

# **SUPPLEMENTAL MATERIAL**

Supplementary Tables

Supplementary Note

HERMES Memorandum of Understanding

Description of studies

**Supplementary Table 1. Summary of participating studies: design, case ascertainment, genotyping and follow-up**

Acronym	Design	Country	Recruitment period	HF definition	Cases (n)	Controls (n)	Genotyping platform	Sequence data	Median HF follow-up (months)	HF mortality (% cases)
<b>ARIC</b>	Cohort	USA	1987-1989	Registers (hospitalization ICD codes)	1,613	7,338	Affy 6.0	6,572 WGS	37	1096 (68)
<b>CHS</b>	Cohort	USA	1989-1990	Re-exam (CHS criteria)	1,123	2,145	Illumina 370CNV	2,126 WGS	45	1021 (91)
<b>deCODE</b>	Cohort	Iceland	-	Registers (hospitalization ICD codes)	13,200	367,730	Multiple Illumina arrays	15,220 WGS	-	-
<b>EGCUT</b>	Cohort	Estonia	2001-	Registers (hospitalization ICD codes)	2,699	10,709	Multiple Illumina arrays	2,284 WGS	-	-
<b>EPIC-Norfolk</b>	Cohort	UK	1993-1997	Registers (hospitalization ICD codes)	1,687	17,631	Affy Axiom UK Biobank	No	-	-
<b>FHS</b>	Cohort	USA	1948 and 1971	Re-exam (FHS criteria)	476	3,290	Affy 500K + focused panel	2,154 WGS and 1670 WES	57	367 (77)
<b>FINRISK</b>	Cohort	Finland	1992-2012	Registers (hospitalization ICD codes or medications)	1,463	20,298	Illumina HumanCoreExome	7,000 WES	43	623 (43)
<b>MDCS</b>	Cohort	Sweden	1991-1996	Registers (hospitalization ICD codes)	1,770	27,529	Illumina OmniExpressExome	29,299 WES	31	1141 (64)
<b>PIVUS</b>	Cohort	Sweden	2001-2004	Registers (hospitalization ICD codes)	116	833	Illumina Omni 2.5M	No	30	26 (22)
<b>PREVEND</b>	Cohort	Netherlands	1997-1998	Patient records (ESC criteria)	163	3,486	Illumina CytoSNP	500 WGS	21	-
<b>Rotterdam</b>	Cohort	Netherlands	1989	Patient records (Rotterdam criteria)	876	3,807	Illumina Hap550K	No	-	-
<b>SHIP</b>	Cohort	Germany	1997-2001	Patient records (Rotterdam criteria)	352	1,126	Affy 6.0	No	-	-
<b>TwinGene</b>	Cohort	Sweden	2004-2008	Registers (hospitalization ICD codes)	604	5,176	Illumina OmniExpress	942 WGS	-	-
<b>UK Biobank</b>	Cohort	UK	2006-2010	Registers (hospitalization ICD codes)	6,504	387,652	Affy Axiom UK Biobank	50,000 WES	-	-
<b>ULSAM</b>	Cohort	Sweden	1970-1974	Registers (hospitalization ICD codes)	215	964	Illumina Omni2.5M	No	25	156 (73)
<b>WGHS</b>	Cohort	USA	1992-1994	Patient records (FHS or CHS criteria)	479	22,791	Illumina HumanHap300 Duo	No	-	-

<b>DiscovEHR</b>	EHR	USA	2007-	Registers (hospital ICD codes)	5,656	31,026	Illumina OmniExpressExo me	50,726 WES	33	2162 (38)
<b>Bio-SHiFT</b>	Case cohort	Netherlands	2011-2018	Inclusion criteria (ESC criteria)	398	-	Illumina GSA beadchip	No	27	46 (12)
<b>HFPGR</b>	Case cohort	USA	2003-2015	Registers (hospitalization ICD codes)	860	-	Affy Axiom UK Biobank	No	116	213 (25)
<b>TRIUMPH</b>	Case cohort	Netherlands	2009-2014	Inclusion criteria (hospitalized)	475	-	Illumina GSA beadchip	No	13	113 (24)
<b>BIOSTAT-CHF</b>	Case cohort	Multiple	2010-2014	Inclusion criteria	4,023	954	Cases: Affy Axiom Controls: Illumina Infinium custom	No	21	1118 (28)
<b>COGEN</b>	Case-control	Denmark	2010-2017	Registers (hospital ICD codes)	1,636	2,215	Illumina CoreExome	No	-	-
<b>GoDARTS</b>	Case-control	UK	1996-2009	Adjudicated	568	3,811	Affy 6.0 Illumina OmniExpress	No	-	-
<b>GRADE</b>	Case-control	USA	2002-2012	Inclusion criteria (HFrEF)	1,060	7,709	Illumina Infinium PsychArray	No	-	-
<b>LURIC</b>	Case-control	Germany	1997-2000	Adjudicated	1,007	2,054	Affy 6.0	No	-	-
<b>Penn HF study</b>	Case-control	USA	2013-2015	Inclusion criteria	2,206	4,523	Illumina OmniExpressExo me	No	56	341 (26)
<b>dal-OUTCOMES</b>	RCT-HF outcome	Multiple	2008-2010	Case report form	911	N/A	Illumina Omni	No	59	48 (5)
<b>ENGAGE AF-TIMI48</b>	RCT-HF outcome	Multiple	2008-2010	Case report form	6,971	-	Illumina MEGA	No	34	810 (12)
<b>EPHESUS</b>	RCT-HF outcome	Multiple	1999-2001 (cases) 2006-2007 (controls)	Inclusion criteria (post-MI HFrEF)	1,094	886	Illumina Cases: OmniExpressExo me Controls: Quad 660	No	16	144 (13)
<b>IDEAL</b>	RCT-HF outcome	Multiple	1999-2001	Case report form	751	N/A	Illumina MEGA	No	60	64 (9)
<b>PROSPER</b>	RCT-HF outcome	Multiple	1997-1999	Adjudicated outcome	211	5,033	Illumina 660K Quad	521 WGS	13	-
<b>PEGASUS-TIMI54</b>	RCT-HF outcome	Multiple	2010-2013	Adjudicated outcome	2,271	-	Illumina MEGA	No	33	211 (9)
<b>SAVOR-TIMI53</b>	RCT-HF outcome	Multiple	2010-2011	Case report form	1,150	-	Illumina MEGA	No	24	125 (11)

