

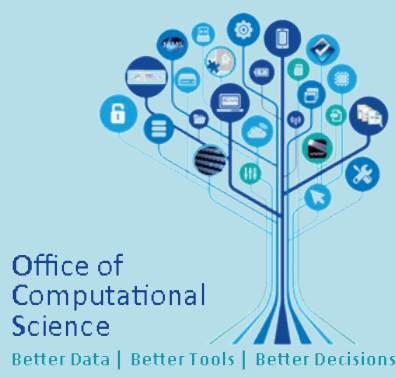
STANDARD ENDPOINTS, STANDARDIZED DATA AND SUBGROUP OUTCOMES IN DIABETES: A PATIENT-LEVEL META-ANALYSIS OF CARDIOVASCULAR OUTCOMES



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INTRODUCTION

Good clinical review requires that efficacy and safety outcomes be assessed by relevant intrinsic patient factors that could modify dose-response or toxicity. Further, section 907 of the Food and Drug Administration Safety and Innovation Act (FDASIA) requires FDA to report on clinical trial participation, as well as safety and efficacy outcomes in relevant demographic subgroups (age, gender, race and ethnicity). However, the clinical trial participation of patients of different genders, ages, races or ethnic groups in submitted new drug applications (NDAs) are often insufficient to enable the required safety and efficacy analyses by subgroup. One possible way to overcome this limitation is to aggregate data from clinical trials across an NDA or across multiple NDAs within the same drug class. The Office of Translational Sciences (OTS) in the Center for Drug Evaluation and Research (CDER) at the FDA converted legacy data from 51 pivotal diabetes clinical trials for 10 NDAs into the Study Data Tabulation Model (SDTM) data. These studies were originally submitted in diverse formats and were not designed a priori to support a specific meta-analytic intent. The legacy conversion mapped all adverse events to the Medical Dictionary for Regulatory Activities (MedDRA) version 13, and reference start day was harmonized to the first day of treatment. In this poster, we present meta-analyses of diabetes clinical trials with thiazolidinediones (TZDs) to assess cardiovascular events within age, gender, and racial subgroups, using an endpoint customized by FDA reviewers and utilized in previous FDA meta-analyses.

OBJECTIVES

- To obtain insightful information on the safety of new drugs in patient subgroups by aggregating patient-level data from clinical trials across an NDA or across multiple NDAs with TZDs.
- To estimate the risks of major adverse cardiac event (MACE) by age, gender and race in aggregated clinical trials of patients with type 2 diabetes (T2D) who receive TZDs through a meta-analytic approach.

ENDPOINT

Time from randomization to the first MACE, where MACE is defined as a composite of cardiovascular death (CV death), non-fatal myocardial infarction (MI) or non-fatal stroke based on MedDRA preferred terms and AE outcomes of death and hospitalization.

TRIAL SELECTION CRITERIA

The following criteria were used to select trials for subject-level meta-analyses performed across NDAs within the TZD class.

- Control: We selected trials with a unique control arm, i.e., different doses of the investigational product were not considered as control.
- Blinding: We preferentially selected double-blind trials.
- Randomization/Parallel follow-up: Randomized control trials were selected in which treatment arms were studied in parallel.
- Sample size/trial durations: We omitted trials with durations exceeding two years or sample sizes exceeding 1000 patients. These were larger trials with longer duration of exposure, and thus patients within these trials are more likely to develop CV events than those within the shorter duration efficacy trials. These trials were analyzed separately.

Abbreviations: AEENDTC, Adverse Event end date; AESI, Adverse Event of Special Interest; AESTCTC, Adverse Event start date; BMI, Body Mass Index; DSSTDTTC, Disposition start date; HbA1c, Glycated hemoglobin; LBDTC, Lab date; RFENDTC, Subject reference end date; SD, Standard Deviation; TZD, Thiazolidinedione; yr, years.

METHODS

The primary analysis for MACE endpoint was an on-study analysis based on the intention-to-treat (ITT) population, defined as all randomized subjects. Additional sensitivity analysis (on-treatment analysis based on the ITT population) was conducted as well (results not shown here). This primary and sensitivity analyses were based on a cox proportional hazards model stratified by study with a fixed effect for treatment.

