Natriuretic Peptides, Body Mass Index and Heart Failure Risk:

Pooled Analyses of SAVOR-TIMI 53, DECLARE-TIMI 58 and CAMELLIA-TIMI 61

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Abstract

Background: N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations are lower in patients with obesity. The interaction between body mass index (BMI) and NT-proBNP with respect to heart failure (HF) risk remains incompletely defined.

Methods: Data were pooled across three randomized clinical trials enrolling predominantly patients who were overweight or obese with established cardiometabolic disease: SAVOR-TIMI 53, DECLARE-TIMI 58 and CAMELLIA-TIMI 61. Hospitalization for heart failure (HHF) was examined across strata of baseline BMI and NT-proBNP. The effect of dapagliflozin vs. placebo was assessed for a treatment interaction across BMI categories in patients with or without an elevated baseline NT-proBNP (≥125 pg/mL).

Results: Among 24,455 patients, the median NT-proBNP was 96 (IQR: 43-225) pg/mL and the median BMI was 33 (IQR 29-37) kg/m^2, respectively, with 68% of patients having a BMI ≥30 kg/m^2. There was a significant inverse association between NT-proBNP and BMI which persisted after adjustment for all clinical variables (p<0.001). Within any range of NT-proBNP, those at higher BMI had higher risk of HHF at 2 years (comparing BMI <30 vs. ≥40 kg/m^2 for NT-proBNP ranges of <125, 125-<450 and ≥450 pg/mL: 0.0% vs. 0.6%, 1.3% vs. 4.0%, and 8.1% vs. 13.8%, respectively), which persisted after multivariable adjustment (HR_{adj} 7.47 [95% CI 3.16-17.66], HR_{adj} 3.22 [95% CI 2.13-4.86], and HR_{adj} 1.87 [95% CI 1.35-2.60], respectively). In DECLARE-TIMI 58, dapagliflozin vs. placebo consistently reduced HHF across BMI categories in those with an elevated NT-proBNP (p-trend for HR across BMI = 0.60), with a pattern of greater absolute risk reduction (ARR) at higher BMI (ARR for BMI <30 to ≥40 kg/m^2: 2.2% to 4.7%; p-trend = 0.059).

Conclusions: The risk of HHF varies across BMI categories for any given range of circulating NT-proBNP. These findings showcase the importance of considering BMI when applying NT-proBNP for HF risk

stratification, particularly for patients with low-level elevations in NT-proBNP (125-<450 pg/mL) where there appears to be a clinically meaningful absolute and relative risk gradient.

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Introduction

The prevalence of obesity and concomitant heart failure (HF) continues to increase, with a resultant increase in HF-associated mortality and morbidity.[1] Obesity is a well-established risk factor for HF, with prior studies demonstrating an association between obesity and HF across the spectrum of ejection fraction.[2] Natriuretic peptides (NPs) are prognostic of future HF risk in the general population irrespective of prior HF, and improve risk stratification when added to clinical risk models.[3-5] Multiple studies have consistently shown circulating NP concentrations to be inversely associated with body mass index (BMI) independent of the clinical situation (e.g., acute and chronic ambulatory HF), with patients with obesity demonstrating lower NP concentrations despite being at increased risk for HF.[6-8] As such, a given NP concentration may be associated with marked differences in risk of HF across the range of BMI, with implications for HF risk stratification and clinical decision making. For example, low-level elevations in NPs may carry relevant prognostic weight for future HF in patients with high BMI. However, the prognostic associations of the NPs in a population with a high prevalence of obesity are not well-defined. Specifically, nearly all prior studies have been constrained by a modest sample size of individuals with greater obesity severity (all with <1,200 patients with BMI ≥35 kg/m^2, with even more sparse data on those with a BMI ≥40 kg/m^2),[9-11] limiting power and precision for a more granular examination of the NP-BMI relationship with respect to HF risk stratification. As well, no prior studies have examined whether treatment implications exist based on risk differences for a given NP concentration across BMI.

Accordingly, we sought to 1) examine the relationship between baseline N-terminal pro-B-type NP (NT-proBNP) and BMI with subsequent HF risk by analyzing patient-level data across three clinical trials which enrolled patients with a high prevalence of obesity and cardiometabolic disease (SAVOR-TIMI 53, DECLARE-TIMI 58, and CAMELLIA-TIMI 61),[12-14] and 2) within the DECLARE-TIMI 58 trial, assess

whether the treatment effect of dapagliflozin on HF differs by BMI among patients at risk for HF on the basis of an elevated baseline NT-proBNP (≥125 pg/mL).

Methods

Trial Populations and Outcomes

The design and primary results of all three trials have been previously reported.[12-17] Briefly, SAVOR-TIMI 53 and DECLARE-TIMI 58 randomized patients with type 2 diabetes and either established atherosclerotic cardiovascular (CV) disease (ASCVD), or multiple CV risk factors to placebo vs. saxagliptin and vs. dapagliflozin, respectively. CAMELLIA-TIMI 61 randomized patients with a BMI ≥ 27 kg/m^2 and established ASCVD or multiple CV risk factors to lorcaserin vs. placebo. Given the established effects of saxagliptin and dapagliflozin on incident HF risk (increasing and decreasing, respectively), only patients randomized to placebo from SAVOR-TIMI 53 and DECLARE-TIMI 58 were included in the analyses examining prognostic associations. As lorcaserin has not been demonstrated to affect future HF risk, patients from both treatment arms in CAMELLIA-TIMI 61 were included. The analysis cohort included all patients across the three trials with available NT-proBNP from randomization. In a separate analysis to examine the treatment effect of dapagliflozin as a function of BMI stratified by NT-proBNP, patients randomized to dapagliflozin in DECLARE-TIMI 58 were compared with placebo. The ethics committees at all participating centers approved the protocols for each trial. Written informed consent was obtained from all patients.

The primary outcome for this analysis was hospitalization for heart failure (HHF). All outcomes were adjudicated centrally by the TIMI Clinical Events Committee (CEC) using established definitions as specified in the trial-specific CEC charters.[12-14]

Biomarker Assessment

Blood samples were collected at the time of randomization in each trial and centrifuged on site. Isolated serum and plasma were stored at -20^{o}C or colder at the site and shipped frozen to the TIMI Clinical Trials Laboratory (Boston, MA) where samples were stored at -80^{o}C or colder. NT-proBNP was measured using

the Roche proBNP II assay in SAVOR-TIMI 53 and DECLARE-TIMI 58, and the Siemens Healthineers Atellica assay in CAMELLIA-TIMI 61. Prior analyses have demonstrated excellent concordance in NT-proBNP concentrations between these assays (Cohen's κ >0.80) around established thresholds.[18] High-sensitivity cardiac troponin T (hsTnT) was measured in all three trials on the Cobas 6000 analyzer (Roche Diagnostics).

