

I-PRESERVE Trial

Irbesartan in heart failure with preserved EF

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On behalf of the I-PRESERVE Investigators and
Patients

Presenter Disclosure Information

The following relationships exist related to this presentation:

P Carson: Bristol-Myers Squibb - sanofi aventis consulting fees

B Massie: Bristol-Myers Squibb - sanofi aventis grant support,
consulting fees

J McMurray: Bristol-Myers Squibb funds for Glasgow University

M Komajda: Bristol-Myers Squibb consulting fees

R McKelvie: Bristol-Myers Squibb - sanofi aventis consulting fees

M Zile: Bristol-Myers Squibb - sanofi aventis consulting fees

C Staiger: sanofi aventis employee and holds stock options

A Ptaszynska: Bristol-Myers Squibb employee and holds stock options

I-PRESERVE was sponsored by
Bristol-Myers Squibb and sanofi aventis

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Subject Accrual by Region/Country

All Randomized Subjects (N=4128)

N. AMERICA 9%

Canada (3%)

U.S.A (6%)

LATIN AMERICA 17%

Argentina (9%)

Brazil (4%)

Mexico (4%)

W. EUROPE 35%

Belgium (4%)

Denmark (<1%)

France (6%)

Germany (6%)

Greece (<1%)

Italy (<1%)

Netherlands (5%)

Norway (<1%)

Portugal (<1%)

Spain (9%)

Sweden (1%)

Switzerland (<1%)

UK and Ireland (2%)

E. EUROPE 36%

CZ Republic (2%)

Hungary (2%)

Poland (7%)

Russia (25%)

AFRICA 1%

South Africa

AUSTRALIA 1%

293 enrolling sites in 25 countries

I-PRESERVE: Background (i)

- Heart failure (HF) has long been associated with a low ejection fraction, yet epidemiologic databases have increasingly reported that nearly half of HF patients have a preserved ejection fraction (LVEF >40-50%).
- Unlike low EF heart failure, HF-PEF affects primarily older patients, especially women; hypertension is the primary underlying condition, with CAD and prior MI being relatively infrequent.
- HF-PEF has been associated with substantial morbidity and mortality.

I-PRESERVE: Background (ii)

- The renin angiotensin system (RAS) has a central position in vascular and myocardial remodeling thought to be involved in this type of heart failure.
- Previous trials with RAS inhibitors in HF-PEF have not provided overall favorable results although encouraging signals were noted.
- There is currently no evidence-based treatment to improve patient outcomes.

I-PRESERVE: Objectives

- To determine whether treatment with the angiotensin receptor blocker irbesartan reduces mortality and morbidity in patients with HF-PEF.
- To better define the characteristics, natural history, and prognosis of heart failure in this population.

I-PRESERVE: Entry Criteria

Age ≥ 60 years
Current HF symptoms
LVEF ≥ 0.45

NYHA class II - IV

- CHF hosp. ≤ 6 months

NYHA Class III/IV

- CXR congestion
- ECG (LVH, LBBB)
- Echo (LVH, LAE)

Key Exclusions: SBP > 160 mm Hg; prior EF $< 40\%$; ACS or stroke ≤ 3 m; hypertrophic or restrictive CM, pericardial or valvular disease; significant co-morbidities: pulmonary disease, creatinine > 2.5 , Hb < 11

Only 1/3 pts could enter on an ACEI

I-PRESERVE: Outcomes

- Primary endpoint: All cause mortality and protocol-specified CV hospitalizations (for heart failure, MI, unstable angina, stroke, ventricular or atrial arrhythmia).
- Secondary endpoints:
 - All cause mortality
 - CV death
 - HF death or HF hospitalization
 - CV death, MI or stroke
 - QoL (MLwHF) at 6 months
 - Change in NT-proBNP levels at 6 months

