

SUPPLEMENTAL MATERIAL

An Evaluation of the Causes of Sex Disparity in Heart Failure Trials

Dr Holly Morgan, Dr Aish Sinha, Dr Margaret McEntegart, Dr Suzanna Hardman, Professor Divaka Perera

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Supplementary Table 1: Full Trial List

Trial	Total no	Females	%	Age	Journal	Year	Notes	Sub-type
SERVE-HF	1325	127	9.6	69.5	NEJM	2015	CPAP, lvef<45%	2
CHART-1	315	32	10.2	61.9	EHJ	2017	ICM, stem cells	1,10 Y
CHRISTMAS	305	31	10.2	62.5	Lancet	2003	Carvediolol, ICM	2,11
STICH	1212	148	12.2	59.5	NEJM	2011	CABG	1,9,10 Y
BeAT-HF	408	53	13.0	62	JACC	2020	Baroreflex, LVEF <35	1,9 Y
MUSTT	2202	301	13.7	66.5	NEJM	2000	ICD	2,6 Y
ESSENTIAL II	950	133	14.0	62	EHJ	2009	Enoximone	1,11
REM-HF	1650	231	14.0	69.5	EHJ	2017	Remote monitoring	1,8
DOT-HF	335	47	14.0	64	Circ	2011	Implanted monitor	1,6 Y
CASTLE-AF	363	52	14.3	64	NEJM	2018	AF ablation	1,9 Y
WATCH	1587	234	14.7	63	Circ	2009	Warfarin/sapt, ef<35%	1,11
DAVID II	600	90	15.0	63.5	JACC	2009	Pacing	2,6 Y
MADIT-II	1232	192	15.6	64.5	NEJM	2002	LVEF <30	1,6 Y
PARR-2	430	67	15.6	63.5	JACC	2007	PET imaging	1,7,10
SENSE-HF	501	79	15.8	65	EHJ	2011	fluid monitor device	1,6 Y
EVITA	400	68	17.0	55	EHJ	2017	Vitamin D	1,11
RAFT	1798	308	17.1	66.2	NEJM	2010	ICD v CRT, LVEF <30%	1,6 Y
EARTH	642	113	17.6	60.3	Lancet	2004	Darusentan	1,11
AF-CHF	1376	248	18.0	67	NEJM	2008	AF in CCF, LVEF 27	1,11
Higgins et al	490	91	18.6	66	JACC	2003	CRT	1,6 Y
IN-TIME	664	128	19.3	65.5	Lancet	2014	Device monitoring	1,6,8
ACCLAIM	2408	476	19.8	64.3	Lancet	2008	IMT	1,8
MOMENTUM-3	366	73	19.9	59.5	NEJM	2018	LVAD	1,6,9 Y
VAL-HEFT	5010	1005	20.1	62.7	NEJM	2001	Valsartan	2,11
MACH-1	2590	521	20.1	62.8	Circ	2000	Mibefradil	1,11
PROTECT-2	452	91	20.1	67.5	Circ	2012	Impella/IABP	1,9,10 Y