Statistical Analyses

Demographics and other baseline characteristics are reported as median (25^{th}-75^{th} percentiles) for continuous variables and as counts and percentages for categorical variables. The χ^2 test was used for categorical variables and the Kruskal–Wallis test was used for continuous variables to compare differences among groups.

NT-proBNP was analyzed both continuously and categorically using previously applied thresholds:[19] <125, 125-<450 and ≥450 pg/mL. BMI was analyzed categorically using commonly accepted thresholds: <30, 30-<35, 35-<40 and ≥40 kg/m^2. For the primary analysis, event rates were estimated in the combined population using Kaplan-Meier estimates of survival probabilities at 2 years, with supplementary analyses stratified by age, sex, and prior HF. As DECLARE-TIMI 58 and CAMELLIA-TIMI 61 had longer follow-up time compared with SAVOR (median follow-up of 4.2, 3.3 and 2.1 years, respectively),[12-14] a supplementary analysis was performed restricted to only patients in those trials with 3-year rates.

A linear regression model was used to evaluate the relationship between NT-proBNP and BMI with multivariable adjustment for the following co-variates: age (continuous), sex, hypertension, diabetes, estimated glomerular filtration rate (continuous), smoking status, established ASCVD, prior HF and hsTnT (continuous). For the linear regression analyses, NT-proBNP was log transformed for normality. Cox regression models were used to examine the association between BMI and HHF across

NT-proBNP strata with adjustment for the same co-variates. All associations were separately examined in subgroups of patients with and without prior HF. Proportionality of the hazards was tested by regressing Schoenfeld residuals over time and no departures from this assumption were detected. Restricted cubic splines were used to examine the relationship between continuous NT-proBNP and HHF stratified by BMI.

The Cochran-Armitage test-for-trend was used to assess associations across the ordinal BMI groups and incident HHF stratified by NT-proBNP. Models were also separately evaluated by allowing a 2-way interaction term for NT-proBNP and BMI. Heterogeneity in the effect of dapagliflozin vs. placebo for HHF across BMI was examined among patients from DECLARE-TIMI 58 with elevated baseline NT-proBNP (≥125 pg/mL). All p-values were 2-sided, and values <0.05 were considered statistically significant. Statistical computations were performed with the statistical software R version 4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

A total of 24,455 patients were included in the overall analyses (**Table 1**) with a median BMI of 33 (25^{th}-75^{th} percentile: 29-37) kg/m^2. Among these, 29.0%, 34.5%, 21.5% and 12.0% had a BMI <30, 30-<35, 35-<40 and ≥40 kg/m^2, respectively. Patients with higher BMI were younger and had greater prevalence of hypertension and established HF (p-trend < 0.001). The overall median NT-proBNP was 96 (25^{th}-75^{th} percentile: 43-225) pg/mL. Baseline characteristics by NT-proBNP are shown in **Supplemental Table 1**. Patients with higher NT-proBNP were older, with greater prevalence of established ASCVD or HF, and with higher baseline hsTnT. There was an inverse relationship between NT-proBNP and BMI when assessed with linear regression, which persisted after multivariable adjustment (p<0.001; **Supplemental Table 2**).

Event Rates for HHF by NT-proBNP and BMI

A total of 688 HHF events occurred during follow-up, with an overall 2-year event rate of 1.9%. Both higher NT-proBNP and higher BMI were each associated with greater probability of HHF (**Supplemental Figure 1**). Of patients who had a HHF event, baseline NT-proBNP was lower in those with a higher BMI (p-trend < 0.001; **Figure 1**). Stratified by the baseline BMI, there was a stepwise risk gradient for HHF across NT-proBNP within each of the BMI groups (**Supplemental Figures 2 and 3**). Conversely, stratified by the baseline NT-proBNP, there was a graded association between higher BMI and the risk of HHF across all NT-proBNP strata, with those having a BMI ≥40 kg/m^2 having a near doubling of the HHF 2-year event rate compared with those with a BMI of <30 kg/m^2 (p-trend < 0.001 for each; **Figure 2**). These associations were generally consistent when further stratified by age (**Supplemental Figure 4**), sex (**Supplemental Figure 5**) and prior HF (**Supplemental Figure 6**).

Restricting only to DECLARE-TIMI 58 (placebo only) and CAMELLIA-TIMI 61 (all patients) so as to examine the effect of a longer follow-up time, there was continued separation in HHF risk and a greater absolute risk difference across BMI categories within each NT-proBNP strata at 3 years (**Supplemental Figure 7**). With continuous modeling of NT-proBNP, a similar relationship was observed (**Figure 3**), with a pattern of progressively greater absolute risk differences for HHF in patients with NT-proBNP >450 pg/mL compared with those with normal NT-proBNP (<125 pg/mL) as BMI increased (p-trend = 0.13**; Supplemental Table 3).** For example, in those with a BMI ≥35 kg/m^2, a 2-year HHF event probability of 2.5% and 5.0% was indicated by an NT-proBNP of 169 and 300 pg/mL, whereas those with a BMI <35 kg/m^2 had an NT-proBNP of 319 and 496 pg/mL for equivalent 2-year risk (**Figure 3**).

Adjusted Hazard for HHF by NT-proBNP and BMI

After multivariable adjustment for clinical risk factors and baseline hsTnT, there was a significant interaction between NT-proBNP and BMI with respect to the hazard of HHF (p-interaction <0.001; **Supplemental Table 4**). Stratifying by baseline NT-proBNP concentration, there was a stepwise increase in the HR for HHF with increasing BMI across all groups of NT-proBNP (p-trend < 0.001 for each; **Figure 4**). The largest relative gradient (>7-fold) across BMI categories was observed in those with normal NT-proBNP (<125 pg/mL), with attenuation of this gradient among those with higher baseline NTproBNP (1.8-fold gradient from the lowest to highest BMI category among patients with NT-proBNP ≥450 pg/mL; **Figure 4**) due to generally higher risk across all BMI categories. Considering absolute risk (**Figure 2**), those with a normal NT-proBNP were all at low absolute risk irrespective of BMI (2y rate ≤0.6%), whereas those with even a low-level elevation in NT-proBNP (125-<450 pg/mL) had a clinically meaningful absolute risk difference (2y KM rate 1.3% to 4.0% across BMI), with a 3-fold gradient in risk for HHF across BMI (BMI ≥40 vs. <30 kg/m^2**:** HR_{adj} 3.22 [95% CI 2.13-4.86], p<0.001; **Figure 4**). These associations were consistent when stratified by prior HF (**Supplemental Table 5**).