<b>SOLID-TIMI52</b>	RCT-HF outcome	Multiple	2009-2011	Adjudicated outcome	186	9,172	Affy Axiom UK Biobank	No	-	-
<b>TNT</b>	RCT-HF outcome	Multiple	1998-1999	Case report form	396	N/A	Illumina MEGA	No	33	59 (15)
<b>ACTION-HF</b>	RCT-HF cohort	USA	2003-2007	Inclusion criteria	584	-	Affy Axiom UK Biobank	No	48	87 (15)
<b>ATHENA-HF</b>	RCT-HF cohort	USA	2014-2016	Inclusion criteria (Hospitalized)	168	-	Illumina Omni	No	1	7 (4)
<b>CARRESS-HF</b>	RCT-HF cohort	USA, Canada	2008-2012	Inclusion criteria (Hospitalized)	64	-	Illumina Omni	No	2	14 (21)
<b>CHARM</b>	RCT-HF cohort	Multiple	1999-2003	Inclusion criteria	2,727	-	Illumina MEGA	No	38	651 (24)
<b>CORONA</b>	RCT-HF cohort	Multiple	2003-2007	Inclusion criteria	2,815	-	Illumina OMEGA	No	35	462 (16)
<b>DOSE-AHF</b>	RCT-HF cohort	USA, Canada	2008-2009	Inclusion criteria (Hospitalized)	44	-	Illumina Omni	No	2	4 (9)
<b>EXACT-HF</b>	RCT-HF cohort	USA, Canada	2010-2013	Inclusion criteria (HFReEF)	110	-	Illumina Omni	No	6	6 (6)
<b>FIGHT</b>	RCT-HF cohort	USA	2013-2015	Inclusion criteria (HFReEF)	136	-	Illumina Omni	No	6	19 (14)
<b>INDIE-HFpEF</b>	RCT-HF cohort	USA	2016-2017	Inclusion criteria (HFpEF)	78	-	Illumina Omni	No	4	1 (1)
<b>IRONOUT</b>	RCT-HF cohort	USA	2014-2015	Inclusion criteria (HFReEF)	146	-	Illumina Omni	No	4	4 (3)
<b>NEAT-HFpEF</b>	RCT-HF cohort	USA	2014	Inclusion criteria (HFpEF)	72	-	Illumina Omni	No	4	0 (0)
<b>PARADIGM-HF</b>	RCT-HF cohort	Multiple	2009-2012	Inclusion criteria (HFReEF)	1,111	-	Illumina Omni	1,111 WES	28	145 (13)
<b>RELAX</b>	RCT-HF cohort	USA, Canada	2008-2012	Inclusion criteria (HFpEF)	142	-	Illumina Omni	No	6	2 (1)
<b>ROSE-AHF</b>	RCT-HF cohort	USA, Canada	2010-2013	Inclusion criteria (Hospitalized HF with renal failure)	192	-	Illumina Omni	No	2	20 (10)
<b>TIME-CHF</b>	RCT-HF cohort	Switzerland, Germany	2003-2008	Inclusion criteria (Hospitalized)	546	-	Affy Axiom UK Biobank	No	61	207 (38)
<b>Val-HeFT</b>	RCT-HF cohort	Multiple	1997-1999	Inclusion criteria (HFReEF)	1,023	-	Illumina Omni	No	25	125 (12)

Full study titles and cohort descriptions are given in the Supplementary Note below. HF follow up refers to median number of months from time of heart failure ascertainment to death or loss to follow-up, and HF mortality refers to the number and proportion of heart failure cases that died during follow-up. EHR, hospital-based population cohort with electronic health records for phenotypes; ESC, European Society of Cardiology; HF, heart failure cases; HFReEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICD, international classification of disease; Illumina Omni, Illumina Infinium Omni2.5-8v1/ Human Exome-12v1 or IlluminaOmni2.5Exome; Illumina MEGA, Illumina Infinium Multi-Ethnic Genotyping Array; RCT, randomized controlled trial; WES, whole exome sequencing; WGS, whole genome sequencing.

**Supplementary Table 2. Characteristics of participating studies**

Study		Age at diagnosis	Age at ascertainment	Male sex	BMI	History of MI/CAD	Diabetes	Hypertension	AF	HFrEF	HFmrEF	HFpEF
<b>ARIC</b>	HF	NA	73.2 ± 8.1	883 (0.55)	29.3 ± 5.9	1298 (0.80) / 787 (0.49)	484 (0.30)	1015 (0.64)	831 (0.53)	NA	NA	NA
	Control	-	77.2 ± 7.2	3343 (0.46)	27.9 ± 5.2	2988 (0.41) / 1030 (0.14)	1515 (0.21)	4049 (0.56)	801 (0.11)	-	-	-
<b>CHS</b>	HF	83.6 ± 6.5	83.6 ± 6.5	461 (41.1)	27 ± 4.7	333 (29.7) / 398 (35.4)	251 (22.5)	870 (77.5)	440 (39.2)	188 (16.7)	99 (8.8)	343 (30.6)
	Control	-	85.6 ± 7	817 (38.1)	26.2 ± 4.5	220 (10.3) / 276 (12.9)	373 (17.5)	1356 (63.2)	472 (22)	-	-	-
<b>deCODE</b>	HF	79.9±12.7	-	5842 (44.3)	-	NA	8751 (66.3)	5524 (41.8)	NA	NA	NA	NA
	Control	43.2±25.5	-	18475 (5.0)	-	NA	29708 (8.1)	9904 (2.7)	NA	-	-	-
<b>EGCUT1 (370)</b>	HF	65.5 ± 12.1	NA	117 (48.1)	29 ± 6.2	26 (10.7) / 149 (61.3)	88 (36.2)	214 (88.1)	94 (38.7)	6 (13)	3 (6.5)	37 (80.5)
	Control	-	NA	802 (47.4)	25.5 ± 4.8	14 (0.8) / 89 (5.3)	96 (5.7)	570 (33.7)	42 (2.5)	-	-	-
<b>EGCUT2 (Exome)</b>	HF	60.4 ± 11.5	NA	208 (34.4)	30 ± 6.2	247 (40.8) / 409 (67.6)	200 (33.1)	548 (90.6)	219 (36.2)	38 (14.5)	39 (14.9)	185 (70.6)
	Control	-	NA	1431 (30.2)	24.4 ± 5.5	71 (1.5) / 157 (3.3)	188 (4)	1051 (22.2)	87 (1.8)	-	-	-
<b>EGCUT3 (Omni)</b>	HF	70.6 ± 12.6	NA	865 (46.7)	28.4 ± 5.7	384 (20.7) / 1218 (65.8)	513 (27.7)	1649 (89.1)	796 (43)	48 (12.9)	54 (14.5)	271 (72.6)
	Control	-	NA	1836 (43)	26 ± 4.8	67 (1.6) / 340 (8)	328 (7.7)	1643 (38.5)	175 (4.1)	-	-	-
<b>EPIC-Norfolk</b>	HF	75.9 ± 8	66.9 ± 7.0	1013 (60)	27.3 ± 4.1	447 (26.5) / 1687 (100)	109 (6.47)	1280 (76)	824 (48.8)	NA	NA	NA
	Control	-	58.4 ± 9.1	8028 (45.5)	26.2 ± 3.8	689 (3.91) / 7915 (44.9)	315 (1.79)	8001 (45.4)	1756 (9.96)	-	-	-
<b>FHS</b>	HF	80 ± 42	NA	236 (49.6)	29 ± 2.4	NA / 152 (4)	100 (21.8)	357 (75)	NA	194 (40.8)	54 (11.3)	194 (40.8)
	Control	-	NA	1447 (44)	27.5 ± 4.9	NA / 258 (6.9)	257 (8)	1374 (41.8)	NA	-	-	-
<b>FINRISK</b>	HF	66.1 ± 11.7	59.6 ± 9.8	1073 (54.5)	29.9 ± 5.4	405 (20.6) / 622 (31.6)	695 (35.3)	1625 (82.6)	NA	NA	NA	NA
	Control	-	46.9 ± 12.9	9466 (46.6)	26.4 ± 4.6	626 (3.08) / 1149 (5.66)	2125 (10.5)	11060 (54.5)	NA	-	-	-
<b>MDCS</b>	HF	74.2 ± 8.1	63.1 ± 6.1	458 (60.7)	25.6 ± 8.4	132 (17.5) / 160 (21.2)	431 (5.7)	657 (87)	46 (6.1)	NA	NA	NA