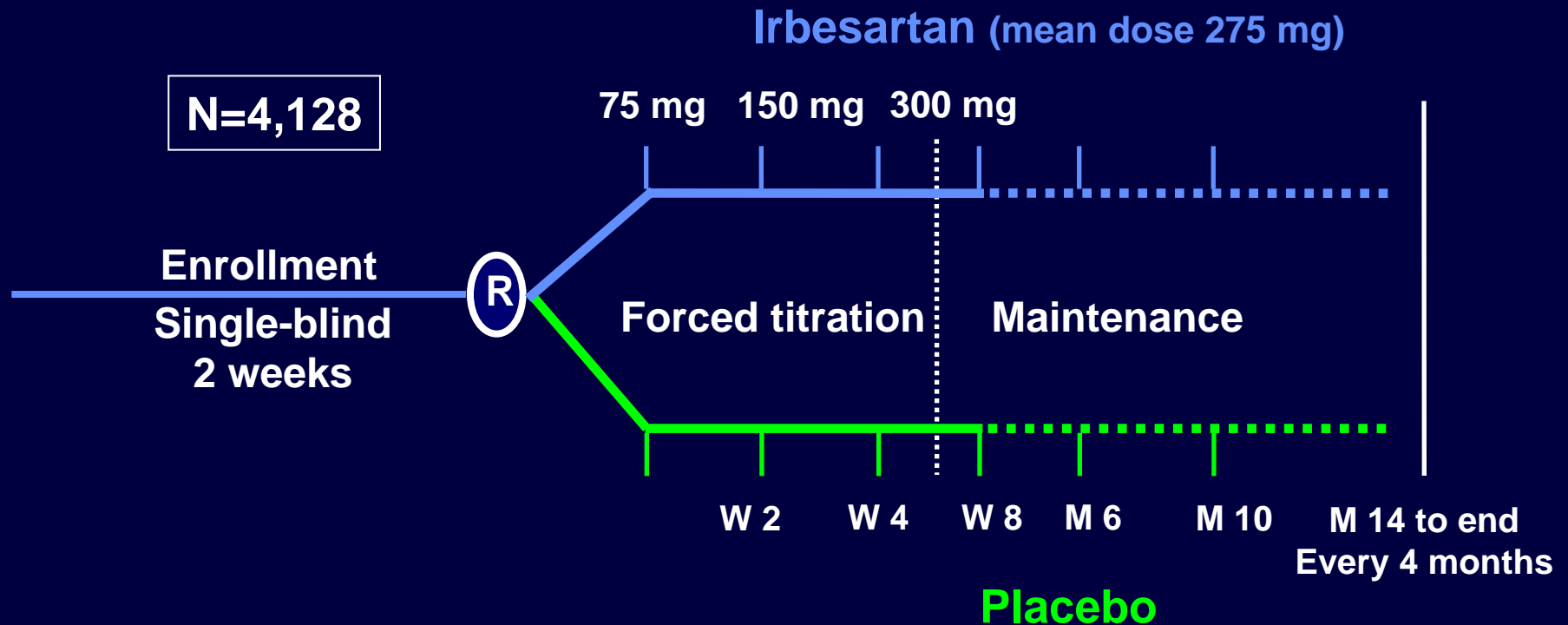
Methods

Statistical assumptions:

- Anticipated annual primary event rate: 18% in the placebo group
- Expected reduction in the annual event rate: 14.5 %
- To provide a statistical power of 90% with a two-sided alpha of 0.05:
 - 1440 events needed, requiring 3600 subjects; the estimated recruitment period was 2 years with a follow-up period of 2 years
 - During the study, based on a blinded assessment of the event rates, the number of subjects was increased to 4100, recruitment to 2.75 years , duration of the study to 6 years

I-PRESERVE: Study Design

Randomized, double-blind, placebo controlled trial



Follow-up continued until 1,440 primary endpoints occurred

I-PRESERVE: Patient Characteristics

	Cohort & Epidemiological <u>Studies</u>	I-PRESERVE <u>(n=4,128)</u>
Age, yr	75	72
Women	65-70%	60%
EF	60%	59%
Hypertension hx	80-90%	88%
Prior MI	<20%	23%
Atrial fibrillation	20-30%	29%
Diabetes	20-30%	27%

I-PRESERVE: Baseline Characteristics (i)

	Placebo (N = 2061)	Irbesartan (N = 2067)
Age (Mean – yr)	72 ± 7	72 ± 7
≥75 yrs (%)	35	34
Female sex (%)	61	59
Race - White (%)	93	94
NYHA class (%) II/III/IV	22/76/3	21/77/3
Ischemic etiology (%)	24	26
Hypertensive etiology (%)	63	64
Hypertension Hx (%)	88	89
Myocardial infarction Hx (%)	23	24
Atrial Fibrillation Hx (%)	29	29
Diabetes Mellitus Hx (%)	27	28