Treatment Interaction of Dapagliflozin vs. Placebo for HHF

In the population with an elevated NT-proBNP at baseline (≥125 pg/mL), dapagliflozin versus placebo was associated with a consistent reduction in HHF across BMI (p-trend for HR = 0.60), with a pattern of greater absolute benefit at greater BMI (ARR 2.2% to 4.7% across BMI <30 to ≥40 kg/m^2; p-trend = 0.059; **Figure 5**).

Discussion

In this cohort of well-phenotyped patients consisting of >15,000 individuals with obesity, we demonstrate that for any given range of NT-proBNP, there is a graded association in the absolute and relative risk for HHF with increasing BMI. Within this cohort, those with an NT-proBNP <125 pg/mL had overall low absolute risk for HHF irrespective of BMI. However, in those with elevated NT-proBNP (≥125 pg/mL), HHF risk for any given NT-proBNP value was significantly higher among individuals with obesity, suggesting a need to consider BMI when applying NP concentrations for HF risk stratification. In particular, clinicians should recognize the meaningful risk of HHF in patients with severe obesity with low-level elevations in NT-proBNP (e.g., 125-<450 pg/ml), where we demonstrate an absolute risk gradient of 2.7% across BMI at 2 years, and a >3-fold relative risk difference after multivariable adjustment. Moreover, for patients with an elevated NT-proBNP (≥125 pg/mL), we demonstrate a pattern of greater absolute benefit with the sodium-glucose co-transporter-2 inhibitor (SGLT2i) dapagliflozin for reduction of HHF risk with increasing obesity severity. Collectively, these findings suggest that reclassification of risk by BMI among patients with low-level elevations in NT-proBNP may have implications for ongoing clinical surveillance and initiation of HF preventative therapies.

Prior studies have probed the prognostic associations between NPs, BMI, and incident HF. In an analysis of the TOPCAT trial, which enrolled patients with established HF and preserved ejection fraction, when BMI and NT-proBNP were assessed dichotomously,[10] only patients with both high BMI (>31.95 kg/m^2) and high NT-proBNP (>984 pg/mL) were shown to have elevated risk of HHF, without a substantial difference observed for patients with a high BMI and low NT-proBNP compared with those with both a low BMI and NT-proBNP.[10] Expectedly, given that TOPCAT exclusively enrolled patients with HF with use of higher NP thresholds as trial eligibility criterion for patient selection, the overall NT-proBNP distribution was markedly higher than in our study. In contrast, in analyses from the ARIC epidemiologic study of patients without established CV disease,[9] patients who were obese (BMI 30-<35

kg/m^2; n=2,356) or severely obese (BMI > 35 kg/m^2; n=1,119) had higher absolute risk of HHF than patients in lower BMI groups across similar NT-proBNP concentrations, though without marked differences in relative risk after multivariable adjustment for clinical factors. Our current study results expand on these prior findings, leveraging a substantially larger cohort of patients who were overweight or obese, in which we demonstrate marked differences in both absolute and relative risk for HHF across BMI for any range of NT-proBNP. Moreover, as nearly all prior studies stem from either epidemiologic cohorts free of established cardiovascular disease at baseline or consist of patients with already established clinically overt HF, we expand on prior research by examining prognostic implications in a patient population with established cardiovascular disease but predominantly without prior HF at baseline (stage A and B HF),[20] a group in which lifestyle modification, closer monitoring and HF preventative therapies have the potential to delay or prevent onset of clinical HF.

These findings may have implications for clinical practice, particularly for decision making centered around patients without established HF. On the basis of findings from STOP-HF,[21] a randomized trial which evaluated the impact of an NP-based screening strategy for reducing left ventricular dysfunction with or without HF, current guidelines recommend the use of NPs for routine screening in those at risk for HF to inform team-based care centered at preventing development of overt HF.[22] However, with respect to this NP screening, our findings illustrate that the absolute risk for HF varies markedly by BMI for any given range of NT-proBNP. Moreover, owing to low absolute rates of HHF in those with a normal NT-proBNP (<125 pg/mL) and consistently high rates in those with an NT-proBNP ≥450 pg/mL irrespective of BMI, the absolute risk difference may be most clinically meaningful for those with low-level elevations in NT-proBNP (125- <450 pg/mL) without HF at baseline, where greater equipoise may exist regarding initiation of HF preventative therapies. To this end, we demonstrate a significant gradient in absolute risk of HHF across BMI in this subset of patients ranging from 1.4% to 4% at 2 years, which becomes even more pronounced in both relative and absolute risk with longer follow-

up (1.8% to 5.6% at 3 years). As well, our findings suggest possible treatment implications on the basis of the NP-BMI relationship. For patients identified as being at risk for HF on the basis of an elevated NT-proBNP concentration (stage B HF), the absolute benefit of dapagliflozin may be greater in those with greater obesity severity. As such, identifying patients at higher risk who stand to derive greater absolute benefit may help to guide allocation of costly therapies such as SGLT2i in patients at risk for HHF, and may be particularly relevant in view of the emerging role of glucagon-like peptide-1 receptor agonists (GLP1RA) in obese patients at risk of HF.

The mechanisms underlying the inverse relationship between BMI and the NPs remain unclear. While adipocytes have been shown to have high expression of natriuretic peptide clearance receptors (NPR-C),[23] the same relationship has been demonstrated for both BNP and NT-proBNP,[10,11] with NPR-C only playing a role in clearance of the former. Moreover, prior studies have shown that lean mass as opposed to fat mass may be better correlated with NT-proBNP levels,[11] and that differences in NT-proBNP based on lean mass may be further explained by differences in free testosterone.[24] Interestingly, several lines of investigation support a bidirectional relationship between obesity and the NPs. Using genetically engineered mouse models, Miyashita et al. demonstrated that increased NP concentrations prevented accumulation of abdominal fat in mice fed with high-fat diets via upregulation of the peroxisome proliferator-activated receptor (PPAR)-γ and PPARδ pathways.[25] However, data regarding the effect of weight loss on natriuretic peptides is conflicting. While prior observational studies have demonstrated an increase in NP concentrations following weight loss,[26-28] with markedly improved NP response to saline loading,[26], the recent STEP HFpEF trial demonstrated a reduction in both weight and NPs with use of the GLP1RA semaglutide, with resultant improvement in HF-related symptoms, functional capacity and a reduction in HF events.[29] As such, the putative mechanisms underlying the relationship between the NP system and obesity warrant further investigation.