Due to missing information about event dates, we developed algorithms (Figure 1), which utilized available dates of related events like disposition date, laboratory test dates, etc. as proxy to calculate person-time at risk to first MACE per patient in each trial. For MACE, the number of patients with the event, the time to an event or censoring (for patients without an event), the incidence rate (IR), and the hazard ratio (HR) with 95% confidence interval (CI) stratified by study were calculated.

Figure 1: Algorithm for missing and incomplete event dates for time-to-event analysis for MACE

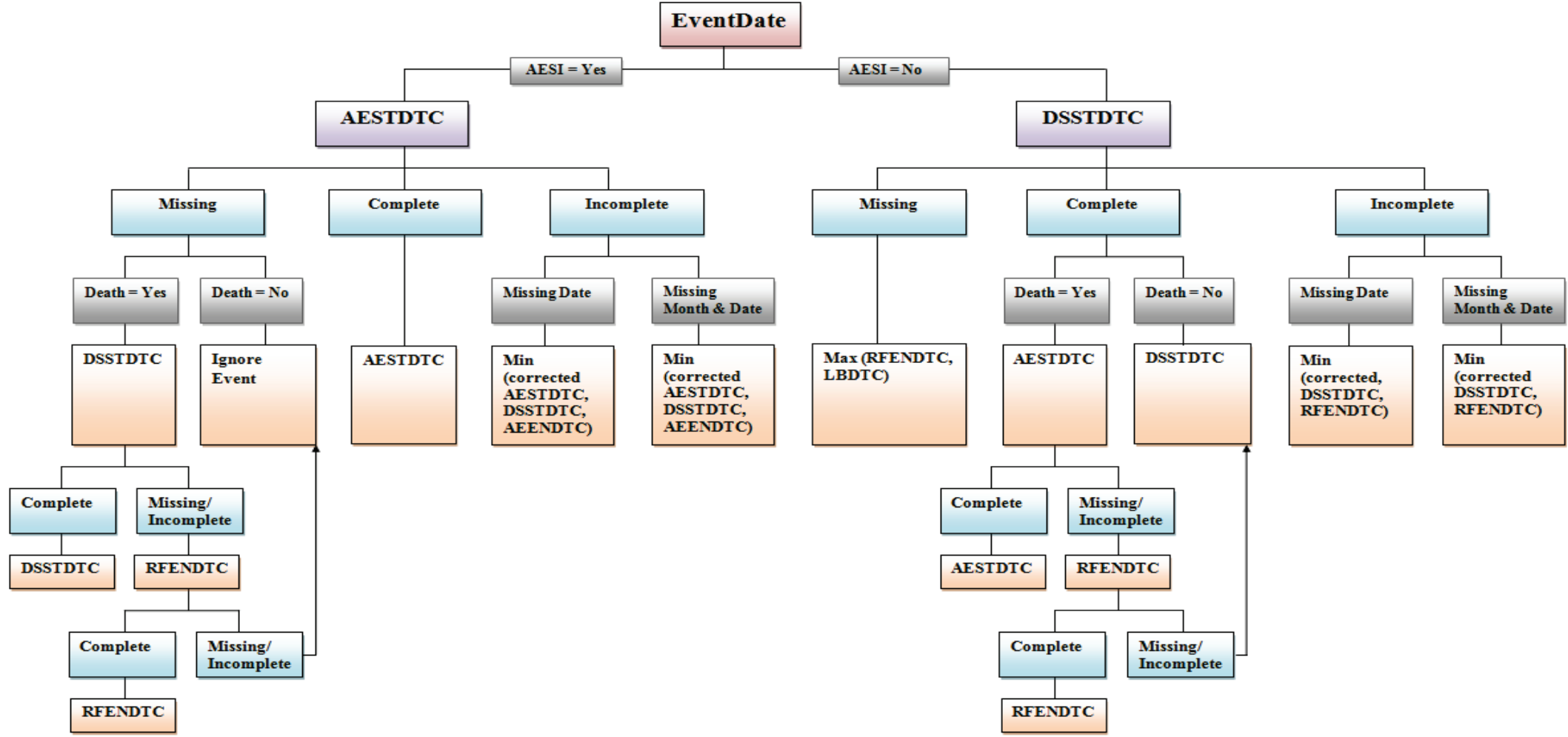


Table 1: Baseline demographics and clinical characteristics

	Small Trials		Large Trials	
	TZD (n = 1849)	Comparator (n = 1096)	TZD (n = 5576)	Comparator (n = 6889)
HbA1c, % (Mean ± SD)	7.39 ± 0.94	7.43 ± 1.08	8.09 ± 1.39	8.11 ± 1.42
BMI, mg/m ² (Mean ± SD)	30.55 ± 6.10	31.14 ± 5.43	31.45 ± 5.34	31.61 ± 5.45
Age, yr (Mean ± SD)	58.57 ± 8.93	59.32 ± 9.41	59.47 ± 8.77	58.92 ± 9.10
Age, n (%)				
<65	1406 (76.04)	787 (71.81)	3994 (71.63)	5028 (72.99)
≥65	443 (23.96)	309 (28.19)	1582 (28.37)	1861 (27.01)
Sex, n (%)				
Female	793 (42.89)	431 (39.32)	2344 (42.04)	2834 (41.34)
Male	1056 (57.11)	665 (60.68)	3232 (57.96)	4055 (58.86)
Race, n (%)				
American Indian/Alaskan Native	3 (0.16)	8 (0.73)	-	-
Asian	376 (20.34)	90 (8.21)	67 (1.20)	92 (1.34)
Black/African American	184 (9.95)	121 (11.04)	73 (1.31)	118 (1.71)
Other	136 (7.36)	70 (6.39)	18 (0.32)	27 (0.39)
White	1150 (62.20)	807 (73.63)	5418 (97.17)	6652 (96.56)
Exposure, days (Median (IQR))	182 (167-193)	185 (175-497)	1125 (972-1961)	1114 (931-1803)

