| Table K-8. Studies evaluating incremental value of NT-proBNP to predict composite outcomes in stable heart failure patients |
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| **Author****Year****Mean Length F/U** | **Study Description** | **Peptide Levels (pg/mL)** | **Prognostic Markers** | **Model Descriptions****Measure(s) of Risk (95%CI)** | **Discrimination Statistics****(C-statistics/C-index)** | **Global Model Fit Statistics✝** | **Calibration Statistics (Hosmer-Lemeshow statistic)** | **Measure of Risk Reclassification (IDI and NRI)** |
| Dini,20 2008 F/U: 22 mo\*\* | Study design: CohortOutpatients with chronic HF, LVEF≤ 45% n, mean Age, %Males: 313, 69yrs (11), 78%Outcomes (#events, #risk): composite (all-cause mortality + HF hospitalization) (111, 313) | Admission mean:1,492 (617 – 3,540)\*\* Discharge: NR Cutpoint: >1,492 | NT-proBNP, age, NYHA class, LVEF, EDT, sex, coronary artery disease, Myocardial E wave velocity | Model: Adjusted (Multivariate) Cox regression Adjusted/Non-adjusted covariates: age, sex, NYHA class, LVEF, EDT, coronary artery disease, Myocardial E wave velocityHR=2.94 (1.83, 4.72) | NA | Base model (demographic & clinical variable)=52.7, Base model (clinical variables + LVEF, Em)=78.6, Base model (demographic & clinical variables + LVEF, Em) + NT-proBNP=97.7 (p<0.0001)  | NR | NR |
| Masson,10 2006 Val-HefF/U: 23 mo | Study design: CohortSecondary analysis of RCT dataPatients with stable symptomatic HF (LVEF <40%) n, mean age, %male: 3,916, NR, 80.2%Outcomes (#events, #risk): composite (mortality and morbidity) (1,194, 3,916) | ADM mean: 895 (375- 1985)\*\*D/C mean: NRCutpoint: >895 | NT-proBNP, BNP  | Model: multivariable cox regression and ROC analysis  Adjusted/Non-adjusted covariates: Age, BMI, NYHA, LVEF, LVIDD, ischemic etiology, AF, SBP, HR, digoxin, Diuretics, ACE inhibitors, beta-blockers, creatinineHR=2.20 (1.92, 2.51), AUC=0.688 (0.009) | NA | Likelihood ratio, add NT-proBNP to Base Model p<0.0001 | NA | NA |