Several limitations of our study should be acknowledged. Since serial biomarker data were not systematically captured across the trials, post-baseline changes in BMI or NT-proBNP over the course of follow-up could not be assessed in the present analyses, and such data may provide further incremental prognostic information. As well, we were unable to account for changes to background medications that may have influenced NT-proBNP concentrations or otherwise affected the risk of HHF during trial follow-up. BMI was used to grade obesity severity in these analyses and may fail to account for differences in body composition which are better assessed with imaging. Further stratification of the NP-BMI categories by age, sex or prior HF history sometimes resulted in very few or no events within a subgroup. As such, some risk estimates in these subgroups have wide CIs. For HHF risk prevention, only dapagliflozin was examined and while this may be generalizable across the SGLT2i class of medications, this cannot be concluded with certainty.

Conclusion

In a large cohort of patients with cardiometabolic disease and a high burden of obesity, the risk of HHF varies across the range of BMI within any given range of NT-proBNP, whether assessed on the basis of absolute or relative risk. Among patients with an elevated NT-proBNP, those with greater severity of obesity potentially derive greater absolute benefit with the SGLT2i dapagliflozin for reduction of HHF risk. These findings showcase the importance of considering BMI when interpreting NT-proBNP assessments for HF risk stratification, particularly for patients with low-level elevations in NT-proBNP, and in assessing the potential benefit of SGLT2i as HF therapy.

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Table 1: Baseline Characteristics by Categories of Body Mass Index

Characteristic	Body Mass Index Category (kg/m^2)			
	<30 (N=7080, 29.0%)	**30-<35 (N=8425, 34.5%)**	**35-<40 (N=5270, 21.5%)**	**≥40 (N=3680, 15.0%)**
Trial				
CAMELLIA	1459 (13.2)	4114 (37.2)	3036 (27.4)	2454 (22.2)
SAVOR (placebo)	2714 (44.2)	1947 (31.7)	980 (15.9)	506 (8.2)
DECLARE (placebo)	2907 (40.1)	2364 (32.6)	1254 (17.3)	720 (9.9)
Demographics				
Age (years)	65 (60-70)	65 (59-70)	64 (58-69)	62 (57-67)
Male	4795 (67.7)	5704 (67.7)	3305 (62.7)	1979 (53.8)
BMI (kg/m^2)	27.7 (25.9-28.9)	32.4 (31.2-33.6)	37.0 (35.9-38.3)	43.5 (41.5-46.9)
Co-morbidities				
Hypertension	5764 (81.4)	7468 (88.6)	4848 (92.0)	3443 (93.6)
Diabetes	6235 (88.1)	6360 (75.5)	4115 (78.1)	3021 (82.1)
Current smoker	1088 (15.4)	966 (11.5)	568 (10.8)	308 (8.4)
Established ASCVD	4578 (64.7)	5719 (67.9)	3534 (67.1)	2210 (60.1)
Heart failure	620 (8.8)	835 (9.9)	590 (11.2)	543 (14.8)
Atrial fibrillation	435 (6.1)	731 (8.7)	588 (11.2)	507 (13.8)
Clinical and Biochemical Markers				
Systolic BP (mmHg)	133 (122-144)	133 (122-144)	133 (122-144)	132 (122-143)
eGFR (mL/min/1.73 m²)	82.0 (67.0-94.0)	78.0 (64.0-91.0)	77.0 (63.0-90.7)	77.4 (62.0-91.0)
NT-proBNP (pg/mL)[a]	101 (45.4-244.0)	93.6 (43.2-214.0)	92.3 (42.0-223.0)	96.0 (42.2-222.0)
hsTnT (ng/L)	9.5 (6.0-15.1)	8.4 (4.4-14.2)	8.2 (4.2-14.2)	7.2 (3.9-13.4)
Baseline Medications				
Aspirin	4722 (66.7)	6043 (71.7)	3698 (70.2)	2495 (67.8)
Statin	5520 (78.0)	6917 (82.1)	4300 (81.6)	2974 (80.8)
Beta-blocker	3779 (53.4)	5219 (61.9)	3348 (63.5)	2286 (62.1)
ACE inhibitor or ARB	4684 (66.2)	6184 (73.4)	3948 (74.9)	2858 (77.7)

Numbers indicate n (%) for categorical variables and median (25^{th}-75^{th} percentiles) for continuous variables. P-trend for each variable across BMI <0.001 with the exception of systolic BP and hsTnT (p-trend = 0.21 and 0.67, respectively)

[a] NT-proBNP was inversely associated with BMI when assessed with linear regression (**Supplemental Table 2**).

Abbreviations: ACE – angiotensin converting enzyme; ARB – angiotensin receptor blocker; ASCVD – atherosclerotic cardiovascular disease; BMI – body mass index; BP – blood pressure; eGFR – estimated glomerular filtration rate; hsTnT – high-sensitivity troponin T; NT-proBNP – N-terminal pro-type Brain Natriuretic Peptide.

Figure Legends

Figure 1: Distribution of Baseline NT-proBNP across Body Mass Index Categories in Patients with Subsequent Hospitalization for Heart Failure.

The median, 25th percentile and 75th percentile of NT-proBNP concentration within each BMI group is shown.

Figure 2: 2-year Event Rates of Hospitalization for Heart Failure by Body Mass Index across NT-proBNP

The 2-year event rates for HHF are shown across BMI groups stratified by the baseline NT-proBNP concentration, demonstrating a stepwise absolute risk gradient across BMI groups in each of the NT-proBNP strata. In patients with normal NT-proBNP (<125 pg/mL), the event rate for HHF is low even in those at high BMI. Conversely, in patients with an NT-proBNP >450 pg/mL, even those at lower BMI have a high event rate for HHF. However, in patients with low-level elevations of NT-proBNP (125-<450 pg/mL), there exists a clinically meaningful reclassification of risk when further contextualizing NT-proBNP by BMI.

