2017 Heart Failure Focused Update Data Supplement

(Section numbers correspond to the 2013 full-text guideline.)

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Key Search Terms: Heart Failure, Angiotensin Receptor-Neprilysin Inhibitor, Ivabradine, Angiotensin Receptor Blockers, Angiotensin-Converting Enzyme Inhibitors, Beta Blockers, Angioedema, Natriuretic Peptides, Ferric Carboxymaltose, Iron deficiency, hypertension, sleep apnea, natriuretic peptide biomarker.

Master Abbreviation List:

1° indicates primary; 2°, secondary; ~, approximately; 6MWT, 6 min walk test; ACE, angiotensin-converting enzyme; ACEI indicates angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; ADHERE, Acute Decompensated Heart Failure National Registry; AF, atrial fibrillation; AHI, apnea-hypopnea index; AHRQ, Agency for Healthcare Research and Quality; AIRE, Acute Infarction Ramipril Efficacy; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ALT, alanine aminotransaminase; AMI; acute myocardial infarction; APE, acute pulmonary embolism; ARB, angiotensin-receptor blocker; AKI/ARF, acute kidney injury/acute renal failure; ARNI, angiotensin receptor-neprilysin inhibitor; ASA, aspirin; AST, aspartate transaminase; ATLAS, Assessment of Treatment with Lisinopril and Survival; AUC, area under the curve; AV, atrioventricular; ; BEAUTIFUL, Morbidity-Mortality Evaluation of the If Inhibitor Ivabradine in Patients With Coronary Disease and

Left-Ventricular Dysfunction; BID, twice a day; BL, baseline; BNP, plasma B-type natriuretic peptide; BP, blood pressure; bpm, beats per minute; BSA, body surface area; CABG, coronary artery bypass graft; CAD, coronary artery disease; CANPAP, Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial; CCB, calcium channel blockers; CKD, chronic kidney disease; cGMP, cyclic guanosine monophosphate; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CHD, chronic heart disease; CI, confidence interval; CM, contrast media; CONFIRM-HF, Ferric carboxymaltose evaluation on performance in patients with iron deficiency in combination with chronic heart failure; CONSENSUS Cooperative North Scandinavian Enalapril Survival Study; COPD, chronic obstructive pulmonary disease; CPAP, Continuous positive airway pressure; Cr, creatinine; CRT, cardiac resynchronization therapy; CSA, central sleep apnea; cTnI, cardiac troponin I; CTR, cardiothoracic ratio ; CV, cardiovascular; CVA, cerebrovascular accident; CVD, cardiovascular disease; C/W, compared with; DBP, diastolic blood pressure; DM, diabetes mellitus; DOSE-AHF, Diuretic Optimization Strategy Evaluation in Acute HF; DPB, diastolic blood pressure; ECG, electrocardiography; ED, emergency department; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ELAN-HF, European Collaboration on Acute Decompensated Heart Failure; ESRD, end-stage renal disease; EMPHASIS, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EQ-5D, EuroQoL five dimensions questionnaire; ET, ; FAIR-HF, Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure; FCM, ferric carboxymaltose; FU, follow-up; GDEM, guideline-directed evaluation and management; GDMT, guideline-directed management and therapy; GP, ; HCM, ; HDL, high density lipoprotein; HEAAL study, effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure; HF, heart failure; HF*p*EF, Heart failure with preserved ejection fraction; h/o, history of; HF*r*EF, Heart failure with reduced ejection fraction; HR, hazard ratio; hs-CRP, high sensitivity C-reactive protein; HTN, hypertension; HYVET, Hypertension in the Very Elderly Trial; Hx, history; ICD, implantable cardioverter defibrillator; ID, iron deficiency; IDI, integrated discrimination improvement; IHD, ischemic heart disease; IMPRESS, Comparison of Vasopeptidase Inhibitor, Omapatrilat, and Lisinopril on Exercise Tolerance and Morbidity; I-PRESERVE, Irbesartan in Heart Failure with Preserved Ejection Fraction Study; IQR, interquartile range; ITT, intent to treat; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LCZ, ; LV, left ventricular; LVD, Left ventricular dysfunction; LVEF, left ventricular ejection fraction; LVEDD; left ventricular end-diastolic dimension; LVH, left ventricular hypertrophy; MACE, major adverse cardiac event; MI, myocardial infarction; MR-proANP, ; MR-proADM, ; MRA, mineralocorticoid receptor antagonists; MTD, maximal tolerated dose; MV, mitral valve; MWT, minute walk test; N/A, not available; NEAT-HFpEF, Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction; NEP, neutral endopeptidase; NNH, number needed to harm; NNT, number needed to treat; NP, natriuretic peptide; NRI, net reclassification improvement; NS, nonsignificant; NSTEMI, non-ST-elevation myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OCTAVE, The Omapatrilat Cardiovascular Treatment vs. Enalapril; ONTARGET, The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; OR, odds ratio; OSA, obstructive sleep apnea; OVERTURE, Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events; PAD, peripheral artery disease; PARADIGM-HF, Prospective Comparison of ARNI With ACE to Determine Impact on Global Mortality and Morbidity in Heart Failure; PARAMOUNT, Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction; PAP, positive airway pressure; PCI, percutaneous coronary intervention; PCP, Primary Care Physician; PDE, phosphodiesterase; PEP-CHF, Perindopril in Elderly People With Chronic Heart Failure; PGA, patient global assessment; PPM, permanent pacemaker; PSG, polysomnography; PTCA, percutaneous transluminal coronary angioplasty; PONTIAC, NT-proBNP Guided Primary Prevention of CV Events in Diabetic Patients; PRIMA, Can Pro-Brain-Natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality?; PROTECT, ProBNP Outpatient Tailored Chronic Heart Failure Therapy; pts, patients; PVD, peripheral vascular disease; QoL, quality of life; RAAS, renin-angiotensin-aldosterone system; RAS, renin-angiotensin system; RCT, randomized controlled trial; RED-HF, Reduction of events by darbepoetin alfa in heart failure; RELAX, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure With Preserved Ejection Fraction; ROC, receiver-operating characteristic; RR, relative risk; SBP, systolic blood pressure; SCr, serum creatinine; SERVE-HF, Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure; SHEP, Systolic Hypertension in the Elderly Program; SHIFT, Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial; SIGNIFY, Study Assessing the Morbidity–Mortality Benefits of the If Inhibitor Ivabradine in Patients with Coronary Artery Disease; SOB, shortness of breath; SPRINT, Systolic Blood Pressure Intervention Trial; SR, systematic review; SSS, sick sinus syndrome; STARBRITE, the Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting; STARS-BNP, Systolic Heart Failure Treatment Supported by BNP; STEMI, ST–elevation myocardial infarction; STOP-HF, St. Vincent's Screening to Prevent Heart Failure; SUPPORT, Supplemental Benefit of ARB in Hypertensive Patients With Stable Heart Failure Using Olmesartan; SURVIVE, Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support; TIA, transient ischemic attack; TIME-CHF, ; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; TRANSCEND, the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease; TSAT, transferrin saturation; UA, unstable angina; UL, ; UPSTEP, Use of Peptides in Tailoring Heart Failure Project; VF, ventricular fibrillation; VHD, valvular heart disease VT, ventricular tachycardia; and w/o, without.

Data Supplement A. RCTs and Meta-analyses With Biomarkers (Section 6.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Biomarker Studies Pertinent to Stage A / B HF Patients					
PONTIAC Huelsmann et al. 2013 (1) 23810874 ● Medical University of Vienna ● Roche Pharma AG	**Aim:** To assess the effectiveness of neurohumoral therapy for the prevention of cardiac events in pts with type 2 DM with increased biomarker NT-proBNP **Study type:** RCT **Size:** 300	**Inclusion criteria:** Pts with type 2 DM, age ≥18 y, elevated NT-proBNP (≥125 pg/mL) **Exclusion criteria:** Free of heart disease, chronic infections or malignancies, systemic cortisone treatment, renal replacement therapy, nondiabetic conditions that lowered life expectancy to <1 y and absence of reliable contraception in women of childbearing age	**Intervention:** Individualized up-titration of RAS antagonists and beta blockers in addition to diabetes treatment (150), treated at cardiology clinic **Comparator:** "Control" group treated for diabetes, (150), treated at diabetes care units	**1° endpoint:** • Hospitalization or death due to cardiac disease following 24 mo • Results: Significant reduction of 1° endpoint in intervention group (HR: 0.351; 95% CI: 0.127–0.975; p=0.044) **1° Safety endpoint:** • BP was significantly reduced in both intervention and control (p<0.05); heart rate was only reduced in the intensified group (p=0.004)	• All-cause hospitalizations, HF hospitalizations and unplanned CV hospitalizations or death (p<0.05 reduction) • Study limitations: Absence of pt randomization for treatment, pt population mainly Caucasian, statistical analysis done without adjustment of co-variates • Pts treated with a RAS antagonist/beta-blocker and the dosage reached higher in intensified group (p<0.0001) • No difference in NT-proBNP levels
STOP-HF Ledwidge et al. 2013 (2) 23821090 ● Heartbeat Trust, Health Research	**Aim:** To establish efficacy of BNP screening and collaborative care in at-risk population in reducing newly	**Inclusion criteria:** Pts ≥40 y, and history of HTN (on meds ≥1 mo), hypercholesterolemia, obesity, vascular disease including	**Intervention:** BNP screening at BL and annually and protocol referral for BNP ≥50 pg/mL for echocardiography and collaborative care. (697)	**1° endpoint:** • LV dysfunction (systolic: LVEF <50% or diastolic: E/E' ratio >15) with or without newly diagnosed HF(with symptoms of HF requiring admission to	•Emergency hospitalizations for major MACE [40 vs. 22 (0.60 OR; 95% CI: .45-0.81; p=.002)]] •CV investigations more likely to be done in the intervention group with BNP levels ≥50 pg/mL •Increase in RAAS agents in the

Board of the Irish Government; and European Commission Framework Programme. The Heartbeat Trust received unrestricted grants from Pfizer, A. Menarini, Alere, Roche,Takeda, Abbott, Covidien, and Servier.	diagnosed HF and prevalence of significant LV systolic and /or diastolic dysfunction. **Study type:** RCT (unblinded) **Size:** 1,374	CAD,, cerebrovascular disease or peripheral vascular disease, DM, arrhythmia therapy, or moderate to severe valvular disease **Exclusion criteria:** Established LV systolic dysfunction, symptomatic HF, diagnosis compromising survival	**Comparator:** Usual 1° care (677)	hospital, confirmed by d/c summary) • 59 (8.7 %) vs. 37 (5.3%) (0.55 OR; 95% CI: 0.37–0.82; p=0.003)	intervention group • In the subgroup with BNP levels ≥50 pg/mL, increase in BNP levels in the intervention group was ~1/2 of that in the control group • The results might not be applicable to general population (single center), non-blinding introduces bias. Event rate was lower than expected. Cost-effectiveness unclear. Incremental value of and cut-off of BNP may change in population studied.
Meta-Analyses or SRs of RCTs of NP Guided Therapy in Stage C HF					
Brunner-La Rocca et al. 2015 (3) 26419999	**Aim:** To assess which HF pts benefit from NT-pro BNP therapy **Study type:** Meta-Analysis **Size:** 2,137 pts from 8 NT-proBNP trials	**Inclusion criteria:** Studies that included individual pt data HF*p*EF and HFrEF. EF ≤45% **Exclusion criteria:** Pts with unknown LVEF, STARBRITE study, 1° meta-analyses that aggregated data	**Intervention:** (NT-pro)BNP-guided therapy and HF*r*EF (1,731) **Comparator:** (NT-pro)BNP-guided therapy and HF*p*EF (301)	**1° endpoint:** • All-cause mortality and admission for HF Results: • Lower mortality in HF*r*EF with guided treatment (HR: 0.78; 95% CI: 0.62–0.97; p=0.03). • Lesser HF admissions in HF*r*EF (HR: 0.80; 95% CI: 0.67–0.97; p=0.02)	• NT pro BNP-guided treatment harmful in HF*p*EF without HTN and in pts with renal failure • Limitations: Bias due to exclusion of aggregate data, Lack of specific testing for diagnosis of comorbidities, absence of comorbidity index, insufficient sample size for pts with HF*p*EF, treatment management aspects unaddressed and statistical tests are not powerful
Don-Wauchope et al. 2015 (4) 25448029	**Aim:** Review evidence of SRs regarding utility of NPs in clinical practice. **Study type:** Review of SRs	**Inclusion criteria:** SRs that authors were aware of through their participation in an AHRQ comparative effectiveness review.	**Intervention:** NP-guided therapy **Comparator:** Clinically-guided care	**1° endpoint** • 8 SRs assessed all-cause mortality and "generally found there was a benefit." • 4 SRs examined all cause-hospitalization and did not find decrease with NP-	• Underlying SRs largely comprised analysis of the same RCTs. • Results were qualitative.

	Size: 9 reviews	**Exclusion criteria:** N/A		guided therapy • 4 SRs assessed HF hospitalization and "consistently" found a significant reduction with NP-guided therapy	
Xin W. et al. 2015 (5) 24888383	**Aim:** To assess the effects of NP-guided treatment of chronic HF on outcomes **Study type:** Meta-analysis **Size:** 14 studies, 3,004 pts	**Inclusion criteria:** Prospective RCTs with adult HF pts comparing the effects of BNP or NT-proBNP-guided therapy with clinically guided therapy	**Intervention:** BNP or NT-proBNP-guided therapy (1,503) **Comparator:** Clinically guided therapy (1,501)	**1° endpoints:** • All-cause mortality, HF hospitalization, all-cause hospitalization, safety (adverse events) **Results**: • Compared with clinical group, BNP-guided treatment significantly decreased the risk of HF-related hospitalization (RR: 0.79; 95% CI: 0.63–0.98; p=0.03), **although did not significantly affect the risk of all-cause mortality** (RR: 0.94, 95% CI: 0.81–1.08, p=0.39) or all-cause hospitalization (RR: 0.97; 95% CI: 0.89–1.07; p=0.56). **1° Safety endpoint:** • NP-guided therapy was not associated with increased risk for serious adverse events.	• BNP-guided therapy improved LV systolic function in HF pts (LVEF: weighted mean difference=2.80%, 95% CI: 0.90–4.69%; p=0.01), • But did not significantly affect NYHA class or QoLs (p=ns)
Troughton RW et al. 2014 (6) 24603309	**Aim:** To assess the effects of NP-guided treatment of chronic HF on outcomes **Study type:** Meta-analysis	**Inclusion criteria:** RCTs reporting all-cause mortality and comparing BNP-guided treatment of HF with clinically guided treatment and 1 study (PROTECT trial) that did not	**Intervention:** BNP-guided therapy (1,006) **Comparator:** Clinically guided therapy (994)	**1° endpoint:** • All-cause mortality Results: • All-cause mortality was significantly reduced by NP-guided treatment [HR: 0.62 (0.45–0.86); p=0.004]	• HF hospitalizations were reduced in the NP-guided group, compared with clinically guided pts [HR: 0.80 (0.67–0.94); p=0.009] as were CV admissions [HR: 0.82 (0.67–0.99); p=0.048] • Each of the included RCTs was relatively small and 2 trials did not

	Size: 11 studies, 2,000 pts	report mortality (11 studies, 9 with individual pt data) **Exclusion criteria:** For 2 studies, data from the 3rd ('usual care') groups were not included.		• Significant interaction between age and treatment efficacy (p=0.028), with a survival benefit for BNP-guided vs. clinical treatment in pts <75 y [HR: 0.62 (0.45–0.85); p=0.004] but not in pts ≥75 y [HR: 0.98 (0.75–1.3); p=ns]	provide individual pt data.
De Vecchis et al. 2014 (7) 24522083	**Aim:** To assess the effects of NP-guided treatment of chronic HF on outcomes **Study type:** Meta-analysis **Size:** 6 studies, 1,775 pts	**Inclusion criteria** • RCT to a strategy of titrating drug therapy based on the level of a circulating NP (BNP or NT-proBNP) compared to clinical conventional criteria, and they reported all-cause mortality. Should have included >60 pts and its follow-up should have been longer than 90 d.	**Intervention:** BNP or NT-proBNP-guided therapy **Comparator:** Clinically guided therapy	**1° endpoint:** • Combined endpoint of all-cause mortality and HF hospitalization **Results:** NP-guided therapy for outpatients with HF was shown to be associated with a decreased risk of death and HF hospitalizations (OR: 0.64; 95% CI: 0.43–0.95; p=0.026)	Limitations: • Each of the included RCTs was relatively small • Benefit was not seen in some of the studies
Balion et al. 2014 (8) 25074674	**Aim:** To assess the effects of NP-guided treatment of chronic HF on outcomes **Study type:** SR **Size:** 9 RCTs; 2,104 pts	Meta-analysis was not done due to study heterogeneity.	**Intervention:** BNP or NT-proBNP-guided therapy (1,503) **Comparator:** Clinically guided therapy (1,501)	**1° Outcome:** • Review: Overall, there was a wide variation in study design and how parameters were reported including pt selection, BL characteristics, therapy goals, BNP/NT-proBNP cutpoint, and outcome types. • The strength of evidence for the outcome of mortality, reported in 7 studies, was found to be low due to inconsistency and	N/A

				imprecision.	
Savarese et al. 2013 (9) 23472172	**Aim:** To determine whether NP-guided (BNP or NT-proBNP) therapy, compared to clinically guided therapy, improves outcomes **Study type:** Meta-analysis **Size**: 12 trials enrolling 2,686 participants (730 in BNP, 1,956 in NT-proBNP related trials)	**Inclusion criteria:** All randomized trials reporting clinical endpoints (all-cause mortality and/or HF related hospitalization and/or all-cause hospitalization) with comparison of BNP or NT-proBNP guided therapy vs. a control group in chronic HF pts	**Intervention:** • BNP-guided therapy: BNP-guided: 373 • NT-proBNP guided: 872 **Comparator:** Clinically guided therapy • BNP group control 357 • NT-proBNP group control 1,084 • Separate analyses on pts ≤ or >75 y using data reported in 3 trials.	**1° endpoints** • All-cause mortality, all-cause hospitalization, HF hospitalization Results: NP-guided therapy (either BNP or NT-proBNP) significantly reduced all-cause mortality (OR: 0.738; 95% CI: 0.596–0.913; p=0.005) and HF related hospitalization (OR: 0.554; 95% CI: 0.399–0.769; p=0.000), but not all-cause hospitalization (OR: 0.803; 95% CI: 0.629–1.024; p=0.077)	• When separately assessed, NT-proBNP-guided therapy reduced all-cause mortality (OR: 0.717; 95% CI:0.563–0.914; p=0.007) and HF hospitalization (OR: 0.531; 95% CI: 0.347–0.811; p=0.003), but not all-cause hospitalization (OR: 0.779; CI:0.414–1.465; p=0.438), whereas BNP-guided therapy did not significantly reduce all-cause mortality (OR: 0.814; CI:0.518–1.279; p=0.371), HF related hospitalization (OR: 0.599; 95% CI: 0.303–1.187; p=0.14) or all-cause hospitalization (OR: 0.726; 95% CI:0. 0.509 – 1.035; p=0.077) • Analysis from 3 trials showed the composite outcome of all-cause mortality and HF hospitalization was significantly reduced by NP-guided therapy in younger pts (≤75 y) (OR: 0.449; 95% CI: 0.207–0.973; p=0.043), but not in older pts (>75 y) (OR: 0.800; 95% CI: 0.423–1.513; p=0.5).
Li et al. 2013 (10) 23602555	**Aim:** To assess the effects of NP-guided treatment of chronic HF on all-cause mortality and HF hospitalization	**Inclusion criteria** Studies with >40 pts and involved comparison of BNP-guided vs. guideline-guided drug therapy of the pts with chronic HF in the outpatient	**Intervention:** BNP-guided therapy **Comparator:** Clinically guided therapy	**1° endpoint:** • Combined end point of all-cause mortality and HF hospitalization Results: Significantly decreased risk of all-cause mortality (RR: 0.83; 95% CI: 0.69–0.99; p=0.035; and HF	In the subgroup analysis, HF rehospitalization was significantly decreased in the pts <70 y (RR: 0.45; 95% CI: 0.33–0.61; p=0.000; or with BL higher BNP (≥2114 pg/mL) (RR: 0.53; 95% CI: 0.39–0.72; p=0.000)

	Study type: Meta-analysis **Size:** 11 studies, 2,414 pts	setting		rehospitalization (RR: 0.75; 95% CI: 0.62–0.91; p=0.004; in the BNP-guided therapy group.	
Felker et al. 2009 (11) 19699866	**Aim**: To determine whether titration of therapy based on NP measurements improves mortality in chronic HF **Study type:** Meta-analysis **Size:** 6 studies; 1,627 pts	**Inclusion criteria** Prospective RCTs of pts with chronic HF randomized pts to a strategy of titrating medical therapy based on the level of a circulating biomarker compared to a parallel control group, reporting all-cause mortality	**Intervention:** BNP-guided therapy **Comparator:** Clinically guided therapy	**1° endpoint:** • All-cause mortality Results: Significant mortality advantage for biomarker-guided therapy (HR: 0.69, 95% CI: 0.55–0.86) compared to control	N/A
Porapakkham et al. 2010 (12) 20308637	**Aim**: To determine whether BNP guided therapy improves CV outcomes in chronic HF **Study type:** Meta-analysis **Size:** 8 studies; 1,726 pts	**Inclusion criteria** Eligible RCTs were those that enrolled >20 pts and involved comparison of BNP-guided drug therapy vs. usual clinical care of the pt with chronic HF in an outpatient setting	**Intervention:** BNP-guided therapy **Comparator:** Clinically guided therapy	**1° endpoint:** • All-cause mortality Results: Significantly lower risk of all-cause mortality (RR: 0.76; 95% CI: 0.63–0.91; p=0.003) in the BNP-guided therapy group compared with the control group	• In pts <75 y, all-cause mortality was significantly lower in the BNP-guided group (RR: 0.52; 95% CI: 0.33–0.82; p=0.005). • No reduction in mortality with BNP-guided therapy in pts ≥75 y (RR: 0.94; 95% CI: 0.71–1.25; p=0.70). • All-cause hospitalization and survival free of any hospitalization was not significantly different between groups (RR: 0.82; 95% CI: 0.64–1.05; p=0.12 and RR: 1.07; 95% CI: 0.85–1.34; p=0.58, respectively). • Additional % pts achieving target doses of ACE-inhibitors and beta blockers 21% and 22% in the BNP group and 11.7% and 12.5% in the control group, respectively.
RCTs of NP Guided Therapy in HF					

