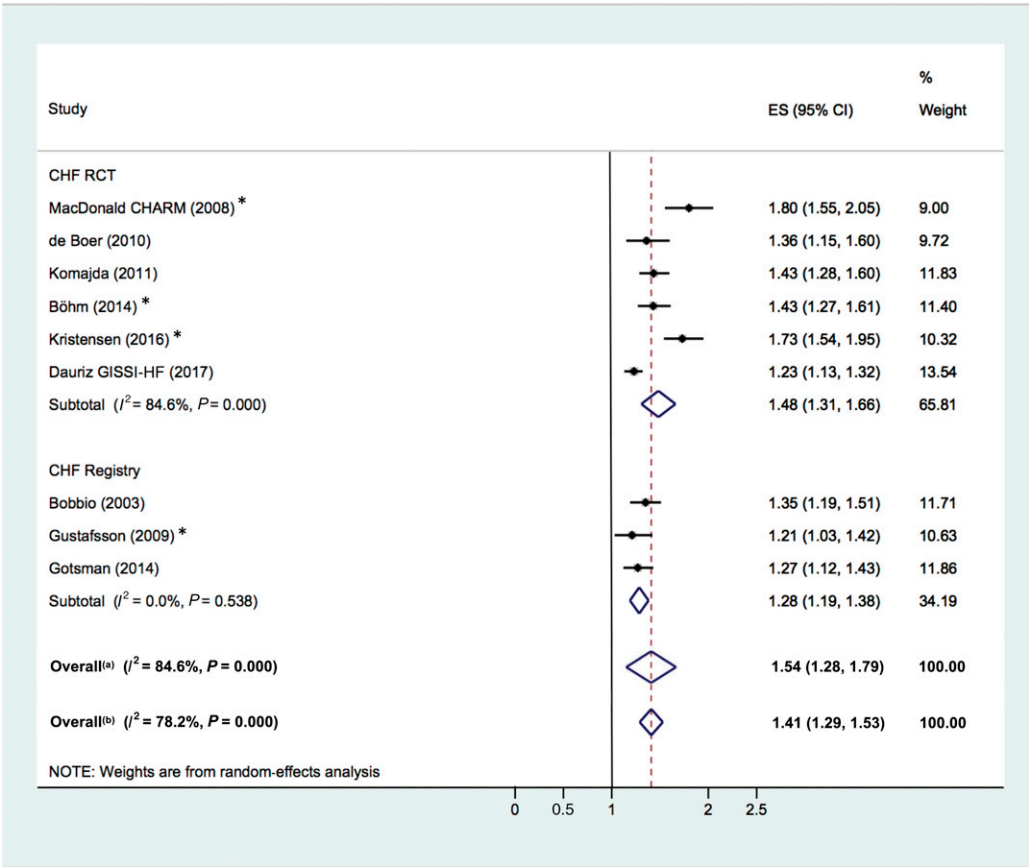

Figure 4—Forest plot and pooled estimates (marked with letter "b") of the effect of diabetes on risk of the combined end point of all-cause death or hospitalization. At the bottom of the forest plot are also reported the pooled estimates (marked with letter "a") of the prognostic effect of diabetes on the risk of hospitalization for HF when the analysis was restricted to the four studies (marked with an asterisk) that examined the combined end point of all-cause death or hospitalization for HF. CHARM, Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity; ES, effect size.

30% increased risk of all-cause death and an approximately 35% increased risk of both cardiovascular death and hospitalization (mostly for HF) over a median follow-up of 3 years; *3*) the association between diabetes and the risk of adverse clinical outcomes remained significant in those studies where analysis was fully adjusted for potentially confounding covariates, and *4*) the adverse impact of diabetes on risk of mortality and hospitalization was greater in patients with chronic HF than in those with acute HF. This latter finding, however, does not detract importance from the adverse impact of diabetes on mortality risk in patients with acute HF, i.e., a subgroup of patients with HF that is typically characterized by remarkably higher rates of all-cause and cardiovascular mortality in the shorter term when compared with patients with chronic HF (36,37,64,75). Notably, the differences observed in mortality risk between patients with acute HF and those with chronic HF are amplified when subgroups of patients with acute HF presenting with de novo or worsening HF are considered separately. As known, patients with worsening HF are typically characterized by a much higher prevalence of comorbidities (76). Additionally, it is important to note that in the setting of acute HF, the presence of diabetes can exert adverse effects on mortality risk during the hospital stay, as elevated admission blood glucose levels have been reported to be associated with higher in-hospital death, especially among those with established diabetes (2,36,37).