Abbreviations: BMI – body mass index; HHF – hospitalization for heart failure; NT-proBNP – N-terminal pro-type brain natriuretic peptide

Figure 3: 2-year Event Probabilities of Hospitalization for Heart Failure as a Function of Continuous NT-proBNP across BMI Groups: A) Dichotomized at 35 kg/m^2 B) Conventional BMI Categories

The 2-year event probability for HHF is shown with continuous modeling of NT-proBNP concentration. Panel A shows the event probabilities across NT-proBNP as a function of BMI groups dichotomized at 35 kg/m^2. Panel B shows the event probabilities across NT-proBNP as a function of conventional BMI groups. The rug plots below the x-axis in each panel depict the distribution of NT-proBNP, with greater density of marks indicating more patients with an NT-proBNP concentration in that range. The absolute risk difference for HHF across BMI groups increases at higher NT-proBNP concentrations.

Abbreviations: BMI – body mass index; HHF – hospitalization for heart failure; NT-proBNP – N-terminal pro-type brain natriuretic peptide

Figure 4: Adjusted Hazard Ratios of Hospitalization for Heart Failure by Body Mass Index across NT-proBNP

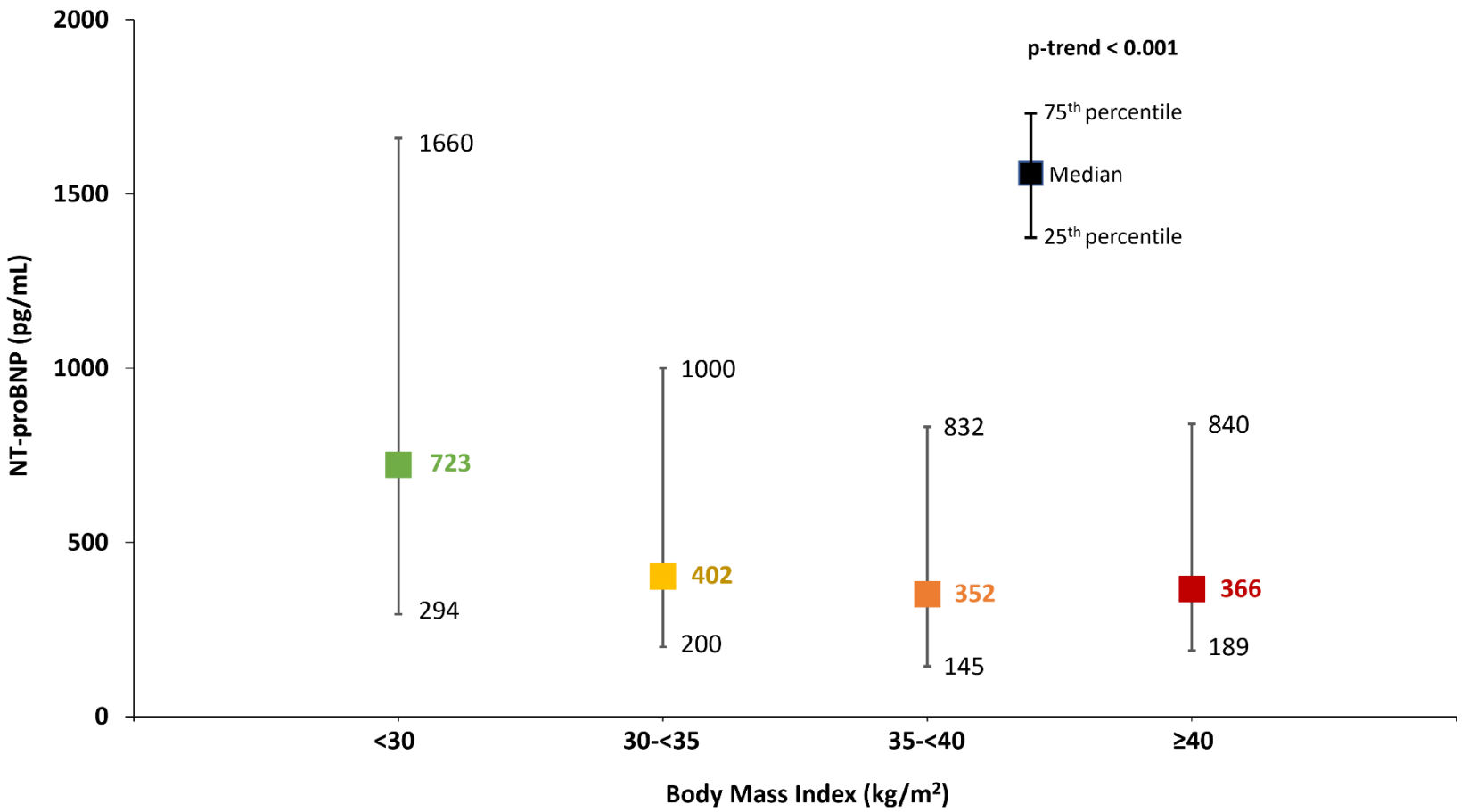
The forest plots depict the adjusted risk gradient for heart failure hospitalization, across BMI groups stratified by baseline NT-proBNP concentration. Within each NT-proBNP stratum, BMI <30 kg/m^2 is used as the reference group. All hazard ratios reflect multivariable adjustment for age (continuous), sex, hypertension, diabetes, estimated glomerular filtration rate (continuous), smoking status, established ASCVD, prior HF and hsTnT (continuous).