I-PRESERVE: Baseline Characteristics (ii)

Clinical measurements	Placebo (N = 2061)	Irbesartan (N = 2067)
Systolic BP, mm Hg	136 ± 15	137 ± 15
Diastolic BP, mm Hg	79 ± 9	79 ± 9
Body Mass Index, kg/m ²	29.6 ± 5.3	29.7 ± 5.3
QoL MLwHF score (median, IQ range)	42 (28 – 58)	42 (27 – 58)
Laboratory measurements		
EF	0.60 ± 0.09	0.59 ± 0.09
ECG - LVH (%)	30	31
Hemoglobin, g/dL	14 ± 2	14 ± 2
Creatinine, mg/dL	1.0 ± 0.34	1.0 ± 0.32
eGFR, ml/min/1.73m ²	72 ± 22	73 ± 23
NT-proBNP, pg/ml (median, IQ range)	320 (131 – 946)	360 (139 – 987)

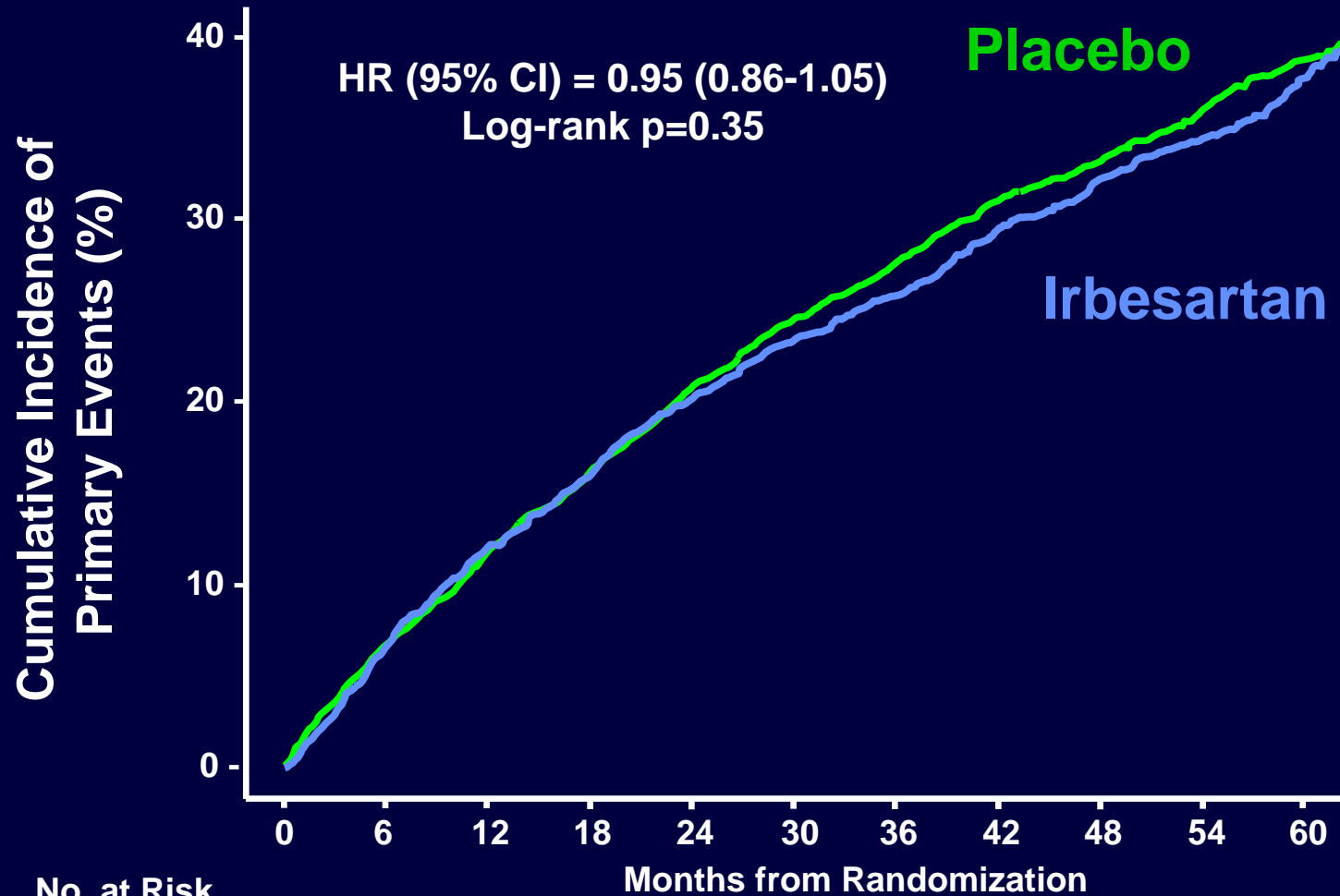
Mean ± sd unless otherwise stated

I-PRESERVE: Baseline Treatments

Treatment (%)	Placebo (N = 2061)		Irbesartan (N = 2067)	
Diuretic	84		82	
Spirolactone	15	28	15	27