| Table K-8. Studies evaluating incremental value of NT-proBNP to predict composite outcomes in stable heart failure patients (continued) |
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| **Author****Year****Mean Length F/U** | **Study Description** | **Peptide Levels (pg/mL)** | **Prognostic Markers** | **Model Descriptions****Measure(s) of Risk (95%CI)** | **Discrimination Statistics****(C-statistics/C-index)** | **Global Model Fit Statistics✝** | **Calibration Statistics (Hosmer-Lemeshow statistic)** | **Measure of Risk Reclassification (IDI and NRI)** |
| Cleland,11 2009 CORONAF/U:24 mo | Study design: Case seriesSecondary analysis of RCT dataChronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40%n, mean age, %male: T1: 1,221, 70.8yrs (6.7), 74%T2: 1,222, 72.7yrs (7.0), 76% T3: 1,221, 74.5yrs (7.2), 50%Composite (CV mortality or nonfatal MI or nonfatal stroke), (883, 3664) | ADM mean: T1: 47(26-78) pmol/L, T2: 173(133-220) pmol/L, T3: 486(367-776) pmol/L D/C mean: NRCutpoint: per log unit | log NT-proBNP, age, AF, diabetes, claudication, CABG, NYHA, ApoA-I, EF, sex, MI, SBP/10, creatinine\*, BMI\*, HR\*, triglycerides\* | Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: age, diabetes, coronary bypass or claudication, NYHA, HR, systolic BP, EFHR=1.587 |   | Base model = 314.9, Base model + NT-proBNP=477.1 (Inc. Chi-square=155.445, p<0.0001) |   |   |
| Cleland,11 2009 CORONAF/U:24 mo | Study design: Case seriesSecondary analysis of RCT dataChronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40%n, mean age, %male: T1: 1,221, 70.8yrs(6.7), 74%T2: 1,222, 72.7yrs(7), 76% T3: 1,221, 74.5(7.2), 52%Composite (Atherothrombotic end point (fatal or nonfatal myocardial infarction, or fatal or nonfatal nonhemorrhagic stroke), (284, 3,664) | ADM mean: T1: 47(26-78) pmol/L, T2: 173(133-220) pmol/L, T3: 486(367-776) pmol/L D/C mean: NRCutpoint: per log unit | log NT-proBNP, hsCRP, age, AF, diabetes, claudication, ApoA-I\*, MI,  | Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: age, diabetes, coronary bypass or claudication, NYHA, HR, systolic BP, EFHR=1.238 | NA | Base model = 85.981, Base model + NT-proBNP=97.7 (Inc. Chi-square=11.719, p=0.0006) | NA | NA |
| Cleland,11 2009 CORONAF/U: 24 mo | Study design: Case seriesSecondary analysis of RCT dataChronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40%n, mean age, %male: T1: 1,221, 70.8yrs(6.7), 74%T2: 1,222, 72.7yrs(7), 76% T3: 1,221, 74.5(7.2), 51%Composite: Coronary events (sudden death , fatal or nonfatal myocardial infarction, coronary revascularization, ventricular defibrillation by an implantable device, resuscitation from cardiac arrest, or hospitalization for unstable angina), (741, 3,664) | ADM mean: T1: 47(26-78) pmol/L, T2: 173(133-220) pmol/L, T3: 486(367-776) pmol/L D/C mean: NRCutpoint: per log unit | log NT-proBNP, age\*, AF, diabetes, claudication, NYHA, Apo A-I, EF, MI, SBP/10, creatinine\*, BMI\*, HR\*, angina pectoris | Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: age, diabetes, coronary bypass or claudication, NYHA, HR, systolic BP, EFHR=1.469 | NA | Base model = 182.3, Base model + NT-proBNP=291.0 (Inc. Chi-Square=95.579, p<0.0001) | NA | NA |
| Cleland,11 2009 CORONAF/U: 24 mo | Study design: Case seriesSecondary analysis of RCT dataChronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40%n, mean age, %male: T1: 1,221, 70.8yrs(6.7), 74%T2: 1,222, 72.7yrs(7), 76% T3: 1,221, 74.5(7.2), 55%death or worsening HF (1,376, 3,664) | ADM mean: T1: 47(26-78) pmol/L, T2: 173(133-220) pmol/L, T3: 486(367-776) pmol/L D/C mean: NRCutpoint: per log unit | log NT-proBNP, age, AF, diabetes, NYHA, claudication, ApoA-I, EF, SBP/10\*, creatinine\*, BMI\*, HR, sex, triglycerides\* | Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: age, diabetes, coronary bypass or claudication, NYHA, HR, systolic BP, EFHR=1.639 | NA | Base model = 463.0, Base model + NT-proBNP=700.8 (Inc. Chi-Square=259.612, p<0.0001) | NA | NA |
| Wedel,14 2009 CORONA F/U: 24 mo | Study design: Case seriesSecondary analysis of RCT dataChronic HF patients, 60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: 3,342, 72.5 (7.1), 75Outcomes (#events, #risk): Composite (Atherothrombotic endpoint (fatal or nonfatal myocardial infarction, or fatal or nonfatal nonhemorrhagic stroke), (284, 3,342) | ADM mean: 166 (70-358)\*\* pmol/L D/C mean: NR Cutpoint: per log unit | log NT-proBNP, age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA-1, s/creatinine, intermittent claudication, HR, MI, stroke, ApoB, ALAT, CK, TSH, hsCRP | Model: multi-variable cox regression  Adjusted/Non-adjusted covariates: age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA-1, s/creatinine, intermittent claudication, HR, MI, stroke, ApoB, ALAT, CK, TSH, hsCRPHR=1.24 (1.10-1.40) | NA | χ2 for base model + (ALAT,CK,TSH,Apo-1,Apo-B,TG-s) = 74, base model +(ALAT,CK,TSH,Apo-1,Apo-B,TG-s) + NT-proBNP= 97.7 (p=0.0001)  | NA | NA |
