

GENDER DIFFERENCES IN HOSPITALIZATION OR DEATH DUE TO HEART FAILURE AS RELATED TO GLYCEMIC CONTROL IN THE ACCORD TRIAL

Tejas Patel¹, Bereket Tesfaldet¹, Neha Amin², Eileen Navarro¹, Jerome Fleg², Helena Saviglin¹, Ruth Kirby², Jue Chen², Gyorgy Csako², Charu Gandotra³, George Sopko², Lawton Cooper², Sean Coady², Frank Pucino¹, Keith Burkhart¹, Karim Calis¹, Henry Chang², Patrice Desvigne-Nickens², Lijuan Liu², Michelle Fennessy⁴, Eric Leifer², Subha Raman⁴, Yves Rosenberg², Ahmed Hasan², for the Meta-Analytical Interagency Group

¹ CDER/FDA, ² NIH/NHLBI, ³ Howard University Hospital, ⁴ Ohio State University



INTRODUCTION

Heart failure (HF) and type 2 diabetes (T2D) are important causes of hospitalizations and mortality. Heart failure is two and five times more common in diabetic men and women, respectively, and associated with a worse prognosis than age-matched non-diabetics. The ACCORD trial (NCT00000620) tested the impact of intensive vs. standard glucose-lowering treatment (target HbA1c <6.0% vs. 7.0%-7.9%) on cardiovascular events in T2D patients (median baseline HbA1c 8.1%). We further explored the treatment effects on hospitalization or death due to heart failure (hdHF).

METHODS

Rates of hdHF were compared by treatment arms across genders, as well as by gender across treatment arms in secondary analyses of publicly available patient-level data from the ACCORD trial.

- We report event rates as Kaplan-Meier estimates and hazard ratios (95% CI) at 2.5, 5, and 7 years (end-of-trial).
- Multivariate analysis was used to adjust for age, gender, race, body mass index (BMI), established cardiovascular disease (CVD), previous HF, baseline HbA1c, use of insulin, sulfonylureas, or thiazolidinediones (TZDs), duration of T2D, estimated glomerular filtration rate (eGFR), and current smoking status.

RESULTS

Table 1. Characteristics of the subjects at baseline.

	Men (N=6299)		Women (N=3952)	
	Intensive Rx (N=3145)	Standard Rx (N=3154)	Intensive Rx (N=1983)	Standard Rx (N=1969)
	n (%)			
Age ≥65 yr	1132 (36)	1133 (36)	610 (31)	629 (32)
BMI ≥30 kg/m ²	1853 (59)	1836 (59)	1351 (68)	1355 (69)
Duration of T2D ≥10 yr	1541 (49)	1574 (50)	1007 (51)	966 (49)
Established CVD	1297 (41)	1289 (41)	530 (27)	493 (25)
Previous HF	162 (5)	147 (5)	87 (4)	98 (5)
HbA1c ≥8%	1746 (56)	1786 (57)	1146 (58)	1170 (60)
eGFR ≤60 mL/min	206 (7)	176 (6)	233 (12)	218 (11)
Insulin	993 (32)	1099 (35)	757 (38)	733 (37)
Sulfonylureas	1786 (57)	1732 (55)	981 (50)	975 (50)
TZD	725 (23)	686 (22)	408 (21)	439 (22)
Current Smoker	435 (14)	412 (13)	205 (10)	195 (10)

During a median follow-up of 4.9 years, hdHF events occurred in:

- 4.7% (298/6299) of men vs. 3.7% (146/3952) of women ($p = 0.013$ by Fisher's exact test);
- 4.7% (148/3145) with intensive vs. 4.8% (150/3154) with standard treatment arms in men ($p = 0.953$); and
- 4.2% (84/1983) with intensive vs. 3.2% (62/1969) with standard treatment arms in women ($p = 0.077$).

Comparing men to women, the rate of hdHF events:

- increased with intensive treatment in men after 3.5 years (Fig. 1A), but the difference was not significant between genders across the entire observation period ($p=0.428$ by log-rank test); and
- significantly decreased with standard treatment in women across the entire study ($p=0.007$) (Fig. 1B).

Comparing intensive to standard glucose-lowering treatment, the rate of hdHF events:

- did not differ significantly at any time point in men ($p=0.974$) (Fig. 2B);
- was non-significantly higher in women ($p=0.077$) (Fig. 2A); and
- exhibited no gender by treatment interaction ($p=0.150$)

Significant risk factors for hdHF included:

- age ≥65 years, BMI ≥30 kg/m², CVD, previous HF, baseline HbA1c ≥8%, insulin use, eGFR ≤60 mL/min, current smoking in the entire population;
- age ≥65 years, CVD, previous HF, baseline HbA1c ≥8%, insulin use, current smoking in men; and
- age ≥65 years, BMI ≥30 kg/m², CVD, previous HF, eGFR ≤60 mL/min in women.