ACE-inhibitor	25	39	26	38
Digoxin	13		14	
Beta-blocker	58	72	59	72
Calcium channel blocker	39		40	
Antiplatelet	58		59	
Lipid lowering	30		32	
Total exposed during the study				

I-PRESERVE: Primary Endpoint

Death or protocol specified CV hospitalization
(Mean follow-up 49.5 months)



No. at Risk

Irbesartan	2067	1929	1812	1730	1640	1569	1513	1291	1088	816	497
Placebo	2061	1921	1808	1715	1618	1539	1466	1246	1051	776	446

Primary Outcome with Component Events

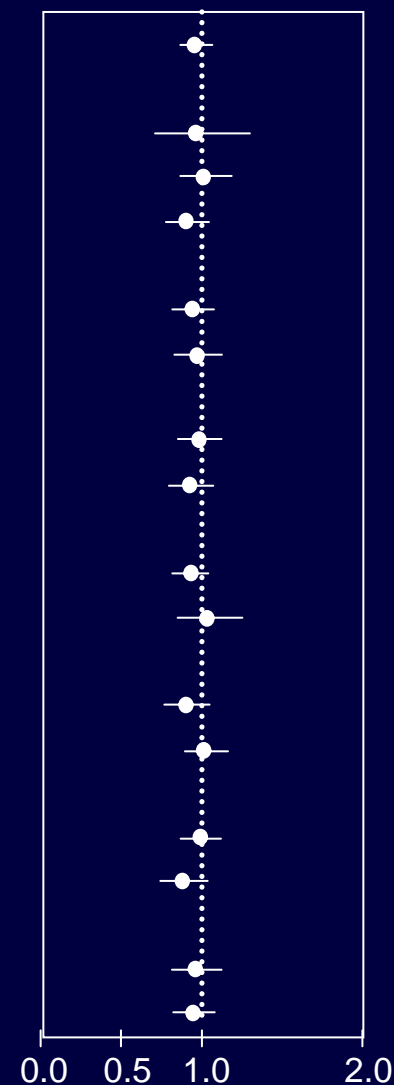
	Placebo (n=2061)	Irbesartan (n=2067)
Primary Outcome	763	742
Death	226	221
CV hospitalization*	537	521
Worsening heart failure	314	291
Myocardial infarction	54	60
Unstable angina	19	20
Stroke	79	68
Atrial arrhythmia	68	77
Ventricular arrhythmia	3	5