WARCEF	2305	465	20.2	61	NEJM	2012	Warfarin v aspirin	1,11
COMET	3029	612	20.2	62	Lancet	2003	Carvedilol/metoprolol	1,11
OPTILINK-HF	1002	203	20.3	66.3	EHJ	2016	Fluid monitoring	1,8
MORE-CRT MPP	467	95	20.3	79.7	EHJ	2019	CRT	2,6 Y
ARTS-HF	458	94	20.5	71.3	EHJ	2013	Finerenone	2,11
COPERNICUS	2289	470	20.5	63.4	NEJM	2001	Carvedilol	1,11
BCIS-1	301	62	20.6	71	JAMA	2010	IABP	1,9,10 Y
REVERSE	610	128	21.0	62.5	Circ	2012	CRT, mild LVSD	2,6 Y
OVERTURE	5770	1211	21.0	63.4	Circ	2002	omapatrilat v enalapril	1,11
INOVATE-HF	707	149	21.1	61.4	JACC	2016	Vagus nerve	2,9 Y
OHCS	1193	254	21.3	66	JACC	2011	Atrial arrhythmia device	2,6
IMPRESS	573	122	21.3	64	Lancet	2000	omapatrilat v enalapril	2,11
FIGHT	300	64	21.3	61.5	JAMA	2016	Liraglutide	2,11
MOXCON	1934	420	21.7	64.2	EHJ	2003	ICM 62%, EF 25%	1,11
GISSI-HF	6975	1516	21.7	67	Lancet	2008	Fatty acids	5,11
ATMOSPHERE	7016	1525	21.7	63.3	NEJM	2016	Aliskiren	1,11
ENDURANCE	446	97	21.7	64.7	NEJM	2017	Lvad	1,6,9 Y
PARADIGM-HF	8399	1832	21.8	63.8	NEJM	2014	Entresto	2,11
BEST	2708	593	21.9	60	NEJM	2001	BB in EF<35	1,11
RENEWAL	2048	450	22.0	64.1	Circ	2004	Etanercept, EF<30	1,11
OPT-CHF	405	89	22.0	64.5	JACC	2008	Oxypurinol	2,11
EMPHASIS-HF	2737	610	22.3	68.6	NEJM	2011	Empagliflozin	1,11
TEN-HMS	426	97	22.8	67.2	JACC	2005	Tele monitoring	2,8
ASTRONAUT	1615	368	22.8	64.6	EHJ	2013	Aliskiren	2,11
COMMANDER HF	5022	1150	22.9	66.4	NEJM	2018	Rivaroxaban	2,10,11
ATOMIC-AHF	613	141	23.0	66	JACC	2016	Omecamtiv, LVEF<40	2,11
NorthStar	921	212	23.0	69	EHJ	2013	Long-term FU	2,8
MIRACLE-ICD	369	86	23.3	67.1	JAMA	2003	CRT	1,6 Y

SCD-HeFT	2521	588	23.3	60	NEJM	2005	Amiodarone v ICD	1,6 Y
DAPA-HF	4744	1109	23.4	66.3	NEJM	2019	Dapagliflozin	2,11
ARTS-HF	1066	250	23.5	71.2	EHJ	2016	Finerenone	2,11
CORONA	5011	1180	23.5	Not reported	JACC	2009	Rosuvastatin	5,11
MOOD-HF	372	89	23.9	62	JAMA	2016	Escitalopram	2,11
EMPEROR-reduced	3730	893	23.9	66.8	NEJM	2020	Empagliflozin	2,11
HeartMate II	309	74	23.9	54	Circ	2009	LVAD	1,6 Y
Cvlprit shock	646	155	24.0	70	NEJM	2017	Cardiogenic shock	5,9 Y
VICTORIA	5050	1212	24.0	67	NEJM	2020	Vericiguat	2,11
SHIFT	6558	1574	24.0	60.4	Lancet	2010	Ivabradine	1,11
RELEVANT	324	78	24.1	64.2	EHJ	2009	CRT, NICM	1,6,12 Y
Qili Qiangxin HF	491	121	24.6	57.3	JACC	2013	Qili Qiangxin	2,11
DAVID	506	125	24.7	65	JAMA	2002	Dual chamber v ICD	2,6 Y
ANDROMEDA	627	155	24.7	71.5	NEJM	2008	Dronedarone	1,11
MADIT CRT	1820	453	24.9	64.5	NEJM	2009	CRT	1,6 Y
SUPPORT	1147	287	25.0	66	EHJ	2015	Olmesartan	5,11
BLOCK-HF	691	174	25.2	73.4	NEJM	2013	CRT	2,6
MITRA-FR	304	77	25.3	36% >75	NEJM	2018	Mitraclip	2,9
EVEREST	4133	1058	25.6	65.8	JAMA	2007	Tolvaptan	2,11
ESSENTIAL I	900	234	26.0	62	EHJ	2009	Enoximone	1,11
ESCAPE	433	113	26.1	56	JAMA	2005	RH catheterisation	1,9 Y
CARE-HF	813	216	26.6	66.5	NEJM	2005	CRT	1,6 Y
ROSE-AHF	360	97	26.9	70	JAMA	2013	Dopamine/Nesiritide	5,11
EchoCRT	809	221	27.3	58	NEJM	2013	CRT in narrow QRS	1,6 Y
CHAMPION	550	151	27.5	61.5	Lancet	2011	Implantable monitor	5,6,8 Y
DANISH	1116	307	27.5	63.5	NEJM	2016	ICD in NICM	1,6,12 Y
TRUST	1339	370	27.6	63.5	Circ	2010	OP ICD	1,6
DOSE	308	86	27.9	66	NEJM	2011	diuretics	5,11

