Table 1: Baseline characteristics for included studies

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Pub Year | Number of patients | Source | Follow-up  (years) | HF phenotype | Age (years)  Mean (SD) | Women  (%) | NYHA class  (%) |
| Haass | 2011 | 4,109 | USA | 4.1 | HFpEF | 72 | 60.4 | II/III/IV:  3/9/0 |
| DeShutter | 2014 | 47,866 | USA | 3.1 | HFpEF | 61.6 (15.4) | 55 | - |
| Kapoor | 2010 | 1,236 | USA | 1.0 | HFpEF | 71 (12) | 4 | - |
| Padwal | 2014# | 22,009 | MAGGIC | 3.0 | HFrEF:15,956 patients  HFpEF: 6,053 patients | 66.8 | 32 | II/III: 46/50 |
| Vest | 2015 | 3,811 | USA | 6.0 | HFrEF | 54.1 (11.6) | 100 | I/II/III/IV:  8/31/59/2 |
| Curtis | 2005 | 7,767 | USA & Canada | 3.1 | HFrEF | 64 (11) | 24.6 | I/II/(III or IV):  14.3/54.5/31.3 |
| Zafrir | 2015 | 630 | Israel | 3.3 | HFrEF | 65 (13) | 20 | III or IV: 53 |
| Clark | 2015 | 1,675 | USA | 2.0 | HFrEF | 52.2 (11.6) | 22.6 | III or V: 79.1 |
| Wu | 2009 | 446 | USA | 0.8 | HFrEF | 62.2 | 27.6 | - |
| McAuley | 2007 | 6,876 | USA | 7.5 | HFrEF | 58 (11) | 10 | - |

NYHA class: New York Heart Association functional classification; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction. # the MAGGIC meta-analysis was based on studies originally reported between 1992 and 2006; data collection will have occurred several years earlier [9].

Table 2: Patients comorbidities and mortalities

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | HF phenotype | BMI group | IHD  (%) | Diabetes  (%) | COPD  (%) | Hypertension (%) | Blood pressure (mean)  (Systolic/diastolic) | Creatinine(mg/  dL)/ eGFR  (mean with SD) | All-cause /  CV mortality  N (%) | Reported natriuretic peptide level |
| Haass 2011 | HFpEF | <23.5  23.5-26.4  26.5-30.9  31.0-34.9  >35.0 | - | 18  20  27  31  41 | 10  10  8  9  13 | 76  87  88  92  92 | 134/77  135/78  136/71  138/72  137/73 | 1 (0.3)/68(23)  1(0.3)/73 (23)  1 (0.3)/73 (22)  1(0.4)/72 (23)  1(0.3)/71 (24) | 108(32%)/68(20%)  205(24)/124(15)  287(19)/168(11)  151(19)/93(12)  123(21)/74(12)  (did not report HR) | Yes |
| DeShutter 2014 | HFpEF | <=30  >30 | - | - | - | - | 135/73  138/77 | - | Did not report CV deaths | No |
| Kapoor 2010 | HFpEF | <20  20-25  26-30  31-35  36-40  41-45  >45 | 59  61  57  64  61  57  37 | 33  35  37  57  66  72  59 | - | 82  86  82  89  90  95  87 | Any diastolic dysfunction (%): 67,93,86,  80  85  70  92 | Creatinine>1.5 (%): 41  34  37  40  36  51  37 | Did not report CV deaths | No |
| Padwal 2014 | HFpEF | <22.5  22.5-24.9  25-29.9  30-34.9  >=35 | 40  45  48  44  35 | 11  15  19  28  36 | - | 32  41  48  61  68 | 135/75  137/77  139/80  140/80  142/81 | - | Did not report CV deaths | No |
| HFrEF | <22.5  22.5-24.9  25-29.9  30-34.9  >=35 | 52  57  59  56  47 | 13  17  22  31  39 | - | 25  31  37  49  59 | 124/74  126/76  129/77  132/79  133/80 | - | Did not report CV deaths | No |
| Vest 2015 | HFrEF | 18.5-24.99  25-29.99  >=30 | 46  51  44 | 17  26  38 | - | 44  54  66 | SBP (media): 104  110  110 | - | Did not report CV deaths | No |
| Curtis 2005 | HFrEF | <18.5  18.5-24.9  25-29.9  >=30 | 61  68  74  63 | 18  20  29  41 | - | 40  40  46  59 | SBP (mean): 124  124  127  132 | 1.2  1.3  1.3  1.2 | 72(45)/45(28)  977(38)/840(33)  998(32)/833(27)  550(28)/473(24)  (reported HR) | No |
| Zafrir 2015 | HFrEF | <25.5  25.5-30.4  >30.4 | - | 34  45  55 | - | 49  59  70 | - | 1.40  1.38  1.33 | Did not report CV deaths | No |
| Clark 2015 | HFrEF | 18.5-24.9  25-29.9  >=30 | - | 19  28  33 | - | 32  44  47 | - | - | Did not report CV deaths | No |
| Wu 2009 | HFrEF | 18.5-24.9  25-24.9  >=30 | - | 20  25  37 | - | 55  59  65 | 135/79  134/80  136/80 | Initial/peak creatinine: 1.40/1.45  1.21/1.51  1.32/1.24 | Did not report CV deaths | No |
| McAuley 2007 | HFrEF | 18.5-24.9  25-29.9  >=30 | - | 7  11  16 | - | 38  47  59 | 130/79  133/82  135/84 | - | Showed a negative relation between BMI and CV deaths  (did not report HR) | No |