Figure 1. Kaplan-Meier estimates for hdHF by gender in intensive (A) and standard (B) treatment arms. Kaplan-Meier estimates and corresponding hazard ratios are presented at 2.5, 5, and 7 years (end-of-trial).

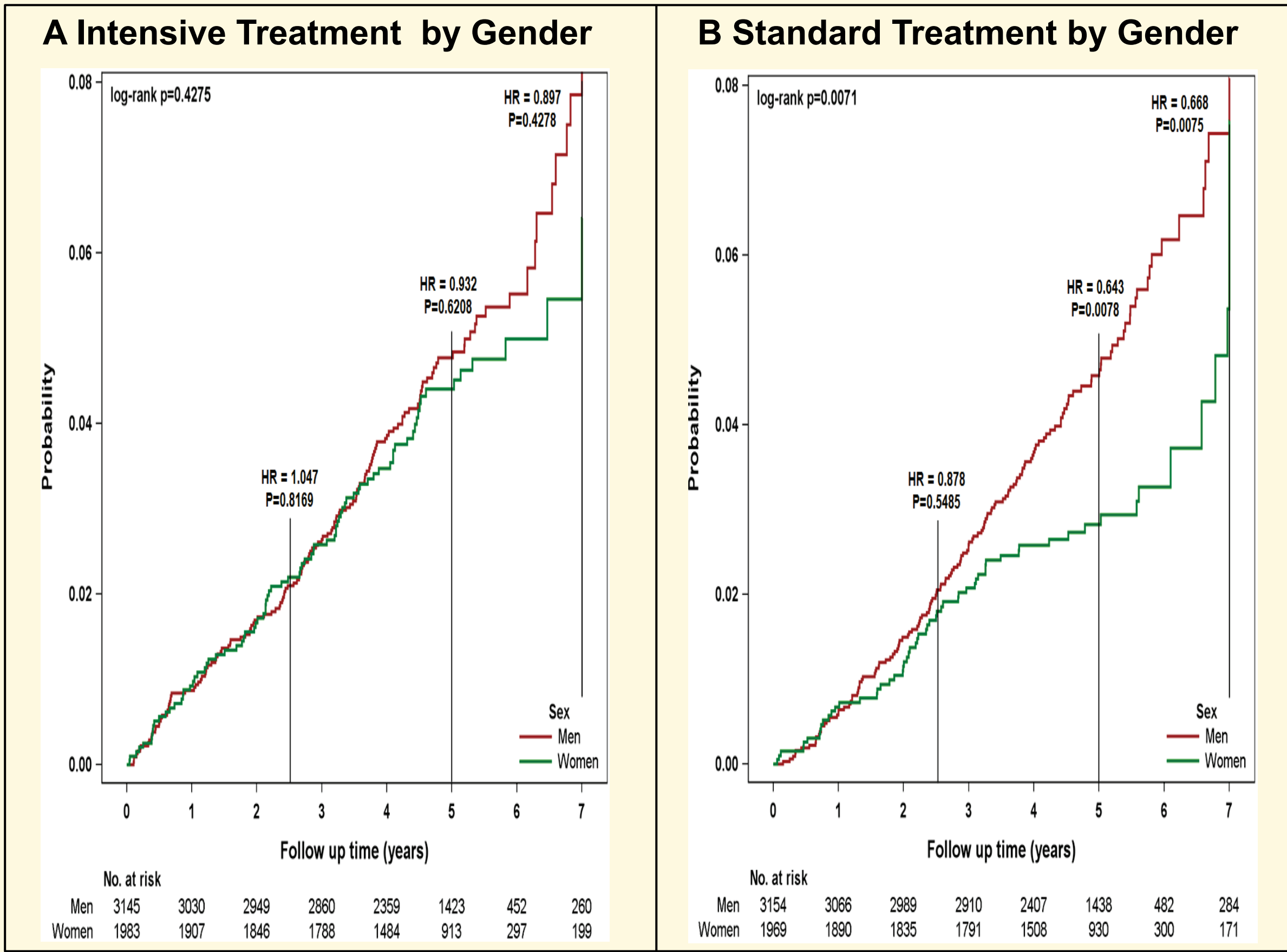
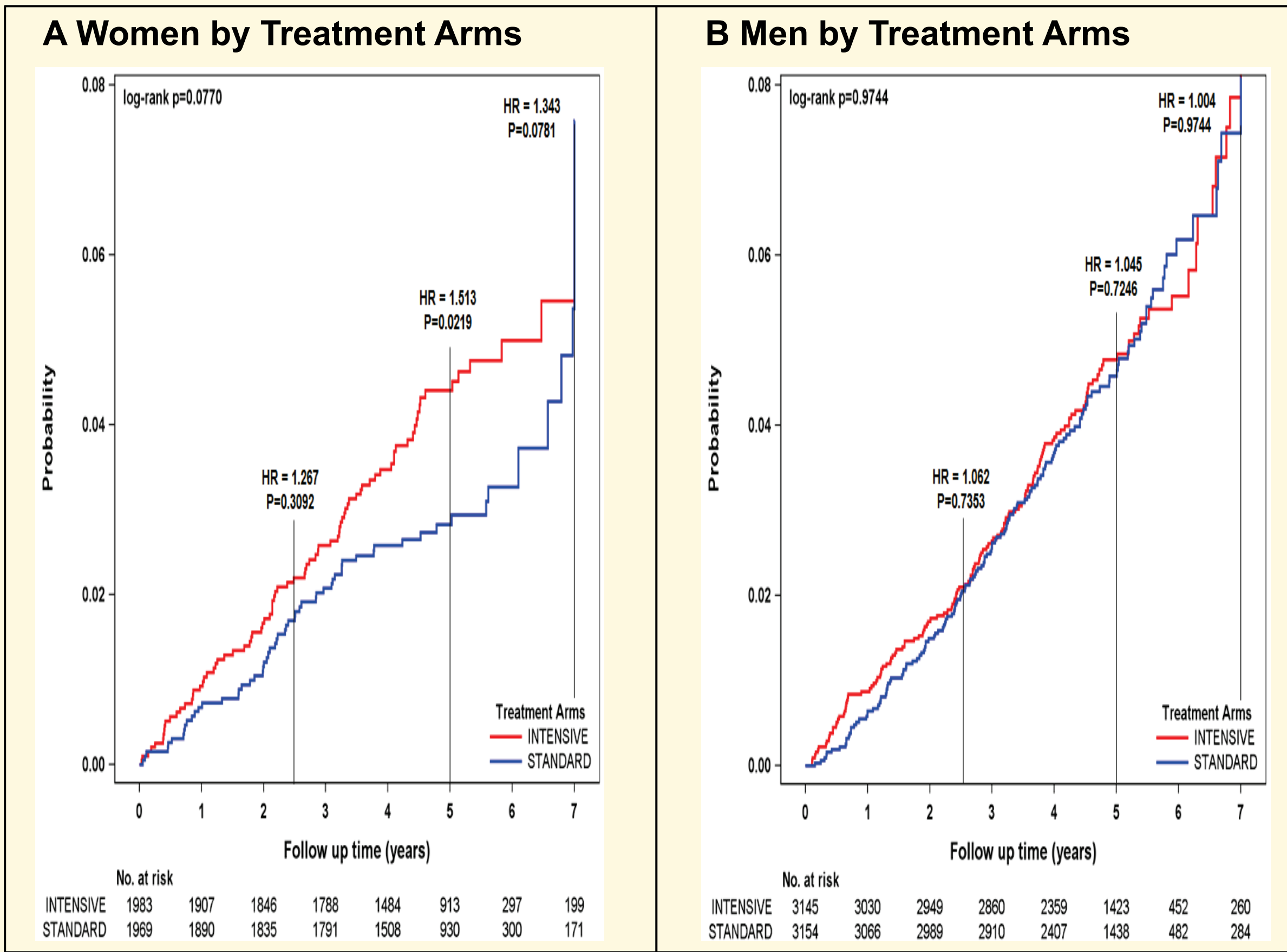


Figure 2. Kaplan-Meier estimates for hdHF by treatment arms in women (A) and men (B). Kaplan-Meier estimates and corresponding hazard ratios are presented at 2.5, 5, and 7 years (end-of-trial).



CONCLUSION

- Women with type 2 diabetes tended to have an increased risk of hdHF events with intensive vs. standard glucose-lowering treatment in the ACCORD trial. No such difference was observed among men.
- This hypothesis-generating secondary analysis, without adjustments for multiple comparisons, warrants confirmatory studies.
- The findings call attention to the importance of outlining gender differences in treatment responses in clinical trials.

DISCLOSURES:
NONE

DISCLAIMER: The contents of this poster are solely the responsibility of the authors, and do not represent the official views of the NIH, the FDA, Howard University, or Ohio State University. These analyses were conducted on publicly available data from BioLINCC.