PIONEER-HF	881	246	27.9	61	NEJM	2019	Entresto	2,11
SURVIVE	1327	371	28.0	66.5	JAMA	2007	Levo v Dobutamine	1,11
HF-action	2331	653	28.0	59	JAMA	2009	Exercise	1
OPTIME-CHF	949	272	28.7	65.5	JAMA	2002	Milrinone	5,11
EPHESUS	6632	1918	28.9	64	NEJM	2003	Eplerenone	2,11
South Texas CHF Disease	1069	310	29.0	70.9	Circ	2004	Disease mx	5,8
DIAL	1518	444	29.2	65	BMJ	2005	OP telephone FU	5,8
ACTIV CHF	319	95	29.8	62	JAMA	2004	Tolvaptan	2,11
HEAAL	3834	1143	29.8	66	Lancet	2009	Losartan	2,11
WISDOM	525	158	30.1	61.7	JACC	2019	Communication	5,8
ELITE II	3152	977	31.0	71.4	Lancet	2000	Losartan/Captopril	2,11
VMAC	489	152	31.1	61.4	JAMA	2002	Nesiritide v GTN	5,11
RESPOND-CRT	998	311	31.2	67	EHJ	2017	CRT	1,6 Y
IABP Shock 2	600	187	31.2	69.5	NEJM	2012	Cardiogenic shock	5,9 Y
OUTSMART-HF	500	156	31.2	59	Circ	2020	CMR, NICM	5,7,12
CHARM	7599	2400	31.6	66	Lancet	2003	Candesartan	2,11
MIRACLE	453	144	31.9	64.3	NEJM	2002	CRT	1,6 Y
TIM-HF	1571	501	31.9	70	Lancet	2018	Telecommunications	1,8
GUIDE-IT	894	286	32.0	63	JAMA	2017	BNL, LVEF <40	2,7
SMART-AV	980	314	32.0	66	Circ	2010	CRT smart delay	2,6 Y
COMPANION	1520	495	32.6	66.8	NEJM	2004	CRT	1,6 Y
PROTECT	2033	671	33.0	70	JACC	2011	Rolofylline	5,11
DECREASE-HF	306	101	33.0	66.7	Circ	2007	CRT	1,6 Y
ASCEND-HF	7141	2391	33.5	67	NEJM	2011	Nesiritide	5,11
TRUE-AHF	2157	737	34.2	68.5	NEJM	2017	Ularitide	5,11
TIME-CHF	499	172	34.5	76.5	JAMA	2009	Intensive mx, age>60	2,3,7,8
BATTLESCARRED	364	131	36.0	76	JACC	2009	BNP	5,7
COAPT	614	221	36.0	72.2	NEJM	2018	Mitraclip	5,9 Y