| Wedel,14 2009 CORONA F/U: 24 mo | Study design: Case seriesSecondary analysis of RCT dataChronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: 3,342, 72.5 (7.1), 75%Outcomes (#events, #risk): all-cause mortality/ HF hospitalization (1,376, 3,342) | ADM mean: 166 (70-358)\*\* pmol/L D/C mean: NR Cutpoint: per log unit | log NT-proBNP, age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA-1, s/creatinine, intermittent claudication, HR, MI, stroke, ApoB, ALAT, CK, TSH, hsCRP | Model: multivariable Adjusted/Non-adjusted covariates: age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA-1, s/creatinine, intermittent claudication, HR, MI, stroke, ApoB, ALAT, CK, TSH, hsCRPHR=1.64-1.74) | demographics and medical history C-statistic: 0.653, lipid variables added C-statistic: 0.666, the addition of NT-proBNP C-statistic: 0.701 (P-value for Step 1 vs. 2 p=0.0.002 and 2 vs. 3 p=0.0001). | Demographic and clinical parameters (χ2= 12.26), LVEF added to the above: χ2= 31.14, the addition of E/Em ratio: χ2=43.64 addition of log transformed NT-proBNP: χ2=49.88 (all P <0.0001) | NA | NA |
| Wedel,14 2009 CORONA F/U: 24 mo | Study design: Case seriesSecondary analysis of RCT dataChronic HF patients, ≥60 years, with NYHA II-IV, ischemic etiology, and EF<35-40% n, mean age, %male: 3,342, 72.5 (7.1), 75%Outcomes (#events, #risk): CV mortality/nonfatal MI/nonfatal stroke (883, 3,342) | ADM mean: 166 (70-358)\*\* pmol/L D/C mean: NR Cutpoint: per log unit | log NT-proBNP, age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA-1, s/creatinine, intermittent claudication, HR, MI, stroke, ApoB, ALAT, CK, TSH, hsCRP | Model: multi-variable cox regression Adjusted/Non-adjusted covariates: age, diabetes, EFx100, BMI, CABG, sex, AF, NYHA, ApoA-1, s/creatinine, intermittent claudication, HR, MI, stroke, ApoB, ALAT, CK, TSH, hsCRPHR=1.59 (1.49-1.71) | NA | χ2 for base model + (ALAT,CK,TSH,ApoA-1,Apo-B,TG-s) = 315, base model +(ALAT,CK,TSH,Apo-1,Apo-B,TG-s) + NT-proBNP= 477 (p=0.0001)  | NA | NA |
| Dini,21 2009 F/U:29 mo | Study design: Cohort Outpatients with chronic HF, and LVEF≤ 45% n, mean age, %male: 232, 69yrs(10), 84%Composite (all-cause mortality + HF hospitalization) (65, 232) | ADM mean: 891 (174)D/C mean: NRCutpoint: >544 | NT-proBNP, age, LVEF, EDT, sex, coronary artery disease, Myocardial E wave velocity | Model: Multivariable Cox regression Adjusted/Non-adjusted covariates: age, LVEF, EDT, sex, coronary artery disease, Myocardial E wave velocityHR=2.66 (1.24, 5.71) | NA | Base model (Demographics & clinical data + EF + EDT + EM) + NT-proBNP = Inc χ2 = p<0.0001 | NA | NA |
| Bajraktari,22 2011 F/U: 37 mo | Study design: Cohort Outpatients with chronic systolic HF, and LVEF≤ 45% n, mean age, %male: 107, 68yrs(12), 75%Outcomes (#events, #risk): Composite (cardiac mortality + HF hospitalization)(55, 107) | ADM mean: 1,257 (553 – 3,212)\*\* D/C mean: NR Cutpoint: ≥2.47 on log scale | logNT-proBNP, age, sex, T-IVT, mean E/Em ratio, LVEF  | Model: Multivariate logistic regression Adjusted/Non-adjusted covariates: age, sex, T-IVT, mean E/Em ratio, LVEF OR=4.162 (1.289, 13.44) | NA | Base model ( age, sex, T-IVT, mean E/Em ratio, LVEF ) Chi-square = 35.9 , Base model + NT-proBNP, χ2 = 38.0 (p<0.0001) | NA | NA |

✝Likelihood-based measures i.e., log likelihood ratio, likelihood ratio χ2, Global χ2, incremental χ2

\*Insignificant

\*\*Median Values

**Abbreviations:** ADM = admission; AHF = Acute heart failure; ApoA1 = apolipoprotein A-I; BMI = body mass index; BMod = behavior modifcation; BNP = B-type natriuretic peptide; BP = Blood pressure; CHF= Congestive heart failure; CP= Cutpoint; D/C= discharge; EDT = Ethylenediaminetetraacetic acid; F/U= followup; GFR = Glomerular filtration rate; HF = Heart failure; HR = Hazard ratio; IDI = integrated risk improvement; IQR= Interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = Not reported; NS = Not stated; NYHA = New York Heart Association; pg/mL = Picograms per milliliter; vs. = Versus; χ2 = chi square; Yrs = years