IHD: Ischaemic heart disease, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, HR: hazard ratio.

Table 3: Baseline medications

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | HF phenotype | BMI group | Diuretic  (%) | Spirono-lactone (%) | ACE inhibitor / ARB (%) | Beta-blocker (%) | Digoxin  (%) | Calcium channel blocker (%) | Lipid-lowering agent (%) | Anti-platelet agent (%) | Statins  (%) | Nitrates (%) |
| Haass 2011 | HFpEF | <23.5  23.5-26.4  26.5-30.9  31.0-34.9  >35.0 | 78  81  82  83  91 | 20  14  15  14  17 | 23  23  25  28  28 | 50  59  59  61  63 | 20  15  13  14  10 | 31  36  39  45  46 | 25  27  33  29  35 | 52  63  61  58  53 | - |  |
| DeShutter 2014 | HFpEF | <=30  >30 | - | - | - | - | - | - | - | - | - |  |
| Kapoor 2010 | HFpEF | <20  20-25  26-30  31-35  36-40  41-45  >45 | 46  49  52  56  59  78  69 | - | 38  52  53  57  52  76  59 | 46  45  45  54  53  59  50 | 17  21  17  15  8  7  7.4 | 29  40  37  42  37  41  37 | - | - | 27  43  47  58  56  54  43 |  |
| Padwal 2014 | HFpEF | <22.5  22.5-24.9  25-29.9  30-34.9  >=35 | 76  76  74  81  86 | 18  17  16  15  20 | 32  35  36  42  36 | 25  34  40  43  42 | 42  35  32  28  25 | - | - | - | - |  |
| HFrEF | <22.5  22.5-24.9  25-29.9  30-34.9  >=35 | 86  83  83  84  89 | 28  25  23  25  25 | 68  72  70  68  65 | 30  38  42  48  49 | 59  53  49  46  46 | - | - | - | - |  |
| Vest 2015 | HFrEF | 18.5-24.99  25-29.99  >=30 | - | - | 91  92  92 | 63  69  73 | 69  62  61 | - | - | - | - |  |
| Curtis 2005 | HFrEF | <18.5  18.5-24.9  25-29.9  >=30 | 94  85  84  89 | - | 96  93  93  94 | - | 42  41  43  44 | - | - | - | - | 42  41  43  44 |
| Zafrir 2015 | HFrEF | <25.5  25.5-30.4  >30.4 | - | - | 85  89  89 | 90  96  94 | - | - | - | - | - | - |
| Clark 2015 | HFrEF | 18.5-24.9  25-29.9  >=30 | 31  41  46 | - | - | 56  64  71 | - | - | - | - | - | - |
| Wu 2009 | HFrEF | 18.5-24.9  25-24.9  >=30 | 38  41  40 | - | 73  76  72 | 73  84  81 | 18  17  8 | 8  6  10 | - | - | 65  70  73 | - |
| McAuley 2007 | HFrEF | 18.5-24.9  25-29.9  >=30 | - | - | - | 15  20  23 | - | 22  23  26 | - | Antihypertensive agent  16  20  23 | - | - |

IHD: Ischaemic heart disease, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction. ‘ –‘ did not report.