Troughton et al. 2000 (13) 10791374	**Aim:** To assess the effects of NT-proBNP-guided treatment of chronic HF on outcomes **Study type:** RCT **Size:** 69 pts	**Inclusion criteria:** Ambulatory pts with LVEF <40% and symptomatic HF (NYHA II-IV) **Exclusion criteria:** Pts with unknown LVEF **Follow up :** Minimum 6 mo (median 9.5 mo)	**Intervention:** (NT-pro)BNP-guided therapy with a target of NT-proBNP level <200 pmol **Comparator:** Standardized clinical assessment (clinical group)	**1° endpoints:** • Death, CV hospitalization and outpatient HF event **Results**: • Fewer CV events (death, hospitals, or HF decompensation) in the NT-proBNP group than in the clinical group (19 vs. 54; p=0.02) • At 6 mo, 27% of pts in the BNP group and 53% in the clinical group had experienced a first CV event (p=0.034).	• Changes in LVEF, QoL, renal function, and adverse events were similar in both groups. • N-BNP-guided treatment of HF reduced total CV events, and delayed time to first event compared with intensive clinically guided treatment. • NP was reduced significantly and NP guidance changed therapy
STARS-BNP Jourdain et al. 2007 (14) 17448376	**Aim:** To evaluate the prognostic impact of a therapeutic strategy using plasma BNP **Study type:** RCT **Size:** 220 pts	**Inclusion criteria:** Ambulatory NYHA class II to III pts considered optimally treated **Exclusion criteria:** N/A **Follow up :** median 15 mo	**Intervention:** BNP-guided therapy Target : BNP <100 pg/mL **Comparator:** Medical treatment according to either current guidelines (clinical group)	**1° endpoint** • HF-related death or hospital stay for HF **Results:** • Mean dosages of ACE inhibitors and beta blockers significantly higher in the BNP group (p<0.05), • BNP-guided strategy reduced the risk of HF related death or hospital stay for HF (24% vs. 52%, p<0.001), mainly obtained through an increase in ACE inhibitor and beta blocker dosages.	• NP guidance changed therapy • Unknown whether BNP-guided therapy resulted in reduction in BNP levels
TIME-CHF Pfisterer et al. 2009 (15) 19176440	**Aim:** To compare 18-mo outcomes of N-terminal BNP-guided vs. symptom guided HF therapy	**Inclusion criteria:** Ambulatory HF pts 60 y with systolic HF (LVEF ≤45%), NYHA class of II or greater, prior HF hospitalization within	**Intervention:** Uptitration of guideline-based treatments to BNP level of ≤2 times of UL (BNP-guided therapy) **Targets**:	**1° endpoints:** • 18 mo survival free of all-cause hospitalizations **Results**: • N-terminal BNP and	• Survival free of hospitalization for HF was higher among those in the N-terminal BNP-guided group (72% vs. 62%, respectively; HR: 0.68 [95% CI: 0.50–0.92]; p=0.01). • N-terminal BNP-guided therapy

	Study type: RCT **Size:** 499 pts	1 y, and N-terminal BNP level of ≥2 times the upper limit of normal.	NT-proBNP <400 pg/mL if age <75 y, NT-proBNP <800 pg/mL if 75 y **Comparator:** Uptitration of guideline-based treatments to reduce symptoms to NYHA class of II or less (symptom guided therapy)	symptom-guided therapy resulted in similar rates of survival free of all-cause hospitalizations (41% vs. 40%, respectively; HR: 0.91 [95% CI: 0.72–1.14]; p=0.39) • BNP guidance changed therapy (higher doses of ACE inhibitors, ARB, Beta blockers and higher use of spironolactone) • NT-ProBNP levels were not different between groups	improved outcomes in pts 60 to 75 y of age but not in those ≥75 y of age (p<0.02 for interaction). • QoL improvements were similar in both the N-terminal BNP-guided and symptom guided strategies
BATTLESCARRED Lainchbury et al. 2009 (16) 20117364	**Aim:** to compare the effects of NT-proBNP)-guided therapy with those of intensive clinical management and with usual care **Study Type:** RCT (Australia hospitals) **Size:** 364 pts	**Inclusion criteria:** Pts admitted to a single hospital with HF, NT-proBNP >50 pmoL/l or 400 pg/mL.(included HF*p*EF)	**Intervention:** Outpatient post d/c therapy guided by NT-proBNP levels Target: NT-proBNP <150 pmoL/l (1,270 pg/mL) **Comparators:** Therapy guided by intensive clinical management, **or** according to usual care	**1° endpoints:** Mortality **Results:** 1-y mortality was less in both the hormone (9.1%) and clinically-guided (9.1%) groups compared with usual care (18.9%; p=0.03)	• 3 y mortality was selectively reduced in pts ≤75 y receiving hormone guided treatment (15.5%) compared with either clinically managed treatment (30.9%; p=0.048) or usual care (31.3%; p=0.021). • NP guidance changed therapy • NT-ProBNP levels were not different between groups
Berger et al. 2010 (17) 20170790	**Aim**: To investigate whether the addition of NT-proBNP-guided, intensive pt management to multidisciplinary care improves outcome in pts following hospitalization due to HF	**Inclusion criteria:** Pts admitted to a hospital with HF, NYHA III or IV on admission, Cardiothoracic Index>0.5 or LVEF <40%	**Intervention:** Outpatient post discharge discontinue • BM: NT-proBNP-guided, intensive up-titration of medication by HF specialists in high-risk pts. • Target: NT-proBNP (<2,200 pg/mL) **Comparators** • Multidisciplinary care: 2 consultations from an HF	**1° endpoints:** Hospitalization **Results**: • Pt management reduced HF hospitalization (488 D) compared with the multidisciplinary care (1254 D) and usual care (1,588 d) groups (p<0.0001) • Combined end point of death or HF rehospitalization was lower	• NT-ProBNP levels were not different between groups: Pt management group had the highest proportion of RAAS inhibition triple-therapy • Death rate was similar between the pt management (22%) and multidisciplinary care groups (22%), but was lower compared with the usual care group (39%; vs. pt management: p<0.02; vs. multidisciplinary care: p<0.02)

	Study Type: RCT (8 Viennese hospitals) **Size:** 278 pts		specialist-therapeutic recommendations and home care by a HF nurse • Usual care	in the BM (37%) than in the multidisciplinary care group (50%; p<0.05) and in the multidisciplinary care than in the usual care group (65%; p=0.04) • NT-ProBNP levels were lowered in guided pt management arm	
PRIMA Eurlings et al. 2010 (18) 21144969	**Aim**: To assess whether management by an individualized NT-proBNP target would lead to improved outcome compared with HF management guided by clinical assessment alone **Study Type:** RCT **Size:** 345 pts	**Inclusion criteria:** Hospitalized HF pts with for decompensated, symptomatic HF with NT-proBNP levels >1,700 pg/mL at admission (included HF*p*EF)	**Intervention:** After discharge discontinue out pt management guided by an individually set NT-proBNP (n=174) defined by the lowest level at discharge or 2 wk thereafter. **Comparators:** Clinically-guided outpatient management (n=171)	**1° endpoints:** Number of d alive outside the hospital after index **Results:** Management guided by NT-proBNP target did not significantly improve the 1° endpoint p=0.49)	• In the NT-proBNP-guided group mortality was lower, as 46 pts died (26.5%) vs. 57 (33.3%) in the clinically guided group, but this was not statistically significant (p=0.21) • Individualized NT-proBNP target increased the use of HF medication (p=0.006)
SIGNAL HF Trial Persson et al. 2010 (19) 20876734	**Aim**: To investigate if NT-proBNP-guided therapy in HF pts in 1° care would improve clinical outcomes over and above treatment according to guidelines **Study Type:** RCT (Sweden 1° care centers)	**Inclusion criteria:** Ambulatory HF pts NYHA class II-IV, LVEF <50% and NT-proBNP levels males >800, females >1,000 ng/	**Intervention:** Structured treatment of HF according to guidelines with or without NT-proBNP monitoring • Target: At least a 50% reduction from BL NT-proBNP	**1° endpoints:** Composite endpoint of d alive, d out of hospital and symptom score **Results:** There were no differences between the groups concerning either the 1° endpoint (p=0.28) or its components (CV) death, p=0.93; CV hospitalization, p=0.88; or symptom score, p=0.28	• Treatment doses of beta blockers and RAS blockers were markedly increased towards target doses a similar degree in **both** groups

	Size: 252 pts				
STARBRITE Trial Shah et al. 2011 (20) 21807321	**Aim:** Whether outpatient diuretic management guided by BNP and clinical assessment better compared with clinical assessment alone **Study Type:** Multicenter (3) RCT **Size**: 130	**Inclusion criteria** Hospitalized HF pts with LEVF ≤35% **Exclusion criteria**: Serum creatinine >3.5 mg/dL and ACS	**Intervention:** Outpatient post discharge BNP and clinical assessment guided therapy **Comparator:** Clinical assessment alone.	**1° endpoints:** Composite endpoint of d alive and d out of hospital, **Results:** No significant difference HR: 0.72; 95% CI: 0.41–1.27; p=0.25	• Change in serum creatinine, or change in SBP not different • BNP strategy pts received significantly more ACE inhibitors, beta blockers
PROTECT Study Gaggin et al. 2012 (21) 22858078	**Aim:** Whether elders benefit from NP-guided HF care **Study Type:** Single center RCT **Size:** 151	**Inclusion criteria** Chronic HF pts with LV systolic dysfunction	**Intervention:** Management guided by NT-proBNP with a goal to lower NT-proBNP ≤1000 pg/mL over 10 mo **Comparator:** Standard of care	**1° endpoints:** Total CV events in 2 age categories 75 and ≥75 y **Results:** Pts ≥75 y with NT-proBNP management had lowest rate of CV events (1.76 events per pt with standard of care vs. 0.71 events per pt with NT-proBNP guide, p=0.03)	• Improvement in QoL, LVEF, and indices of LV volume with guided approach • NP guidance changed therapy: greater use of aldosterone antagonists and lesser use of loop diuretics in the guided therapy group (no difference in ACE inhibitors or beta blockers)
UPSTEP-study group Karlstrom et al. 2011 (22) 21715446	**Aim:** To determine whether BNP-guided HF treatment improves morbidity and/or mortality	**Inclusion criteria** Ambulatory HF NYHA II-IV, LVEF <40% and elevated BNP levels	**Intervention:** BNP-guided (BNP) with a goal <150 or 300 ng/L for elderly **Comparator:** Conventional (CTR) HF treatment	**1° endpoints:** Combined death and worsening/hosp for HF **Results:** No significant differences 1° outcome (p=0.18)	• No differences for d out of hospital, and younger vs. elderly. • Subgroup analysis: improved survival (p<0.0001 for the 1° outcome) among responders with >30% decrease in BL BNP value vs. nonresponders.

	Study Type: Multicenter RCT-probe design **Size:** 279				
Maisel et al. 2002 (23) 12124404	**Aim:** To validate and characterize the use of BNP in the diagnosis of HF in pts with dyspnea **Study type:** Prospective, blinded, diagnostic accuracy study **Size:** 1,856	**Inclusion criteria:** Pts who came to the emergency department with acute dyspnea **Exclusion criteria:** Age <18 y and those whose dyspnea was clearly not secondary to HF (i.e., those with trauma or cardiac tamponade), acute myocardial infarction, unstable angina, or renal failure	**Intervention:** Comparisons of BNP values among diagnostic groups including HF and non HF pts **Comparator:** Non-HF pts such as pulmonary disease, cor pulmonale	**1° endpoint:** Diagnostic accuracy of BNP at a cutoff of 100 pg/mL was 83.4%. The negative predictive value of BNP <50 pg/mL was 96%. **Secondary endpoint :** In multiple logistic-regression analysis, measurements of BNP added significant independent predictive power to other clinical variables in models predicting which pts had HF	•Used in conjunction with other clinical information, rapid measurement of BNP is useful in establishing or excluding the diagnosis of acute HF failure in pts with acute dyspnea
van Kimmenade et al. 2006 (24) 16860029	**Aim:** To analyze the role of NT-pro-BNP in diagnosis of HF in pts presenting with dyspnea, the so-called natriuretic peptide gray zone. NT-pro-BNP concentrations, clinical characteristics, and 60-d mortality were studied in acutely dyspneic pts from an international	**Inclusion criteria:** Acutely dyspneic pts **Exclusion criteria:** With trauma or cardiac tamponade), acute myocardial infarction, unstable angina, or renal failure	**Intervention:** Comparisons of NT-pro-BNP among diagnostic groups including HF and non-HF pts **Comparator:** Non-HF pts such as pulmonary disease, cor pulmonale	**1° endpoint:** Subjects with HF and diagnostically elevated NT-pro-BNP concentrations had the highest mortality rates, subjects without HF and NT-pro-BNP concentrations < 300 ng/L had the lowest mortality rates, and subjects with gray-zone NT-pro-BNP had intermediate outcomes, irrespective of their final diagnoses.	•Adding specific clinical information to NT-pro-BNP improves diagnostic accuracy in subjects with intermediate NT-pro-BNP concentrations. Mortality rates in subjects with intermediate NT-pro-BNP concentrations are lower than in those with NT-pro-BNP concentrations diagnostic for HF but are higher than in subjects with NT-pro-BNP concentrations less than the gray zone

	multicenter study **Study type:** Prospective, blinded, diagnostic accuracy study **Size:** 1,256				
Maisel et al. 2004 (25) 15364340	**Aim:** To examine the relationships among BNP levels and HF severity, clinical decision making, and outcomes **Study type:** Multicenter, prospective, blinded, diagnostic accuracy study **Size:** 464	**Inclusion criteria:** Pts over the age of 18 y presenting to the ED with HF and who received treatment in the ED or hospital admission for HF were included. **Exclusion criteria:** Current MI or ACS with ST-segment deviation of ≥1 mm, renal failure requiring dialysis, or pts with a baseline BNP concentration of ≤100 pg/mL were excluded	**Intervention:** Physicians were blinded to the actual BNP level and subsequent BNP measurements. **Comparator:** Comparison between severity of HF determined by physicians or BNP and outcomes	**1° endpoint:** ED doctor's intention to admit or discharge a pt had no influence on 90-d outcomes, while the BNP level was a strong predictor of 90-d outcome. The 90-d combined event rate (HF visits or admissions and mortality) in the group of pts admitted with BNP <200 pg/mL and >200 pg/mL was 9% and 29%, respectively (p=0.006).	• In pts presenting to the ED with HF, there is a disconnect between the perceived severity of HF by ED physicians and severity as determined by BNP levels. The BNP levels can predict future outcomes and thus may aid physicians in making triage decisions about whether to admit or discharge pts. Emerging clinical data will help further refine biomarker-guided outpatient therapeutic and monitoring strategies involving BNP.
O'Connor et al. 2010 (26) 20185037	**Aim:** To identify high-risk HF pts at hospital discharge **Study type:** Predictive modeling using variables obtained during hospitalization in the ESCAPE trial	**Inclusion criteria:** hospitalized with severe HF, LVEF ≤30%, SBP ≤125 mmHg, **Exclusion criteria:** creatinine >3.5 mg/dL, prior inotrope use	**Derivation cohort:** ESCPAPE trial, n=423 **Validation cohort:** FIRST trial, n=471	**1° endpoint:** •6-mo mortality and death or rehospitalization rates (64%) •Multivariate discharge predictors of death included: BNP, per doubling (HR: 1.42), cardiac arrest or mechanical ventilation, yes/no (HR: 2.54), BUN, per 20 mg/dL increase (HR: 1.22) and sodium, per unit mEq/L increase (HR: 0.93)	• A simplified discharge score discriminated mortality risk from 5% (score=0) to 94% (score=8). • Bootstrap validation demonstrated good internal validation for the model (c-index 0.78) •Limitations: ESCAPE represented pts with severe LV dysfunction and advanced symptoms (not the general population of acute HF) managed at experienced centers; exclusion of pts with characteristics

	Size: 423				known to be associated with worse outcomes (e.g., creatinine >3.5 mg/dL, requiring inotropes)

Search Terms and Date: natriuretic peptides, heart failure, human, last 5 years. Last search done on April 18, 2016.

Data Supplement B. Nonrandomized Trials/ Observational Studies/ Registries for Changes in or Discharge NP Levels in ADHF – Biomarkers (Section 6.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Primary Endpoint and Results (P values, OR or RR & 95 % CI)	Summary / Conclusion / Comments
Bayés-Genís et al. 2005 (27) 15948093	**Aim:** Percentage of NT-proBNP reduction during admission and its prognostic significance **Study type:** NR Prospective cohort **Size:** 74 pts	**Inclusion criteria:** Pts diagnosed with acute HF in emergency department and who had follow-up evaluation for 6 & 12 mo after admission **Follow up :**12 mo	**1° endpoints:** • Percent reduction in NT-proBNP and its association with CV mortality **Results:** • The area under the ROC curve for % NT-proBNP reduction to predict CV death was 0.78 (95% CI: 0.66–0.90; p=0.002)	• 30% NT-proBNP reduction percentage cutoff value had 75% accuracy for the identification of high-risk pts and was the only variable that was associated with CV death in multivariate analysis (OR: 4.4; 95% CI: 1.12–17.4; p=0.03). • Study relatively old and small
Verdiani et al. 2008 (28) 18545069	**Aim:** To evaluate the prognostic significance of NT-proBNP % reduction during ADHF **Study type:** Prospective cohort **Size:** 120 pts	**Inclusion criteria:** Pts consecutively admitted with ADHF **Follow up:** 6 mo	**1° endpoint** • Percent reduction in NT-proBNP and its association with CV mortality **Results:** • In ROC, the mean AUC for NT-ProBNP % reduction was 0.63 (95% CI: 0.51–0.75; p=0.04) for the composite endpoint (death or readmission), and 0.81 (95% CI: 0.65–0.97, p=0.01) for CV mortality at risk of events.	• NT-ProBNP reduction percentage <30% was the best cut off for the identification of pts • Study relatively old and small

Bettencourt et al. 2004 (29) 15451800	**Aim:** To compare 18 mo outcomes of NT-BNP-guided vs. symptom guided HF therapy **Study type:** Prospective cohort single center study **Size:** 182 pts	**Inclusion criteria:** Consecutive ADHF pts defined by ESC or Framingham criteria **Follow up:** 6 mo	**1° endpoints:** • Death or readmission **Results:** • Pts were classified into 3 groups: (1) decreasing NT-proBNP levels by at least 30% (n=82), (2) no significant modifications on NT-proBNP levels (n=49), and (3) increasing NT-proBNP levels by at least 30% (n=25). • Among the 64 pts discharged without volume overload, a positive association between change in NT-proBNP and outcome was observed (HR: 2.66; 95% CI: 0.77–9.18 for change <30%; HR: 16.04; 95% CI: 9.49 – 52.02 for increase ≥30% compared with those with decreasing NT-proBNP by at least 30%	• Pts demonstrating a ≥30% increase in NT-proBNP levels during the course of their admission had the most adverse prognosis • Study relatively old and small
Kociol et al. 2013 (30) 23250981	**Aim:** Examine relationship between markers of decongestion and symptom relief and clinical outcomes **Study type:** retrospective analysis of the RCT, DOSE-AHF **Size:** 308 pts	**Inclusion criteria:** Pts enrolled in DOSE-AHF **Follow up:** 60 d	**1° endpoints:** • Time to death, first rehospitalization or emergency department visit **Results:** • Of the weight loss, fluid loss, and NT-proBNP reduction, only % reduction in NT-proBNP was significantly associated with symptom relief (r=0.13; p=0.04). • Reduction in NT-proBNP Associated with better outcome (NT-proBNP HR: 0.95; 95% CI: 0.91–0.99 per 10% reduction).	• Favorable changes in each of the 3 markers of decongestion were associated with improvement in time to death, rehospitalization, or emergency department visit at 60 d
Kociol et al. 2011 (31) 21743005	**Aim:** To examine if admission, discharge, or change from admission to discharge BNP measure is the most important predictor of long-term outcomes	**Inclusion criteria:** Linked pts ≥65 y of age from hospitals in OPTIMIZE-HF to Medicare claims **Follow up:** 1 y	• The discharge BNP had the best performance and was the most important characteristic for predicting 1 y mortality (HR for log transformation: 1.34; 95% CI: 1.28–1.40) and 1 y death or rehospitalization (HR: 1.15; 95% CI: 1.12–1.18).	• Compared with a clinical variables, discharge BNP model improved risk reclassification and discrimination in predicting each outcome (1 y mortality: NRI: 5.5%, p<0.0001; IDI: 0.023, p<0.0001; 1-y mortality or rehospitalization: NRI: 4.2%, p<0.0001; IDI: 0.010, p<0.0001)

	Study type: Retrospective analysis –from OPTIMIZE HF Trial **Size:** 7,039 pts			
Flint KM et al. 2014 (32) 24922626	**Aim:** To examine if admission, discharge, or change from admission to discharge BNP measure is the most important predictor of outcomes **Study type:** Retrospective analysis from VA database **Size:** 109,875 pts	**Inclusion criteria:** All hospital discharges with a 1° diagnosis of HF in the Veterans Affairs Health Care System from 2006 to 2009. **Follow up:** 30 d	**1° endpoints:** • 30 d readmission rate for HF **Results:** 30 d HF readmission was associated with elevated admission BNP, elevated discharge BNP, and smaller percent change in BNP from admission to discharge. • Pts with a discharge BNP ≥1,000 ng/L had an unadjusted 30 d HF readmission rate over 3 times as high as pts whose discharge BNP was ≤200 ng/L (15% vs. 4.1%).	• Discharge BNP had the greatest effect (C-statistic, 0.639–0.664 [p<0.0001]; NRI, 9% [p<0.0001]). • Large sample size
ELAN-HF Score Salah et al. 2014 (33) 24179162	**Aim:** To examine if admission, discharge, or change from admission to discharge BNP measure is the most important predictor of outcomes **Study type:** Individual pt data meta-analyses of prospective cohort studies **Size:** 1,301 pts	**Inclusion criteria:** Pts from 7 prospective cohorts with pts admitted because of clinically validated ADHF, discharged alive, and NT-proBNP measurements available at admission and at discharge **Follow up:** 180 d	**1° endpoints:** All-cause mortality and a composite of all-cause mortality and/or first readmission for CV reason within 180 d after discharge **Results:** • NT-proBNP levels at discharge and the changes in NT-proBNP during hospitalization yielded the best C-statistic (AUC: 0.78; 95% CI: 0.74–0.82).	• In pts hospitalized for ADHF, the addition of the discharge NT-proBNP values as well as the change in NT-proBNP to known risk markers, generates a relatively simple yet robust discharge risk score that importantly improves the prediction of adverse events