* Protocol-specified

I-PRESERVE: Primary Endpoint subgroup analyses

Time to First Primary Event by Baseline Subgroup

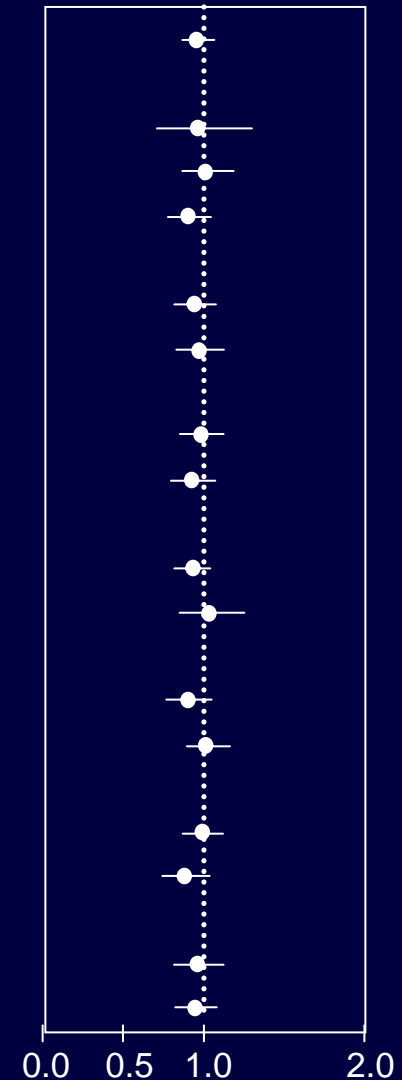
<u>Baseline Subgroup</u>	<u>Irbesartan</u>	<u>Placebo</u>
ALL PATIENTS	742/2067 (36%)	763/2061 (37%)
Age Group		
< 65	86/376 (23%)	86/364 (24%)
65-75	331/994 (33%)	322/981 (33%)
>= 75	325/697 (47%)	355/716 (50%)
Sex		
Female	392/1228 (32%)	420/1263 (33%)
Male	350/839 (42%)	343/798 (43%)
Ejection Fraction		
<= 59	433/1054 (41%)	423/1027 (41%)
> 59	309/1011 (31%)	339/1033 (33%)
ACEi		
No	529/1529 (35%)	566/1551 (36%)
Yes	213/538 (40%)	197/510 (39%)
Beta-blocker		
No	299/842 (36%)	336/859 (39%)
Yes	443/1125 (36%)	427/1202 (36%)
Diabetes		
No	491/1495 (33%)	494/1496 (33%)
Yes	25/570 (44%)	269/564 (48%)
Hosp. for HF within 6 Months		
No	323/1157 (28%)	334/1155 (29%)
Yes	419/910 (46%)	429/906 (47%)



I-PRESERVE: Primary Endpoint subgroup analyses

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Secondary Endpoints

Outcome	Patients with Events		HR (95% CI)
	Placebo (n=2061)	Irbesartan (n=2067)	
Death	436	445	1.00 (0.88-1.14)
Cardiovascular death	302	311	1.01 (0.86-1.18)
HF death or HF hospitalization	438	428	0.96 (0.84-1.09)
Cardiovascular death, MI or stroke	400	402	0.99 (0.86-1.13)

P=NS for all

Secondary Endpoints

	Placebo (n=2061)	Irbesartan (n=2067)
Change in MLwHF score at 6 months*	-7.0 (-19.0, 0.0)	-8.0 (-19.0, 1.0)
Change in NT pro-BNP (pg/mL) at 6 months*	-2 (-125, 119)	-13 (-149, 100)

Other Outcomes

Patients with Events	Placebo (n=2061)	Irbesartan (n=2067)	HR (95% CI)
HF hospitalization	336	325	0.95 (0.81-1.10)
All cause hospitalization	1126	1152	1.02 (0.94-1.11)

* median, IQ range; P=NS for all

Discontinuations and Adverse Events

	<u>Placebo</u> <u>(N = 2061)</u>	<u>Irbesartan</u> <u>(N = 2067)</u>	<u>P value</u>
Patients who discontinued study drug - no. (%)			
Any reason	684 (33.2)	702 (34.0)	0.60
Adverse event	288 (14.0)	331 (16.1)	0.07
Subject choice	223 (10.8)	208 (10.1)	0.43
Specific serious adverse events - no. (%)			
Hypotension	62 (3.0)	60 (2.9)	0.84
Renal failure	57 (2.8)	69 (3.3)	0.29
Hyperkalemia	9 (0.4)	12 (0.4)	0.34

I-PRESERVE: Conclusions

- The I-PRESERVE study enrolled a population of older, predominantly female, patients similar to those enrolled in epidemiologic HF-PEF databases.
- Although this was a well-treated population, they experienced substantial mortality and cardiovascular morbidity .
- Irbesartan did not reduce the primary endpoint of death and protocol-specified CV hospitalizations, nor did it reduce prespecified secondary endpoints. The medication was well-tolerated.

I-PRESERVE: Conclusions

- Our results are consistent with the two previous trials utilizing RAS blockers in patients with HF-PEF that did not demonstrate an overall positive effect.
- For this large group of patients constituting up to half of all heart failure, there continues to be no specific evidence-based therapy.
- In order for this field to move forward, a better understanding is needed of the mechanisms underlying this syndrome and additional potential targets for treatment.