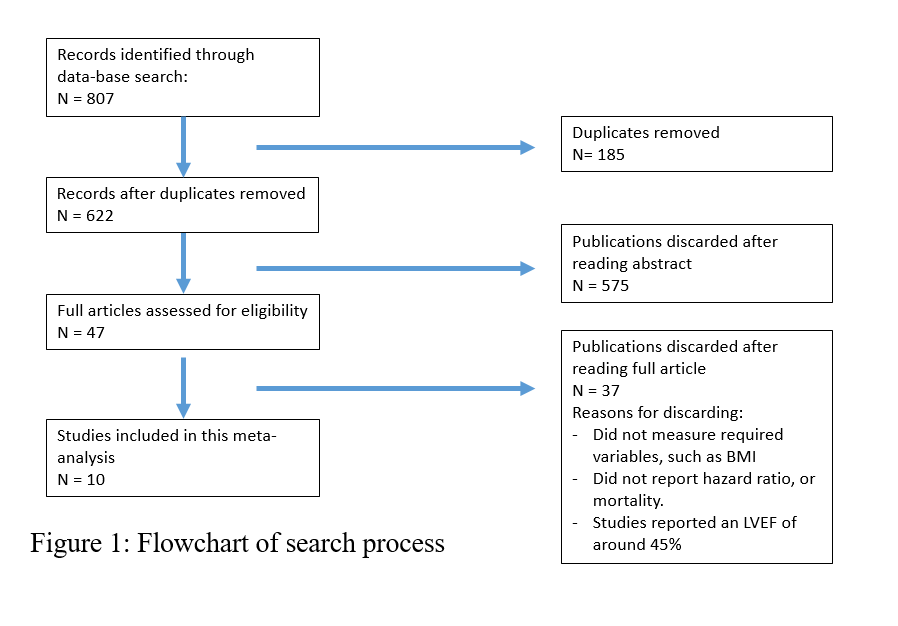
Table 4: Hazard and Odds Ratios for All-cause Mortality by BMI Category for the included studies