Our meta-analysis has some important limitations (strictly inherent to the nature of the included studies) that should be mentioned. First, the data for all-cause mortality are most comprehensive, while data related to hospitalizations are least. Second, although we used a random-effects model, the interpretation of the results of this meta-analysis requires some caution, given the (expected) high heterogeneity observed in the overall analysis. It is plausible to assume that this high heterogeneity largely reflects a mix of different patients with acute or chronic HF with varying degrees of LVEF dysfunction and different etiologies of HF at the study entry and who were enrolled both in RCTs and in observational registries. We systematically explored and identified all these possible sources of statistical heterogeneity using stratified analyses and sensitivity analyses (as detailed in the RESULTS section and Supplementary Table 3). Notably, no relevant differences in risk of mortality and hospitalization were observed by stratifying the patients according to their LVEF ($\leq$35% vs. $>$35%) at baseline. For all clinical outcomes, the lowest degrees of heterogeneity were usually observed for observational registries enrolling patients with chronic HF (with I^2 values = 0% for registries analyzing the impact of diabetes on risk of hospitalization and the combined end point of all-cause death or hospitalization). However, we believe that more detailed analyses

of the causes of heterogeneity will require collaborative pooling of individual participant data from large prospective studies as these become available over time.

Another potential limitation of the meta-analysis, which is also inherent to the nature of the included studies, is that the varying degree of confounder adjustment across the individual studies hampered a systematic assessment of the impact of known risk factors on the outcomes of interest. As shown in Supplementary Tables 1 and 2, some studies reported incomplete adjustments for known risk factors and potential confounding variables; as such, it was impracticable to combine models in studies that adjusted for the same set of potential confounding factors. Other potential limitations include inability to discern differences in mortality risk between specific ethnic populations and patient subgroups (e.g., presence/absence of aortic stenosis or atrial fibrillation, etc.). Additionally, since the diagnosis of diabetes was not always consistent among the included studies, some inaccuracy in the estimated prevalence of diabetes and in the identification of diabetes subtypes may not be excluded, although the vast majority of diabetes cases were likely to be type 2 diabetes. Finally, the follow-up periods were fairly short for some of the eligible studies, at just over 1 year, and most of the eligible studies did not provide detailed information about HbA_{1c} levels, duration of diabetes, use of different classes of glucose-lowering medications at baseline, or HbA_{1c} levels over the follow-up. In light of the recent advancements in the pharmacological options for diabetes (77) and as also recommended by the 2016 ESC guidelines for the management of HF (3), the early recognition of these important diabetes-related variables (which may provide more accurate information about the severity of diabetes) may have potential clinical implications for a more accurate, patient-centered, team-based approach to the management of patients with coexistent HF and diabetes. Further studies will be needed to account for all these diabetes-related variables (especially pharmacologic therapy for diabetes and HbA_{1c} measurements), similar to those recently conducted in the ESC-HFA (Heart Failure Association) Heart Failure Long-Term Registry (36,64) or in the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure) trial (65). Moreover, future large RCTs will be also needed to examine the effects of intensive glucose control on risk of mortality and hospitalization in patients with acute or chronic HF.

Notwithstanding these limitations, the present meta-analysis has also several important strengths. As discussed previously, this meta-analysis provides the most comprehensive assessment to date on the independent prognostic impact of diabetes on the long-term risk of all-cause death, cardiovascular death, and hospitalization in patients with acute or chronic HF. These results, obtained by analyzing more than 100,000 total deaths among more than 380,000 patients with HF (incorporating data from both RCTs and observational registries that are likely to be an accurate reflection of patients commonly seen in clinical practice), provide clear evidence that survival of patients with coexistent HF and diabetes is significantly lower than that of patients without diabetes. Moreover, the large number of total deaths ensured adequate statistical power to quantitatively assess the association between diabetes and long-term survival outcomes. We also employed standardized risk estimates from all eligible studies to allow a consistent combination of estimates across studies. Finally, selective reporting of studies was not a concern in our analyses, as our comprehensive search and contact with investigators made it unlikely that any published report was missed and visual inspection of plots and formal tests demonstrated no statistical evidence of publication bias.

In conclusion, this largest and most comprehensive meta-analysis to date showed that the presence of diabetes per se adversely affects long-term survival and risk of hospitalization in patients with acute and chronic HF. These findings further highlight the urgent need of a multidisciplinary team–based approach to the management of this particularly high-risk patient population.

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