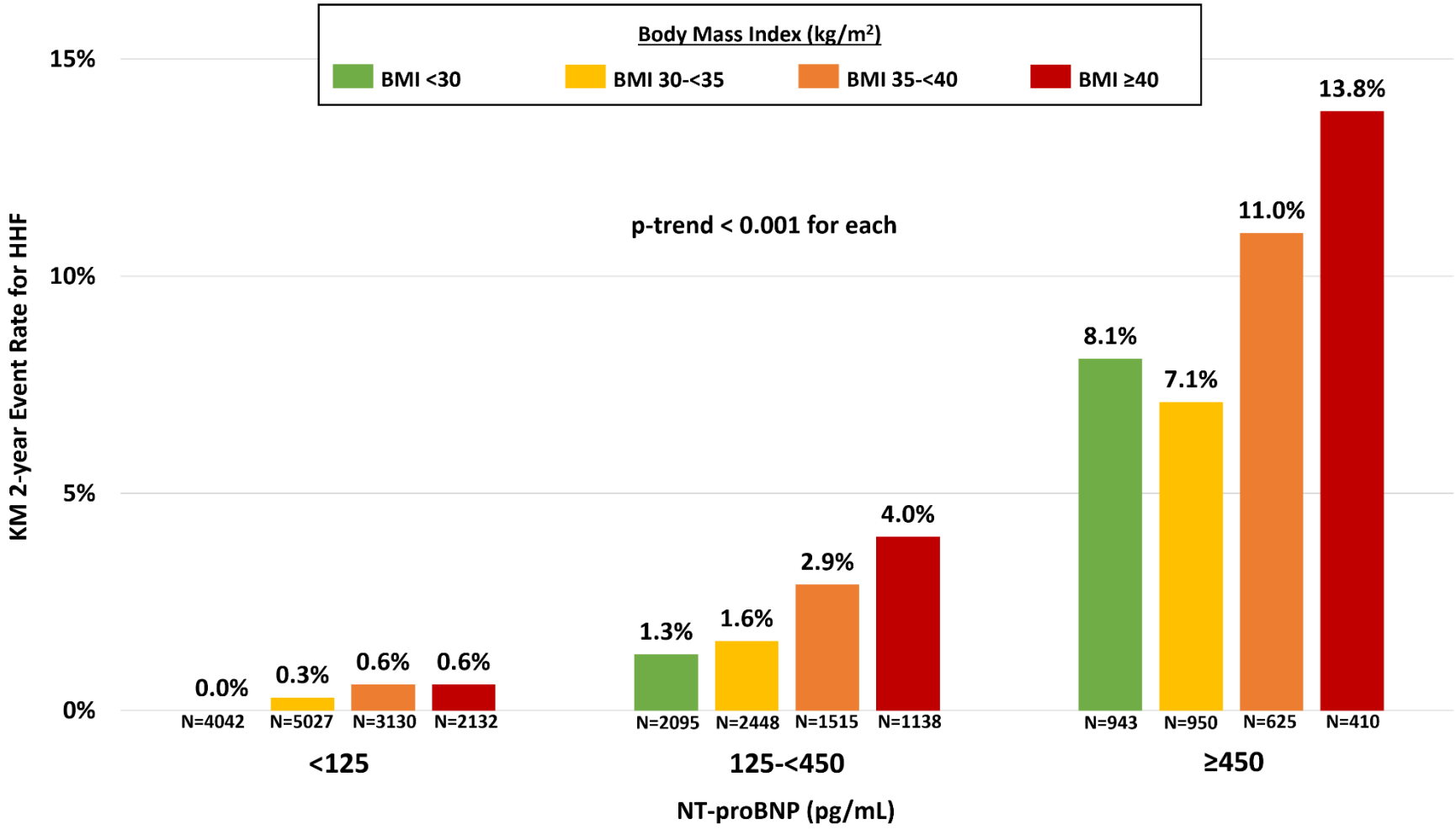
Abbreviations: aHR – adjusted hazard ratio; BMI – body mass index; NT-proBNP – N-terminal pro-type brain natriuretic peptide

Figure 5: Treatment Interaction of Dapagliflozin versus Placebo in DECLARE-TIMI 58 Patients with Elevated NT-proBNP (≥125 pg/mL) as a Function of Body Mass Index

The 3-year event rates and hazard ratios across BMI are shown for the subset of patients from DECLARE-TIMI 58 with an elevated NT-proBNP (≥125 pg/mL) at baseline, further stratified by treatment allocation to dapagliflozin or placebo. Dapagliflozin consistently reduced HHF risk across BMI categories, with a pattern of increasing absolute benefit at higher BMI.

Abbreviations: ARR – absolute risk reduction; BMI – body mass index; KM – Kaplan Meier; HHF – hospitalization for heart failure; HR – hazard ratio; NT-proBNP – N-terminal pro-type brain natriuretic peptide


2000
1500
1000
500
0
NT-proBNP (pg/mL)
p-trend < 0.001
75th percentile
Median
25th percentile
1660
723
294
1000
402
200
832
352
145
840
366
189
<30
30-<35
35-<40
≥40
Body Mass Index (kg/m²)