GALACTIC	781	288	36.9	78	JAMA	2019	Vasodilators	1,11
SENIORS	2128	787	37.0	76	EHJ	2005	Nebivolol, >70	3,5,11
STAMINA-HeFT	319	118	37.0	69	Circ	2008	Erythropoietin	2,11
RELAX-AHF	1161	436	37.6	72	Lancet	2013	Serelaxin	5,11
BLAST-AHF	621	236	38.0	70	EHJ	2017	TRV027	5,11
CHARM-preserved	3023	1212	40.1	67.2	Lancet	2003	Candesartan	4,11
A-HeFT	1050	421	40.1	56.8	NEJM	2004	ISMN/hydralazine	2,11
RELAX-AHF-2	6545	2637	40.3	73	NEJM	2019	Serelaxin	5,11
VERITAS	1435	580	40.4	70	JAMA	2007	Tezosentan	5,11
SADHART-CHF	469	190	40.5	62.1	JACC	2010	Sertraline	2,3,11
RED-HF	2278	934	41.0	72	NEJM	2013	Erythropoietin	2,11
WHICH? II	787	323	41.0	74	EHJ	2017	Intensive mx	5,8
TELE-HF	1653	694	42.0	61	NEJM	2010	Telemonitoring	5,8
PRIMA	345	148	42.9	72	JACC	2010	BNP target	5,7,8
AFFIRM-AHF	1132	494	43.6	71.1	Lancet	2020	IV iron, ef<50%	2,11
NCT00490958	332	153	46.1	62.8	JACC	2010	Telmisartan dialysis	2,11
CONFIRM-HF	304	141	46.4	69.2	EHJ	2015	IV iron	2,11
IMPACT-HF	363	170	46.8	67	JACC	2004	Carvedilol, EF 25%	2,9,10,11
HART	902	424	47.0	63.6	JAMA	2010	Education, any EF	5,8
ACUTE	1983	951	48.0	81	Circ	2019	Risk score, HFH	5,7
socrates-preserved	477	229	48.0	73	EHJ	2017	Vericiguat	4,11
NCT00378950	605	291	48.1	60.7	Circ	2012	Education	5,8
RUSSLAN	504	244	48.4	67	EHJ	2002	Levosimendan, ICM	5,10,11
VITALITY-HFpEF	789	385	48.8	72.7	JAMA	2020	Vericiguat	4,11
ICON-RELOADED	1461	717	49.1	56.4	NEJM	2018	BNP in acute HF	5,7
TORIC	1377	689	50.0	68.5	EHJ	2002	Torasemide, any EF	5,11
PACT-HF	2494	1258	50.4	77.7	Circ	2019	Discharge care	5,8
PRIMA II	405	207	51.1	77.5	Circ	2018	BNP, acute HF	5,7

TOPCAT	3445	1775	51.5	68.7	NEJM	2014	Spironolactone	4,11
PARAGON-HF	4796	2479	51.7	72.7	NEJM	2019	Entresto	4,11
Aldo-DHF	422	219	51.9	67	JAMA	2013	Spiro, HFpEF	4,11
PANACHE	305	160	52.5	73.6	JAMA	2019	neladenoson bialanate	4,11
FAIR-HF	459	244	53.2	67.7	NEJM	2009	IV iron, LVEF <45	2,11
PEP-CHF	850	468	55.1	76	EHJ	2006	Perindopril in >70s	3,5,11
ELISABETH	503	298	59.2	87	JAMA	2020	ED care bundle, >75	3,5,7
I-PRESERVE	4128	2477	60.0	72	NEJM	2008	Irbesartan HFpEF	4,11

Subtypes: 1. LVEF<35% 2. LVEF<50% 3. Older age group, 4. HFpEF, 5. HF all comers, 6. Device 7.

Diagnostics/scores 8. Outpatient care 9. Invasive procedure/surgery 10. ICM 11. Drug trial 12. NICM.

Invasive/procedural: Y.

Supplementary Table 2: Registries

Search term: (*heart failure*[MeSH Major Topic]) AND (*registry*[Text Word]) AND ((*"The New England journal of medicine"*[Journal]) OR (*"Lancet (London, England)"*[Journal]) OR (*"British medical journal"*[Journal]) OR (*"JAMA"*[Journal]) OR (*"Journal of the American College of Cardiology"*[Journal]) OR (*"Circulation"*[Journal]) OR (*"European heart journal"*[Journal])) AND (2000:2021[*pdat*])

