Sex and Permanent Drug Discontinuation in Clinical Trials: Insights from the TIMI Trials

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BACKGROUND

- Women remain underrepresented across cardiovascular clinical trials, but the underlying barriers remain poorly understood.

- Whether women are more likely than men to prematurely discontinue study drug once enrolled in a clinical trial remains unknown.

METHODS

- Eleven phase 3 TIMI trials with 187,691 individuals (51,812 [28%] women) were included (**Table 1**).

- Multivariable logistic regression models were used to evaluate the association of sex with premature study drug discontinuation adjusting for relevant confounders for each individual trial including age, BMI, and baseline comorbidities such as HTN, DM, or prior MI.

- Random effects models were then used to examine the independent relationship of sex with study drug discontinuation across trials.

Table 1: TIMI Cardiovascular Outcomes Trials

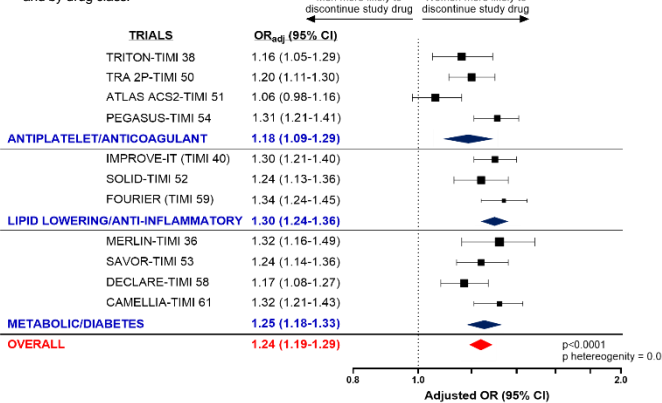| Type	Trial	Year	Intervention	Male, n (%)	Female, n (%)
Antiplatelet/ Anticoagulant	TRITON-TIMI 38	2007	Prasugrel vs. Clopidogrel	10072 (74%)	3536 (26%)
	TRA 2P-TIMI 50	2012	Vorapaxar vs. placebo	20123 (76%)	6326 (24%)
	ATLAS ACS2-TIMI 51	2012	Rivaroxaban vs. placebo	11600 (75%)	3926 (25%)
	PEGASUS-TIMI 54	2015	Ticagrelor vs. placebo	16102 (76%)	5060 (24%)
Lipid Lowering	IMPROVE-IT (TIMI 40)	2015	Simvastatin + ezetimibe vs. simvastatin	13728 (76%)	4416 (24%)
	SOLID-TIMI 52	2014	Darapladib vs. placebo	9700 (75%)	3264 (25%)
	FOURIER (TIMI 59)	2017	Evolocumab vs. placebo	20795 (75%)	6769 (25%)
Metabolic/ Diabetes	MERLIN-TIMI 36	2007	Ranolazine vs. placebo	6269 (65%)	2291 (35%)
	SAVOR-TIMI 53	2013	Saxagliptin vs. placebo	11037 (67%)	5455 (33%)
	DECLARE-TIMI 58	2018	Dapagliflozin vs. placebo	10738 (63%)	6422 (37%)
	CAMELLIA-TIMI 61	2018	Lorcaserin vs. placebo	7702 (64%)	4298 (36%)
	TOTAL			135,879 (72%)	51,812 (28%)

RESULTS

- Among participants enrolled, women tended to be older, had a higher BMI, and were more likely than men to have a history of hypertension, DM, and reduced eGFR, and less likely to have had a prior MI or PCI (**Table 2**).

**Table 2**: Baseline Demographics Pooled Across Trials

	Women (n=51,812)	Men (n=135,879)	P value
Age, years, median (IQR)	65 (59-72)	62 (56-69)	<0.0001
BMI, kg/m², median (IQR)	29.5 (25.7-34.1)	28.4 (25.7-32.0)	<0.0001
Current smoker	18%	26%	<0.0001
White race	82%	85%	<0.0001
Hypertension	82%	73%	<0.0001
Hyperlipidemia	73%	72%	0.007
Diabetes mellitus	52%	42%	<0.0001
Prior MI	35%	46%	<0.0001
Prior PCI	34%	46%	<0.0001
Prior HF	14%	13%	<0.0001
Baseline eGFR <60 mL/min/1.73m²	26%	16%	<0.0001

Figure 1: Adjusted odds of premature study drug discontinuation in women vs men across TIMI trials and by drug class.

TRIALS	OR_{adj} (95% CI)
TRITON-TIMI 38	1.16 (1.05-1.29)
TRA 2P-TIMI 50	1.20 (1.11-1.30)
ATLAS ACS2-TIMI 51	1.06 (0.98-1.16)
PEGASUS-TIMI 54	1.31 (1.21-1.41)
ANTIPLATELET/ANTICOAGULANT	**1.18 (1.09-1.29)**
IMPROVE-IT (TIMI 40)	1.30 (1.21-1.40)
SOLID-TIMI 52	1.24 (1.13-1.36)
FOURIER (TIMI 59)	1.34 (1.24-1.45)
LIPID LOWERING/ANTI-INFLAMMATORY	**1.30 (1.24-1.36)**
MERLIN-TIMI 36	1.32 (1.16-1.49)
SAVOR-TIMI 53	1.24 (1.14-1.36)
DECLARE-TIMI 58	1.17 (1.08-1.27)
CAMELLIA-TIMI 61	1.32 (1.21-1.43)
METABOLIC/DIABETES	**1.25 (1.18-1.33)**
OVERALL	**1.24 (1.19-1.29)**

p<0.0001
p heterogenity = 0.02

- After adjusting for baseline differences, women had a 24% higher odds of premature drug discontinuation prior to study end compared with men (OR_{adj} 1.24, 95% CI 1.19-1.29, **Figure 1**).

- Consistent results were observed for women vs men in the placebo (OR_{adj} 1.22, 95% CI 1.16-1.28, p<0.001) and active therapy arms (OR_{adj} 1.27, 95% CI 1.21-1.33, p<0.001 **Figure 2**).

Figure 2: Adjusted odds of drug discontinuation in women vs men across TIMI trials stratified by treatment arm

THERAPY ARM	OR (95% CI)
Active Therapy	1.27 (1.21-1.33)
Placebo	1.22 (1.16-1.28)
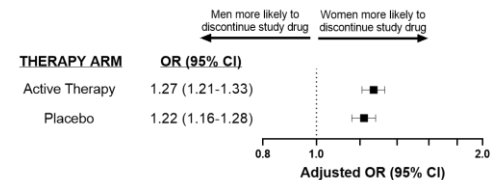
- Women and men on active drug had similar rates of drug discontinuation due to a reported adverse event (36% vs 36%, p=0.60), while women in the placebo arm were marginally less likely than men to stop study drug due to an adverse event (28% vs 30%, p=0.001).

CONCLUSIONS

- Across contemporary TIMI trials, women were more likely than men to prematurely discontinue study drug.

- This observation was not explained by baseline differences or more frequent reporting of adverse events.

- Future trials should better capture reasons for drug discontinuation to understand barriers to continued study drug use, particularly among women.

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