Cohen-Solal et al. 2009 (34) 19539144	**Aim:** Examine whether decreases in BNP levels during the first few d of hospitalization were associated with greater survival in pts with ADHF **Study type:** Retrospective analysis of SURVIVE **Size:** 1,327 pts	**Inclusion criteria:** Of 1,327 SURVIVE pts, this analysis included 1,038 who had BNP samples at both BL and d 5 **Follow up:** 180 d	**1° endpoints:** All-cause mortality and a composite of all-cause mortality and/or first readmission for CV reason within 180 d after discharge **Results:** • A pt was classified as a "responder" if the follow-up BNP level was ≥30% lower than BL BNP • Short-term 30 d mortality risk reduction was 67% in d 5 BNP responders compared with nonresponders, whereas long-term (180-d) all-cause mortality risk reduction was 47%	• Pts with lowered BNP on treatment for ADHF had reduced mortality risks (31- and 180-d) compared to those with little or no BNP decrease
Logeart et al. 2004 (35) 14975475	**Aim:** To determine the value of BNP predicting post-discharge outcome of pts admitted for ADHF **Study type:** Prospective cohort **Size:** 105 pts	**Inclusion criteria:** Serial BNP measurements were performed from admission to discharge in 2 samples of consecutive pts	**1° endpoints:** Combined death or first re-admission for HF **Results:** The predischarge BNP assay had the best discriminative power (AUC for ROC=0.80) and remained the lone significant variable in multivariate analysis (HR: 1.14; 95% CI: 1.02–1.28; p=0.027	• High predischarge BNP assay is a strong, independent marker of death or readmission after decompensated HF, more relevant than common clinical or echocardiographic parameters and more relevant than changes in BNP levels during acute cares • Study relatively old and small
O'Brien et al. 2003 (36) 12921811	**Aim:** To determine the value of BNP predicting post-discharge outcome of pts admitted for ADHF **Study type:** Prospective cohort **Size:** 96 pts	**Inclusion criteria:** NT-proBNP was measured at admission in 96 pts hospitalized with acute LVF **Follow up:** 180 d	**1° endpoints:** Combined death or HF **Results:** Only pre-discharge plasma NT-proBNP (OR: 15.30; 95% CI: 1.4–168.9], p=0.026) was independently predictive of the composite endpoint. The AUC ROC curve for pre-discharge NT-proBNP was superior to that for admission NT-proBNP for prediction of death or HF (AUC ROC 0.87 cf 0.70), for death (0.79 cf 0.66), LVF hospitalization (0.78 cf 0.70) or HF as an outpatient (0.71	• Plasma NT-proBNP measured pre-discharge provides useful prognostic information following hospitalization with acute LVF. • Study relatively old and small

			cf 0.61	
Richards et al. 2001 (37) 11401111	**Study type:** Observational study within a randomized trial **Size:** 297	**Inclusion criteria:** Ischemic CM, EF<45%, chronic stable CHF, NYHA II-III or prior II--IV **Exclusion criteria:** Current NYHA IV, HR<50 bpm, BP<90 or >160/100, coronary event/procedure last 4 weeks, IDDM, CKD, hepatic/renal disease, sick sinus syndrome, 2nd or 3rd degree heart block, treatment with beta-blocker, beta-agonist or verapamil	**1° endpoint:** Association of plasma N-BNP and adrenomdeullin with mortality and HF events at 18 mo **Results:** • Above median proBNP increased risk of mortality (HR: 4.7; CI 2–10.9) and HF admission (HR: 4.7; CI: 2–10) • Above median adrenomedullin increased risk of mortality (HR 3.9,CI 1.8-8.7) and HF admission (HR 2.4, CI 1.3-4.5) • Associations persist in multivariable modeling	• NT-proBNP and adrenomedullin levels are independently associated with outcome in pts with heart failure from an ischemic cardiomyopathy
Tang et al. 2003 (38) 14662703	**Study type:** Retrospective, observational **Size:** 558	**Inclusion criteria:** Chronic systolic HF >3 mo duration, stable medical therapy, LVEF<50%, NYHA class I-III, followed in outpatient HF clinic at a single center who had BNP obtained at clinic visit **Exclusion criteria:** Congenital heart disease, cardiac transplant, primary valvular disease, active ischemia requiring urgent revascularization	**1° endpoint:** Prevalence, clinical characteristics, and characteristics of a BNP<100 pg/mL in a HF clinic population **Results:** • 21% of symptomatic HF pts had BNP <100 pg/mL • Characteristics associated with this phenotype include younger age, female gender, nonischemic etiology, better preserved cardiac and renal function, less have atrial fibrillation	• A sizeable minority (21%) of ambulatory pts with chronic HF have a BNP <100 pg/mL • This phenotype (HF with non-diagnostic BNP) is associated with identifiable clinical characteristics
Januzzi et al. 2008 (39) 18243855	**Study type:** Review paper regarding utility of NT-proBNP testing for diagnosis or exclusion of HF in pts with acute HF **Size:** N/A	**Inclusion criteria:** Studies using NT-proBNP assays used commercially **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** • NT-proBNP had comparable sensitivity/specificity to BNP for diagnosis of acute HF in dyspneic pts • NT-proBNP testing may be superior to	• NT-proBNP testing can help with the diagnosis and triage of the patients with acute dyspnea."

			clinical assessment in diagnosing HF	
Santaguida et al. 2014 (40) 25052418	**Study type:** Systematic review **Size:** 7 publications included	**Inclusion criteria:** Study assessing incremental value of BNP or NT-proBNP for predicting morbidity and mortality in acute decompensated HF **Exclusion criteria:** Studies of stable HF; natriuretic peptide could not be included in base model to allow assessment of incremental value	**1° endpoint:** BNP or NT-proBNP improved prognostic model performance for mortality as assessed by discrimination and or likelihood statistics **Results:** • 5 BNP publications consistently predicted all-cause mortality in short (3–6 mo) and long (9,12 mo) beyond base model but not all statistically significant • Two NT-proBNP publications both showed incremental value at 22 mo and 6.8 y with 1 being statistically significant	• Clinical heterogeneity precluded formal meta-analysis
Hill et al. 2014 (41) 24957908	**Study type:** Systematic review **Size:** 76 publications included (37 BNP alone, 25 NT-proBNP alone, 14 both)	**Inclusion criteria:** • Age >18 y presenting to ED or urgent care center with signs/symptoms suggestive acute HF • English language articles from 1989-2012 • FDA-approved assays **Exclusion criteria:** • Studies with pts who had conditions that may impact NP levels (transplant, HCM, valvular)	**1° endpoint:** Test performance characteristics **Results:** •BNP pooled sensitivity=95%, 95% CI: 93–97%), specificity 67% (58–75%) • NT-proBNP pooled sensitivity 91% (95% CI: 88–93), specificity 67% (50–80%)	• Both BNP and NT-proBNP had high sensitivity but low specificity • Overall strength of evidence for sensitivity and all decision cutpoints for both peptides was high; strength of evidence for specificity rated as moderate. • Both BNP and NT-proBNP performed well to rule out, but less well to rule in, for the diagnosis of heart failure among patients presenting to the ED or urgent care centers.
Zaphiriou et al. 2005 (42) 15921792	**Study type:** Diagnostic accuracy study (observational) **Size:** 306 pts	**Inclusion criteria:** Pts with new symptoms suggestive of HF referred by GP to rapid access HF clinics at 5 centers in UK between 201 and 2003	**1° endpoint:** Sensitivity, specificity, PPV, NPV, LR, AUC for diagnosis of HF **Results:** • 104 (34%) of pts had HF	• 2 of 5 sites withdrew after recruiting 18 and 14 pts • Both BNP and NT-proBNP are useful for ruling out HF in pts presenting to PCP with possible HF symptoms

		Exclusion criteria: None listed	• AUC BNP 0.84 (95% CI: 0.79–0.89), Nt-proBNP 0.85 (0.81–0.9) • BNP: NPV: 0.87, PPV: 0.59 • NT-proBNP NPV: 0.97, PPV: 0.44	
Son et al. 2012 (43) 22564550	**Study type:** Observational, decision making model using rough set and decision tree approaches **Size:** 159 subjects (71 HF, 88 control)	**Inclusion criteria:** • ED presentation for dyspnea (HF vs. Noncardiac control) • Complete medical records **Exclusion criteria:** • HF excluded if other diagnosis made	**1° endpoint:** HF diagnosis **Results:** NT-proBNP was one of 6 variables identified in decision-tree rough set and one of 4 variables in logistic regression model	• NT-proBNP identified as a critical variable for decision making of HF in pts with dyspnea presenting to ED
Kelder et al. 2011 (44) 22104551	**Study type:** Cross-sectional, diagnostic accuracy (observational) **Size:** 721 subjects	**Inclusion criteria:** Pts presenting with signs/symptoms of HF who were referred to 1 of 8 rapid access clinics in the Netherlands **Exclusion criteria:** Known, established HF Acute HF requiring immediate therapeutic intervention	**1° endpoint:** Diagnosis of HF **Results:** • 207/721 (29%) had HF • C-statistic without proBNP =0.83 • C-statistic with proBNP =0.86 NRI 69%	• NT-proBNP had utility beyond the history and physical for diagnosing HF among primary care outpatients presenting with signs/symptoms of HF
Booth et al. 2014 (45) 24969534	**Study type:** Systematic review **Size:** 12 BNP publications; 20 NT-proBNP publications	**Inclusion criteria:** • Pts presenting with signs or symptoms of HF or were at risk of HF a time of presentation • Primary care setting **Exclusion criteria:** Studies with subjects with: • Age <18 y • Acute HF • Known exacerbation of chronic stable HF	**1° endpoint:** Diagnostic accuracy of BNP or NT-proBNP **Results:** • BNP pooled sensitivity (lowest cutpoint 0.85, optimal 0.8, manufacturer 0.74) and specificity (0.54, 0.5, 0.58, respectively) • NT-proBNP pooled sensitivity (lowest cutpoint 0.90, optimal 0.86, manufacturer 0.82) and specificity (0.5, 0.58, 0.58, respectively)	• Both BNP and NT-proBNP have good diagnostic utility for diagnosing HF in the primary care setting in those with signs/symptoms of HF or at risk of developing HF • Tests have better sensitivity than specificity • Authors felt that it was unlikely that further studies will change these conclusions

		• Conditions that may interfere with NP levels (heart transplant, obesity, HCM, valvular lesion)		
Dao et al. 2001 (46) 11216950	**Study type:** Observational, convenience sample at 1 VA urgent care center **Size:** 250	**Inclusion criteria:** SOB as prominent complaint **Exclusion criteria:** • Dyspnea clearly not from HF • ACS (unless predominant presentation was HF	**1° endpoint:** Diagnostic utility of point-of-care BNP for diagnosis of HF **Results:** • BNP C-statistic =0.98 • Treating physician C statistic =0.88 • BNP remained independently associated with HF diagnosis in multivariable model beyond H+P, xray, ECG	• BNP had diagnostic utility for HF diagnosis in the urgent care setting
Davis et al. 1994 (47) 7905953	**Aim:** Assessed value of ANP and BNP in pts presenting with dyspnea **Study type:** Observational **Size:** 52	**Inclusion criteria:** Suspected HF among elderly pts presenting with acute dyspnea requiring admission **Exclusion criteria:** Pneumonia, pulmonary thromboembolism, or pneumothorax	**1° endpoint:** Strong negative correlations between LVEF and log BNP (r=-0.7; p<0.001) and log ANP (r=-0.59; p<0.001). **Results** Admission plasma BNP more accurately reflected the final diagnosis of HF (93% sensitivity and 90% specificity when BNP ≥22 pmol/L) than LVEF or plasma ANP concentration.	• One of the original studies that showed that plasma BNP was raised in dyspneic pts with HF • But not in acutely breathless pts with lung disease • Rapid BNP assays may assist in the diagnosis of pts with acute dyspnea
Cheng et al. 2001 (48) 11216951	**Aim:** To determine if BNP levels predict outcomes of pts admitted with decompensated HF **Study type:** Observational **Size:** 72	**Inclusion criteria:** Pts admitted with decompensated NYHA class III to IV HF, measuring daily BNP levels **Exclusion criteria:** Lack of levels	**1° endpoint:** Association between initial BNP and the predischarge or premoribund BNP measurement and subsequent death and 30-d readmission **Results:** In pts surviving hospitalization, BNP discharge concentrations were strong predictors of subsequent readmission (area under the receiver operator curve of 0.73).	• In pts admitted with decompensated HF, changes in BNP levels during treatment are strong predictors for mortality and early readmission. • BNP levels might be used successfully to guide treatment of pts admitted for decompensated HF
Fonarow et al. 2008 (49) 18178412	**Aim:** To determine additive prognostic value of	**Inclusion criteria:** Hospitalizations for HF from April 2003 to December	**1° endpoint:** BNP above the median and increased Tn were associated with significantly increased	• Admission BNP and cardiac Tn levels are significant, independent predictors of in-hospital mortality in

	admission BNP and Tn levels in acutely decompensated HF **Study type:** Registry analysis **Size:** 48,629	2004 entered into ADHERE were analyzed. BNP assessment on admission was performed in 48,629 (63%) of 77,467 hospitalization episodes **Exclusion criteria:** Absence of BNP levels	risk of in-hospital mortality (OR: 2.09 and 2.41 respectively, each p<0.0001).	acutely decompensated HF.
Zairis et al. 2010 (50) 19157603	**Aim:** To investigate the combined prognostic value of admission serum levels of BNP, cTnI and hs-CRP, in pts hospitalized because of acutely decompensated severe (NYHA class III/IV) low-output chronic HF. **Study type:** Multicenter Prospective cohort **Size:** 577	**Inclusion criteria:** Consecutive hospitalized acute decompensated HF pts with NYHA class III/IV recruited in the 5 participating centers **Exclusion criteria:** Competing diagnoses of renal failure, MI	**1° endpoint:** Cardiac mortality by 31 d **Results:** There was a significant gradual increased risk of 31-d cardiac death with increasing in the number of elevated biomarkers (p<0.001). By multivariate Cox regression analysis, elevated serum levels of BNP (p=0.002), cTnI (p<0.001) and hs-CRP (p=0.02) were independent predictors of the study end point.	• In pts hospitalized for acute decompensation of severe (NYHA III/IV) low-output HF, BNP, cTnI and hs-CRP upon admission offers enhanced early risk stratification.
Peacock et al. 2008 (51) 18480204	**Aim:** Describe the association between elevated cardiac troponin levels and adverse events in hospitalized pts with acute decompensated HF **Study type:** Registry analysis	**Inclusion criteria:** Hospitalizations for acute decompensated HF between 2001 and 2004 in ADHERE. Entry criteria included a troponin level that was obtained at the time of hospitalization **Exclusion criteria:** Pts with a serum creatinine level ≥ 2.0 mg per deciliter	**1° endpoint:** Overall, 4,240 pts (6.2%) were positive for troponin. **Results:** Pts who were positive for troponin had lower SBP on admission, a lower EF, and higher in-hospital mortality (8.0% vs. 2.7%, p<0.001) than those who were negative for troponin. The adjusted odds ratio for death in the group of pts with a positive troponin test was 2.55 (95% CI: 2.24–2.89; p<0.001)	• In pts with acute decompensated HF, a positive cardiac troponin test is associated with higher in-hospital mortality, independently of other predictive variables.

	Size: 67,924	(177 micromol per liter).		
Lee et al. 2012 (52) 22665814	**Aim:** To derive and validate a model for acute HF mortality applicable in the ED. **Study type:** Multicenter Registry analysis **Size:** 12,591	**Inclusion criteria:** Population-based random sample of 12,591 pts presenting to the ED from 2004 to 2007 **Exclusion criteria:** No lab availability	**1° endpoint:** Death within 7 d of presentation **Results:** Mortality risk increased with higher triage heart rate (OR: 1.15; [95% CI: 1.03–1.30] per 10 beats/min) and creatinine concentration (OR: 1.35; [CI: 1.14–1.60] per 1 mg/dL [88.4 micro mol/L]), and lower triage SBP (OR: 1.52 [CI: 1.31–1.77] per 20 mm Hg) and initial oxygen saturation (OR, 1.16 [CI: 1.01–1.33] per 5%).	• A multivariate index comprising routinely collected variables stratified mortality risk with high discrimination in a broad group of pts with acute HF presenting to the ED.
Dhaliwal et al. 2009 (53) 19398076	**Aim:** Compare the relationship between absolute and relative changes in BNP with future clinical events, and whether serial BNP measurements add prognostic information in pts treated for decompensated HF **Study type:** Retrospective registry analysis **Size:** 203	**Inclusion criteria:** Pts hospitalized for acute decompesated HF by Framingham criteria **Exclusion criteria:** Renal failure, severe lung disease, acute coronary syndrome	**1° endpoint:** For the combined end point of total mortality or readmission for HF **Results:** • Increasing tertiles of BNP levels after treatment had a hazard ratio of 1.4 (1.1–1.7, p<0.01) and increasing tertiles of percent reduction in BNP, had a HR:0.7 (0.6–0.9; p=0.005), respectively, for the combined end point of total mortality or readmission for HF • Follow-up BNP performed better than did baseline BNP or percent reduction in BNP. • More BNP measurements other than the follow-up BNP did not improve the fit of the model further.	• Both lower absolute BNP levels and greater percentage reduction in BNP with treatment of decompensated HF are associated with better event-free survival. • Advocating a threshold BNP to which pts should be treated may not be possible given that high BNP levels tend not to decrease to levels associated with better outcomes during the short period of treatment. • More BNP measurements do not add prognostic information beyond that provided by a single BNP level after treatment
Alonso-Martinez et al. 2002 (54) 12034159	**Aim:** To determine usefulness of CRP in predicting need for readmission in HF	**Inclusion criteria:** Intervention group: admission with HF; control group: admission with syncope	**1° endpoint:** 18-mo HF readmission • CRP levels were higher in pts with HF compared to syncope (3.94 vs. 0.84, p<0.0007)	• Multivariate predictors of readmission were CRP levels, NYHA class and plasma K on discharge • Limitation: small, single-center

	Study type: Observational **Size:** 76	**Exclusion criteria:** Clear cause for elevated CRP (e.g., inflammation, infection)	• Higher CRP levels were associated with higher NYHA class, increased risk of HF readmission, shorter time to readmission, and increased mortality **Safety endpoint:** NYHA class on discharge and death	observational study
Dieplinger et al. 2010 (55) 20153308	**Aim:** To evaluate the prognostic value of established and novel biomarkers in pts with acute dyspnea **Study type:** Observational **Size:** 251	**Inclusion criteria:** Pts presenting to ED with acute dyspnea **Exclusion criteria:** STEMI, NSTEMI or ACS troponin pos. **Biomarkers**: BNP, MR-proANP, MR-proADM, copeptin, C-terminal pro-ET-1, soluble ST2, chromogranin A (CgA), adiponectin, proguanylin, prouroguanylin	**1° endpoint:** All-cause mortality at 1 y • 25% died within 1 y • At baseline, decedents (n=62) had higher median plasma concentrations of all 10 biomarkers than survivors (n=189) • In multivariate model, only MR-proANP (RR: 1.6), ST2 (RR: 1.7) and CgA (RR: 1.5) were independent predictors of death	• Low systolic BP and advanced age were also independent predictors of 1-y mortality • Limitations: post-hoc analysis; sub-group (87 of 251) had dyspnea due to acute HF alone; single-center, majority men (94%)
Ilva et al. 2008 (56) 18599345	**Aim:** To evaluate prevalence and prognostic significance of elevated cTnI and cTnT in acute HF **Study type:** Observational substudy **Size:** 364	**Inclusion criteria:** Hospitalized with acute HF **Exclusion criteria:** ACS pts; missing sample for cardiac TnI/TnT **Biomarkers on admission and 48 hours**: cTnT, cTnI, cystatin C, NT-proBNP	**1° endpoint:** 6 -mo mortality • 51% of pts had +cTnI and 30% had +cTnT • 6-mo all-cause mortality was 18.7% • Both cTnI (OR: 2.0; 95% CI: 1.2–3.5) and cTnT (OR: 2.6; 95% CI: 1.5–4.4) were associated with adverse outcome in pts with previous, but no de novo HF	• On multivariable analysis, cystatin C (OR: 6.3; 95% CI: 3.2–13), logNT-proBNP (OR: 1.4; 95% CI: 1.0–1.8) and SBP on admission (/10 mm Hg increase; OR: 0.9; 95% CI: 0.8–0.9) were independent risk predictors, whereas troponins were not • Mortality was proportional to troponin release • Limitations: exclusion of pts with ACS was based on clinician judgment; cut-off values for troponins was based on 2000 ESC/ACC guidelines
Januzzi et al. 2007 (57) 17692745	**Aim:** To examine the value of measuring ST2 in pts	**Inclusion criteria:** Pts presenting to ED with acute dyspnea	**1° endpoint:** •death at 1 y • ST2 levels were significantly higher in pts	• ST2 levels were higher in pts with HF*r*EF (0.67 ng/ml; IQR 0.31–1.50) vs. HF*p*EF (0.42 ng/ml; IQR 0.22–

	with acute dyspnea **Study type:** Observational **Size:** 593 (pts with acute HF 209, other causes of acute dyspnea 384)	**Exclusion criteria:** Not reported	with acute HF (0.50 ng/ml; IQR 0.27–1.22) vs. those without (0.15 ng/ml; IQR 0.06–0.42) • 1-y mortality was 15.7% • ST2 levels were significantly higher in decedents than survivors (1.03 vs. 0.18 ng/ml; p<0.001) • In multivariable analysis, ST2 ≥0.20 ng/ml strongly predicted death at 1 y	0.90) • A multi-marker approach with both ST2 and NT-proBNP levels identified subjects with the highest risk for death • Limitations: single-center study; biologic role of ST2 in acute HF poorly understood
Manzano-Fernandez et al. 2011 (58) 21211603	**Aim:** To determine whether risk of mortality associated with ST2 differs in pts with acute HF*p*EF vs. HF*r*EF **Study type:** Observational study combining 3 databases (Boston, MA; Linz, Austria; Murcia, Spain) **Size:** 447	**Inclusion criteria:** Acute HF **Exclusion criteria:** N/A **Biomarkers**: ST2, troponin T, NT-proBNP, CRP	**1° endpoint:** •1 y vital status • During 1-y follow-up, 117 pts (26%) died • ST2 levels were higher among deceased than survivors (median 0.80 ng/ml vs.0.38 ng/ml; p<0.001); and this pattern was true for HF*r*EF and HF*p*EF • On multivariate analysis, elevated ST2 levels were associated with greater risk of 1-y mortality for HF*p*EF (HR: 1.41; 95% CI: 1.14–1.76) than HF*r*EF (HR: 1.20; 95% CI: 1.10–1.32)	• Pts with HF*r*EF had higher ST2 levels than HFpEF (median 0.55 ng/ml vs. 0.38 ng/ml; p<0.001) • Addition of ST2 to NT-proBNP improved C statistic and both net reclassification improvement and integrated discrimination improvement, regardless of LVEF • Limitations: pooled multinational analysis that lacked predefined endpoints and complete echocardiographic measures; no pre-discharge ST2 levels
Rehman et al. 2008 (59) 19017513	**Aim:** To examine patient-specific characteristic of ST2 in pts with acute HF **Study type:** Observational study combining 2 databases (Boston, MA; Linz, Austria) **Size:** 346	**Inclusion criteria:** Acute HF **Exclusion criteria:** N/A **Biomarkers**: ST2, BNP, NT-proBNP, CRP	**1° endpoint:** •ROC curves and multivariable Cox proportional hazards analyses • ST2 levels correlated with severity of HF (p<0.001), LVEF and creatinine clearance • ST2 levels correlated with BNP, NT-proBNP and CRP • In a multivariable model, ST2 remained a predictor of mortality (HR: 2.04; 95% CI: 1.30–3.24)	• Pts with HFpEF had lower ST2 levels compared to HF*r*EF •1-y mortality was 42% among 116 pts with elevation in both ST2 and BNP/NT-proBNP • In the presence of a low ST2 level, BNP/NT-proBNP did not predict mortality • Limitations: lack of serial measures of ST2; biologic role of ST2 in acute HF poorly understood

Shah et al. 2010 (60) 20525986	**Aim:** To determine the relationship between galectin-3 and cardiac structure and function in pts with acute dyspnea **Study type:** Observational **Size:** 115	**Inclusion criteria:** PT presenting to ED with acute dyspnea, detailed echo exams during admission **Exclusion criteria:** N/A **Biomarkers:** galectin-3, NT-proBNP	**1° endpoint:** •Association between galectin-3 and echo and clinical indices •Higher levels of galectin-3 associated with older age, poorer renal function, and higher NT-proBNP •Significant relationship between galectin-3 and poorer RV function, higher RV systolic pressure and more severe MR and TR	•Galectin-3 levels higher in pts who died at 1 and 4 y •In multivariate analysis, galectin-3 remained a significant predictor of 4-y mortality independent to echocardiographic markers of risk •Limitations: delay between collection of biomarkers and echocardiograms; small, single-center cohort

Search Terms and Date: natriuretic peptides, heart failure, human, last 5 years. Last search done on April 18, 2016.