Body Mass Index (kg/m²)
BMI <30
BMI 30-<35
BMI 35-<40
BMI ≥40
p-trend < 0.001 for each
KM 2-year Event Rate for HHF
15%
10%
5%
0%
0.0%
0.3%
0.6%
0.6%
1.3%
1.6%
2.9%
4.0%
8.1%
7.1%
11.0%
13.8%
N=4042
N=5027
N=3130
N=2132
N=2095
N=2448
N=1515
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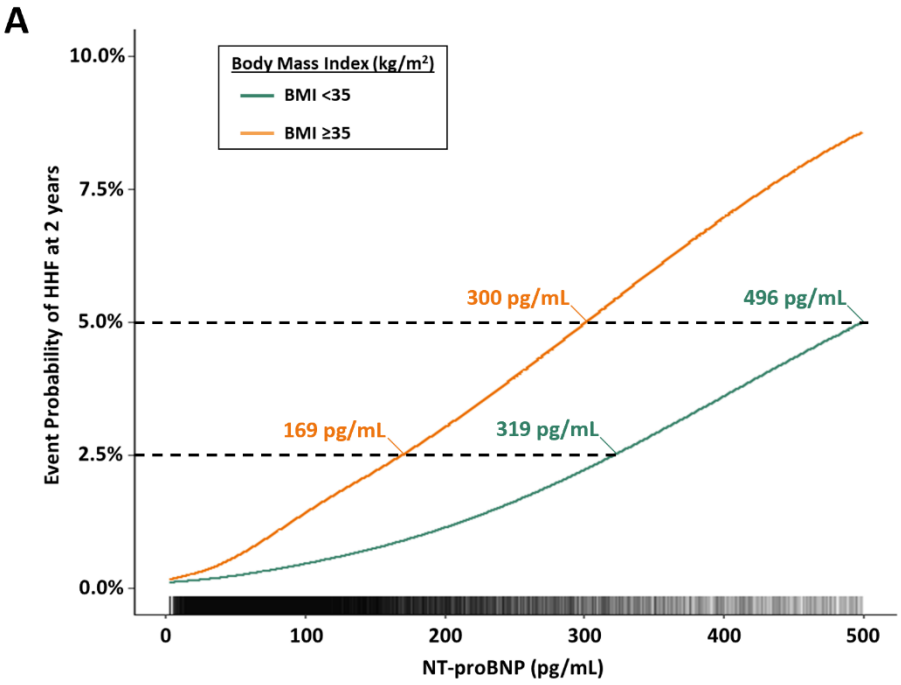
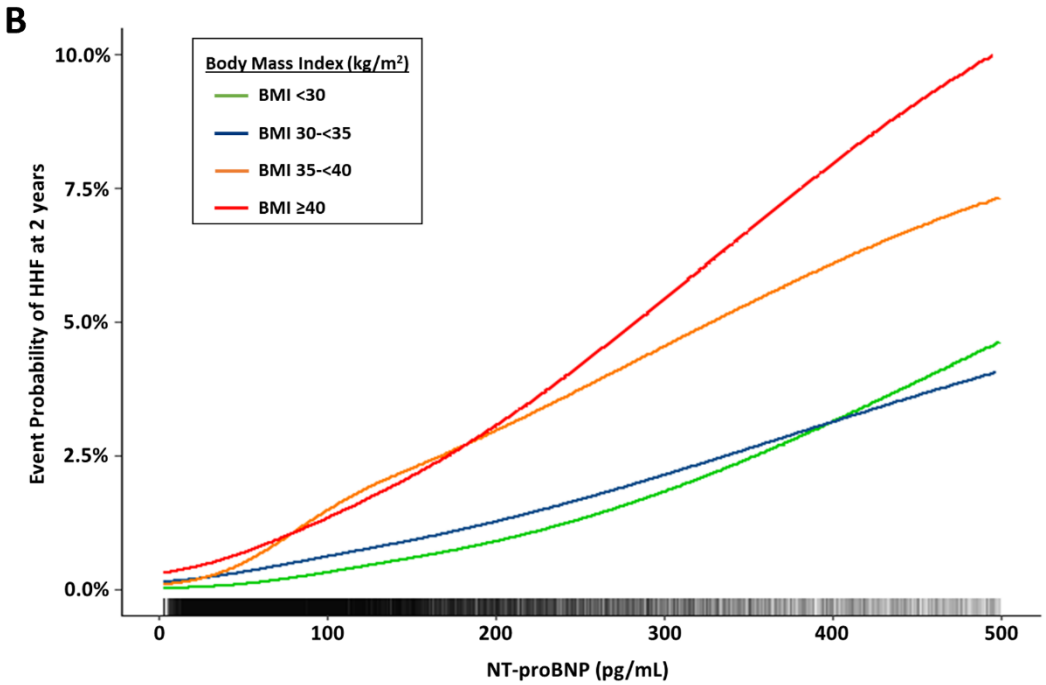
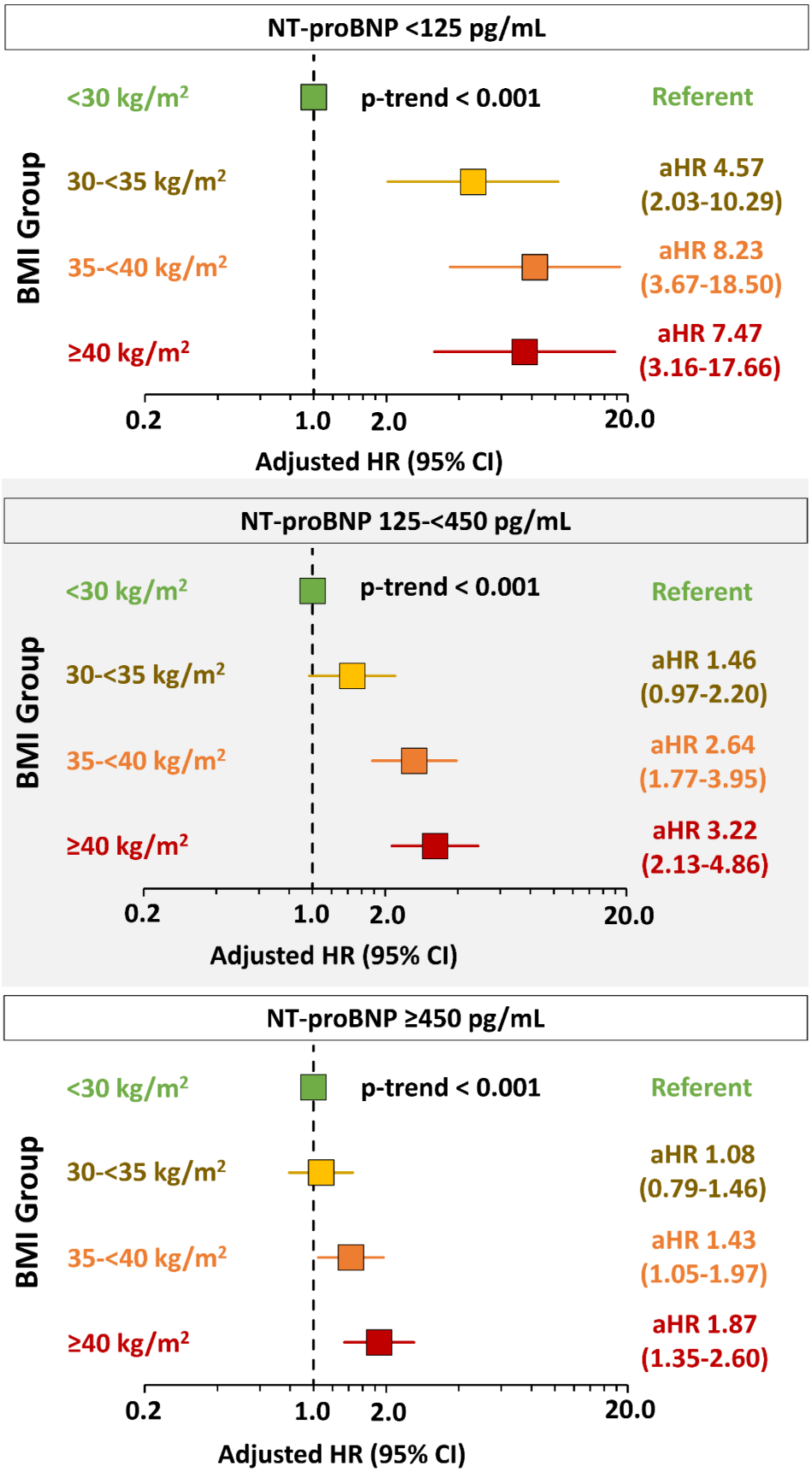
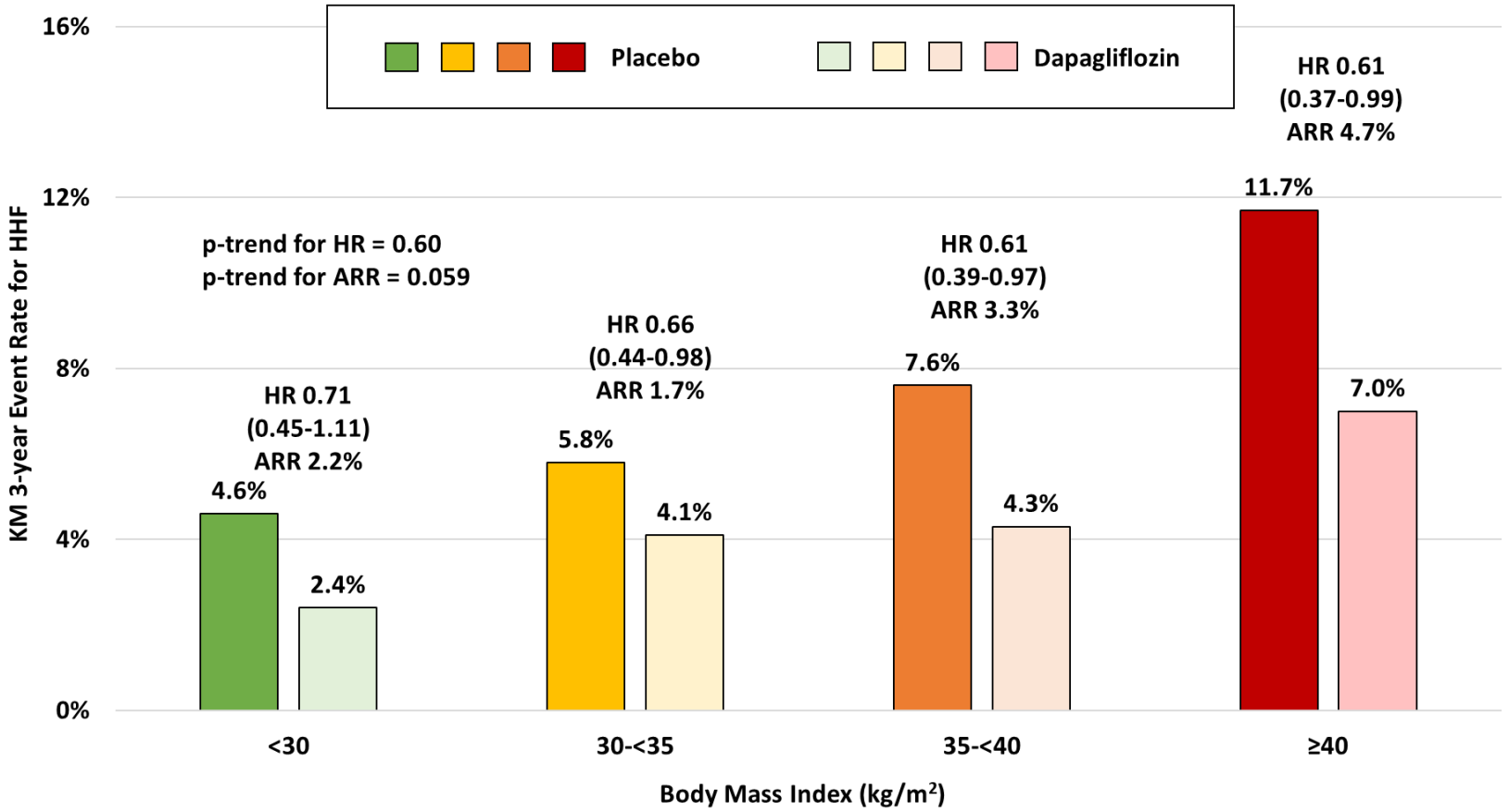
N=410
<125
125-<450
≥450
NT-proBNP (pg/mL)