	Control	-	58.9 ± 6.9	3577 (47.1)	24.1 ± 7.4	377 (5.0) / 422 (5.6)	128 (17.0)	5183 (68.3)	73 (1.0)	-	-	-
<b>PIVUS</b>	HF	76.1 ± 5	70.1 ± 0.2	80 (61.5)	28.5 ± 5.5	29 (22.7) / NA	22 (16.9)	108 (83)	15 (11.5)	NA	NA	NA
	Control	-	70.2 ± 0.2	427 (48.2)	26.8 ± 4.1	38 (4.3) / NA	97 (10.9)	624 (70.4)	10 (1.1)	-	-	-
<b>PREVEND</b>	HF	69.4 ± 10.4	61.3 ± 9.8	109 (66.9)	27.9 ± 4.4	29 (22.7) / NA	19 (11.8)	119 (73)	52 (33.5)	57 (37.3)	NA	96 (62.7)
	Control	-	49.1 ± 12.3	1771 (50.8)	26 ± 4.2	38 (4.3) / NA	132 (3.83)	1119 (32.6)	95 (2.79)	-	-	-
<b>Rotterdam</b>	HF	71.6 ± 7.4	NA	607 (45)	27.6 ± 4.2	150 (11.1) / 184 (13.6)	0 (0.00)	156 (11.6)	NA	-	-	-
	Control	-	NA	2436 (38.2)	15.2 ± 3.9	352 (5.53) / 424 (6.66)	1 (0.00)	1182 (18.6)	NA	-	-	-
<b>SHIP</b>	HF	NA	60.0 ± 13.9	160 (45.5)	29.1 ± 4.7	72 (20.5) / 352 (100)	87 (10.7)	274 (70.2)	34 (9.7)	NA	NA	NA
	Control	-	51.2 ± 16.0	613 (54.4)	27.2 ± 4.5	69 (6.1) / 326 (29)	120 (24.7)	596 (52.9)	15 (1.4)	-	-	-
<b>TwinGene</b>	HF	74.5 ± 9.9	NA	365 (60.4)	27.2 ± 4.4	210 (34.8) / 350 (5.8)	158 (26.2)	423 (70.3)	NA	NA	NA	NA
	Control	-	NA	2432 (47)	26.4 ± 4	229 (4.4) / 457 (8.8)	438 (8.5)	1449 (28)	NA	-	-	-
<b>UK Biobank</b>	HF	64.8±6.7	62.4±6.2	4562 (70.1%)	29.8±5.8	2712(41.7) / 3062 (47.1)	1711 (26.3)	4866 (74.8)	2848 (43.8)	NA	NA	NA
	Control	-	57.3±7.9	177932 (45.9%)	27.4±4.7	11748 (3.0) / 16106 (4.2)	23555 (6.1)	123838 (31.9)	12297 (3.2)	-	-	-
<b>ULSAM</b>	HF	80.6 ± 6	71.1 ± 0.7	293 (100)	26.9 ± 3.6	39 (13) / NA	71 (24)	241 (83)	18 (6)	11 (3.8)	11 (3.8)	96 (32.8)
	Control	-	71 ± 0.6	928 (100)	26.1 ± 3.4	60 (6.5) / NA	160 (17.3)	668 (72.1)	37 (4.3)	-	-	-
<b>WGHS</b>	HF	73.3 ± 10	NA	0 (0)	28.3 ± 5.8	68 (14.1) / 105 (21.9)	110 (23)	258 (53.9)	141 (29.4)	-	-	-
	Control	-	NA	0 (0)	25.9 ± 4.9	396 (1.7) / 1006 (4.4)	2515 (11)	5456 (23.9)	1245 (5.5)	-	-	-
<b>DiscovEHR</b>	HF	NA	73.9 ± 12	3198 (56.2)	32.3 ± 7.3	1942 (34.1) / 3898 (68.5)	2263 (39.8)	5151 (90.5)	2719 (47.8)	442 (7.77)	380 (6.68)	2647 (46.5)
	Control	-	56.1 ± 16.6	11792 (36.3)	31.5 ± 7.5	1650 (5.08) / 4763 (14.7)	6471 (19.9)	17071 (52.6)	726 (2.24)	-	-	-
<b>Bio-SHiFT</b>	HF	57 ± 14	63.6 ± 13	284 (71)	27.3 ± 5	148 (37) / NA	104 (26)	175 (44)	147 (37)	178 (79)	34 (15)	14 (6)
<b>HFPGR</b>	HF	70.1 ± 10.8	70.1 ± 10.8	540 (62.8)	31.1 ± 7.2	540 (62.8) / NA	340 (40)	754 (88)	364 (42)	282 (33)	201 (23)	363 (42)

<b>TRIUMPH</b>	HF	67 ± 15	71 ± 13	298 (63)	28 ± 6	190 (40) / NA	172 (36)	242 (51)	198 (42)	254 (68)	54 (15)	64 (17)
<b>BIOSTAT-CHF</b>	HF	NA	68.9 ± 12.0	1805 (73.3)	-	942 (38.3) / 1106 (44.9)	805 (32.7)	1536 (62.4)	1120 (45.5)	1778 (81.0)	275 (12.5)	141 (6.4)
	HF (validation)	70 ± 11	NA	1042 (66.7)	29 ± 6.3	768 (49.2) / 1488 (95.3)	490 (31.4)	916 (58.7)	694 (44.5)	785 (50.3)	198 (12.7)	149 (9.55)
<b>COGEN</b>	HF	67.6 ± 10.3	67.6 ± 10.3	243 (38.2)	28.3 ± 5.2	180 (28.3) / 344 (54.1)	148 (23.3)	453 (71.2)	80 (12.6)	143 (22.5)	88 (13.8)	245 (38.5)
	Control	-	64.2 ± 10.9	907 (41)	27.5 ± 5.0	292 (13.2) / 943 (43.9)	407 (18.4)	1277 (57.7)	115 (5.2)	-	-	-
<b>GoDARTS1 (Affy)</b>	HF	73.6 ± 9.19	73.1 ± 9.8	1100 (59)	30.2 ± 5.2	NA	1864 (100)	NA	NA	NA	NA	NA
	Control	-	74.6 ± 9.1	110 (53.9)	32.2 ± 6.2	NA	204 (100)	NA	NA	-	-	-
<b>GoDARTS2 (Illumina)</b>	HF	74.6 ± 9.14	74.6 ± 9.1	110 (53.9)	32.2 ± 6.2	NA	204 (100)	NA	NA	NA	NA	NA
	Control	-	71.6 ± 11.9	1215 (62.4)	31.1 ± 5.9	NA	1947 (100)	NA	NA	-	-	-
<b>GRADE</b>	HF	NA	63.9 ± 11.4	887(83.7)	29.1±6.1	602 (56.9) / NA	361 (34.0)	621 (58.6)	111 (18.4)	NA	NA	-
	Control	-	64.8 ± 12.4	4872 (63.1)	27.7±5.2	302 (3.9) / NA	1226 (16.0)	5096 (66.8)	0 (0)	-	-	-
<b>LURIC</b>	HF	NA	65.3	727 (72.2)	27.8 ± 4.3	501 (49.8) / 792 (78.6)	516 (51.2)	744 (73.9)	285 (28.3)	200 (19.9)	112 (11.1)	184 (18.3)
	Control	-	61.5	1417 (69)	27.3 ± 3.9	817 (39.8) / 1627 (79.2)	720 (35.1)	1481 (72.1)	83 (4)	-	-	-
<b>Penn HF study</b>	HF	NA	56.7 ± 13.6	1562 (70.8)	28.3 ± 6.6	60 (6.5) / NA	498 (23)	1044 (47)	745 (34)	1490 (72.3)	224 (10.9)	346 (17.0)
	Control	-	64.3 ± 12.8	2687 (59.4)	29 ± 6.7	NA / 529 (23)	NA	NA	NA	-	-	-
<b>dal- OUTCOMES</b>	HF	NA	62.2 ± 9.3	721 (73)	29.5 ± 5.2	869 (95) / 911 (100)	281 (31)	693 (76)	NA	NA	NA	NA
	Control	-	-	-	-	-	-	-	-	-	-	-
<b>ENGAGE AF-TIMI48</b>	HF	NA	69.6 ± 9.3	4236 (61)	30.7 ± 6.0	1119 (16) / 3134 (45)	2248 (32)	6695 (96)	6971 (100)	1048 (15)	1423 (20)	3068 (44)
	Control	-	72.9 ± 8.5	2562 (61)	29.9 ± 5.6	366 (9) / 1120 (27)	1899 (45)	3988 (95)	4214 (100)	-	-	-
<b>EPHESUS</b>	HF	NA	63.4 ± 11.5	792 (72.6)	27.6 ± 4.5	1091 (100) / 1091 (100)	323 (29.6)	579 (53.5)	99 (9.14)	1091 (100)	-	-