Data Supplement 1. RCTs Comparing ARNI (Section 7.3.2.10)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
PARAMOUNT Solomon et al. 2012 (61) 22932717	**Aim:** To address safety and efficacy of LCZ696 (ARNI) in pts with HF*p*EF **Study type:** RCT **Size:** 308	**Inclusion criteria:** Pts ≥40 y of age, LVEF ≥45%, NYHA class II-III HF, NT-pro BNP >400 pg/mL. **Exclusion criteria:** Right HF due to pulmonary disease, dyspnea due to noncardiac causes, valvular/myocardial disease, CAD or CVD needing revascularization within 3 mo of screening.	**Intervention:** LCZ696 (149) target dose 200 mg BID achieved in 81% **Comparator:** Valsartan (152) target dose 160 mg BID achieved in 78%	**1° endpoint:** • Change from BL at 12 wk for NT-proBNP • Results: Reduction in LCZ696 group vs. valsartan (ratio of change from BL: 0.77, 95% CI: 0.64–0.92; p=0.005) **1° Safety endpoint:** • LCZ-696 well tolerated. • Serious adverse events: 15% in LCZ696 vs. 20% in valsartan group	• No difference in change in NT-proBNP from BL at 36 wk • BP reduced in the LCZ696 group vs. valsartan at 12 wk (p=0.001 for SBP and p=0.09 for DBP) • Change in BP correlated poorly with the change in pro-BNP • No difference in improvement in NYHA class at 12 wk (p=0.11) and 36 wk (p=0.05). • No difference in KCCQ scores • Trial not powered to ascertain clinical outcomes. Further studies needed to assess safety and efficacy in HF*p*EF pts.
PARADIGM-HF McMurray et al. 2014	**Aim:** To compare survival rates with the use of	**Inclusion criteria:** ≥18 y of age, NYHA class II, III, IV; EF ≤35%, BNP of at least 150	**Intervention:** LCZ696 (4,187) target dose 200 mg BID (mean	**1° endpoint:** • Composite of death (CV causes) or a first	• Less CV death in LCZ696 arm (558 vs. 693) HR: 0.8 (95% CI: 0.71–0.89; p<0.001)

(62) 25176015	LCZ696 with enalapril in HF **Study type:** RCT **Size:** 8,442	pg/mL, hospitalized for HF ≤12 mo (≥BNP100 pg/mL), on ACE inhibitors or ARBs ≥4 wk before screening, required to take stable dose of beta blockers and an ACE inhibitor (or ARB) equal to 10mg of enalapril. Prior to randomization pts were required to complete 2 wk each of enalapril 10 mg BID and LCZ 100 BID. **Exclusion criteria:** Symptomatic hypotension, SBP <95 mm Hg, eGFR <30 mL/min/min/1.73m^2 of body surface area, serum K level >5.2 mmol/L, angioedema history, unacceptable side effects of ACE inhibitors or ARBs	375±71 mg daily) **Comparator:** Enalapril (4,212) target 10 mg BID (mean 18.9±3.4 mg daily)	hospitalization for HF • Results: Composite less in LCZ696 group vs. enalapril, 914 (21.8%) vs. 1,117, (26.5%) HR: 0.80 (95% CI: 0.73–0.87; p<0.001)	• Less HF hospitalizations in LCZ696 arm (537 vs. 658) HR: 0.79 (95% CI: 0.71–0.89; p<0.001) • Less death from any cause in LCZ696 arm (711 vs. 835), HR: 0.84 (95% CI: 0.76–0.93; p<0.001) • The change from baseline to 8 mo in the score on the KCCQ in LCZ696 arm (2.99 points reduction vs. 4.63 points), HR: 1.64 (95% CI: 0.63–2.65; p=0.001) • No difference in new onset of AF (84 vs. 83; p=0.84) • No difference in protocol defined decline in renal function, HR: 0.86 (95% CI: 0.65–1.13; p=0.28). • More symptomatic hypotension (14% vs. 9.2%; p<0.001) • No difference in angioedema, 19 vs.10 (p=0.13)

Search Terms and Date: 3 trials identified by chairs in December 2015.

Data Supplement 2. RCTs Comparing RAAS Inhibition (Section 7.3.2.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
ONTARGET ONTARGET Investigators et al. 2008 (63) 18378520	**Aim:** Compare ACE (ramipril), ARB (telmisartan), and combination ACE/ARB in pts with CVD or high-risk DM **Study Type:** RCT **Size**: 25,620	**Inclusion Criteria:** Pts >55 y of age, CAD, PVD, previous stroke, or high-risk DM with end-organ damage **Exclusion Criteria:** HF at trial entry, ACE or ARB intolerance, revascularization planned or <3 mo	**Intervention:** Run in, then randomization to ramipril (8,576) target dose 10 mg daily, telmisartan (8,542) target dose 80 mg daily or combination (8,502), titrated to BP	**1° endpoint:** • Composite of CV death, MI, stroke, or HF hospitalization at 5 y **Results:** No difference in outcome (16.5% ACE, 16.7% ARB, 16.3% combination; CI: ARB RR: 1.01 (95% CI: 0.94–1.09)	• Compared to the ramipril arm: • Telmisartan had more hypotensive symptoms (p<0.001); less cough (p<0.001) and angioedema (p=0.01); same syncope. • Combination arm had more hypotensive symptoms (p<0.001); syncope (p=0.03); and renal dysfunction (p<0.001) • BP fell by 6.4/7.4/9.8 mm Hg • Less angioedema with telmisartan
TRANSCEND Yusuf et al. 2008 (64) 18757085	**Aim:** To assess the effectiveness of ARB in ACE-intolerant pts with CVD or high-risk DM **Study Type:** RCT **Size:** 5,926	**Inclusion Criteria:** ACE-intolerant pts with CAD, PVD, previous stroke, or high-risk DM with end-organ damage **Exclusion Criteria:** HF at trial entry, revascularization planned or <3 mo	**Intervention:** Run in, then randomization to telmisartan titrated to 80 mg as tolerated (2,954) **Comparator:** Titration of other mediations as needed to control BP (2,944)	**1° endpoint:** • Composite of CV death, MI, stroke, or HF hospitalization at 5 y **Results**: No significant difference RR: 0.92 (95% CI: 0.81–1.05); p=0.216	• No difference in 2° outcomes; ARB was safe in this pt population - no angioedema
SUPPORT Sakata et al. 2015 (65) 25637937	**Aim:** Discover whether addition of ARB to ACE and beta blockers in pts with chronic HF will	**Inclusion Criteria:** Pts 20–79 y of age with hypertension, NYHA class II-IV, stable on ACE ± beta blockers	**Intervention:** Randomization to olmesartan (578) titrated up to 40 mg as tolerated (578) (mean dose achieved at 5 y, 17.9	**1° endpoint:** • Composite of all-cause death, MI, stroke, or HF hospitalization at 4.4 y **Results:** No significant difference RR: 1.18 (95% CI: 0.96–1.46); p=0.11	• Pts on triple therapy with ACE/ARB/Beta blocker had more of 1° composite outcome, 38.1 vs. 28.2%, HR: 1.47 (95% CI: 1.11–1.95; p=0.006); all-cause death, 19.4 vs. 13.5%, HR: 1.50 (95% CI:

	improve clinical outcomes **Study Type:** Open label blinded endpoint **Size:** 1,147	**Exclusion Criteria:** Creatinine >3.0, MI or, revascularization within 6 mo	mg/d) **Comparator:** Titration to control BP without use of an ARB (568)		1.01–2.23; p=0.046); and renal dysfunction (21.1 vs. 12.5%, HR: 1.85 (95% CI: 1.24–2.76; p=0.003).
Mineralocorticoids Antagonist Trials					
EMPHASIS subgroup analysis Eschalier et al. 2013 (66) 23810881	**Aim:** Investigate the safety and efficacy of eplerenone in pts at high risk for hyperkalemia **Study Type:** Prespecified subgroup analysis of RCT **Size:** 2,737	**Inclusion Criteria:** Pts enrolled in EMPHASIS at high risk for hyperkalemia of worsening renal function (>75 y, DM, eGFR <60, or SBP <123) **Exclusion Criteria:** eGFR<30	**Intervention:** Randomization to eplerenone **Comparator:** Placebo	**1° endpoint:** • Efficacy: Hospitalization for HF or worsening renal failure. **Safety:** K >5.5, >6.0, <3.5, hospitalization for significant hyperkalemia, hospitalization for worsening renal function **Results**: Efficacy: reduced composite endpoint. Safety: increased risk of K+ >5.5 mmol/L, hospitalization for hyperkalemia or discontinuation of study medication due to adverse events. No differences from the main trial results in the high-risk subgroups. K >5.5 was increased in the whole cohort and the subgroups, but K >6.0, clinically significant hyperkalemia, and change in eGFR were not substantially higher.	• The beneficial effects of eplerenone were maintained in the high-risk subgroups.
RALES Pitt et al. 1999 (67) 10471456	**Aim:** To investigate the effect of spironolactone on mortality and morbidity in pts with severe HF. **Study Type:**	**Inclusion Criteria:** NYHA class III, IV; HF≤6 mo, Left EF≤35%, On ACE inhibitors, loop diuretic. Digitalis and vasodilators allowed. **Exclusion Criteria:** 1° operable VHD (other than	**Intervention:** Spironolactone 25 mg daily (822) **Comparator:** Placebo (841)	**1° endpoint:** • Death from all causes **Results**: • Placebo vs. Spironolactone group (46% vs. 35%; RR: 0.70; 95% CI: 0.60–0.82; p<0.001) • Trial stopped early due to favorable results at 24 mo.	• Reduction in death from cardiac causes and Hospitalization for cardiac causes (p<0.001) • Improvement in NYHA class (p<0.001) • No clinically important safety concerns for electrolytes. Gynecomastia/breast pain more frequent in the spironolactone

	RCT **Size:** 1,663	mitral or tricuspid), ACHD, unstable angina, 1° heaptic failure, active cancer, life threatening disease, heart transplant, serum Cr ≥2.5 mg/dL, serum K ≥5.0 mmoL/L			group (p<0.001)

The ARB evidence table from the 2013 Heart Failure Guideline is included at the end of this document.

The ACE inhibitor evidence table from the 2013 Heart Failure Guideline is also included at the end of this document.

The Beta Blocker evidence table from the 2013 Heart Failure Guideline is included at the end of this document.

Data Supplement 3. RCTs Comparing Pharmacological Treatment for of ARNI With ACE (Section 7.3.2.10)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint; Study Limitations; Adverse Events
IMPRESS Rouleau et al. 2000 (68) 10968433	**Aim:** Determine if inhibition of neutral endopeptidase and ACE with the vasopeptidase inhibitor omapatrilat is better than ACE inhibition alone with lisinopril **Study type:** Double blind RCT **Size:** 573 pts	**Inclusion criteria:** • Informed consent • Age ≥18 • Stable (>3 mo) symptomatic HF (NYHA class II–IV HF) • Decreased LVEF ≤40 • ≥4 wk dose of ACE inhibitors • Seated SBP ≥90 mm Hg **Exclusion criteria:** • Uncontrolled hypertension • Acute coronary events within 3 mo • Revascularization within 3 mo • Serum potassium <3.5 or >5.3 mmol/L • Creatinine >221 mcmol/L • Transaminases >2 upper limit of normal • Leucocytes <3.0x10^9/L, neutrophils <1.5x10^9/L, or platelets <120x10^9/L	**Intervention:** Omapatrilat (289) target dose 40 mg daily **Comparator:** Lisinopril (284) target dose 20 mg daily	**1° endpoint:** Change in exercise duration from baseline to wk 12 **Results**: Similar exercise duration at 12 wk (p=0.45)	**2° endpoint:** • No difference in combined endpoint of death and admission for worsening HF (p=0.52) • Combined endpoint of death and comorbidity for worsening HF was better for omapatrilat HR: 0.52 (95% CI: 0.28–0.96; p=0.035) • Angioedema occurred in no pts taking omapatrilat vs. 1 taking enalapril **Comments:** Vasopeptidase inhibitor omapatrilat did not improve exercise tolerance compared with ACE inhibitor lisinopril

		• Use of beta blockers <6 mo • Calcium channel blockers for use other than AF • Pts included in previous RCTs of omapatrilat			
OVERTURE Packer et al. 2002 (69) 12186794	**Aim:** Determine dual ACE and NEP inhibitors provides greater benefit in pts with HF than ACE inhibitors alone **Study type:** Double blind RCT **Size:** 5,770 pts	**Inclusion criteria:** • NYHA class II–IV HF due to non/ischemic cardiomyopathy for ≥2 mo, or • LVEF ≤30% and hospitalized for HF within 12 mo **Exclusion criteria:** • Surgically correctable or reversible cause of HF • Likely to receive cardiac transplant or left ventricular assist device • Severe 1° pulmonary, renal, or hepatic disease • Hx of intolerance to ACE inhibitors • ACS within 1 mo • Coronary revascularization or an acute cerebral ischemic event within 3 mo • Hx of ventricular tachycardia, ventricular fibrillation, or sudden death who did not have an ICD placed and had not fired within 2 mo • Hx or hospitalization or intravenous therapy for HF within 48 h • IV positive inotropic agent within 2 wk • SBP >180 or <90 mm Hg • Heart rate >130 bpm • Serum creatinine >2.5 mg/dL • Serum potassium <3.5 or >5.2 mmol/L	**Intervention:** Omapatrilat (2,886), target dose 40 mg daily achieved 82.5% **Comparator:** Enalapril (2,884) target dose 10 mg BID achieved 86.4%	**1° endpoint:** Combined risk of death or hospitalization for HF requiring IV treatment **Results**: No significant difference HR: 0.94 (95% CI: 0.86–1.03; p=0.187)	• Omapatrilat reduced risk of death and hospitalization for chronic HF HR: 0.89 (95% CI: 0.82–0.98; p=0.012). For this analysis, pts were treated with intensification of oral medications. • More frequent angioedema with omapatrilat (0.8% vs. 0.5%)
OCTAVE Kostis et al. 2004 (70) 14751650	**Aim:** Compare safety and efficacy of dual ACE and NEP inhibitors to ACE inhibitors alone **Study type:** Double blind RCT	**Inclusion criteria:** • Age ≥18 • 3 separate BP criteria for 3 groups: Group 1 untreated hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg); Group 2 hypertension and persistent mild hypertension (trough SBP 140–159 mm Hg and DBP <100 mm Hg, or trough DBP 90–99 mm Hg and SBP <160 mm Hg);	**Intervention:** Omapatrilat target dose 80 mg daily **Comparator:** Enalapril target dose 40 mg daily	**1° endpoints:** • Reduction in SBP at wk 8 • Need for new adjunctive antihypertensive therapy by wk 24	**2° endpoints:** • Reduction in DBP at wk 8 • Reduction in SBP and DBP at wk 24 • BP control (SBP <140 mm Hg and DBP <90 mm Hg) at wk 8 and 24 **Comments:**

	Size: 25,302 pts	Group 3 hypertension with persistent moderate to severe hypertension (trough SBP 160–179 mm Hg and DBP <110 mm Hg, or trough DBP 100–109 mm Hg and SBP <180 mm Hg) **Exclusion criteria:** • Contraindication to therapy with ACE inhibitors or angiotensin II receptor antagonists • Hx of angioedema, anaphylaxis, drug-induced or chronic urticarial, or multiple drug sensitivities • Recent hospitalization for MI, unstable angina, stroke, TIA or COPD • Recent treatment for malignancy, chronic renal disease 2° to autoimmune disease, or end-stage renal disease of any etiology • Hypertensive pts treated with ACE inhibitors whose BP placed them in study group 3			• Greater reductions in BP in omapatrilat within each study (p<0.001) • Overall mean reduction in SBP ≥3.6 mm Hg • Larger reductions in BP in black pts with omapatrilat than with enalapril. But overall reduction smaller with both drugs than in other subgroups. • Adverse events, serious adverse events, and deaths were the same for omapatrilat and enalapril • More angioedema with omapatrilat (2.17% vs. 0.68%) • More angioedema in blacks with omapatrilat (5.54% vs. 1.62%) and current smokers (3.93% vs. 0.81%)

Search Terms and Date: March 2016, angioedema, neprilysin inhibitors, omapatrilat.

Data Supplement 4. RCTs Comparing Pharmacological Treatment for Stage C HF*r*EF (Section 7.3.2.11)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
SHIFT HF Böhm et al. 2015 (71) 26508709	**Aim:** To assess influence of comorbidities on outcomes and ivabradine treatment effect of heart rate reduction in stable HF. **Study type:** Post hoc analysis of RCT	**Inclusion criteria:** Pts ≥18 y of age in sinus rhythm, heart rate at rest ≥70 bpm, MTD for HF meds **Exclusion criteria:** N/A	**Intervention:** Ivabradine **Comparator:** Placebo	**1° endpoint:** • CV death or HF hospitalization rate increased with the comorbidity load (p<0.0001) with most events in pts with >3 comorbidities for both drug and placebo. • Hospitalization rate lower for comorbidity loads of ivabradine	• Number of comorbidities was related to outcomes • Heart rate reduction with Ivabradine is conserved at all comorbidity loads

	Size: 6,505				
SHIFT Swedberg K et al. 2010 (72) 20801500 Ivabradine and outcomes in chronic HF (SHIFT)	**Aim**: To assess the effect of heart rate reduction by the selective sinus-node inhibitor ivabradine on outcomes in HF **Study type**: randomized, double-blind placebo-controlled trial. 677 centers 37 countries **Size**: 6,558 6,505 analyzed 3,241 ivabradine 3,264 placebo	**Inclusion criteria**: Over 18 y of age, in sinus rhythm, resting heart rate of ≥70 bpm, stable symptomatic chronic HF (NYHA class II-IV) for ≥4 wk, previous admission to the hospital for HF within 12 mo, LVEF ≤35% **Exclusion criteria**: HF due to congenital heart disease or 1° severe valvular disease. MI within 2 mo, ventricular or AV pacing for ≥40% of the d, AF or flutter, symptomatic hypotension The following treatments not allowed during study: • diltiazem and verapamil (nondihydropyridine CCB) • class I antiarrhythmics • strong inhibitors of CYP450 3A4	**Intervention**: Ivabradine **Comparator**: Placebo	**1° endpoint**: • Composite of CV death or hospital admission for worsening HF • Primary endpoint: ivabradine better. Event rate 24% vs. 29%. HR 0.82 (0.75–0.90); p<0.0001 • Hospitalization for worsening HF: ivabradine better. 16% vs 21%, HR: 0.74 (95% CI: 0.66–0.83; p<0.001) • Death from HF: ivabradine better. 3% vs. 5%; HF: 0.74 (0.58–0.94); p=0.014	• Composite of CV death or hospital admission for worsening HF among those receiving at least 50% of target beta blocker dose at time of randomization. All cause death; any CV death; HF hospitalization; all-cause hospitalization; any CV hospitalization; death from HF; composite of CV death HF hospitalization, nonfatal MI. • No difference in all-cause mortality or CV mortality • Ivabradine better for all-cause hospitalization, HF hospitalization, CV hospitalization, and composite 2° endpoint • Analyzed as time to first event. Median follow-up of 22.9 mo • In subgroup analysis, effect limited to those with higher baseline heart rate (≥77 bpm) • Use of devices was low (CRT in 1% and ICD in 4%) • Mean age 61 y • When added to GDEM, including beta blocker at optimal dose, ivabradine reduced adverse events, driven largely by HF mortality or HF hospitalization Adverse Effects: • 1% withdrew due to bradycardia (p<0.001) • Phosphenes 3% (p<0.001) • Comparable across age groups • AF - ivabradine 9% vs. placebo 8% (p=0.012)
SIGNIFY Fox et al. 2014 (73)	**Aim**: Assess the mortality-morbidity	**Inclusion criteria**: Stable CAD without clinical HF and heart rate of ≥70	**Intervention**: Ivabradine (n=9,550)	**1° endpoint**: • Composite of CV death and nonfatal MI	• Adverse Events: Increased bradycardia, AF, phosphenes and cardiac disorders.