Figure 2: Split violin plots of treatment exposure

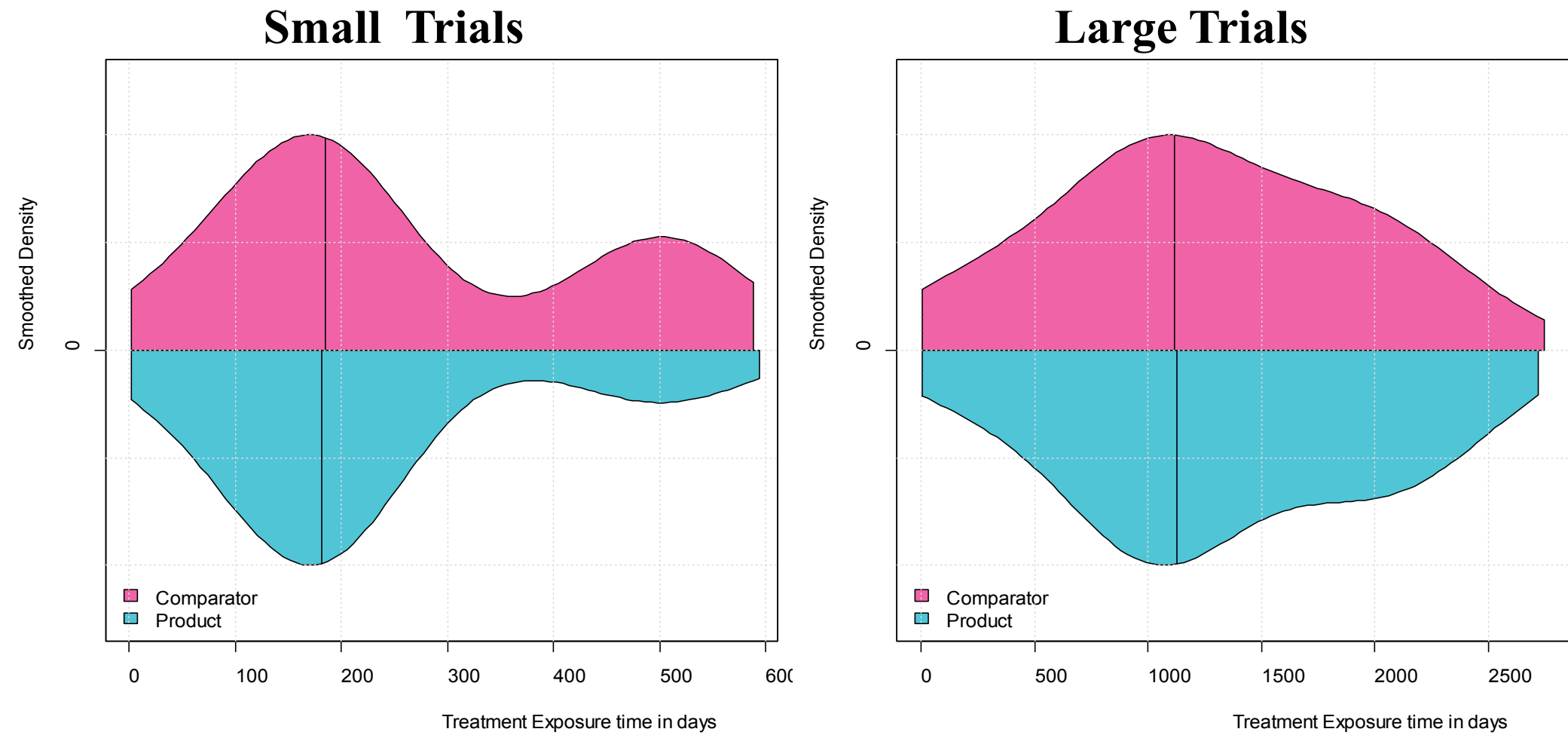
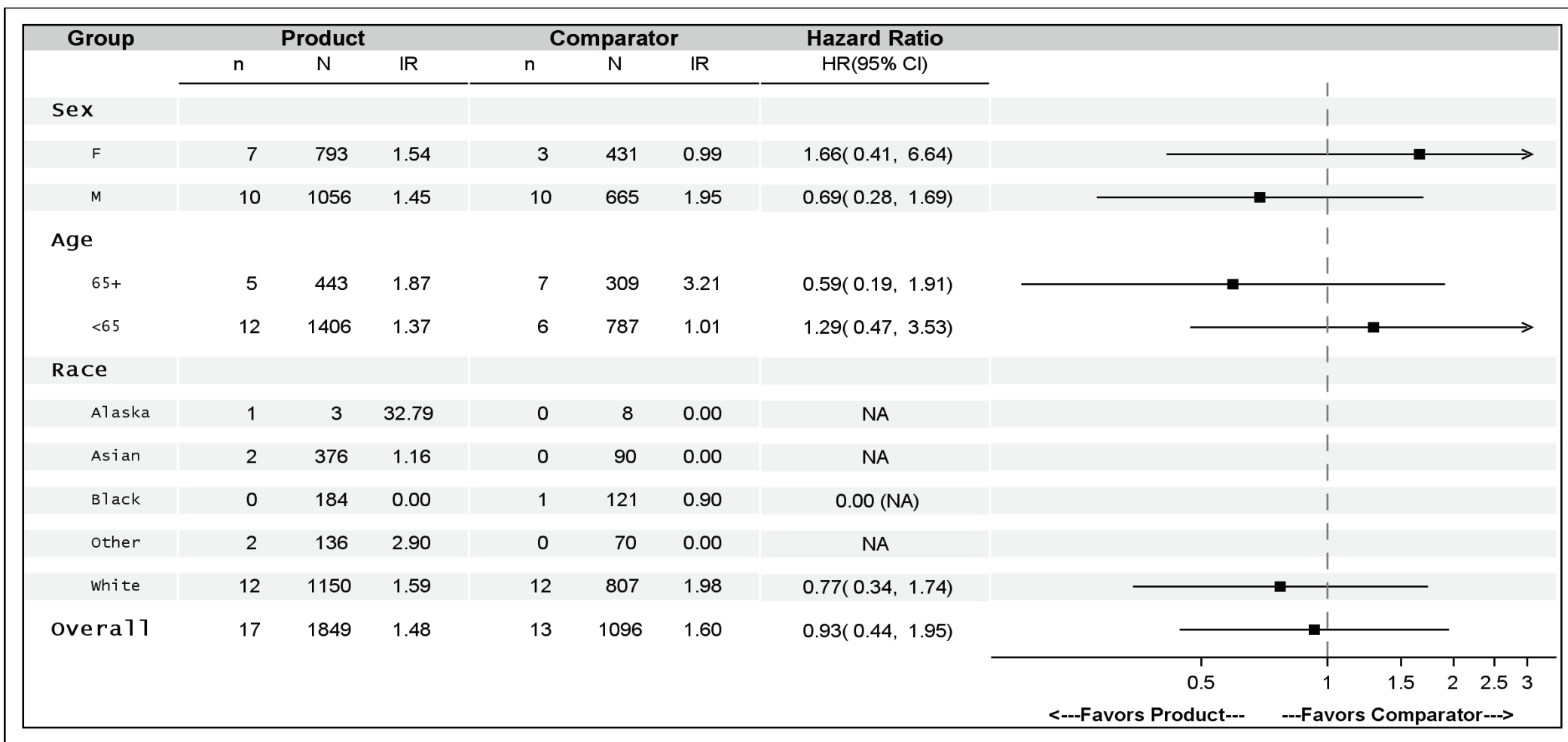