	Control	-	72.8 ± 7.5	427 (48.6)	27.7 ± 5.5	15 (1.7) / 17 (1.9)	90 (10.2)	383 (43.6)	22 (2.5)	-	-	-
<b>IDEAL</b>	HF	NA	64.6 ± 8.8	587 (78)	27.6 ± 4.0	751 (100) / 751 (100)	128 (17)	208 (28)	116 (15)	NA	NA	NA
	Control	-	-	-	-	-	-	-	-	-	-	-
<b>PEGASUS-TIMI54</b>	HF	NA	66.4 ± 8.7	1618 (71)	29.5 ± 5.1	2270 (100) / 2270 (100)	892 (39)	1957 (86)	192 (8)	NA	NA	NA
	Control	-	65.3 ± 8.2	6501 (78)	29.0 ± 4.8	8329 (100) / 8329 (100)	2304 (28)	6205 (74)	314 (4)	-	-	-
<b>PROSPER</b>	HF	NA	78.1 ± 3.71	123 (58.3)	27.4 ± 4.5	649 (12.9) / 649 (12.9)	30 (14.2)	122 (57.8)	88 (41.7)	NA	NA	NA
	Control	-	78.5 ± 3.4	2401 (47.7)	26.8 ± 4.2	1942 (34.1) / 3898 (68.5)	514 (10.2)	3135 (62.3)	417 (8.3)	-	-	-
<b>SAVOR-TIMI53</b>	HF	NA	66.1 ± 9.0	754 (66)	33.1 ± 5.8	653 (57) / 926 (81)	1150 (100)	1011 (88)	232 (20)	NA	NA	NA
	Control	-	65.9 ± 7.9	3892 (69)	32.0 ± 5.3	2020 (36) / 3389 (60)	5614 (100)	4625 (82)	442 (8)	-	-	-
<b>SOLID-TIMI52</b>	HF	NA	67.7 ± 10.3	124 (66.7)	29.9 ± 5.6	88 (47.3) / 186 (100)	100 (53.8)	87 (46.8)	38 (20.4)	NA	NA	NA
	Control	-	64.3 ± 9.2	6830 (74.5)	28.8 ± 5.0	2827 (30.8) / 9172 (100)	2967 (32.4)	3428 (37.4)	347 (3.8)	-	-	-
<b>TNT</b>	HF	NA	64.3 ± 7.9	296 (75)	30.0 ± 6.0	282 (71) / 396 (100)	103 (26)	275 (69)	NA	NA	NA	NA
	Control	-	-	-	-	-	-	-	-	-	-	-
<b>ACTION-HF</b>	HF	61.2 ± 12.2	61.2 ± 12.2	456 (78.1)	30.0 ± 6.0	NA	172 (29.5)	NA	43 (7.4)	569 (97.3)	16 (2.7)	-
<b>ATHENA-HF</b>	HF	64.8 ± 14.2	69.0 ± 13.6	122 (72.6)	32.8 ± 9.4	52 (31) / 80 (47.6)	68 (41)	138 (82)	107 (64)	93 (55)	22 (13)	53 (32)
<b>CARRESS-HF</b>	HF	62.7 ± 14.0	70.0 ± 11.8	55 (82)	33.9 ± 8.7	31 (46) / 43 (64)	38 (57)	51 (76)	41 (61)	41 (61)	7 (10)	19 (27)
<b>CHARM</b>	HF	62.8 ± 11.5	66.5 ± 10.9	1822 (66.8)	28.7 ± 5.8	1514 (56) / 2006 (74)	787 (29)	1529 (56)	817 (30)	1608 (59)	441 (16)	678 (25)
<b>CORONA</b>	HF	68.5 ± 8.0	72.5 ± 6.9	2166 (77)	27.4 ± 4.5	1716 (61) / 2458 (87)	780 (28)	1842 (65)	1131 (40)	2617 (93)	198 (7)	-
<b>DOSE-AHF</b>	HF	65.1 (11.6)	73.3 (9.2)	31 (71)	32.0 ± 7.4	23 (52) / 32 (73)	25 (57)	37 (84)	31 (71)	27 (61)	4 (9)	13 (29)
<b>EXACT-HF</b>	HF	58.3 ± 13.6	65.9 ± 12.2	92 (84)	31.3 ± 7.2	47 (43) / 63 (57)	60 (55)	86 (78)	64 (58)	107 (97)	3 (3)	-
<b>FIGHT</b>	HF	54.3 ± 10.6	63.5 ± 10.1	122 (90)	31.1 ± 8.1	73 (54) / 90 (66)	83 (61)	101 (74)	81 (60)	134 (99)	2 (1)	-



<b>INDIE-HFpEF</b>	HF	64.5 ± 11.2	68.2 ± 10.3	35 (45)	34.7 ± 6.6	5 (6) / 23 (30)	22 (28)	59 (76)	38 (49)	-	-	78 (100)
<b>IRONOUT</b>	HF	58.1 ± 13.6	65.4 ± 11.7	106 (73)	29.3 ± 5.7	74 (51) / 90 (62)	58 (40)	98 (67)	64 (44)	133 (91)	13 (9)	-
<b>NEAT-HFpEF</b>	HF	67.1 ± 10.0	69.6 ± 9.4	36 (50)	34.7 ± 7.5	8 (11) / 18 (25)	25 (35)	63 (88)	27 (38)	1 (1)	-	71 (99)
<b>PARADIGM-HF</b>	HF	NA	66.5 ± 10.0	942 (81)	29.9 ± 5.2	527 (46) / 751 (66)	445 (39)	905 (80)	565 (50)	1111 (96)	48 (4)	-
<b>RELAX</b>	HF	65.8 ± 9.9	68.6 ± 10.1	70 (48)	33.6 ± 7.1	14 (10) / 45 (31)	54 (37)	123 (84)	71 (49)	-	-	146 (100)
<b>ROSE-AHF</b>	HF	66.0 ± 13.0	72.7 ± 10.4	147 (77)	31.8 ± 7.7	70 (37) / 114 (59)	98 (51)	153 (80)	140 (73)	101 (53)	20 (10)	70 (36)
<b>TIME-CHF</b>	HF	77.0 ± 7.7	77.0 ± 7.7	323 (59.2)	25.6 ± 4.5	257 (47.1) / 355 (65.0)	192 (35.2)	403 (73.8)	186 (34.1)	353 (64.7)	89 (16.3)	104 (19.0)
<b>Val-HeFT</b>	HF	58.6 ± 10.8	63.1 ± 10.3	805 (79)	26.7 ± 4.2	- / 600 (59)	245 (24)	970 (95)	NA	1023 (100)	1 (0.1)	1 (0.1)