25176136	benefits of Ivabradine in pts with stable CAD without clinical HF **Study type:** RCT **Size:** 19,102	bpm and in sinus rhythm, persistence and confirmation of ≥1 CV risk factors **Exclusion criteria:** Serum creatinine >200 mcmol /L, significant anemia, ALT or AST >3 times upper normal value, unstable CV condition, LVEF ≤40%; MI, coronary revascularization, stroke <3 mo.	**Comparator:** Placebo (n=9,552)	• Results: No significant difference in incidence of 1° endpoint (HR: 1.08; 95% CI: 0.96–1.20; p=0.20), death from CV causes (HR: 1.10; 95% CI: 0.94–1.28; p=0.25), nonfatal MI (HR: 1.04; 95% CI: 0.90–1.21; p=0.60) and rate of death (HR: 1.06; 95% CI: 0.94–1.21; p=0.35) **1° Safety endpoint:** • Incidence of bradycardia higher in Ivabradine group (p=0.001)	• Significant interaction between ivabradine and presence of angina in a subgroup analysis (p=0.02).
BEAUTIFUL Fox et al. 2008 (74) 18757088	**Aim:** Assess the mortality-morbidity benefits of Ivabradine in pts with CAD and LV systolic dysfunction **Study type:** Randomized, double-blind, placebo-controlled **Size:** 10,917 5,479 ivabradine 5438 placebo	**Inclusion criteria:** • Pts ≥55 y of age with stable CAD defined as: previous MI, previous revascularization (PCI or surgery), or angiographic evidence of ≥1 stenosis of ≤50%) AND LVEF <40% and end diastolic internal dimension of >56 mm. Sinus rhythm with resting heart rate of ≥60 bpm. • Angina and HF symptoms stable for 3 mo • Appropriate conventional CV medication for 1 mo. **Exclusion criteria:** MI or coronary revascularization within the previous 6 mo; stroke or TIA within 3 mo, PPM or ICD, valvular disease likely to	**Intervention:** Ivabradine n=5,479 **Comparator:** • Placebo in addition to appropriate CV medication n=5,438	**1° endpoint:** • Composite of CV death, admission for MI and admission for HF • No difference in composite 1° endpoint (22.5% vs. 22.8%; HR: 1.00; 0.91–1.1; p=0.94) • No differences in any prespecified subgroup.	**2° endpoints:** 1) All-cause mortality 2) Cardiac death (death from MI or HF or related to a cardiac procedure) 3) CV death (death from a vascular procedure, presumed arrhythmic death, stroke death, other vascular death or sudden death of unknown cause) or admission for HF, 4) Composite of admission for fatal and nonfatal MI or UA 5) Coronary revascularization 6) CV death 7) Admission for HF 8) Admission for MI • No differences in 2° endpoints in overall population. • In subgroup with heart rate of ≥70, ivabradine reduced 1) admission for AMI (fatal and nonfatal) (HR 0.64; 0.49–0.84; p=0.001) 2) composite of admission for AMI or UA (HR 0.78; 0.62–0.97; p=0.023)

		need surgery within 3 y, SSS, sinoatrial block, congenital long QT, complete AV block, severe or uncontrolled hypertension, NYHA class IV HF			3) coronary revascularization (HR 0.7; 0.52–0.93; p=0.16) • 28% in Ivabradine group discontinued medication (vs. 16%), largely due to bradycardia (13% vs. 2%) • No significant difference in adverse effects (23% vs. 23%; p=0.70)

Search Terms and Date: studies identified by chairs in December 2015, one study added by Jan 2016.

Data Supplement C. RCTs Comparing Pharmacologic Treatment for HF*p*EF: Recommendations (Section 7.3.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
HYVET Beckett et al. 2008 (75) 18378519	**Aim:** To determine whether treatment of HTN is beneficial in the elderly. **Study type:** RCT **Size:** 3,845	**Inclusion criteria:** Age >80, persistent HTN (SBP >160) **Exclusion criteria:** Known HF, creatinine >150 µmol/L (1.7 mg/dL), CVA <6 mo	**Intervention:** Indapamide + perindopril if needed for BP control. Target 150/80 mm Hg (1,933) **Comparator:** Placebo (1,912)	**1° endpoint:** • Fatal or nonfatal stroke. • Trend for improved outcome with active treatment 51 strokes (12.4/1,000 pt-y) vs. placebo 69 (17.7/1,000 pt-y), HR: 0.70; 95% CI: 0.49–1.01; p=0.06) and significantly reduced fatal stroke 27 (6.5/1000 pt-y) vs. placebo 42 (10.7/1000 pt-y), HR: 0.61; 95% CI: 0.38–0.99; p=0.046)	• Significantly reduced all-cause death HR: 0.79 (95% CI: 0.65–0.95; p=0.02) and HF incidence HR: 0.36 (95% CI: 0.22–0.58, p<0.001) with active treatment •Trend for decreased CV and HF death (p=0.06 for both)
ALLHAT Long-term Follow-up Piller et al. 2011 (76) 21969009	**Aim:** To compare diuretic-based to ACE-inhibitor or CCB-based treatment of HTN **Study type:** RCT	**Inclusion criteria:** Age >55, HTN (SBP ≥140, DBP≥90), at least 1 CV risk factor (MI, stroke, LVH, diabetes, low HDL, PVD) **Exclusion criteria:**	**Intervention:** Amlodipine (8,898) 572 with in-trial HF, Lisinopril (8,904); 469 with in-trial HF **Comparator:** Chlorthalidone (15,002); 720 with in-trial HF	**1° endpoint:** • Adjusted mortality risk • Increased mortality with in-trial incident HF, both HF*p*EF: HR: 2.42 (95% CI: 2.08–2.81, p<0.001) and HFrEF: HR: 3.06; 95% CI: 2.67–3.51; p<0.001)	• Increased HF mortality with incident HF, both HF*p*EF: HR: 3.81 (95% CI: 2.18–6.67, p<0.001) and HF*r*EF: HR: 6.80; 95% CI: 4.36–10.62; p<0.001) • No difference in mortality in pts with incident HF by drug treatment

	Size: 32,804	Symptomatic HF, EF <35% at trial entry			
SHEP HF Results Kostis et al. 1997 (77) 9218667	**Aim:** To assess the effect of antihypertensive treatment in isolated systolic HTN **Study type:** RCT **Size:** 4,736	**Inclusion criteria:** Age > 60, SBP 160–219, DBP<90 **Exclusion criteria:** Recent MI or CABG, pts with DM, stroke, AF	**Intervention:** Antihypertensive therapy: step 1, chlorthalidone, step 2, atenolol (2,365) **Comparator:** Placebo (2,371)	**1° endpoint:** • Incident HF • Active treatment decreased BP from mean of 170/77 to mean of and decreased HF events from 105 (4.4%) with placebo to 55 (2.3%) RR: 0.51 (95% CI: 0.37–0.71, p<0.001) at 4.5 y	• 1° results of SHEP showed decreased stroke risk with active treatment 149 (8.2%) with placebo to 96 (5.4%) RR: 0.64 (95% CI: 0.49–0.82, p=0.003) at 4.5 y • LV function was not measured
CHARM-Preserved Yusuf et al. 2003 (78) 13678871	**Aim:** To ascertain efficacy of candesartan in pts with HF*p*EF. **Study type:** RCT **Size:** 3,023	**Inclusion criteria:** HF pts in NYHA class II-IV with EF >40% **Exclusion criteria:** Creatinine >265 µmol/L (3.0 mg/dL), potassium >5.5 mmol/L, MI, stroke, or open-heart surgery in the previous 4 wk	**Intervention:** Candesartan (1,514) **Comparator:** Placebo (1,509)	**1° endpoint:** • CV death or admission for HF. • No difference for candesartan 333 (22%) vs. placebo 366 (24%) at 3.5 y, HR: 0.89; 95% CI: 0.77–1.03; p=0.12) covariate adjusted HR: 0.86 (95% CI: 0.74–1.00); p=0.051)	• No differences for 2° endpoints except for covariate adjusted risk of HF admission HR: 0.84 (95% CI: 0.70–1.00; p=0.047). CV death 11.2 vs. 11.3% HR: 0.99 (95% CI: 0.80–1.22; p=0.918). • Adverse effects requiring discontinuation: hypotension (2.4 vs. 1.1%; p=0.009; increased creatinine, 4.8 vs. 2.4%; p=0.005; hyperkalemia 1.5 vs. 0.6%; p=0.029) • Limitations: Some pts may have had previous EF <40%.
PEP-CHF Cleland et al. 2003 (79) 16963472	**Aim:** To ascertain efficacy of perindopril in pts with HF*p*EF. **Study type:** RCT **Size:**	**Inclusion criteria:** Age ≥70, Rx with diuretics for clinical diagnosis of HF, echo criteria for diastolic dysfunction **Exclusion criteria:**	**Intervention:** Perindopril (424) **Comparator:** Placebo (426)	**1° endpoint:** • All-cause mortality or admission for HF. • No difference for perinopril 107 (25.1%) vs. placebo 131 (23.6%) at 3 y, HR: 0.92; 95% CI: 0.70– 1.21; p=0.5. .	• HF hospitalization lower at 1 y with perindopril: 34 events (8.0%) vs. placebo 53 (12.4%), HR: 0.63; 95% CI: 0.41–0.97; p=0.033). •Limitations: Many pts withdrew (40% by 18 mo), often to take open-label ACE inhibitors (36% by study end).

	850	Creatinine >200 µmol/L (2.3 mg/dL), potassium > 5.4 mmol/L			
I-PRESERVE Massie et al. 2008 (80) 19001508	**Aim:** To ascertain efficacy of irbesartan on in pts with HF*p*EF. **Study type:** RCT **Size:** 4,128	**Inclusion criteria:** Age > 60, HF pts in NYHA class II-IV with EF >45% **Exclusion criteria:** Previous EF <40%, creatinine >222 µmol/L (2.5 mg/dL) ACS, stroke, or revascularization in the previous 3 mo	**Intervention:** Irbesartan (2,067) **Comparator:** Placebo (2,061)	**1° endpoint:** • CV death or hospitalization for CV cause. • No difference for irbesartan vs. placebo (742 (36%) vs. 763 (37%), HR: 0.95; 95% CI: 0.86 – 1.05; p=0.35)	• No differences for mortality or any other 2° endpoints • Minnesota living with HF scale improved in both, groups to the same • No difference in BNP levels • No difference in adverse effects requiring discontinuation: doubling of creatinine, 6% vs. 4%; p<0.001; K >6.0 3% vs. 2%; p=0.01) •Limitations: Study drug discontinuation in 34% of pts by end of study. High rate of concomitant ACE-I (40%)
NEAT-HF*p*EF Redfield et al. 2015 (81) 26549714	**Aim:** To ascertain efficacy of isosorbide mononitrate on daily activity in pts with HF*p*EF. **Study type:** Double-blind crossover **Size:** 110	**Inclusion criteria:** Age ≥50 y on stable HF therapy, EF ≥50%, activity limited by dyspnea, fatigue, or chest pain **Exclusion criteria:** SBP <110mm Hg and >180 mm Hg, current nitrates or PDE-5 inhibitors	**Intervention:** Isosorbide mononitrate (110) **Comparator:** Placebo (110)	**1° endpoint:** • Average daily activity assessed by accelerometer units during 120 mg phase. • Nonsignificant trend for lower daily activity in the treatment group. (-381 accelerometer units; 95% CI: -780–17; p=0.06) and significant decrease in h of activity/d (-0.30 h; 95% CI: -0.55– -0.05; p=0.02)	• No differences for any of the 3 doses on QoL scores, 6MWT and levels of NT-proBNP (trend unfavorable for nitrates) • Limitations: Rapid dose escalation of study drug.
RELAX Redfield et al. 2013 (82) 23478662	**Aim:** To ascertain effects of sildenafil on exercise capacity in pts with HF*p*EF. **Study type:**	**Inclusion criteria:** Age ≥18 on stable HF therapy, EF ≥50%, peak VO_2 <60% normal and either nt-proBNP >400 or elevated	**Intervention:** Sildenafil (113) **Comparator:** Placebo (103)	**1° endpoint:** • Change in peak VO_2 from BL at 24 wk • No difference between sildenafil (-0.20, IQR -1.7–1.11) and placebo (-0.20,	• No differences in clinical rank score or 6-min walk •Limitations: Urinary cGMP levels were not increased in sildenafil group, raising questions about dosing. High prevalence of

	Double-blind **Size:** 216	PCWP **Exclusion criteria:** Systolic BP <110mm Hg and >180 mm Hg, MMI or revascularization within 60 d, eGFR <20 mL/min		IQR -0.70–1.0) • More worsening of renal function in sildenafil group (p=0.047)	chronotropic incompetence in study population.
TOPCAT Pitt et al. 2014 (83) 24716680 ● New England Research Institutes Post-hoc analysis that captures differences in outcomes by geography - for reference list only	**Aim:** To assess the effects of spironolactone in pts with HF*p*EF. **Study type:** RCT **Size:** 3,445	**Inclusion criteria:** Symptomatic HF, Age ≥50y, LVEF ≥45% stratified according to - HF Hospitalization within past y - Elevated NPs **Exclusion criteria:** Renal disease (eGFR <30 or creatinine >22 µmol/L (2.5 mg/dL), systemic illness with life expectancy <3 y. Specific co-existing conditions, meds, and acute events	**Intervention:** Spironolactone (1,722) **Comparator:** Placebo (1,723)	**1° endpoint and results:** • Composite of CV mortality, HF hospitalization, or aborted cardiac arrest. • No difference with spironolactone vs. placebo 320 (18.6%) vs. 351 (20.4%), HR: 0.89; 95% CI: 0.77–1.04; p=0.138)	• HF hospitalization was reduced with spironolactone 206 (12.0%) vs. 245 (14.2%), HR: 0.83; 95% CI: 0.69–0.99; p=0.04) • Increased hyperkalemia (18.7% vs. 9.1%), decreased hypokalemia (16.2% vs. 22.9%) and more doubling of creatinine (10.2% vs. 7.0%) with spironolactone

TOPCAT Regional Analysis Pfeffer et al. 2015 (84) 25406305 Post-hoc analysis that captures differences in outcomes by geography	**Aim:** To assess regional differences in the effects of spironolactone in pts with HF*p*EF. **Study type:** RCT **Size:** 3,445	**Inclusion criteria:** Symptomatic HF, Age ≥50y, LVEF ≥45% stratified according to • HF Hospitalization within past y • Elevated NPs **Exclusion criteria:** Renal disease (eGFR <30 or creatinine >22 µmol/L (2.5 mg/dL), systemic illness with life expectancy <3 y. Specific co-existing conditions, meds, and acute events	**Intervention:** Spironolactone (1,722) **Comparator:** Placebo (1,723)	**1° endpoint and results:** • Composite of CV mortality, HF hospitalization, or aborted cardiac arrest across regions. • 1° outcome events in 522 (29.5%) pts in the Americas and 149 (8.9%) in Russia/Georgia. 1° outcome event rates with spironolactone and placebo 10.4/100 pt y and 12.6/100 pt y in the Americas and 2.5/100 pt y and 2.3/100 pt y in Russia/Georgia. HR spironolactone vs. placebo 0.82; 95% CI: 0.69–0.98; p=0.026) in the Americas and 1.10 95% CI: 0.79–1.51; p=0.12) in Russia/Georgia.	• Spironolactone had markedly greater effects on BP (4.2 mm Hg drop vs. 0.6 mm Hg; p<0.001, potassium change relative to placebo (0.26 mmol/L vs. 0.08 mmol/L), and increase in creatinine (0.10 vs. 0.02 mg/dL; p<0.001) • Limitations: post-hoc analysis
Chen et al. 2015 (85) 25598008	**Aim:** To assess effects of MRAs in pts with HF*p*EF. **Study type:** Meta-analysis **Size:** 14 RCTs with 6,428 pts	**Inclusion criteria:** Prospective, RCTs that enrolled adult pts with LVEF ≥40% (including post-MI and those with symptomatic or asymptomatic HF) with a study duration of ≥4 mo that assessed at least 1 clinical outcome of interest.	**Intervention:** MRAs (3,249) **Comparator:** Placebo (2,861) Or standard therapy (301) Or active comparator (31)	**1° endpoint and results:** • All-cause mortality and HF hospitalization • No difference in all-cause mortality (RR: MRAs vs. placebo 0.90; 95% CI: 0.78–1.04; p=0.17) • Reduced risk of HF hospitalization (RR: MRA vs. placebo 0.83; 95% CI: 0.70–0.98; p=0.03) **1° Safety endpoint :** • More hyperkalemia with MRAs (12.2% vs. 6.2%, p<0.001)	• MRAs improved QOL (weighted mean difference −5.2; 95% CI: −8.0– −2.3). • MRA's improved echo indices of LV function: E/e', E/A ratio, deceleration time, interventricular relaxation time • Renal failure in 1.19% of pts with MRAs vs. 0.39% • Gynecomastia in 2.81%R vs. 0.3% • Limitations: discrepancies in definitions of HF*p*EF in different trials; heterogeneity of trial outcomes and their assessment, including follow-up duration; 1° outcome results driven by

					TOPCAT
PARAMOUNT Solomon et al. 2012 (61) 22932717	**Aim:** To address safety and efficacy of LCZ696 in pts with HF*p*EF. **Study type:** RCT **Size:** 308	**Inclusion criteria:** Pts ≥40 y of age, LVEF ≥45%, NYHA class II-III HF, NT-pro BNP >400 pg/mL **Exclusion criteria:** Previous EF <45%, isolated right HF, noncardiac dyspnea, CAD or CVD needed revascularization <3 mo Right HF due to pulmonary disease, dyspnea due to noncardiac causes, valvular/myocardial disease, CAD or CVD needing revascularization within 3 mo of screening.	**Intervention:** LCZ696 (149) **Comparator:** Valsartan (152)	**1° endpoint:** • Change in BNP at 12 wk • Greater reduction with LCZ696 (ratio of change compared to valsartan 0.77; 95% CI: 0.64–0.92; p=0.001) **1° Safety endpoint:** •Serious adverse events 15% in LCZ676 group and 20% in valsartan group (p=NS)	• Effect persisted after adjustment for more lowering of BP in LCZ676 group • Improvement in NYHA class at 36 wk in LCZ676 group compared to valsartan. • Reduction of LA size at 36 wk in LCZ676 group compared to valsartan. • BNP levels higher than in other HF*p*EF trials, perhaps because this was an entry criterion.

Date: Some studies added by chairs in December 2015, others added by the writing committee.

Data Supplement D. RCTs Comparing Anemia (Section 9.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events

CONFIRM-HF Ponikowski et al. 2015 (86) 25176939 ● Vifor Inc. ● ICON Clinical Research	**Aim:** To assess benefits and safety of long term FCM in iron-deficient pts with HF **Study type:** RCT (1:1) **Size:** 304	**Inclusion criteria:** Pts at least 18 y, NYHA class II or III, LVEF≤45%, elevated NPs, ID defined as ferritin <100 ng/mL, or ferritin 100–300 ng/mL if TSAT <20%, Hb <15 mg/dL **Exclusion criteria:** Pts in need of transfusion, if not able to complete 6MWT, uncontrolled HTN, infection, malignancy, impaired liver or renal function	**Intervention:** FCM (152) **Comparator:** Placebo (152)	**1° endpoint:** • Change in 6MWT distance from BL to wk 24 • Results: Change in 6MWT distance FCM vs. placebo of 33±11 m (p=0.002)	**2°Endpoints:** • Changes in NYHA class • PGA • 6MWT distance • Fatigue score • KCCQ • EQ-5D • Assessed at wk 6, 12, 24, 36, 52 • Rate of any hospitalization, rate of hospitalization for any CV reason, and rate of hospitalization due to worsening HF; • Time to first hospitalization for any reason, time to first hospitalization for any CVCV reason and time to first hospitalization due to worsening HF; • Time to death for any reason, time to death for any CV reason, and time to death due to worsening HF. **Results:** • Significant improvements in NYHA class, PGA, QoL and Fatigue scores, 6 MWD up to 52 wk • Significant reduction in the risk of hospitalizations for deteriorating HF, HR: 0.39 (95% CI: 0.19–0.82) (p=0.009) • Preserved treatment effect across subgroups • No differences in adverse events when compared to placebo • Study was not designed to test morbidity and mortality outcomes of the ID therapy with FCM

FAIR-HF Anker et al. 2009 (87) 19920054	**Aim:** To evaluate the effects of intravenous iron (FCM) on HF symptoms in pts with systolic HF and ID, with and without anemia. **Study type:** RCT (2:1) **Size:** 459	**Inclusion criteria:** • Chronic HF • NYHA class II or III, • LVEF ≤40% (for pts in NYHA class II) or ≤45% (for pts in NYHA class III), • Hemoglobin level 95–135 g/L • ID **Exclusion criteria:** • Uncontrolled HTN • Other clinically significant heart disease • Inflammation • Clinically significantly impaired liver or renal function.	**Intervention:** Ferric carboymaltose 200 mg weekly until hemoglobin was corrected (n=304) **Comparator**: Placebo (n=155)	**1° endpoint:** • PGA at 24 wk • Results: improvement in the FCM group compared to placebo • 50% much or moderately improved vs. 28% (OR for being in a better rank, 2.51; 95% CI: 1.75–3.61; p<0.001) • NYHA class at 24 wk • Results: improvement in the FCM arm compared to placebo • 47% with NYHA I or II vs. 30% in the placebo arm (OR for improvement by 1 class, 2.40; 95% CI: 1.55–3.71; p<0.001) **1° Safety endpoint:** Trend towards fewer HF hospitalizations in the FCM group (p=0.08)	• Improvement in the FCM group in PGA and NYHA at wk 4 and 12 (p<0.001) •Mean improvement in 6MWT of 35±8m at 24 wk (p<0.001); also significant improvements at 4 and 12 wk •Significant improvement in the EQ-5D and in KCCQ
RED-HF Swedberg et al. 2013 (88) 23473338 ● Amgen	**Aim:** To assess effects of darbepoetin alfa on pts with systolic HF and anemia. **Study type:** RCT **Size:** 2,278	**Inclusion criteria:** NYHA class II, III, or IV HF; LVEF≤40%; Hgb: 9.0–12.0 g/dL; on guideline-recommended HF treatment. **Exclusion criteria:** Transferrin saturation <15%, bleeding or other causes of anemia, serum creatinine >3 mg/dL, BP	**Intervention:** Darbepoetin alfa (1,136) **Comparator:** Placebo (1,142)	**1° endpoint:** • Composite of death from any cause or hospitalization for worsening HF • Results: 1° outcome occurred in 576 pts in the darbepoeitin alfa group vs. 562 in the placebo group (HR: 1.01; 95% CI: 0.90–1.13; p=0.87) **1° Safety endpoint :** • Increased thromboembolic adverse events in the treatment group (p=0.01);	• Limitation: pts with severe anemia were excluded

		>160/100 mm Hg.		No significant increase in fatal/nonfatal strokes in treatment group and similar cancer-related adverse events between groups	

Date: Chairs selected trials in December 2015. One trial added by writing committee.