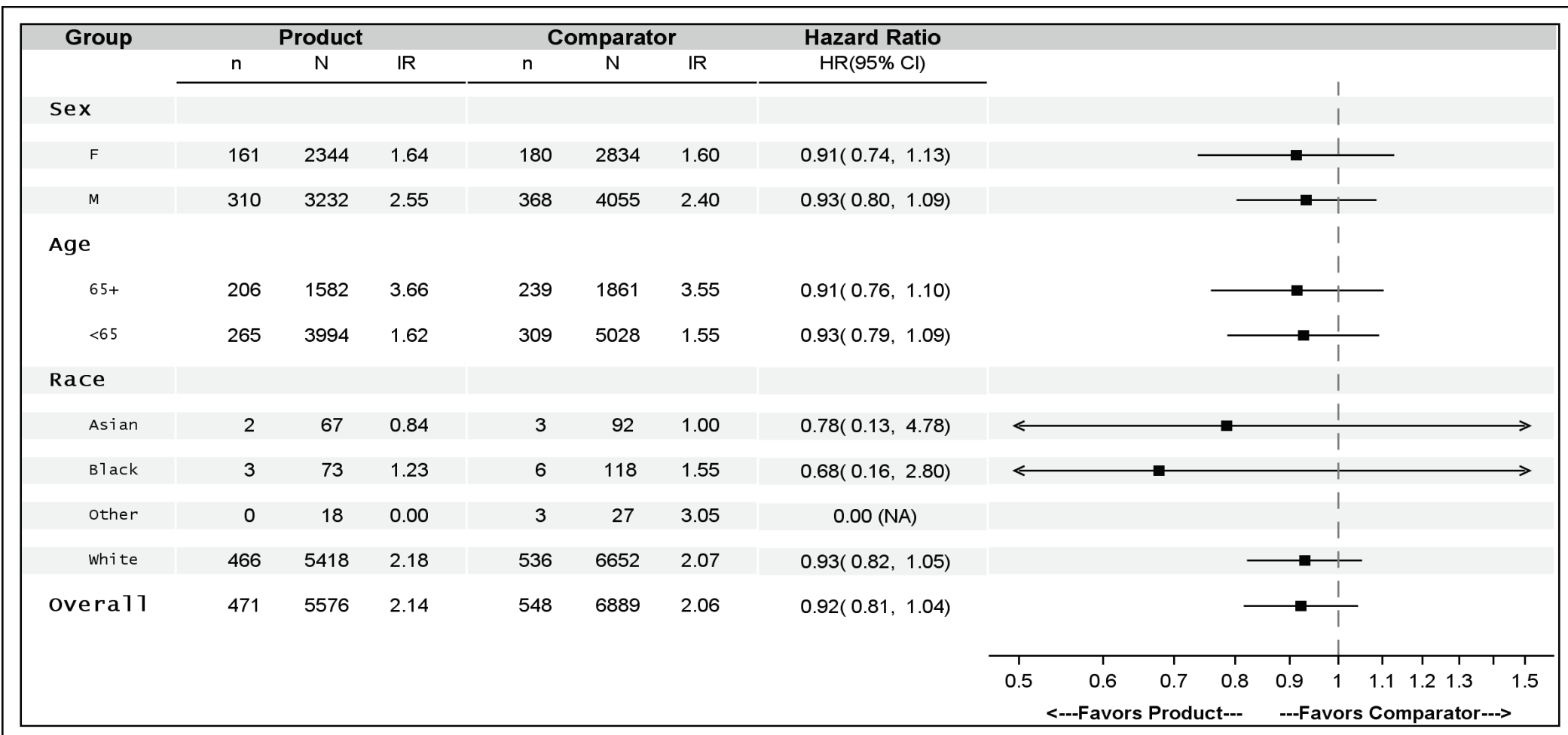