Individual characteristics of cases and controls from 51 cohorts participating in HERMES. Continuous variables are presented as mean ± standard deviation and categorical variables as number (percentage). Baseline characteristics refer to baseline for prospective cohorts, and at the time of diagnosis for case-control studies and clinical trials. Subtypes based on ejection fraction are presented for subjects with available echocardiography. Full titles and references for each cohort can be found in the Supplementary Note below. AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; HF, heart failure cases; HFrEF, heart failure with reduced ejection fraction (<40%); HFmrEF, Heart Failure with mid-range ejection fraction (40-49%); HFpEF, heart failure with preserved ejection fraction (≥50%); MI, myocardial infarction; NA, not available.

## SUPPLEMENTARY NOTE

### **HERMES Memorandum of Understanding** (13 December 2019)

This document seeks to outline the terms of reference for the oversight, governance, activity and output of the HERMES Consortium.

**Aim** HERMES is an international research collaboration to explore the genetic determinants of heart failure risk and prognosis in order to identify and validate therapeutic targets and causal risk factors.

**Ethos** The scientific strength of HERMES lies in its collaborators. The guiding principles for HERMES are scientific excellence; collaborative spirit; transparency and openness, 'no surprises'; equal opportunities for contribution across cohorts; open communication; and mutual trust and confidentiality. The aim of this collegial approach is to maximize the scientific potential of the consortium and to ensure that all members receive appropriate recognition in the publications that will be generated. The consortium will be inclusive and, as such, open to collaboration with both academic, industrial and charitable partners who agree to participate according to the terms of this memorandum.

**Organisation** The management of HERMES will be divided amongst teams: scientific leadership and oversight will be provided by the Scientific Committee (SC); general management and logistic support will be provided by Executive Committee (EC); and primary research projects will be delivered by project working groups. Further detail on each of these groups is given below.

#### *Scientific Committee*

The SC will comprise representatives from each of the participating cohorts and invited members with particular expertise in relevant disease areas or research methodologies. It is

envisaged that a senior investigator from each of the cohorts will join the SC. The SC will provide scientific leadership and overall oversight for HERMES Consortium and HERMES Projects. The SC will meet at approximately two-monthly intervals 'all-hands meeting' (with the option of more frequent meetings). Quorum will be set at 30%. Key roles will include:

- Transparent operation, open and timely communication, effective coordination;
- Ensuring equitable sharing of responsibilities, challenges, and opportunities amongst HERMES members;
- Oversight and steering of the HERMES scientific strategy;
- Review, and approval of submitted project proposals, and suggestion of new projects;
- Establish a working group for each approved project and to agree on the project leader;
- Review and approve study designs, analysis plans, publication strategies and authorship criteria for each project;
- To form additional sub-committees as needed, for instance, to harmonize specific endpoints between cohorts.

#### *Executive Committee*

The EC will form a subgroup of the SC and will be responsible for providing administrative support and project management for the consortium (Appendix 1). Key roles include:

- Registration of new cohorts based on member recommendation, publication or application;
- Provide and maintain a database summarizing the phenotypic data and genetic data available for participating studies (HERMES Dataview);
- To coordinate initial meta-GWA studies of heart failure phenotypes to validate the HERMES analysis platform and operationalise the consortium;
- Curate and store securely summary statistics contributed by participating cohorts;

- As needed or appropriate, curate and store individual participant level data contributed by participating cohorts;
- Create, maintain and make available a website with secure web-based access to HERMES Dataview;
- Create, maintain and make available to the SC a list of HERMES projects approved or pre-approved by the SC;
- Preparing and providing letters of support and other administrative support required by consortium members to facilitate funding or publication;
- The EC will meet at least monthly. Quorum will be set at 50%

### *Project Working Groups*

The primary scientific work of the HERMES consortium will take place in working groups around specific meta-analysis projects. Any consortium member may propose a new project and working group at an SC all hands meeting. Each working group will consist of 1-2 coordinator(s) who will be responsible for the design, analysis and reporting of the project, as well as day-to-day operational management of the project. In addition, working group will include 1-2 representatives from participating cohorts and a nominated lead analyst(s). Key roles will include:

- Following preliminary agreement for a project, the working group will prepare full proposals and submit them to the SC for discussion and revision prior to final agreement.
- The working group lead will contact individual member cohorts to invite formal participation in the specific project
- The working group will establish analysis plans, analysis scripts, and coordinate data management.
- working groups will evaluate results, perform meta-analyses of summary level data, write papers and decide on the need for additional follow-up studies

- working groups will decide the publication strategy and authorship criteria, before final approval by the SC.
- Each working group lead will run meetings and coordinate calls for practical management.
- Working groups may encourage joint ancillary-study application to accomplish new scientific aims.

### **Data sharing policies**

Cohort PIs retain all rights to their data. Only summary statistics are shared for meta-analysis. Aggregate (meta-analysis) data may not be used for other purposes than the working group aims without permission from the working group or the specific study, respectively. Sharing of unpublished results to non-members of the working group that have not explicitly opted-in to the analysis may only occur after approval by the working group. This may, for example, be desirable in situations where a working group is seeking lookup-replication, statistical advice, or functional analyses by groups that are not participating in HERMES.

For HERMES GWAS meta-analysis, individual study results will be transferred to the HERMES analysis centre for QC and meta-analysis (currently University College London), and then shared with a second analysis centre for meta-analysis replication (currently Boston University). Individual study results will not be used for any other purpose and will be treated as confidential by the HERMES analysis centres. Upon completion of the meta-analysis, results will be made available to HERMES Contributing Members (defined below) for review and then made publically available online upon publication of the relevant results paper.

1. Data freeze for studies contributing to HERMES meta-analysis (week -5)
2. Completion of QC and meta-analysis replication (week 0)
3. Confidential release of summary-level data to HERMES Contributing Members only (week +1)

4. Summary-level data made publically available online upon publication of relevant results paper (approx. week 36 - 52)

For the purposes defining rights to pre-publication data access, HERMES members are classified as follows:

#### HERMES Contributing Member

Definition: Cohorts/ organisations who have agreed to the MOU and have contributed genome-wide summary statistics to a HERMES GWAS project either directly, or indirectly by supporting another participating cohort (e.g. genotyping or analyst support), or who have provided project funding to the HERMES core analysis centres.

Data access: Contributing members will have equal access to the results of HERMES GWAS meta-analyses according to the internal data-sharing policy (1 week after final meta-analysis results generated). Contributing data to one analysis will grant access to all subsequent GWAS and sub-group analyses. Genome-wide meta-analysis estimates will be downloadable from a password protected site managed by the coordinating centre.