Data Supplement E. RCTs Comparing HTN (Section 9.5)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Xie et al. 2016 (89) 26559744	**Aim:** To assess the efficacy and safety of intensive BP lowering strategies. **Study Type**: SR and meta-analysis **Size**: 19 trials with 44,989 pts; 3.8 y of follow-up.	**Inclusion Criteria**: RCTs with different BP targets or different BP changes between more vs. less intense therapy with at least 6 mo follow-up. **Exclusion Criteria**: Trials that did not assess a different target or relevant outcome.	5 RCTs (6,960 pts) enrolled only pts with DM and 6 trials (2,809 pts) specifically recruited pts with CKD.	**1° Outcomes**: Major CV events, defined as MI, stroke, HF or CV death, separately and combined; nonvascular and all-cause mortality; ESRD; and adverse events; new onset microalbuminuria/macroalbuminuria or change from micro- to macroalbuminuria and retinopathy in pts with DM. **Results**: Pts in the more intensive BP-lowering treatment group had mean BP 133/76 mm Hg compared with 140/81 mm Hg in the less intensive group. Intensive BP-lowering treatment achieved RR reductions for major CV events: 14% (95% CI: 4, 22), MI: 13% (95% CI: 0, 24), stroke: 22% (95% CI: 10, 32), albuminuria: 10% (95% CI: 3, 16), and retinopathy progression: 19% (95% CI: 0–34). However, more	**Study Limitations**: Only 6,960 pts with DM were included in the total study size of 44,989 pts. **Conclusions**: The absolute CV benefits were greatest in trials in which all enrolled pts had vascular disease, renal disease or DM. However, only 6,960 of the 44,989 pts had DM and no subanalysis for DM was provided; however, the outcome benefits were qualitatively most striking for pts with DM, CKD and/or vascular disease.

				intensive treatment had no clear effects on HF: RR: 15% (95% CI: -11, 34), CV death: 9% (-11, 26), total mortality: 9% (95% CI: -3, 19), or ESRD: 10% (95% CI: -6, 23). The reduction in major CV events was consistent across pt groups, and additional BP lowering had a clear benefit even in pts with SBP <140 mm Hg. The absolute benefits were greatest in trials in which all enrolled pts had vascular disease, renal disease, or DM. Serious adverse events associated with BP lowering were only reported by 6 trials and had an event rate of 1·2% per y in intensive BP lowering group pts, compared with 0.9% in the less intensive treatment group (RR: 1.35 (95% CI: 0.93, 1.97)). Severe hypotension was more frequent in the more intensive treatment regimen (RR: 2.68 (95% CI: 1.21, 5.89), p=0·015), but the absolute excess was small (0.3% vs. 0.1% per pt-y for the duration of follow-up).	
SPRINT Wright et al. 2015 (90) 26551272	**Aim:** To test the effectiveness of a goal SBP <120 mm Hg vs. a goal SBP <140 mm Hg for the prevention of CVD in pts with SBP ≥130 mm Hg at BL. **Study type:**	**Inclusion criteria:** SBP ≥130 mm Hg, with upper limit varying as number of pre-trial BP-lowering meds increased. Age ≥50 y Presence of at least 1: • Clinical or subclinical CVD	**Intervention:** Intensive BP lowering treatment to goal SBP <120 mm Hg (4,678) **Comparison:** • Standard BP lowering treatment to goal SBP <140 mm Hg (4,678) • Net treatment difference ~3 drugs (2.8) on average vs. 2 drugs (1.8) on	**1° Endpoint:** • Composite of MI, non-MI ACS, stroke, ADHF, CV death; HR: 0.75 (95% CI: 0.64, 0.89) • Lower BP target reduced composite outcome 243 pts (1.65%/y) vs. higher target 319 (2.19%/y), HR: 0.75; 95% CI: 0.64–0.89; p<.001) and death: lower target 155 vs. 201, HR: 0.73; 95% CI: 0.60–0.90;	**Summary:** • More intensive SBP lowering to a goal of <120 mm Hg with achieved mean of ~121 mm Hg resulted in less CVD and lower total mortality over 3.26 y in comparison with a goal SBP <140 mm Hg and achieved SBP of ~135 mm Hg. • There were small increases in some expected SAEs. Perhaps unexpected, a sizable increase

	RCT **Size:** 9361 pts followed median of 3.26 y.	• CKD stage 3 or greater • Age ≥75 • Framingham General CVD risk ≥15% in 10 y **Exclusion criteria:** DM, history of stroke, ESRD (eGFR <20 mL/min), anticipated survival <3 y	average • During the trial, mean SBP was 121.5 vs. 134.6.	p=0.003) **Other endpoints:** • Total deaths HR: 0.73 (95% CI: 0.60–0.90) • 1° or death HR: 0.78 (95% CI: 0.67–0.90) • Components of 1° composite mostly consistent in direction other than ACS – no difference. **CKD outcomes:** • 1° in CKD pts: reduction in GFR of ≥50% or ESRD HR: 0.89 (95% CI: 0.42, 1.87) • Incident albuminuria HR: 0.72 (95% 0.48, 1.07) • In pts without CKD: reduction in GFR ≥30% and to <60 • HR: 3.49 (95% CI: 2.44–5.10) • Incident albuminuria HR: 0.81 (95% CI: 0.63–1.04) **Adverse events:** • SAEs: 1.04, p=0.25 • Significant absolute increases seen in intensive group for hypotension (1%), syncope (0.6%), electrolyte abnormality (0.8%), AKI/ARF (1.6%) over the study period. • 1.7% fewer pts had orthostatic hypotension in intensive group, p=0.01.	in reduced eGFR in the non-CKD group and AKI/ARF overall was observed in the intensive group. While of uncertain etiology and significance, there is speculation this could be an acute hemodynamic effect, especially given the findings regarding albuminuria. • Low target significantly reduced HF: HR: 0.62 (95% CI: 0.45–0.84; p=0.002) • No difference in composite or individual renal outcomes with lowering of BP **Limitations:** Few pts were untreated at BL ~9%, so SPRINT provides little if any insight at present regarding BP lowering medication initiation for untreated people with SBP 130–139.

SPRINT Senior Williamson et al. 2016 (91) 27195814	**Aim:** Intensive SBP goal <120mmHg) vs standard (SBP goal <140) **Study Type:** RCT **Size:** 2,636 30% met criteria for being classified as ambulatory frail **Mean follow-up**: 3.1 y	**Inclusion:** Men and women age 75+; mean age 79.8 y; 38% women; 17% black, 74% Caucasian; Exclusions: Nursing home residents; diabetes, Stroke, symptomatic HF in past 6 mo or EF <35%, dx or treatment of dementia, unintentional wt loss >10% in past 5 mo. SBP<110 after standing 1 min, expected survival <3y	**Intervention:** Medications and dietary advice to achieve SBP of <120 mm Hg **Comparator:** Medications and dietary advice to achieve SBP of <140 mm Hg **Achieved SBP:** Intensive= 123.4 mm Hg Standard= 134.8 mm Hg	**1 endpoint:** Composite CVD outcome (AMI, non-MI ACS, Stroke, HF, CVD death. **Results**: 102 events in the intensive treatment group vs 148 events in the standard treatment group; HR: 0.66; 95%CI: 0.51–0.85 and all-cause mortality (73 deaths vs. 107 deaths, respectively; HR: 0.67; 95%CI: 0.49–0.91. No significant difference in falls, orthostatic hypotension, or overall SAEs. NNT for primary outcome=27 and NNT for all-cause mortality=41	**Limitations**: Does not apply to nursing home patients or those with dementia **Conclusions:** Intensive SBP is safe and effective for lowering CVD events and total mortality in persons age 75 and older
TOPCAT Regional Analysis Pfeffer et al. 2015 (84) 25406305 Post-hoc analysis that captures differences in outcomes by geography	**Aim:** To assess regional differences in the effects of spironolactone in pts with HF*p*EF. **Study type:** RCT **Size:** 3,445	**Inclusion criteria:** Symptomatic HF, Age ≥50y, LVEF ≥45% stratified according to • HF Hospitalization within past y • Elevated NPs **Exclusion criteria:** Renal disease (eGFR <30 or creatinine >22 µmol/L (2.5 mg/dL), systemic illness with life expectancy <3 y. Specific co-existing	**Intervention:** Spironolactone (1,722) **Comparator:** Placebo (1,723)	**1° endpoint and results:** • Composite of CV mortality, HF hospitalization, or aborted cardiac arrest across regions. • 1° outcome events in 522 (29.5%) pts in the Americas and 149 (8.9%) in Russia/Georgia. 1° outcome event rates with spironolactone and placebo 10.4/100 pt y and 12.6/100 pt y in the Americas and 2.5/100 pt y and 2.3/100 pt y in Russia/Georgia. HR spironolactone vs. placebo 0.82; 95% CI: 0.69–0.98; p=0.026) in the Americas and 1.10 95% CI: 0.79–1.51; p=0.12) in Russia/Georgia.	• Spironolactone had markedly greater effects on BP (4.2 mm Hg drop vs. 0.6 mm Hg; p<0.001, potassium change relative to placebo (0.26 mmol/L vs. 0.08 mmol/L), and increase in creatinine (0.10 vs. 0.02 mg/dL; p<0.001) • Limitations: post-hoc analysis

		conditions, meds, and acute events			
Law et al., 2009 (92) 19454737	**Study type:** Meta-analysis of use of BP lowering drugs in prevention of CVD from 147 randomized trials **Size:** Of 147 randomized trials of 464,000 pts, 37 trials of beta blockers in CAD included 38,892 pts, and 37 trials of other antihypertensive drugs in CAD included 85,395 pts	**Inclusion criteria:** The database search used Medline (1966-Dec. 2007 in any language) to identify randomized trials of BP lowering drugs in which CAD events or strokes were recorded. The search also included the Cochrane Collaboration and Web of Science databases and the citations in trials and previous meta-analyses and review articles. **Exclusion criteria:** Trials were excluded if there were <5 CAD events and strokes or if treatment duration was <6 mo.	**1° endpoint:** CAD events; stroke **Results:** In 37 trials of pts with a history of CAD, beta blockers reduced CAD events 29% (95% CI: 22%–34%). In 27 trials in which beta blockers were used after acute MI, beta blockers reduced CAD events 31% (95% CI: 24%–38%), and in 11 trials in which beta blockers were used after long term CAD, beta blockers insignificantly reduced CAD events 13%. In 7 trials, beta blockers reduced stroke 17% (95% CI: 1%–30%). CAD events were reduced 14% (95% CI: 2%–25%) in 11 trials of thiazide diuretics, 17% (95% CI: 11%–22%) in 21 trials of ACE inhibitors, insignificantly 14% in 4 trials of angiotensin receptor blockers, and 15% (95% CI: 8%–22%) in 22 trials of CCBs. Stroke was reduced 38% (95% CI: 28%–47%) in 10	• With the exception of the extra protective effect of beta blockers given shortly after a MI and the minor additional effect of CCBs in preventing stroke, all the classes of BP lowering drugs have a similar effect in reducing CAD events and stroke for a given reduction in BP.	

			trials of thiazide diuretics, 22% (95% CI: 8%–34%) in 13 trials of angiotensin-converting enzyme inhibitors, and 34% (95% CI: 25%–42%) in 9 trials of CCBs.		
Aronow et al. 1997 (93) 9230162	**Aim:** To determine effect of propranolol vs. no propranolol on mortality plus nonfatal MI in pts with prior MI and HF*p*EF	**Inclusion criteria:** Pts ≥62 y with MI and LVEF ≥40% and HF NYHA class II or III treated with diuretics and ACE inhibitors for 2 mo	**Intervention:** 79 pts were randomized to treatment with propranolol **Comparator:** 79 pts were randomized to no propranolol. All pts continued diuretic and ACE inhibitor therapy.	**1° endpoint:** At 32-mo mean follow-up, multivariate Cox regression analysis showed that compared with no propranolol, propranolol reduced mortality 35% (p=0.03) and mortality plus nonfatal MI 37% (p=0.018)	**Relevant 2° Endpoint:** At 1-y follow-up, LVEF was increased by propranolol from 57% to 63% (p<0.001) and LV mass was decreased by propranolol from 312 grams to 278 grams (p=0.001) Propranolol was stopped because of adverse effects in 11 of 79 pts (14%)
Van Veldhuisen et al. 2009 (94) 19497441	**Aim:** To determine the effect of nebivolol vs. placebo in pts with HF*r*EF and HF*p*EF	**Inclusion criteria:** Pts ≥70 y history of HF and HF*r*EF or HF*p*EF	**Intervention/Comparator:** 1,359 pts with a history of HF*r*EF and 752 pts with a history of HF*p*EF were randomized to nebivolol or to placebo	**1° endpoint:** At 21-mo follow-up, the primary endpoint of all-cause mortality or CV hospitalization was reduced by nebivolol 14% (95% CI: 0.72–1.04) in pts with HF*r*EF and 19% (95% CI: 0.63, 1.04) in pts with HF*p*EF	**Relevant 2° Endpoint:** HR for reduction of all-cause mortality by nebivolol: 0.84 (95% CI: 0.66–1.08) for HF*r*EF and 0.91 (95% CI: 0.62–1.33) for HF*p*EF
Yusuf et al. 2003 (78) 13678871	**Aim:** To determine the effects of candesartan vs. placebo in pts with HF*p*EF	**Inclusion criteria:** 3,023 pts, mean age 67 y, with HF*p*EF and NYHA class II-IV HF	**Intervention/Comparator:** 3,023 pts were randomized to candesartan or placebo	**1° endpoint:** At 36.6 m follow-up, the primary outcome of CV death or hospitalization for HF was reduced 11% (p=0.118) by candesartan	**Relevant 2° Endpoint:** Hospitalization was reduced 16% (p=0.047) by candesartan
Massie et al. 2008 (80) 19001508	**Aim:** To determine the effect of irbesartan vs. placebo on all-cause mortality or hospitalization for a CV cause in pts with HF*p*EF	**Inclusion criteria:** Pts 60 y and older with HF*p*EF and NYHA class II, III, or IV HF	**Intervention/Comparator** 4,128 pts were randomized to irbesartan or placebo	**1° endpoint:** At 49.5-mo follow-up, the primary outcome of all-cause mortality or hospitalization for CV cause was reduced 5% by irbesartan (p=0.35)	**Relevant 2° Endpoint:** Irbesartan did not significantly reduce the secondary outcomes of death from HF or hospitalization for HF, death from any cause and from CV causes, and quality of life

Piller LB, et al., 2011 (76) 21969009	**Aim:** To determine mortality rates in pts who developed HF in ALLHAT	**Inclusion criteria:** 1,761 pts, mean age 70 y, developed HF during ALLHAT	**Intervention/Comparator** At 8.9-y mean follow-up, 1,348 of 1,761 pts (77%) with HF died	**1° endpoint:** Post-HF all-cause mortality was similar for pts treated with chlorthalidone, amlodipine, and lisiopril. 10-y adjusted rates for mortality were 86% for amlodipine, 87% for lisinopril, and 83% for chlorthalidone	**Relevant 2° Endpoint:** All-cause mortality rates were similar for those with HF*r*EF (84%) and for those with HF*p*EF (81%) with no significant differences by randomized treatment arm
Lv et al. 2013 (95) 23798459	MA of RTC that randomly assigned individuals to different target BP levels	15 trials including a total of 37,348 pts.	7.5/4.5 mm Hg BP difference. Intensive BP lowering achieved. RR for • Major CV events: 11%; 95% CI: 1%–21%) • MI: 13%; 95% CI: 0%–25% • Stroke: 24%; 95% CI: 8%–37% • ESRD: 11%; 95% CI: 3%–18% • Albuminuria: 10%; 95% CI: 4%–16% • Retinopathy 19%; 95% CI: 0%–34% p=0.051	More intensive strategy for BP control reduced cardio-renal end point	

Date: Chairs selected trials in October 2016.

Data Supplement F. Nonrandomized Trials for Hypertension (Section 9.5)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Primary Endpoint and Results (P values, OR or RR & 95 % CI)	Summary / Conclusion / Comments
Thomopoulos et al. 2016 (96) 26848994	Meta-analysis of RCT's of more versus less intense BP control	16 trials (52,235 pts) compared more vs. less intense treatment 34 (138,127 pts) active vs. placebo	More intense BP • Stroke RR: 0.71; 95% CI: 0.60–0.84) • Coronary heart disease RR: 0.80; 95% CI: 0.68–0.95) • Major CV events RR: 0.75; 95% CI: 0.68–0.85 • CV mortality RR: 0.79; 95% CI: 0.63–0.97 Stratification of SBP cutoffs (150, 140 and 130	• Intensive BP reduction improves CV outcomes compared to less intense • Achieved BP of <130/80 mm Hg may be associated with CV benefit.

			mmHg) showed that a SBP/DBP difference of _10/_5mmHg across each cutoff reduced risk of all outcomes	

Date: Chairs selected trials in October 2016.

Data Supplement G. RCTs Comparing Treatment of Sleep Disorders (CPAP makers) (Section 9.6)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint; Study Limitations; Adverse Events
SAVE McEvoy et al. 2016 (97) 27571048	**Aim:** To whether treatment with CPAP prevents major CV events. **Study type:** RCT with 1 wk run-in on sham CPAP **Size:** n=2,717	**Inclusion criteria:** • Adults 45 - 75 y of age • Moderate-to-severe OSA • Coronary or cerebrovascular disease **Exclusion criteria:**	**Intervention:** CPAP treatment plus usual care (CPAP group) **Comparator:** Usual care alone (usual-care group)	**1° endpoint:** Composite of death from CVD, MI, stroke, or hospitalization for UA, HF, or TIA **Results:** • Duration of CPAP=3.3 h/night; AHI events/h decreased from baseline to end of follow up at 3.7 y, 29.0–3.7 events/h • Primary endpoint – no significant difference in CPAP vs usual-care group (n=229, 17.0% vs. n=207; 15.4%; HR: 1.10 with CPAP; 95% CI: 0.91–1.32; p=0.34). • No significant difference in any individual or other composite CV end point. • CPAP significantly reduced snoring and daytime sleepiness and improved health-related quality of life and mood.	**Secondary end points:** • Other CV outcomes • Health-related quality of life • Snoring symptoms • Daytime sleepiness • Mood **Study Limitations:** • Primarily men with moderate-to-severe OSA and minimal sleepiness **Adverse Events:**
ORBIT-AF Holmqvist et al. 2015 (98) 25965712	**Aim:** 1) Define frequency of diagnosed	**Inclusion criteria:** • ≥18 years of age • Electrocardiographic evidence of AF	**Intervention:** N/A **Comparator:** N/A	**1° endpoint:** • All-cause mortality; • First all-cause hospitalization; • Composite of first event of CV	**Secondary end points:** N/A **Study Limitations:**

	OSA among nationwide AF population; 2) Determine whether OSA is associated w/: a) Worse outcomes; b) Arrhythmic AF progressi on; & 3) Determine whether CPAP treatment is associated w/ outcomes in patients w/ AF & OSA. **Study type:** • Prospective descriptive, correlational / comparative, time-series design • Data collection at enrollment & 6-month intervals for minimum of 2 years **Size:** Nationally representative	**Exclusion criteria:** • Life expectancy of <6 months or AF secondary to reversible conditions	Multicenter, ambulatory-based registry	death, stroke/non–central nervous system embolism, TIA, or MI; • First major bleed within 2 years of baseline enrollment in registry **Results:** Frequency of diagnosed OSA among nationwide AF population • 18% (n =1,841) OSA associations w/ outcomes • Higher risk of: o Hospitalization (43 vs 35 events/100 patient-years among patients without OSA [adjusted hazard ratio (HR), 1.12; 95% confidence interval (CI), 1.03-1.22; p=.0078] • No higher risk of: o Death (HR, 0.94; 95% CI, 0.77-1.15; p=.54); o Composite of CV death, stroke/non–central nervous system embolism, TIA, or MI (HR, 1.07; 95% CI, 0.85-1.34; p=.57); o First major bleeding (HR, 1.18; 95% CI, 0.96-1.46; p=.11) OSA associations w/ AF progression • Not associated w/ higher risk of AF progression (HR, 1.06; 95% CI, 0.89-1.28; p=.51). CPAP treatment association w/ outcomes in patients w/ AF & OSA Less likely to progress to more permanent forms of AF versus patients w/out CPAP (HR, 0.66; 95% CI, 0.46-0.94; p=.021).	• Voluntary, observational study - selection & reporting biases o No randomization - Voluntary, observational study - selection & reporting biases o OSA diagnosis made on basis of physician report & medical records. • No data on average duration of CPAP use per night • Maturation – changes in subjects over 2 years not accounted for in data **Adverse Events:** N/A

	sample enrolled consecutively • n=10,132 w/ AF ○ n=1,841 w/ AF & OSA ○ n=1,837 patients w/ OSA & complete CPAP data ○ n =1,763 patients w/ OSA & 2-year outcomes data ○ n=937 patients w/ AF, OSA, & CPAP treatment **Sites:** 176 national sites that w/ provider & geographic heterogeneity				
SERVE-HF Cowie et al. 2015 (99) 26323938 • ResMed • The Clinical Research Institute GmbH	**Aim:** Effects of adaptive servo-ventilation in HF pts with reduced EF and CSA **Study type:** RCT **Size:**	**Inclusion criteria:** • Chronic HF (defined as ≥12 wk since diagnosis) according to current ESC guidelines • LVEF ≤45% • Hypopnea index of ≥10/h • Stable, GDMT • NYHA class III or IV, or NYHA class II with ≥1 hospitalization for HF in the last 24 mo • No hospitalization for HF in 4 wk prior to enrolment	**Intervention:** Adaptive servo ventilation use ≥5h/night, 7d/wk. (n=666) **Comparator:** GDMT (n=659)	**1° endpoint:** • Death from any cause • Lifesaving CV intervention (cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest, or appropriate lifesaving shock) or • Unplanned hospitalization for HF **Significant Results** • All-cause mortality was higher with the intervention (34.8%) than	**2° Endpoint** • CV death • Unplanned hospitalization from any cause • Time to death from CV causes • Change in NYHA class • Change in 6-MWT (both at follow-up visits). • General QoL (EuroQOL) • HF-specific QoL (MLWHF) • Daytime sleepiness