	No of females	Total patients	Female %	Age	Category	Started	Country
Duke CVD Databank	392	1411	27.8	62	ICM	1969	US
BIOSTAT-CHF	402	1710	23.5	67	HFrEF (<40%)	2010	Europe
IMPROVE-HF	10060	34810	28.9	68.7	HFrEF (<35%)	2007	US
ASIAN-HF	1153	5276	21.9	60.1	HFrEF (<35%)	2012	Asia
	597	1204	49.6	68.5	HFpEF		
CHAMP-HF	807	2588	31.2	68	HFrEF	2016	US
SWEDE-HF	10281	32421	31.7	72.6	HFrEF (<50%)	2003	Sweden
	5260	9640	54.5	77	HFpEF		
ESC-HF-LT	4011	12440	32.2	66.6	HHF/CHF	2015	Europe
ESC-HF pilot	1666	5118	32.6	67.1	AHF/CHF	2014	Europe
DATA-HELP	1489	4253	35.0	69	ICM	2009	Poland
	562	1310	42.9	64.1	NICM		
REPORT-HF	7003	18553	37.7	67	HHF	2015	International
GWTG-HF (by LVEF)	26966	70267	38.4	77.5	HFrEF (<50%)	2005	US
	25423	40354	63.0	78	HFpEF		
ADHERE-HFpEF	10346	25865	40.0	73.9	HFpEF	2001	International
GWTG-HF (by Dx)	41040	92361	44.4	76	ICM	2005	US
	36186	63652	56.8	72	NICM		
GARFIELD-AF	1903	4717	40.3	70.2	ICM	2010	International

	3128	7021	44.6	70.0	NICM		
OPTIMIZE-HF	7444	20118	37.0	70.4	HFrEF (<40%)	2003	US
	6849	10072	68.0	75.6	HFpEF		
ADHERE	54802	105388	52.0	74.2	AHF	2001	International
RICA	2226	4200	53.0	78	HHF	2008	Spain
EAHFE	3273	5845	56.0	79	AHF	2007	Spain
Euro Heart HFpEF	1739	3148	55.0	71	HFpEF	2000	Europe
Total	265,008	583,742	40.2	70.3			

Supplementary Table 3: Population Statistics

(heart failure[MeSH Major Topic]) AND (registry[Text Word]) AND ("The New England journal of medicine"[Journal]) OR ("Lancet (London, England)"[Journal]) OR ("British medical journal"[Journal]) OR ("JAMA"[Journal]) OR ("Journal of the American College of Cardiology"[Journal]) OR ("Circulation"[Journal]) OR ("European heart journal"[Journal])) AND (2000:2021[pdat]). NB: if paper referred to a separate original source, this source was used as the reference.

Diagnosis	Population studied	Proportions of females	Age	Reference
All HF	UK	All - 49%; HF+IHD - 43%	76.7	Conrad et al Lancet 2017
HFpEF / HFrEF	UK	HFpEF - 71%; HFrEF 41.5%	83	Dulai, Br J Cardiol 2016
HFpEF / HFrEF	Italy	HFpEF - 51%; HFrEF - 30%	77	Iorio EJHF 2018
All HF	UK	All - 36.4%	Not reported for HF alone	BHF Heart Circulatory Disease Statistics 2019
All HF	Minnesota	All - 57%	74	Roger JAMA 2004
HFrEF / HFpEF	Minnesota	HFpEF 64%; HFrEF 42%	76.4	Gerber JAMA 2015
All HF	Italy	All - 51.7%; HFpEF 50.9%, HFrEF 29%; HF+IHD - 40.7%	Not reported; 63% 55-75 years	Piccini C 2017
All HF	US	All - 45%	57	Loehr, AJC 2008
All HF	Portugal	HFpEF 73.3%; HFrEF 28.2%	68.1	Ceia EJHF 2002
All HF	UK	All - 49%	77.8	Lawson, Lancet 2019
All HF	UK	HF+IHD - 42%; HFpEF - 65%; HFrEF - 40%	78	Lee Circ 2009
All HF	US	All - 52%; HFpEF 55.9%; HFrEF - 29%	74	Gottdiener AIM 2002
All HF	Minnesota	HFpEF - 55.7%; HFrEF - 34.6%	73.0	Owan NEJM 2006
All HFH	Denmark	Hfpef - 50%; HFrEF - 33%; HFrEF (<35%) - 24%	71.7	Gustafsson EHJ 2004

All HF	US	HFpEF – 57.1%, HFrEF (<35%) - 32.6%	72.4	Gurwitz 2013 AJM
All HF	UK	All - 51.2%	79.7	Koudstaal EJHF 2017
IHD/ICM	International	HF+IHD - 41.3%	Not reported	Moran 2014 Circ
ICM/NICM	US	NICM - 48%; HF+IHD - 33%	61.6	Bart, JACC 1997
Total			74	

Supplementary Table 4: Summary of trials and registries; divided by LVEF and aetiology.