#### HERMES Affiliate Member

Definition: Cohorts/ organisations that have agreed to the MOU and have expressed interest in contributing data to future HERMES analyses (when data/ analysis capacity permits).

Data access: Participation in SC meetings to steer scientific strategy. SC meetings may present results in tables and figures for discussion. Affiliate members will not be able to download GWAS meta-analysis estimates.

#### **Opt-in and opt-out policy**

Investigators may join each working group or may opt out of one or more working groups for any reason. The decision to 'opt in' represents a commitment to collaborate only with the HERMES working group for that particular analysis, until the initial proposed manuscript is accepted for publication. This includes a commitment not to accept new replication requests

for the topic under study from researchers not participating in the HERMES working group. No restrictions will be put upon publishing the data that an individual study would contribute to the meta-analysis before opting in to the meta-analysis. Uploading data for meta-analysis will be assumed to imply opting-in to that specific project. At the time of opting in, researchers are required to disclose potentially conflicting ongoing work on the topic of the project ('no surprises' ethos). The decision to opt out of an analysis must take place before the first occurrence of sharing of any research results. After the results have been shared, investigators cannot opt out to publish their findings on their own or with other partners. Only investigators from studies that have opted-in have access to shared results and will be invited to teleconferences in which these results are discussed.

**Industrial collaborators** HERMES will seek to enrol clinical trials cohorts and as such welcomes the participation of industrial collaborators. Industrial and academic collaborators who contribute cohorts to the consortium will participate on an equal basis to the consortium. All results from HERMES analyses will be made publically available in due course through online repositories and in scientific publications.

**Publication planning** An initial publication plan will be developed at the time of working group formation and may be modified based on the results following agreement from the SC. Publications should be prepared and submitted as rapidly as possible after the results have been reviewed and confirmed. For parallel publications, one month is a tolerable wait time; three months may not be tolerable. Each working group needs to balance rapid publication, strength of findings from replication, and equal partnership. Working group members will assure that parent-study disclaimers, reviews, and approvals are managed as required to avoid any delay in submission. These approvals should occur within one month of the completion of the final draft. Abstracts should follow the same rules as publications.

**Authorship** The goal is fair scientific representation from cohort members participating in the working group. Multiple first and multiple senior authors may be designated as such. First and senior authors, including the overall first and the overall last author, should generally come from different cohorts. Long lists of authors are permitted if all authors meet standards for authorship (such as those required by major journals, for instance the criteria used by Nature Genetics and JAMA). Contributing scientists from outside the working group may be co-authors, however, in the event that two people propose similar projects at the same time priority will be given to the internal team. Authorship position in first papers will be determined in advance by a group consensus by the researchers actively participating in the proposed pooled study. Some of the factors that may be considered include effort in working group and size of participating cohorts study. In later papers, successful efforts to obtain additional funding for new scientific work is another criteria. The SC will mediate any differences of opinion regarding authorship representation.

Rapid publication from a working group should generally include authors from all member cohorts contributing summary statistics from the specified analysis. The number of authors per study should generally reflect the contribution of the study to the paper and will be flexible and determined on a case by case basis. Consortium authorship for the writing group is another possible model that may be considered as an alternative model if there is no group consensus on named authorship.

**Involvement of Other Collaborating Studies** Other collaborating studies may be proposed for inclusion in individual working group analyses. Collaborating studies will be asked to abide by all of the principles set out in this memorandum for the purpose of the proposed working group project.

**Data posting** For the purposes of transparency and quality control, meta-analyses results of will be made available to consortium members through HERMES Dataview as soon as they



are available following appropriate quality control processes. Following publication in a scientific journal, shared summary-level results including results from joint analyses will be posted on [www.hermesconsortium.org](http://www.hermesconsortium.org) for the benefit of the wider community, under terms of use that will be agreed by the SC in advance of posting.

**Intellectual property** Concerning meta-analyses performed within the HERMES Consortium (GWAS, pathway analyses and Mendelian randomisation studies) the principles outlined for NIH funded GWAS studies (Federal Register; 72 (166) 28 Aug 2007: 49290-7) will be followed: “genotype-phenotype associations identified through NIH-supported and NIH-maintained GWAS datasets and their obvious implications will remain available to all investigators, unencumbered by intellectual property claims.” In the event that intellectual property related to the GWA studies covered under these principles is pursued by a participating investigator, their institution, or the study itself, the SC must be promptly made aware of the pursuit of such claims. An abstract of the claim(s) needs to be made available to the consortium at the time of submission to the relevant governing body (e.g. US Patent Office).

**Acknowledgements** HERMES thanks iGeneTrain, GENIUS-CHD, CHARGE and PACE consortia for sharing their memoranda of understanding upon which this document is based.

## **DESCRIPTION OF STUDIES**

### **Atherosclerosis Risk in Communities (ARIC)**

*Reference PubMed ID (PMID): 2646917*

The ARIC study is a population-based prospective cohort study of cardiovascular disease sponsored by the National Heart, Lung, and Blood Institute (NHLBI). ARIC included 15,792

individuals, predominantly European American and African American, aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities. Cohort members completed three additional triennial follow-up visits, a fifth visit in 2011-2013, a sixth visit in 2016-2017, and a seventh visit in 2018-2019. The ARIC study has been described in detail previously.

Incident heart failure was defined as the first HF hospitalization or presence of HF code on death certificate since baseline visit through 2014. Discharge records and death certificates that showed a HF code in any position with International Classification of Diseases Code, Ninth Revision (ICD-9) code 428.x, and deaths with ICD-9/10 codes of either 428.x or I50 were considered as HF. Prevalent heart failure at Visit 1 will have a value '1' for 'yes', a value of '0' for 'no', or '.' for missing values. If the participant reported to have taken any medication for heart failure or qualifies for the Gothenburg Criteria then the participant had prevalent heart failure at baseline.

The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services (contract numbers HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700004I and HHSN268201700005I), R01HL087641, R01HL059367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research.

### **Cardiovascular Health Study (CHS)**

*Reference PMID: 1669507, 26538580*

The Cardiovascular Health Study (CHS) is a population-based cohort study of risk factors for coronary heart disease and stroke in adults  $\geq 65$  years conducted across four field centers. The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African American cohort of 687 persons was enrolled for a total sample of 5,888. Participants were excluded from the GWAS study sample due to the presence at study baseline of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack or lack of available DNA. For this analysis, only participants with European ancestry were included.

Incident HF events were identified by self-report or administrative data validated by physician's review of medical records, as described in previous reports (PMID: 1669507). Controls were defined based on no prevalent heart failure at study enrollment and no incident heart failure during study follow-up

This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL120393, and U01HL130114 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at [CHS-NHLBI.org](http://CHS-NHLBI.org).

The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR001881, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

### **deCODE Heart Failure Study (deCODE)**

*Reference PMID: 25807286, 19165921*

The deCODE Icelandic heart failure (HF) sample set included patients diagnosed with HF at Landspítali – The National University Hospital (LUH) in Reykjavik. Case status was assigned based on ICD-9 or ICD-10 codes for discharge diagnoses (ICD-10: I50 and subcodes, ICD-9: 428 and subcodes).

Case status was assigned based on ICD-9 or ICD-10 codes for discharge diagnoses (ICD-10: I50 and subcodes, ICD-9: 428 and subcodes).

The controls included population controls from the Icelandic genealogical database and individuals recruited through different genetic studies at deCODE genetics. Individuals of non-Icelandic origin were excluded from the study.