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **HFpEF** | | | **HFrEF** | | |
| Study | BMI  Category | HR/OR  (95% CI) | Adjusted covariates | BMI  Category | HR/OR  (95% CI) | Adjusted covariates |
| Haass 2011 | <23.5  23.5-26.4  26.5-30.9  31.0-34.9  >35.0 | 1.44 (1.12-1.84)  1.18 (0.9 - 1.4)  1 (1 – 1)  1.07 (0.90-1.41)  1.31 (1.03-1.67) | Age, sex, NYHA class, heart rate, systolic blood pressure, left ventricular hypertrophy, LVEF, cause of HF, hospitalization for HF within the last 6 months, hypertension, myocardial infarction, stroke, COPD and/or diabetes, use of diuretics, digoxin, a calcium-channel blocker, lipid-lowering agents, an ACE-inhibitor, or a beta-blocker, and NT-proBNP. | - | - | - |
| DeShutter 2014 | <18.5  18.5-20  20-25  25-30  30-35  35-40  >40 | 1.9 (1.6-2.3)  1.5 (1.3 -1.7)  1 (1 - 1)  0.8 (0.7 - 0.9)  0.7 (0.6 - 0.8)  0.8 (0.8 - 1.1)  1.2 (0.9 -1.3) | Left ventricular mass index, age, sex, ejection fraction, and relative wall thickness. | - | - | - |
| Padwal 2014 | <22.5  22.5-24.9  25-29.9  30-34.9  >=35 | 1.12 (0.8 -1.57)  1 (1 -1)  0.74 (0.56 -0.97)  0.64 (0.46 -0.88)  0.71 (0.49 -1.05) | Age, sex, aetiology (ischaemic or non-ischaemic), hypertension, diabetes and baseline blood pressure | <22.5  22.5-24.9  25-29.9  30-34.9  >=35 | 1.31 (1.15 -1.5)  1 (1 – 1)  0.85 (0.76 -0.96)  0.64 (0.55 -0.74)  0.95 (0.78 -1.15) | Age, sex, aetiology (ischaemic or non-ischaemic), hypertension, diabetes and baseline blood pressure |
| Vest 2015 | - | - | - | 18.5-24.99  25-29.99  >=30 | 1 (1 -1)  1.08 (1.03 -1.13)  1.09 (1.04 -1.14) | Age, race, ischemic etiology, NYHA, digoxin, ACE inhibitor/ARB, beta-blocker, diabetes, smoking, HTN, hypercholesterolemia, AF, resting SBP, HRR, peak VO2, peak RER, peak Vt, subsequent transplant or LVAD. |
| Kapoor 2010 | <20  20-25  26-30  31-35  36-40  41-45  >45 | 1.68 (1.04 -2.65)  1.25 (0.92 -1.68)  1 (1 -1)  0.99 (0.71 -1.36)  0.58 (0.35 -0.97)  0.79 (0.44 -1.4)  1.38 (0.74 -2.6) | Age, history, medications, and laboratory and echocardiographic  variables. | - | - | - |
| Curtis 2005 | - | - | - | <18.5  18.5-24.9  25-29.9  >=30 | 1.21 (0.95 -1.53)  1 (1 -1)  0.88 (0.8 -0.96)  0.81 (0.72 -0.92) | Age; sex; LVEF; New York Heart  Association class; history of myocardial infarction; dyspnea; duration of HF symptoms; diabetes; hypertension; HF etiology; blood pressure; heart rate; rales; elevated jugular venous pressure; peripheral oedema. |
| McAuley 2007 | - | - | - | 18.5-24.9  25-29.9  >=30 | 1 (1-1)  0.70 (0.63-0.79)  0.65 (0.57-0.76) | Age, sex, CVD, smoking, hypertension, hypercholesterolemia, myocardial infarction, stroke or surgery for CVD and metabolic equivalent. |
| Zafrir 2015 | - | - | - | <25.5  25.5-30.4  >30.4 | 1.11 (0.79-1.55)  1.02 (0.73-1.44)  1 (1-1) | Sex, hypertension, history of myocardial infarction, left ventricular ejection fraction, permanent/paroxysmal atrial fibrillation,left atrial dimension, QRS width, haemoglobin and creatinine level, NYHA grade and  beta-blockers. |
| Clark 2015 | - | - | - | 18.5-24.9  25-29.9  >=30 | Peak oxygen uptake<=14:  1 (1-1)  0.91(0.66-1.25)  0.64 (0.44-0.91);  Peak oxygen uptake>14:  1 (1-1)  0.75(0.43-1.32)  0.87(0.43-1.75) | Age, diabetes, left ventricular ejection fraction, ACE inhibitor/ARB use, New York Heart Association class, and heart failure etiology (ischemic vs non-ischemic). |
| Wu, 2009 | - | - | - | 18.5-24.9  25-24.9  >=30 | 1 (1-1)  0.63 (0.42-0.94)  1.06 (0.69-1.64) | Sex, age, diabetes, LVEF, blocker prescribed at hospital discharge, angiotensin-converting enzyme inhibitor or angiotensin receptor  blocker prescribed at discharge, initial creatinine, and hemoglobin. |

HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction.

Table 5: The associations between BMI and all-cause mortality by different age groups

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | HFrEF | | | | HFpEF | | | |
| Age groups | N | HR  (95% CI) | I2 (%) | P-heterogeneity  (in the group of studies) | N | HR  (95% CI) | I2 (%) | P-heterogeneity  (in the group of studies) |
| ≥60 | 4 | 0.95 (0.92-0.97)  (p<0.05) | 42% | 0.16 | 4 | 0.93 (0.89-0.97)  (p<0.05) | 76% | 0.006 |
| <60 | 3 | 0.97 (0.91-1.03)  (p>0.05) | 97% | <0.001 | 0 | - | - | - |
|  | | | | | | | | |
| ≥65 | 2 | 0.95 (0.91-1.00)  (p>0.05) | 69 % | 0.07 | 3 | 0.95 (0.92-0.97)  (p<0.05) | 0% | 0.57 |
| <65 | 5 | 0.96 (0.92-1.01)  (p>0.05) | 95% | <0.001 | 1 | 0.89 (0.87-0.91)  (p<0.05) | - | - |



A) HFpEF



B) HFrEF



Figure 2: Adjusted relative risk (HR) for all-cause mortality per 5 units increment in BMI. (A): HFpEF; B): HFrEF). HR and 95% CI are represented by the black dot and horizontal line, respectively; the area of the grey square is proportional to the specific-study weight to the overall meta-analysis.

A): HFpEF (LVEF ≥ 50%)



B). HFrEF (LVEF < 40%)



Figure 3: Association between BMI and all-cause mortality. A reference is set at BMI=23.8 (the top (A): HFpEF; the bottom (B): HFrEF). The middle boxes show the range of BMI for which the relative risk is <1.0 compared to the reference BMI.