Category	Registries		Trials	
	Number of patients	Female prevalence	Number of patients	Female prevalence
Unspecified LVEF	151544	44.9 [33.9-52.8]	58,101	36.5 [29.2-47.2]
LVEF				
HF, LVEF <35%	40086	25.4 [23.7-27.2]	88,787	21.4 [17.7-25.7]
HF, LVEF <50%	127104	31.7 [31.2-37.0]	84,348	24.3 [21.7-32.0]
HF, LVEF >50%	90283	54.8 [50.8-61.0]	17,385	51.6 [48.6-52.0]
Aetiology				
ICM	102742	37.7 [33.2-41.3]	8541	17.9 [11.7-21.2]
NICM	71983	44.6 [43.8-50.7]	1940	27.5 [25.8-29.4]
Total	583,742	40.2 [32.3-52.8]	238,813	25.8 [21.3-36.0]

Supplementary Table 5: Trials reporting sex-specific characteristics and outcomes.

Trial	Females	Age (yrs)	Baseline characteristics	Outcomes
STICH	12%	59.3 (males 63.4)	Women had higher BMI, higher rates of diabetes, hypertension, hyperlipidemia. Lower rates of smoking.	Overall all-cause and CV mortality lower in women. No difference in rates of surgical deaths (despite higher preoperative risk). No significant interaction between sex and treatment group for mortality of CV hospitalisation.
MUSTT	14%	53% women <70y/o (67% of men)	Women were more likely to have a history of HF and recent angina. No differences in LVEF, presence of 3 vessel coronary artery disease, prior coronary artery bypass graft or other revascularization.	On EP testing, Men were more likely to have inducible sustained VT than women. Over a 2 year period, there were no significant differences in risk of arrhythmic death or cardiac arrest (9% v 12% in men) or overall mortality (32% vs 21% in men).
TOPCAT	50%	72.1 (males 71.0)	Women had less <u>coronary artery disease</u> , tobacco use, atrial <u>fibrillation</u> , <u>chronic obstructive pulmonary disease</u> , and diabetes	Compared to men, women demonstrated a significantly greater increase in creatinine at 4 months. In the spironolactone arm, event rates were also numerically lower in women

			mellitus. Women had higher LVEF, blood pressure, BMI but lower eGFR and hemoglobin	than in men, of which the differences in all-cause mortality and non-CV mortality were statistically significant.
PARAGON-HF	52%	73.6 (males 71.8	Women had more obesity, less coronary disease, and lower eGFR and NT-proBNP levels than men. Median lvef 60% in women, 55% in men. Lower rates of smoking.	In the control group women had more HFH and less CV death. Greater reduction in events for women than men (primarily driven by reduction in HFH - 33% relative risk reduction in women versus men). Greater improvement in quality of life scores in men.

NT-proBNP : N-terminal pro-B-type natriuretic peptide; *HFH*: heart failure hospitalisation, *eGFR*: estimated glomerular filtration rate

Trial Acronyms in Figure 4

I-PRESERVE - Irbesartan in Heart Failure With Preserved Systolic Function

PARAGON-HF - Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Receptor Blocker Global Outcomes in HF with Preserved Ejection Fraction

TOPCAT - Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist

CHARM-preserved - Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity (Clinical Study of Candesartan in Patients With Heart Failure and Preserved Left Ventricular Systolic Function)

CHARM - Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity

EPHESUS - Evaluation of Perceptions, Knowledge and Compliance With tHE Guidelines for Secondary Prevention in Real Life Practice: A Survey on the Under-treatment of hypercholeSterolemia

VICTORIA - VerICiguaT GIObal Study in Subjects With Heart Failure With Reduced EjectIon FrAction

PARADIGM-HF - Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Converting–Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial

ATMOSTPHERE - Aliskiren Trial of Minimizing OutcomeS in Patients With HEart Failure

OVERTURE - Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events

COMET - Carvedilol Or Metoprolol European Trial

STICH - Surgical Treatment for Ischemic Heart Failure