The study was approved by The Icelandic Data Protection Authority and the National Bioethics Committee of Iceland (approval no. VSNb2015030013/03.01 with amendments). All participating subjects donating biological samples signed informed consents. Personal identities of the participants and biological samples were encrypted by a third-party system approved and monitored by the Icelandic Data Protection Authority.

### **Estonian Genome Center at the University of Tartu (EGCUT)**

*Reference PMID: -*

The Estonia biobank is a population-based cohort of the Estonian Genome Center at the University of Tartu (EGCUT), which was established in 2001. Subjects were recruited at random and represent about 5% of the Estonian population. Cases were identified from ICD code I50. Ethics approval was obtained as 234/T-12 „Omics for health: an integrated approach to understand and predict human disease. Funding was obtained from the Estonian Research Council Grant IUT20-60, EU, H2020 grant 692145, European Union

through the European Regional Development Fund (Project No. 2014-2020.4.01.15-0012) GENTRANSMED.

### **European Prospective Investigation of Cancer (EPIC)-Norfolk**

*Reference PMID: 10466767*

The EPIC-Norfolk study is a prospective population-based cohort study which recruited 25,639 men and women aged 40-79 years at baseline between 1993 and 1997 from 35 participating general practices in Norfolk, UK. Individuals attended for a baseline health check including the provision of blood samples for concurrent and future analysis. They provided consent to future linkage to medical record information and a wide range of follow-up studies for different disease endpoints (including incident T2DM) have subsequently been undertaken, and further health check visits have been conducted since the baseline visit (see [www.srl.cam.ac.uk/epic](http://www.srl.cam.ac.uk/epic)). DNA has been extracted from all EPIC participants and stored blood has been analysed for an extensive range of classical and novel biomarkers. Sample quality control was performed including gender check, relatedness check, and ancestry check. Samples that failed quality control were removed from further analysis. Data used in this analysis includes 19,318 participant. Heart failure definition was based on hospital admission or death record listing Heart failure code - I50 (ICD10). Ethical approval for EPIC-Norfolk was granted by the Norfolk and Norwich Research Ethics Committee.

### **Framingham Heart Study (FHS)**

*Reference PMID: 14819398, 1208363, 17372189*

Framingham Heart Study (FHS) is a community based cohort that enrolled three generations of participants. The objective of the FHS was to identify common factors or characteristics that contribute to CVD by following its development over a long period of time in a large group of participants who had not yet developed overt symptoms of CVD or suffered a heart attack or stroke. The researchers recruited 5,209 men and women between the ages of 30 and 62 from the town of Framingham, Massachusetts, and began the first round of extensive

physical examinations and lifestyle interviews that they would later analyze for common patterns related to CVD development. Since 1948, the subjects have continued to return to the study every two years for a detailed medical history, physical examination, and laboratory tests, and in 1971, the Study enrolled a second generation - 5,124 of the original participants' adult children and their spouses - to participate in similar examinations. In 1994, the need to establish a new study reflecting a more diverse community of Framingham was recognized, and the first Omni cohort of the Framingham Heart Study was enrolled. In April 2002 the Study entered a new phase, the enrollment of a third generation of participants, the grandchildren of the Original Cohort. In 2003, a second group of Omni participants was enrolled. The study was approved by the Institution Review Board of Boston Medical Center, and all participants gave written consent. The data has been deposited to dbGaP (phs000007.v29.p10).

Criteria for defining heart failure in the FHS have been described previously (PMID: 5122894, 16837677). In brief, heart failure was considered to be present if two major or one major plus two minor criteria were present in the absence of an alternative explanation for the symptoms and signs. Major criteria are defined as paroxysmal nocturnal dyspnea, orthopnea, jugular venous distention, hepatojugular reflux, pulmonary rales, radiographic evidence of cardiomegaly, acute pulmonary edema, third heart sound, central venous pressure >16 cm of water, and weight loss >4.5 kg during first 5 days of treatment for suspected heart failure. Minor criteria are defined as bilateral ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, and heart rate >120 beats per minute.

This work was conducted using data and resources from the Framingham Heart Study (FHS) of the National Heart Lung and Blood Institute and Boston University School of Medicine. The study was supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195, HHSN268201500001I,

75N92019D00031) and its contract with Affymetrix, Inc for genotyping services (Contract No.N02-HL-6-4278). The work was also supported by R01 HL093328, R01 HL105993, and R01 HL71039 (PI: Ramachandran).

## **FINRISK**

*Reference PMID: 29165699*

FINRISK is a series of health examination surveys carried out by the National Institute for Health and Welfare (formerly National Public Health Institute) of Finland every five years since 1972. The surveys are based on random population samples from five (or six in 2002) specified geographical areas of Finland. The samples have been stratified by 10-year age group, sex and study area. The sample sizes have varied from approximately from 7,000 to 13,000 individuals and the participation rates from 90% to 60% in different study years. The age-range was 25-64 years until 1992 and 25-74 since 1997. The survey included a self-administered questionnaire, a standardized clinical examination carried out by specifically trained study nurses and drawing of a blood sample. Details of the examination have been previously described<sup>1,2</sup>. The participants were instructed to fast totally for four hours before the scheduled examination and to avoid heavy meals earlier during the day. The length of the fast was recorded. The blood samples were analyzed immediately for routine cardiovascular risk factors at the laboratory of the National Institute for Health and Welfare, which participates in the quality control and standardization program of the Centers of Disease Control and Prevention, Atlanta, GA. The same laboratory has been used in each survey. In addition to the routine risk factors measurements, serum and plasma have been frozen in -70 C for future use. DNA has been collected since the 1992 survey from approximately 34,000 participants. The surveys have appropriate ethical approvals following the usual practices of each survey-year and the participants have signed an informed consent. The follow-up of FINRISK participants takes place with annual record linkage of FINRISK data to the country-wide electronic health care registers, the National Causes-of-Death Register, Hospital Discharge Register including ambulatory visits to specialist health

care facilities, Drug Reimbursement Registers and the Cancer register. The record linkage is carried out using the personal ID code, which is unique to every permanent resident of Finland. Thanks to the country-wide registers, the follow-up is virtually 100% complete. The validity of clinical diagnoses in these registers has been documented in several publications 3-6.

Participants of the FINRISK 1997-2012 surveys have all signed an informed consent, allowing the use of their data and samples for studying environmental and genetic risk factors of chronic diseases. Each FINRISK survey obtained ethical approval according to the law prevailing at that period.

Cases were defined as individuals with a diagnosis corresponding to heart failure in the nationwide hospital discharge or cause of death registers (ICD-10: I50, I110, I130 and I132; ICD-9: 4029B, 404, 4148, 428; ICD-7: 42700, 42710, 428) or special drug reimbursement for heart failure medications (requires a medical certificate that meets predefined criteria for heart failure).

### **Malmö Diet and Cancer Study (MDCS)**

*Reference PMID: 19936945, 21070922*

MDCS is a community-based prospective cohort of middle-aged individuals from Southern Sweden. In total, 30,447 subjects attended a baseline exam in 1991-1996 when they filled out a questionnaire, underwent anthropometric measurements and donated peripheral venous blood samples<sup>1</sup>. The study was approved by the local ethics committee and all participants provided written informed consent. Prevalent or incident cases of heart failure were ascertained from nation-wide hospital registers with high validity as described previously (PMID 21070922). Genome-wide genotyping of single nucleotide variants in the full cohort was by the Regeneron Genetics Center performed using the Illumina Human Omni Express Exome BeadChip kit.