Figure 3: Meta-analysis of small TZD trials: Forest plot of subgroup analyses - MACE (On-study ITT)



Note: IRs represent crude incidence rates, not stratified by study.

Figure 4: Meta-analysis of large TZD trials: Forest plot of subgroup analyses - MACE (On-study ITT)



Note: IRs represent crude incidence rates, not stratified by study.

Disclaimer: The views expressed in this poster are those of the authors and do not represent the policy of FDA.

RESULTS

The baseline demographics and clinical characteristics (Table 1) were well-balanced between both treatment groups in both meta-analyses. Overall, the populations included in the meta-analyses of TZD trials was predominantly White, male and <65 years of age. Treatment exposure for TZD trials was similar between TZD group and comparator group for subjects who had both start and end dates of treatment recorded, as illustrated by the violin plot in Figure 2.

Subgroup analyses of the on-study meta-analyses illustrated in Figure 3 and 4 showed that the HR for the MACE endpoint associated with TZDs versus comparators was not affected by the following factors: age, sex and race. The results of on-treatment subgroup analyses (not shown here) are consistent with the results of on-study subgroup analyses.

DISCUSSION

Both TZD meta-analyses (12465 T2D patients from three large TZD trials and 2945 T2D patients from seven phase-3 clinical trials) showed that the treatment with TZDs did not significantly increase or decrease the risk of MACE compared to comparator (placebo or active comparator). Similarly, subgroup analyses of the on-study meta-analyses showed that the treatment with TZDs was not associated with either a decrease or increase in the risk of MACE endpoint within age, sex and racial subgroups.

Strength of these meta-analyses:

- Inclusion of patient-level data, as it facilitates time-to-event analyses and analyses by patient subgroups of interest.
- PTs in all 51 trials were harmonized to the same version of MedDRA, which facilitates the use of same endpoint definition.
- Standardized data facilitates the aggregation of trials across NDAs, and it also allows creating algorithms to handle missing dates making it possible to calculate person-time at risk to first MACE event per patient in each trial.

Limitations of these meta-analyses:

- These trials were not prospectively designed to support a specific meta-analytic intent. We selected trials using specific criteria, but additional variation in study design, sample size, randomization ratio, duration of exposure, and period of observation could have influenced the observed event rates in the meta-analyses.
- Among the trials included in these meta-analyses, individual patient exposure was up to one year (except three large TZD trials where individual patient exposure was approximately three years), so the time available for the development of CV events was limited.
- Endpoints were not adjudicated in any trial, allowing for misclassifications.

CONCLUSION

- Populations enrolled in the aggregated database do not reflect the full range of patients with diabetes in the US.
- Heterogeneity in event rates observed in trials needs to be explored and understood.
- There is limited representation from some of the minority racial subgroups (American Indian/Alaskan Natives, Asians, and Blacks) to draw conclusions. Even after using the aggregated dataset, under representation prevents a comparison of rates by subgroups. To resolve this issue, future trials need to have a balanced representation of patients with diabetes. This is particularly relevant as the risk of cardiovascular events differs across race groups.

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