	1,325	• Optimized GDMT • No new class of disease-modifying drug for prior ≥4 wk • AHI >15/h with ≥50% central events and a central AHI ≥10/h **Exclusion criteria:** • Significant COPD with a forced expiratory volume in 1 s in 4 wk before randomization • O_2 saturation ≤90% at rest during d • Currently receiving PAP therapy • Cardiac surgery, PCI, MI or UA within the previous 6 mo • Cardiac resynchronization therapy implantation scheduled or performed within 6 mo prior to randomization • TIA or stroke within the previous 3 mo • 1° hemodynamically-significant uncorrected VHD (obstructive or regurgitant) or any valvular disease expected to require surgery during the trial; • Acute myocarditis/pericarditis within the previous 6 mo • Untreated or therapy-refractory restless legs syndrome • Contraindication to the use of AutoSet CS2 because of symptomatic hypotension or significant intravascular volume depletion or pneumothorax or pneumomediastinum • Pregnancy		control (29.3%; HR: 1.28; 95% CI: 1.06–1.55; p=0.01). • CV mortality was higher with the intervention (29.9%) than control (24.0%; HR: 1.34; 95% CI: 1.09–1.65; p=0.006). • 6MWT decreased over time and were significantly lower with the intervention than with the control (p=0.02). • Daytime sleepiness decreased over time and was significantly lower with the intervention than with the control (p<0.001). **Non-Significant Results** • Unplanned hospitalization for HF was not significantly higher with the intervention (43.1%) than control (41.3%; HR: 1.13; 95% CI: 0.95–1.33; p=0.16) • Of the lifesaving CV interventions, none were significantly higher with the intervention than control (p=0.08–0.61) • Unplanned hospitalization for any cause was not significantly lower with the intervention (67.9%) than control (68.0%; HR: 1.05; 95% CI: .92–1.20; p=0.47) • The NYHA class change was not significantly different with the intervention than with the control (p=0.46) • General QoL trends were not significantly higher with the intervention than with the control (p=0.09). • HF-specific QoL trends were not significantly higher with the	(Epworth Sleepiness Scale) **Limitations:** • Unblinded study - more likely to favor treatment group, particularly for QOL, but no QOL improvement seen • HF pts with reduced EF only • HF pts with predominantly CSA not obstructive sleep apnea. • Sample had very limited # of women but reflects epidemiology of CSA with HF*r*EF

				intervention than with the control (p=0.92).	
CANPAP Arzt et al. 2007 (100) 17562959	**Aim:** Investigate whether suppression of CSA below threshold by CPAP would LVEF & ht tx–free survival. **Study type:** Post hoc analysis of RCT **Size:**100	**Inclusion criteria:** • Age 18 to 79 y • NYHA II-IV • HF due to ischemic, hypertensive, or idiopathic DCM • Stabilized w/ optimal medical therapy for ≥1 mo • LVEF <40% • CSA **Exclusion criteria:** • Pregnancy • MI • Unstable angina • Cardiac surgery w/in 3 mo of enrollment • OSA	**Intervention:** • CPAP=CSA suppressed, n=57 • CPAP=CSA suppressed, n=43 **Comparator:** Control, n=110:	**1° endpoint:** • Transplant free survival - Combined rate of all-cause mortality & ht tx **Significant Results** **1° endpoint:** **Transplant free survival** • Significantly different between 3 groups (p=0.016) • Significantly higher in CPAP-suppressed vs. control group (p<0.043) • No difference between CPAP-unsuppressed vs. control group (p<0.26) **2° endpoint:** **•AHI** • AHI significantly > reduction in both CPAP-suppressed (p<0.001) and CPAP-unsuppressed (p<0.001) groups • AHI significantly > reduction in CPAP-suppressed (p<0.001) and CPAP-unsuppressed (p<0.002) than control groups **Mean nocturnal SaO2** • Mean nocturnal SaO_2 significantly > increased in CPAP-suppressed vs. control group (p<0.001) • No significant difference between CPAP-unsuppressed and control group **LVEF**	**2° endpoint:** • AHI • Mean nocturnal SaO2 • LVEF **Limitations:** • Post hoc analysis • Stratification of CPAP-treated pts based on polysomnogram performed 3 mo after randomization. • Because suppressed and unsuppressed status could not be ascertained until completion of PSG, events that occurred during the first 3 mo could not be included • The CPAP-CSA–suppressed group was younger, had a lower AHI, and had a slightly lower proportion of central events than the CPAP CSA–unsuppressed group

				• LVEF significantly increased over time in CPAP-suppressed group (p<0.001) • LVEF significantly increased in CPAP-suppressed vs. CPAP-unsuppressed (p=0.006) and vs. control (p<0.001) groups. • No significant difference between CPAP-unsuppressed and control group (p=0.984)	
CPAP for CSA & HF (CANPAP) Bradley et al. 2005 (101) 16282177	**Aim:** Test long-term treatment of CSA w/ CPAP in HF pts receiving optimal medical therapy on combined rates of death & ht tx. **Study type:** 11 center RCT **Size:** 258	**Inclusion criteria:** • 18-79 y • NYHA II-IV • HF due to ischemia • HTN, Idiopathic DCM • Stable condition • Optimal medical therapy for 1+ mon • LVEF <40% • CSA w/ ≥15 AHI >50% of AHI had to be central. **Exclusion criteria:** • Pregnancy • MI • UA • Cardiac surgery within prior 3 mon, OSA	**Intervention:** CPAP n=128 **Comparator:** No CPAP n=130	**1° endpoint:** Transplant free survival • No significant difference in transplant free survival between CPAP and control groups (p=0.54) **2° endpoints:** • Hospitalizations: No significant difference between CPAP and control groups (p=0.45) • EF: Significant increase in EF between CPAP vs. control groups (p=0.02) • Frequency of apnea and hypopnea episodes • Significant reduction between CPAP vs. control groups (p=0.001) • Mean Nocturnal SaO2 • Significant increase between CPAP vs. control groups (p≤0.001) • 6MWT: Significant increase in 6MWT between CPAP vs. control groups (p=0.016) • QoL: No significant difference between CPAP and control groups	**2° endpoints:** • Hospitalizations • EF • Frequency of apnea and hypopnea episodes • Mean nocturnal SaO_2 • 6MWT • QoL • Neurohormones – norepinephrine and atrial NP **Limitations:** • Underpowered because trial stopped early for low enrollment

				• Neurohormones: Norepinephrine • Significant reduction in CPAP vs. control groups (p=0.009) • Atrial NP: No significant difference between CPAP and control groups	
Ruttanaumpawan et al. 2009 (102) 19189783	**Aim:** To determine whether attenuation of CSA by CPAP in pts w/ HF reduces the frequency of arousals from sleep or improves sleep structure. **Study type:** RCT **Size:** 205	**Inclusion criteria:** • Age 18 - 79 y of age; • NYHA II -IV HF due to ischemic, hypertensive, or idiopathic DCM, stabilized on optimal medical therapy ≥1 mo • LVEF <40% by radionuclide angiography • CSA defined as an AHI ≥15, w/ >50% central apneas & hypopneas **Exclusion criteria:** • Pregnancy • MI • UA • Cardiac surgery within 3 mo of enrollment • OSA	**Intervention:** CPAP n=97 **Comparator:** Control n=108	**1° endpoint:** • AHI (central and obstructive) • Mean and lowest SaO_2 **Significant Results** In the CPAP group, • Central and obstructive AHI decreased significantly over BL and vs. the control group (p<0.001) • Mean and lowest SaO_2 improved in both the CPAP (p<0.001) and control (p<0.04) but the improvement was significantly better in the CPAP vs. the control group (p<0.001). **2° endpoints:** • **No significant improvement in** arousals from sleep or sleep structure within or between groups (p=0.14–0.99)	**2° endpoints:** • Arousals from sleep • Sleep structure (time in bed, sleep period time, total sleep time, sleep efficiency, sleep onset latency, percentage in each sleep stage, periodic leg movement index) **Limitations:** • 2° analysis of CANPAP data • Did not classify arousals as being respiratory or non-respiratory related, and did not examine their timing.
Kaneko et al. 2003 (103) 12660387	**Aim:** To determine the effect of CPAP on LVEF when awake and daytime BP in pts with HF and OSA **Study type:** RCT	**Inclusion criteria:** • HF due to ischemic or nonischemic dilated CM for >6 mo; • LVEF <45% by radionuclide angiography • NYHA class II–IV; • Absence, in last 3 mo, of HF exacerbations while receiving optimal pharmacologic therapy at highest tolerated doses;	**Intervention:** CPAP n=12 **Comparator:** Control n=12	**1° endpoint:** • LVEF when awake • LVEDD • LVESD • Heart rate • Daytime BP **Significant Results** **1° endpoint:** **LVEF when awake**	**2° endpoint:** • **BMI** • Episodes of apnea and hypopnea • Total • Obstructive • Central • Desaturation index (# hr of sleep) • Lowest oxyhemoglobin saturation (%)

	Size: 24	• OSA defined as ≥20 episodes of apnea and hypopnea /h of sleep of which >50% were obstructive **Exclusion criteria:** • 1° valvular heart disease; • Presence of implanted cardiac pacemaker; • UA; • MI: • Cardiac surgery within 3 mo of enrollment		• Significant increase in CPAP (p<0.001) but not control group and difference between groups was significant (p=0.009) **LVEDD** • No significant difference for either group or between groups **LVESD** • Significant reduction in CPAP (p=0.009) but not control group and difference between groups was significant (p=0.02) **Heart Rate** • Significant decrease in CPAP (p=0.007) but not control group and difference between groups was significant (p=0.02) **Daytime BP** • Significant decrease in systolic BP in CPAP (p=0.02) but not control group and difference between groups was significant (p=0.008) • No significant difference in diastolic BP for either group or between groups **2° endpoint**: **BMI** • No significant difference for either group or between groups **Episodes of apnea and hypopnea** **Total** • Significant reduction in CPAP (p<0.001) but not control group and difference between groups	• Total sleep time • Stage I and II sleep (% of total sleep time) • Stage III and IV sleep (% of total sleep time) • REM sleep (% of total sleep time) • Arousals/hr of sleep **Limitations:** • No placebo • Small sample size • Pts unblinded to group

				was significant (p=0.002) **Obstructive** • Significant reduction in CPAP (p<0.001) but not control group and difference between groups was significant (p<0.001) • Central • No significant difference for CPAP group or between groups **Desaturation index (# hr of sleep)** • Significant reduction in CPAP (p<0.001) but not control group and difference between groups was significant (p=0.008) **Lowest oxyhemoglobin saturation (%)** • Significant increase in CPAP (p=0.004) but not control group and difference between groups was significant (p=0.01) **Total sleep time** • No significant difference for CPAP group or between groups **Stage I and II sleep (% of total sleep time)** • No significant difference for CPAP group or between groups **Stage III and IV sleep sleep (% of total sleep time)** • No significant difference for CPAP group or between groups **REM sleep (% of total sleep time)**	

				• No significant difference for CPAP group or between groups **Arousals/h of sleep** • Significant reduction in CPAP (p=0.003) but not control group and difference between groups was significant (p=0.03)	
Mansfield et al. 2004 (104) 14597482	**Aim:** To assess long-term effect of OSA treatment with nocturnal CPAP on systolic heart function, sympathetic activity, BP, and QoL in pts with HF **Study type:** RCT **Size:** 44	**Inclusion criteria:** • HF due to ischemic or nonischemic dilated CM for >6 mo; • LVEF <45% by radionuclide angiography • NYHA class II–IV; • Absence, in last 3 mo, of HF exacerbations while receiving optimal pharmacologic therapy at highest tolerated doses; • OSA defined as ≥20 episodes of apnea and hypopnea /h of sleep of which >50% were obstructive **Exclusion criteria:** • 1° valvular heart disease; • Presence of implanted cardiac pacemaker; • UA; • MI: • Cardiac surgery within 3 mo of enrollment	**Intervention:** CPAP X 3 mo n=19 **Comparator:** Control n=21	**1° endpoint:** • LVEF • Overnight urinary norepinephrine excretion • BP • QoL **Significant Results** **1° endpoint:** **LVEF** • Significant improvement in CPAP group (p<0.001) and vs. control group (p=0.04) **Overnight urinary norepinephrine excretion** • Significant reduction in CPAP group (p<0.05) and vs. control group (p=0.036) **BP** • No significant difference in CPAP group or between groups **QoL** • Significant improvements in most domains within CPAP group **SF-36** • Significant improvements between groups in 4/8 domains ○ Physical (p=0.03) ○ Vitality (p=0.02) ○ Social (p=0.03) ○ Mental health (p=0.01)	**2° endpoint:** • Peak Vo_2 • NYHA class • Epworth sleepiness scale • BMI • AHI events per h • Minimum SpO_2 saturation **Limitations:** • No placebo • Significant difference between groups in peak Vo_2 and mean BP at BL • Dropout rate = 27% • Higher than expected death rate • Higher than expected rate of interventions initiated that may have effected end points • Small sample size with only 3 females

				Chronic HF questionnaire • Significant improvements between groups in 3/4 domains ○ Fatigue (p=0.01) ○ Emotional well-being (p=0.02) ○ Disease mastery (p=0.02) **<u>2° endpoint:</u>** **Peak Vo_2** • No significant difference in CPAP group or between groups **NYHA class** No significant difference CPAP group or between groups **Epworth sleepiness scale** • Significant reduction in CPAP vs. control group (p=0.01) **BMI** No significant difference CPAP group or between groups **AHI events per h** • Significant reduction in CPAP group (p<0.001) and vs. control group (p<0.001) **Minimum SpO_2 saturation** • Significant improvement in CPAP group (p<0.001) and vs. control group (p=0.001)	

Date: Study selected by the chairs in December 2015 and some trials added by the writing committee.

2013 HF Guideline Data Supplement 18. ACE Inhibitors (Section 7.3.2.2)

Study Name, Author, Year	Aim of Study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Endpoints		Mortality	Trial Duration (Years)	Absolute Benefit	P Values & 95% CI:
			Pretrial standard treatment	*N (Total)* *n (Experimental)* *n (Control)*	*Ischemic/ NonIschemic*	*Inclusion Criteria*	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*	*1st Year Mortality*			
CONSENSUS 1987 2883575 (105)	To Evaluate influence of enalapril on prognosis of NYHA class IV HF	RCT	Diuretics (spironolactone 53%, mean dose 80mg), digitalis (93%), other vasodilators, except ACEI (ie, nitrates 46%)	253; 127;126	CAD 73%	Severe HF/symptoms at rest/NYHA class IV; Increased heart size >600 mL; BP: 120/75; HR: 80; AF 50%	APE; hemodynamically import aortic/MV stenosis; MI w/in prior 2 mo Unstable angina; planned cardiac surgery; right HF b/c of pulm disease; Cr >300 mmol/L	Mortality	Change in NYHA-FC, LV size, Cr level	52% placebo group and 36% enalapril group (6 mo mortality: 26% in enalpril group and 44% in placebo group)	0.51 y	N/A	Crude mortality at end of 6 mo (primary endpoint), 26% in enalapril group and 44% in placebo group—40% reduction (p =0.002). Mortality was reduced by 31% at 1 y (p=0.001)
10 y FU of CONSENSUS 1999 10099910 (106)	Report on the survival at the 10-y follow up of the pts randomized in CONSENSUS. (1st study to show prognostic improvement by an ACEI. Pts in NYHA class IV HF treated with enalapril or placebo. After study completion all pts were offered open-label enalapril therapy).	10-y open-label follow-up study (via completion of a questionnaire) on the survival status of pts in CONSENSUS -a RCT.	All pts were offered open-label enalapril therapy	315; 77; 58		253 randomized pts included in analysis of time from randomization to death; Survivors (135) of the double-blind period included in analysis of the time from end of double-blind period to death; Severe, NYHA IV		Mortality			10 y		5 pts, all in the enalapril group, were long-term survivors (p=0.004). Averaged over the trial (double-blind plus open-label extension) risk reduction was 30% (p=0.008), 95% CI: 11% - 46%. At end of double-blind study period, mortality considerably higher among pts not receiving open ACEI therapy
SOLVD 1991 2057034 (107)	Study the effect of enalapril on mortality and hospitalization in pts with chronic HF and EF ≤35%	RCT	Diuretics + Digoxin	2569; 1285; 1284	Ischemic heart disease 72%	LVEF <35%; Mild to severe (11% class I/<2% class IV); LVEF 25%; BP: 125/77; HR: 80; AF: 8-12%	Age >80 y; Unstable angina; MI w/in past mo; Cr>2.0 mg/dL	Mortality	Hospitalizations; Incidence of MI; Mortality by specific causes; Combined mortality and morbidity from both SOLVD+/SOLVD-	15.70%	3.45 y	Treating 1000 SOLVD+ pts with enalapril for ~3 y would save ~50 premature deaths and 350 hospitalizations.	Reduced mortality by 16%; (95% CI, 5-26%; p=0.0036)

SOLVD 1992 1463530 (108)	Study effect of ACEIs on total mortality and mortality from CV causes, the development of HF, and hospitalization for HF in pts with EF ≤35%	RCT	No drug treatment for HF	4228; 2111; 2117	History of ischemic heart disease 85%	EF <35%; Asymptomatic; NYHA class I (67%) + II; EF: 28%; BP: 126/78; HR: 75; AF: 4%	As per SOLVD+	Mortality; Combined mortality and the incidence of HF and rate of hospitalization for HF	Incidence of HF and rate of hospitalization for HF		3.12 y		Reduced mortality: p=0.30; 95% CI: -8-21%
SOLVD F/U 2003 12788569 (109)	12-y FU of SOLVD to establish if the mortality reduction with enalapril among pts with HF was sustained, and whether a subsequent reduction in mortality would emerge among those with asymptomatic ventricular dysfunction.	12 y f/u of RCTs [SOLVD+ and SOLVD-]	N/A	6784; 3391; 3393	N/A	Participation in SOLVD+ and SOLVD- Asymptomatic to severe; NYHA I-IV	N/A	Mortality	N/A	N/A	N/A	Enalapril extended median survival by 9.4 mo in the combined trials (95% CI: 2.8–16.5, p=0.004).	In the prevention trial, 50.9% of the enalapril group had died c/w 56.4% of the placebo group (p=0.001). In the treatment trial, 79.8% of the enalapril group had died c/w 80.8% of the placebo group (p=0.01). Combined prevention and treatment trials: HR for death was 0.90 for the enalapril group c/w placebo group (95% CI: 0.84–0.95, p=0.0003).
ATLAS 1999 10587334 (110)	To compare the efficacy and safety of low and high doses of ACEI on the risk of death and hospitalization in chronic HF. than the large doses that have been shown to reduce morbidity and mortality in pts with HF. AIM: Investigate if low doses and high doses of ACEIs have similar benefits.	RCT	N/A	3164; 1596 to the low-dose strategy and 1568 to the high-dose strategy.	CAD 65%	LVEF <=30%; NYHA class II, III, or IV, despite treatment with diuretics for ≥2 mo (Treatment for HF in ED or hospital within 6 mo required for pts in class II); Prior use of digitalis, ACEIs, or vasodilators allowed but not mandated; NYHA II-IV (mainly class II); LVEF 23%; SBP 126 mmHg; HR 80; NYHA class: III (few II and IV)	Acute coronary ischemic event or revascularization procedure within 2 mo; History of sustained or symptomatic ventricular tachycardia; Intolerant of ACEIs; SCr >2.5 mg/dL	Mortality from all causes	Combined risk of all-cause mortality and hospitalization for any reason; CV mortality, CV hospitalizations; All-cause mortality combined with CV hospitalizations; CV mortality combined with CV hospitalizations; Combined risk of fatal and nonfatal MI plus hospitalization for unstable angina		5 y		High-dose group had 8% lower risk of all-cause mortality (p=0.128) and 10% lower risk of CV mortality (p=0.073) than low-dose group. Death or hospitalization for any reason, high-dose group had 12% lower risk than low-dose group, p=0.002. Total number of hospitalizations: high-dose group 13% fewer hospitalizations for any reason (p=0.021), 16% fewer hospitalizations for CV reason (p=0.05), and 24% fewer hospitalizations for HF (p=0.002).
Post-MI ACEI Use													

SAVE, 1992 1386652 (111)	To test the hypothesis that the long-term administration of captopril to survivors of acute MI who had baseline LV dysfunction but did not have overt HF requiring vasodilator therapy would reduce mortality, lessen deterioration in cardiac performance, and improve clinical outcome.	RCT	Beta-blockers 36%; Digitalis 26%; Nitrates 51%	2231; 1115; 1116	Ischemic 100%	Alive 3 d after MI; LVEF <40%; >21 y of age, but <80; Killip class I — 60% (60% of the ps did not have even transient pulmonary congestion at baseline/the time of their acute MI; EF 31%; BP 113/70; HR 78;	Failure to undergo randomization within 16 d after the MI; Relative contraindication to the use of an ACEIs or the need for such an agent; SCr > 2.5 mg/dl	Mortality from all causes	Mortality from CV causes; Mortality combined with a decrease in the EF of at least 9 units in surviving pts; CV morbidity (development of severe CHF or the recurrence of MI); Combination of CV mortality and morbidity; 2 endpoints of severe HF (treatment failure): 1st, development of overt HF necessitating treatment with ACEI and 2nd, hospitalization to treat CHD.		3.5 y		Mortality from all causes was significantly reduced in the captopril group (228 deaths, or 20%) as c/w the placebo group (275 deaths, or 25%); the RR: 19% (95% CI, 3-32%; p=0.019). RR:21% (95% CI, 5 -35%; p=0.014) for death from CV causes, 37% (95% CI, 20-50%; p<0.001) for the development of severe HF, 22% (95% CI, 4-37%; p=0.019) for CHF requiring hospitalization, and 25% (95% CI, 5-40%; p=0.015) for recurrent MI.
AIRE 1993 8104270 (112)	Investigated the effect of therapy with ACEI ramipril, on survival in pts who had shown clinical evidence of HF at any time after an acute MI. Also, to compare the incidences of progression to severe or resistant HF, nonfatal reinfarction and stroke between the 2 groups.	RCT		2006; 1014; 992		Aged ≥18 y, with a definite acute MI 3-10 d before randomization; Clinical evidence of HF at any time since acute MI	Use of an ACEI considered to be mandatory	Mortality from all causes			1.3 y		Mortality from all causes was significantly lower for pts on ramipril compared to pts on placebo. RR: 27%; 95% CI: 11-40%; p=0.002. Prespecified secondary outcomes: risk reduction of 19% for the 1st validated outcome—namely, death, severe/resistant HF, MI, or stroke (95% CI: 5% - 31%; p=0.008).