A
Body Mass Index (kg/m²)
BMI <35
BMI ≥35
10.0%
7.5%
5.0%
2.5%
0.0%
Event Probability of HHF at 2 years
300 pg/mL
496 pg/mL
169 pg/mL
319 pg/mL
0
100
200
300
400
500
NT-proBNP (pg/mL)


B
Body Mass Index (kg/m²)
BMI <30
BMI 30-<35
BMI 35-<40
BMI ≥40
10.0%
7.5%
5.0%
2.5%
0.0%
Event Probability of HHF at 2 years
0
100
200
300
400
500
NT-proBNP (pg/mL)


NT-proBNP <125 pg/mL
BMI Group
<30 kg/m²
p-trend < 0.001
Referent
30-<35 kg/m²
aHR 4.57
(2.03-10.29)
35-<40 kg/m²
aHR 8.23
(3.67-18.50)
≥40 kg/m²
aHR 7.47
(3.16-17.66)
0.2
1.0
2.0
20.0
Adjusted HR (95% CI)
NT-proBNP 125-<450 pg/mL
BMI Group
<30 kg/m²
p-trend < 0.001
Referent
30-<35 kg/m²
aHR 1.46
(0.97-2.20)
35-<40 kg/m²
aHR 2.64
(1.77-3.95)
≥40 kg/m²
aHR 3.22
(2.13-4.86)
0.2
1.0
2.0
20.0
Adjusted HR (95% CI)
NT-proBNP ≥450 pg/mL
BMI Group
<30 kg/m²
p-trend < 0.001
Referent
30-<35 kg/m²
aHR 1.08
(0.79-1.46)
35-<40 kg/m²
aHR 1.43
(1.05-1.97)
≥40 kg/m²
aHR 1.87
(1.35-2.60)
0.2
1.0
2.0
20.0
Adjusted HR (95% CI)


Placebo
Dapagliflozin
16%
12%
8%
4%
0%
KM 3-year Event Rate for HHF
p-trend for HR = 0.60
p-trend for ARR = 0.059
HR 0.71
(0.45-1.11)
ARR 2.2%
4.6%
2.4%
HR 0.66
(0.44-0.98)
ARR 1.7%
5.8%
4.1%
HR 0.61
(0.39-0.97)
ARR 3.3%
7.6%
4.3%
HR 0.61
(0.37-0.99)
ARR 4.7%
11.7%
7.0%
<30
30-<35
35-<40
≥40
Body Mass Index (kg/m²)