TRACE 1995 7477219 (113)	To determine whether pts who LV dysfunction soon after MI benefit from long-term oral ACE inhibition.	RCT	Beta blocker 16%; Calcium antagonist 28%; Diuretic 66%; Nitrates 53%; Digoxin 28%.	1749; 876; 873	Ischemic 100%	Consecutive pts >18 y hospitalized with MI; Criteria for MI: chest pain or electrocardiographic changes, accompanied by >2X increase in ≥1 cardiac enzymes; LV dysfunction (EF <35%); NYHA class 1 - 41%; BP 121/76; HR 81	Contraindication to ACEI or a definite need for them; Severe, uncontrolled DM; Hyponatremia (<125 mmol/L); Elevated SCr level (2.3 mg/dL)	Death from any cause	Death from a CV cause, sudden death; Progression to severe HF (hospital admission for HF, death due to progressive HF, or HF necessitating open-label ACEI); Recurrent infarction (fatal or nonfatal); Change in the wall-motion index (EF)	The mortality from all causes at 1 y was 24%.		24 lives were saved after 1 mo of treating 1,000 pts	During the study period, 304 pts in the trandolapril group died (34.7%), as did 369 in the placebo group (42.3%). RR: 0.78 (95% CI, 0.67 - 0.91; p=0.001). In every subgroup, treatment with trandolapril was associated with a reduction in risk.

ACEI indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; AIRE, Acute Infarction Ramipril Efficacy; APE, acute pulmonary embolism; ATLAS, Assessment of Treatment with Lisinopril and Survival; BP, blood pressure; CAD, coronary artery disease; CHD, chronic heart disease; CHF, congestive heart failure; CONSENSUS Cooperative North Scandinavian Enalapril Survival Study; Cr, creatinine; CV, cardiovascular; C/W, compared with; DM, diabetes mellitus; ED, emergency department; FU, follow-up; HF, heart failure.

2013 HF Guideline Data Supplement 19. ARBs (Section 7.3.2.3)

Study Name, Author, Year	Aim of Study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Severity	Endpoints		Mortality	Trial Duration (Y)	Statistical Results
			Pre-trial standard treatment.	*N (Total)* *n (Experimental)* *n (Control)*	*Ischemic/ Non-Ischemic*	*Inclusion Criteria*	*Exclusion Criteria*		*Primary Endpoint*	*Secondary Endpoint*	*1st Y Mortality*		
CHARM Alternative; Granger et al; (2003) 13678870 (114)	Discover whether ARB could improve outcome in pts not taking an ACEI (intolerant)	RCT	Diuretics, Beta-blockers (55%), spironolactone 24%, Digoxin 45-46%	2028; 1013; 1015	Ischemic 67-70%	Symptomatic HF, EF <40%, no ACEI (b/c of intolerance)		NYHA II-IV; mild to severe (<4% class IV); EF: 30%; BP: 130/70; HR: 74-75; AF: 25-26%	Composite of CV death or hospital admission for CHF	CV death, hospital admission for CHF or nonfatal MI; CV death, CHF admission, nonfatal MI, nonfatal stroke; CV death, CHF admission, nonfatal MI, nonfatal stroke, coronary revascularization; Death (any cause); New DM		2.8 y	Absolute reduction of 7 major events per 100 pts threated - NNT 14 pts to prevent 1 CV death or hospitalization. HR: 0.77 (95% CI: 0.67-0.89); p=0.0004
CHARM-ADDED; McMurray et al; (2003) 13678869 (115)	To investigate if ARB + ACEI in pts with chronic HF improve clincal outcomes	RCT	Beta blocker-55%; spironolactone 17%; Digoxin 58-59%	2548; 1276; 1272	Ischemic 62-63%	Symptomatic HF; EF <40%; Treatment with ACEI; Age >18 y		NYHA class II-IV; mild to severe (<3% class IV); EF 28%; BP 125/75; HR 74; AF 27%	Composite of CV death or hospital admission for CHF	CV death, hospital admission for CHF or nonfatal MI; CV death, CHF admission, nonfatal MI, nonfatal stroke; CV death, CHF admission, nonfatal MI, nonfatal stroke, coronary revascularization; Death (any cause); New DM		3.4 y	Absolute reduction of 4.4 pts with events per 100 pts treated- NNT of 23 to prevent 1 first event of CV death or CHF hospitalization. RR: 0.85 (95% CI: 0.75-0.96); p=0.011

VALIANT; Pfeffer et al; (2003) 14610160 (116)	Compare the effect of an ARB, ACEI and the combination of the 2on mortality	Randomized double blind multicenter trial	Beta-blockers; ASA	14,703 Valsartan:4909 Captopril-: 4909 VAL + CAP: 4885	Ischemic 100% (MI inclusion criteria)	Age >18 y; Acute MI complicated by HF; LV systolic dysfunct (EF <35%), (<40% on radionuclide ventriculography); SBP >100 mmHg; Cr <2.5 mg/dL	Prior intolerance or contra-indication to ACEI/ ARB	NYHA I-IV; asymptomatic-severe, EF 35%; BP: 123/72; HR: 76	Death from any cause		12.5% VAL 12.3% VAL--CAP 13.2% CAP	2.1 y	VAL and CAP: 1.0 (97.5% CI-- 0.90-1.11); p=0.98 ; VAL+CAP and CAP: 0.98 (97.5% CI-- 0.89-1.09); p=0.73
Val-HeFT; Cohn et al; (2001) 11759645 (117)	Evaluate long term effects of adding ARB to standard therapy for HF	RCT	Diuretics; Digoxin 67%; Beta blocker 35%; ACEI 93%	5010; 2511; 2499	Ischemic 57%	Age >18 y; NYHA II, II, IV; At least 2 wk of background meds including ACEIs; EF <40% and LVID >2.9 cm/BSA		NYHA II-III, IV (only ~2% class IV); Mild to severe; EF 27%; BP 123/76; AF 12%	Mortality; Combined endpoint of mortality and morbidity	Change in EF; • NYHA class, QoL scores; Signs and symptoms of HF		1.92 y	Mortality similar for the 2 treatment groups. For the combined endpoint: RR: 0.87; 97.5% CI, 0.77-0.97; p=0.009
HEAAL study; Lancet 2009; 374: 1840-48. 19922995 (118)	Compared the effects of high-dose vs low-dose losartan on clinical outcomes in pts with HF.	RCT	Diuretic drugs (77%), beta blockers (72%), and ARBs (38%).	3846 losartan 150 mg (n=1927) or 50 mg daily (n=1919).	IHD 64%	>18 y; NYHA class II–IV; LVEF <40%, with stable CV medical therapy for at least 2 wk; Intolerance to ACEI; Investigators encouraged to start beta blocker and titrate to a maximum, whenever possible	Pregnancy or lactation; known intolerance to ARBs; Systolic arterial blood pressure <90 mm Hg; Significant stenotic valvular heart disease; Active myocarditis; active pericarditis; Planned heart transplantation w/in 6 mo; coronary angioplasty, CABG, acute MI, UA pectoris, cerebrovascular accident, or TIA within the previous 12 wk; Suspected significant renal artery stenosis	NYHA II-IV (70% II); EF: 33%; BP: 124/77; HR: 71; AF; 28%	Death or admission for HF	Composite endpoint of death or CV admission. Additional prespecified outcomes included: death, death or all-cause admission, CV death, all-cause admission, CV admission, admission for HF, and changes in the severity of heart disease		4.7 y median f/u	Treating pts with 150 mg dose instead of 50 mg dose would result in 1 additional pt w/out the primary event at 4 y for every 31 pts treated. Composite: 828 (43%) pts in 150 mg group vs. 889 (46%) in 50 mg group died or admitted for HF (HR: 0.90; 95% CI: 0.82-0.99; p=0.027) • Components: 635 pts in 150 mg group vs. 665 in 50 mg group died (HR: 0.94, 95% CI: 0.84-1.04; p=0.24), and 450 vs. 503 pts admitted for HF (0.87, 0.76–0.98; p=0.025)
CHARM-Overall 13678868 (116)	Aimed to find out whether the use of an ARB could reduce mortality and morbidity.	RCT-parallel, randomized, double-blind,	Diuretics 83% Beta blockers 55% ACEI 43% Spironolactone 17% Digoxin 43%	7601 pts (7599 with data) 3803 3796		>18 y; NYHA class II–IV for at least 4 wk; 3 distinct populations: pts with LVEF <40% who were not receiving ACEIs (previous intolerance) or who were currently receiving ACE, and pts with LVEF >40%	SCr > 265 mcmol /L, serum potassium >5.5 mmol/L Bilateral renal artery stenosis; symptomatic hypotension Women of childbearing potential not using adequate contraception; Critical aortic or mitral stenosis; MI, stroke, or open-heart surgery in the previous 4 wk; Use of an ARB in the previous 2 wk	NYHA II-IV NYHA II-IV Only 3% class IV	The primary outcome of the overall program: all-cause mortality; For all the component trials: CV death or hospital admission for CHF.		The annual CV death rate among the placebo group who had reduced LVEF was around 9% and was only 4% in the placebo group of CHARM-Preserved.	3.1 y	886 (23%) pts in candesartan and 945 (25%) in placebo group died (unadjusted HR: 0.91; 95% CI: 0.83–1.00; p=0.055; covariate aHR: 0.90 95% CU: 0.82–0.99; p=0.032) • Fewer CV deaths (691 [18%] vs 769 [20%], unadjusted HR: 0.88; 95% CI: 0.79–0.97; p=0.012; covariate aHR: 0.87; 95% CI: 0.78–0.96; p=0.006) • Hospital admissions for CHF (757 [20%] vs 918 [24%], p<0.0001)

ACEI indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blockers; ASA, aspirin; BP, blood pressure; BSA, body surface area; CABG, coronary artery bypass graft; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CHD, chronic heart disease; CHF, congestive heart failure; Cr, creatinine; CV, cardiovascular; DM, diabetes mellitus; EF, ejection fraction; FU, follow-up; HEAAL study, effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure; HF, heart failure; HR, heart rate; IHD, ischemic heart disease; LV, left ventricular; LVD, left ventricular dilatation; MI, myocardial infarction; MV, mitral valve; N/A, not applicable; NNT, number needed to treat; NYHA, New York Heart Association; QoL, quality of life; pts, patients; SBP, systolic blood pressure; RCT, randomized control trial; SCr, serum creatinine; TIA, transient ischemic attack; UA, unstable angina; Val-HeFT, Valsartan Heart Failure Trial; and VALIANT, Valsartan in Acute Myocardial Infarction.

2013 HF Guideline Data Supplement 20. Beta Blockers (Section 7.3.2.4)

Study Name, Author, Year	Aim of Study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Severity	Endpoints		Mortality		Trial Duration	Statistical Results
				N (Total) *n (Experimental)* *n (Control)*		*Inclusion Criteria*	*Exclusion Criteria*		*Primary Endpoint*	*Secondary Endpoint*	*Annualized Mortality*	*1st Y Mortality*		

CIBIS II CIBIS II investigators and committee members (1999) 10023943 (119)	Investigate the efficacy of bisoprolol in decreasing all-cause mortality in chronic HF	RCT-multicenter double-blind randiomised placebo controlled trial (Europe)	Diuretics + ACEI; [amiodarone allowed--14-l6%]	2647; 1327; 1320	Documented Ischemic 50%	NYHA class lll or IV EF: <35% 18-80 y old	Uncontrolled HTN; MI/UA w/in previous 3 mo; PTCA/CABG w/in previous 6 mo; AV-block >1st degree w/o PPM; Heart rate < 60bpm; resting SBP <100mmHg; renal failure; Reversible obstruct lung disease; Use of beta blocker	Moderate to severe. Mean BP: 130/80; Mean HR: 80; Mean EF: 28%; Mean LVEDD: 6.7 cm; AF: 20%	All-cause mortality	All-cause hospital admissions All CV deaths Combined endpoints Permanent treatment withdrawal	13.2% Placebo group 8.8% Treatm't group	N/A	1.3 y	HR: 0.66 (95% CI: 0.54-0.81); p<0.0001
MERIT-HF; MERIT study Group; (1999) 10376614 (120)	Investigate whether Metoprolol CR/XL lowered mortality in pts with decreased EF and symptoms of HF	RCT--multicenter double-blind randiomised placebo controlled trial (Europe + USA)	Diuretics + ACEI [Amiodarone NOT allowed]	3991; 1991; 2001	Ischemic 65%	NYHA ll-IV; 40-80 y old; LVEF <40% (36-40 if 6-min walk <450m); heart rate >68 bpm	MI/UA w/in 28 d; Contra-indication or current use of beta blocker; PTCA/CABG w/in 4 mo Planned transplant or ICD; Heart block >1st degree w/o PPM; SBP <100mmHg	Mild to severe. Mean BP: 130/78; Mean HR: 78; Mean EF 28%; AF 16-17%	All-cause mortality All-cause mortality in combination with all-cause admission to hospital	N/A	11.0% Placebo group 7.2% Treatm't group	N/A	1 y	Treatment of 27 pt for 1 y can prevent 1 death. 0.66 (95% CI: 0.53-0.81); p=0.00009
COPERNICUS ; Packer et al; (2002) 12390947 (121)	Investigate whether Carvadiolo is beneficial in severe HF	RCT--double blind	Diuretics (PO or IV) + ACEI (or ARB); [Amiodarone allowed 17-18%]	2289; 1156; 1133	Ischemic 67%	Euvolumic NYHA class IV; LVEF <25%; No positive inotropes or vasodilators w/in 4 d	Pt requiring hospitalized intensive care; Use of positive inotropes or IV; vasodilators w/in 4-d; Coronary revascularization/MI/CVA/ sign VT or VF w/in 2 mo; SBP < 85 mmHg, Heart rate <68, Cr >2.8 mg/dL	Severe Mean BP: 123/76; Mean HR: 83; Mean EF 20%;	All-cause mortality	Combined risk of death or hospitalization-any reason; Combined risk of death or hospitalization--CV reason; Combined risk of death or hospitalization--HF reason; Pt global assessment	19.7% placebo [24.0% in pts with recent or recurrent cardiac decompensations]	18.5% in placebo group 11.4% in Carvedilol group	10.4 mo	Treating 1000 pt for 1 y led to savings of 70 premature deaths p=0.0014
SENIORS; Flather et al; (2005) 15642700 (122)	Assess effects of the beta blocker Nebivolol in pts >70 y regardless of EF.	RCT	Diuretics + ACEI (+aldosterone antagonist in 29%)	2128; 1067; 1061	Prior h/o CAD in 69%	Age >70 CHF with 1 of the following: hospitalization with CHF w/in a year or EF <35% w/in the past 6 mo	New HF therapy w/in 6 wk or change in drug therapy w/in 2 wk Contraindication to beta blockers, current use of beta blockers Significant renal dysfunction CVA w/in 3 mo.	Mild to severe Mean BP: 139/81; Mean HR: 79; Mean EF 36% (1/3 with EF >35%);	Composite of all-cause mortality or CV hospital admission	All-cause mortality Composite of all-cause mortality or all-cause hospital admissions All cause hospital admissions CV hospital admissions CV mortality Composite of CV mortality or CV hospital admissions NYHA class assessment; 6 MWT	N/A	N/A	1.75 y	Absolute risk reduction 4.2%; 24 pts would need to be treated for 21 mo to avoid one event RR: 0.86; 95% CI: 0.74-0.99; p=0.039
A Trial of the Beta-Blocker Bucindolol in Pt with Advanced Chronic HF The Beta-Blocker Evaluation of Survival Trial Investigators 11386264 (123)	Designed to determine whether bucindolol hydrochloride, a nonselective beta-adrenergic blocker and mild vasodilator, would reduce the rate of death from any cause among pt with advanced HF	RCT	ACEIs (if tolerated) [91% ACE; 7% ARB], for at least 1 mo. Before the publication of the results of the DIG trial, 12 digoxin therapies were	2708; 1354; 1354	Ischemic 59%	NYHA class III or IV HF LVEF <35% >18 y	Reversible cause of HF present Candidates for heart transplantation Cardiac revascularization procedure within the previous 60 d UA Heart rate <50 bpm, SBP <80mmHg Decompensated HF.	NYHA III or IV (92% class III) EF 23%; HR 82; BP 117/71; AF 12%	Death from any cause	Death from CV causes (death due to pump failure or an ischemic event or sudden death) Hospitalization for any reason Hospitalization because of HF Composite of death or heart transplantation LVEF at 3 and 12 mo MI; QoL; and any change in	For pt in NYHA functional class III, the annual mortality rate was 16% in the placebo group; For pt with NYHA class IV, the annual mortality rate in the placebo group was 28% **Overall**: annual mortality of 17% in placebo group c/w	N/A	~2 y	449 pt in placebo group (33%) died, 411 in the bucindolol group (30%; HR: 0.90; 95% CI, 0.78-1.02; unadjusted p=0.10; adjusted p=0.13)

	and to assess its effect in various subgroups defined by ethnic background and demographic criteria — specifically women and members of minority groups.		required, but thereafter its use became discretionary [DIG 94%].							the need for concomitant therapy	15% in the bucindolol group.			
COMET; Poole-Wilson et al; (2003) 12853193 (124)	To compare the effects of carvedilol and metoprolol on clinical outcome in pts with HF	RCT	Diuretics, ACEIs	3029; 1511 carvedilol; 1518 metoprolol tartrate	N/A	NYHA class II-IV EF <35% Previous CV admission	N/A	Mild to severe	All-cause mortality Composite endpoint of all-cause mortality, or all-cause admission	N/A	N/A	N/A	4.8 y	All-cause mortality 34% carvedilol and 40% metoprolol (HR: 0.83; 95% CI 0.74-0.93; p=0.0017)
(CIBIS) III; 2005 16143696 (125)	Sufficient data do not currently exist to establish the optimum order of initiating chronic HF therapy (ACEI vs. beta blocker). This was the objective of the CIBIS III trial-- it compared the effect on mortality and hospitalization of initial monotherapy with either bisoprolol or enalapril for 6 mo, followed by their combination for 6 to 24 mo.	Multicenter, prospective, randomized, open-label, blinded endpoint evaluation (PROBE) trial,24 with 2 parallel groups.	Diuretics 84%; Digoxin 32%	1010 Bisoprolol 505; Enalapril 505	CAD 62%	>65 y, NYHA class II or III, and LVEF <35% (By echo within the 3 mo) Clinically stable HF (without clinically relevant fluid retention or diuretic adjustment within 7 d)	Treatment with an ACEI, an ARB, or a beta blocker for >7 d during the 3 mo before randomization Heart rate at rest <60 bpm without a functioning pacemaker Supine SBP <100 mm Hg at rest SCr≥220 mmol/L AV block>1° without a functioning pacemaker Obstructive lung disease contraindicating bisoprolol treatment	NYHA II or III; mild to moderate CHF LVEF 29%; Heart rate 79; SBP 134	The primary endpoint was time-to-the-first-event of combined all-cause mortality or all-cause hospitalization	Combined endpoint at the end of the monotherapy phase and the individual components of the primary endpoint, at study end and at the end of the monotherapy phase. CV death CV hospitalization	N/A	N/A	Mean of 1.22±0.42 y (maximum of 2.10 y).	In the ITT sample, 178 pt (35.2%) with a primary endpoint in the bisoprolol-1st group, and 186 (36.8%) in the enalapril-1st group (absolute difference -1.6%; 95% CI: -7.6 to 4.4%; HR: 0.94; 95% CI: 0.77–1.16; noninferiority for bisoprolol-first versus enalapril-1st treatment p=0.019)

ACEI indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; AV, atrioventricular; BP, blood pressure; CABG, coronary artery bypass graft; CHF, congestive heart failure; CIBIS II, Cardiac Insufficiency Bisoprolol Study II; COMET, Carvedilol Or Metoprolol European Trial; COPERNICUS, carvedilol prospective randomized cumulative survival; Cr, creatinine; CR/XL, controlled release/extended release; CV, cardiovascular; CVA, cerebrovascular accident; c/w, compared with; DIG, Digitalis Investigation Group; EF, ejection fraction; HF, heart failure; h/o, history of; HR, hazard ratio; ICD, ICD, implantable cardioverter defibrillator; ITT, intent to treat; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MI, myocardial infarction; MWT, minute walk test; NYHA, New York Heart Association; PPM, permanent pacemaker; PTCA, percutaneous transluminal coronary angioplasty; Pts, patients; QoL, quality of life; RCT, randomized control trial; RR, relative risk; SBP, systolic blood pressure; SCr, serum creatinine; UA, unstable angina; USA, United States of America; VF, ventricular fibrillation; VT, ventricular tachycardia; and w/o, without.

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