This work was supported by grants (to Dr J.G. Smith) from the European Research Council (ERC-STG-2015-679242), the Swedish Research Council (2017-02554), the Swedish Heart-Lung Foundation (2016-0134 and 2016-0315), the Crafoord Foundation, Skåne University Hospital, the Scania county, governmental funding of clinical research within the Swedish National Health Service, a generous donation from the Knut and Alice Wallenberg foundation to the Wallenberg Center for Molecular Medicine in Lund, and funding from the Swedish Research Council (Linnaeus grant Dnr 349-2006-237, Strategic Research Area Exodiab Dnr 2009-1039) and Swedish Foundation for Strategic Research (Dnr IRC15-0067) to the Lund University Diabetes Center. Genotyping was funded by the Regeneron Genome Center.

### **Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)**

*Reference PMID: 16141402*

PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) The PIVUS study, initiated in 2002, is a community-based prospective cohort comprising 1016 randomly selected men and women aged 70 years in Uppsala county. Subjects were re-investigated at age 75 and age 80 years. The PIVUS-study is unique in its detailed characterization of vascular and cardiac function and morphology. The cohort is also well characterized with regards to genomics, epigenomics, proteomics and metabolomics. Ten year follow-up data on cardiovascular events and mortality is available. For heart failure cases, the medical records for all individuals with heart failure diagnosis in any position in the Swedish hospital discharge register were reviewed by two physicians who were blinded to the baseline data. They classified the cases as definite, questionable, or miscoded according to the European Society of Cardiology recommendations. They considered ICD heart failure codes 427.00, 427.10, 428 (ICD-9), I50 (ICD-10) and hypertensive heart disease with heart failure, I11.0 (ICD-10) as possible diagnosis of heart failure. The study is approved by the ethical committee of Uppsala University.

## **Prevention of RENal and Vascular ENd-stage Disease (PREVEND)**

*Reference PMID: 11004219*

The PREVEND Study is a prospective, observational cohort study, focussed to assess the impact of elevated urinary albumin loss in non-diabetic subjects on future cardiovascular and renal disease. This study started with a population survey on the prevalence of micro-albuminuria and generation of a study cohort of the general population. The goal is to monitor this cohort for the long-term development of cardiac-, renal- and peripheral vascular end-stage disease. For that purpose the participants receive questionnaires on events and are seen every three/four years for a survey on cardiac-, renal- and peripheral vascular morbidity. The population is formed of Groningen inhabitants aged 28 to 75 years, who agreed to give a morning urine sample and to answer a short questionnaire. Of the 85,421 subjects invited to participate, 40,856 responded. The final sample is consisted of 8,592 consenting subjects with a morning urinary albumin concentration (UAC) of >10 mg/L and an a-select sample of those with an UAC <10 mg/L who completed the first screening; half of which were genotyped. The PREVEND study was approved by the local medical ethics committee of the University Medical Center Groningen and conformed to the principles outlined in the Declaration of Helsinki. All participants gave written informed consent.

Heart failure cases were collected using criteria in accordance with the Heart Failure Guidelines of the European Society of Cardiology (ESC). In- and outpatient files were inspected for the presence of heart failure at baseline and for new onset heart failure, by recording signs, symptoms, and objective evidence of heart failure. In total 586 individual cases were identified as suspected heart failure. An endpoint adjudication committee of seven independent experts in the field of heart failure evaluated all cases suspected for the diagnosis of new onset heart failure. Each case was validated by two different experts by reviewing anonymized clinical charts, hospitalization, and physician office records in order to ascertain the incidence of heart failure. In case of consensus, patients were classified as

'definite new onset heart failure', 'definite no new onset heart failure', or 'definite heart failure, with date of onset before time of recruitment in PREVEND'. In case of difference of opinion about an individual case, the committee made a joint decision.

The Prevention of Renal and Vascular Endstage Disease Study (PREVEND) genetics is supported by the Dutch Kidney Foundation (Grant E033), the EU project grant GENECURE (FP-6 LSHM CT 2006 037697), the National Institutes of Health (grant LM010098), the Netherlands organisation for health research and development (NWO VENI grant 916.761.70), and the Dutch Inter University Cardiology Institute Netherlands (ICIN).

### **The Rotterdam Study**

*Reference PMID: 29064009*

The Rotterdam Study is a prospective population-based cohort study that addresses determinants and occurrence of cardiovascular, neurological, ophthalmologic, psychiatric, and endocrine diseases in the elderly. At present the Rotterdam Study incorporates three cohorts that were established in 1989, 2000, 2006, and 2015 respectively. RS-I: The first cohort. In 1989 all residents of Ommoord, a suburb of Rotterdam, aged 55 years and over were invited to participate. A total of 7,983 out of 10,275 men and women entered the study (response rate 78 percent). Baseline data were collected from 1990 until 1993. From 2009 onwards we are seeing these participants for the fifth time.

Assessment of heart failure Prevalent heart failure at baseline was assessed using a validated score, that was based on the heart failure definition of the European Society of Cardiology. More details of the assessment have been described previously. Prevalent heart failure cases were obtained through a database containing hospital discharge diagnoses from all hospitals in the Rotterdam area as of January 1, 1991. Furthermore, all medical records were screened in retrospect for the occurrence of heart failure in most (97%) participants of the Rotterdam Study. With these three methods, information on the presence

of heart failure at baseline was available for all participants. Cases of incident heart failure were obtained by continuously monitoring participants of the Rotterdam Study for the occurrence of heart failure during follow-up through automated linkage with files from general practitioners. Also, we used verified hospital discharge diagnoses for case finding, gathered from all hospitals in the Rotterdam area. The date of incident heart failure was defined as the day of the first occurrence of symptoms suggestive of heart failure, obtained from the medical records, or the day of receipt of a first prescription for a loop diuretic or an ACE inhibitor indicated for treatment of heart failure, whichever came first. The diagnosis of heart failure was classified as definite, probable, possible, or unlikely. Only definite and probable cases were considered in the analyses. In accordance with the criteria of the European Society of Cardiology, definite heart failure was defined as a combination of heart failure diagnosed by a medical specialist and the presence of typical symptoms of heart failure, such as breathlessness at rest or during exertion, ankle edema, and pulmonary crepitations, confirmed by objective evidence of cardiac dysfunction (chest X-ray, echocardiography). Probable heart failure was defined as heart failure diagnosed by a general practitioner, with at least two typical symptoms suggestive of heart failure, and at least 1 of the following: history of cardiovascular disease, response to treatment of heart failure, or objective evidence of cardiac dysfunction, whereas symptoms could not be attributed to another underlying disease. Two research physicians independently classified all information on potential heart failure events. If there was disagreement, a consensus was reached in a separate session. Finally, a cardiologist verified all probable cases, and all cases in which the two physicians could not reach consensus. If the cardiologist disagreed with the research physicians, the cardiologist's judgment was considered decisive.

### **Study of Health in Pomerania (SHIP)**

*Reference PMID: 20167617*

The Study of Health in Pomerania (SHIP) is a population-based project in West Pomerania, the north-east area of Germany. A sample from the population aged 20 to 79 years was drawn from population registries. First, the three cities of the region (with 17,076 to 65,977 inhabitants) and the 12 towns (with 1,516 to 3,044 inhabitants) were selected, and then 17 out of 97 smaller towns (with less than 1,500 inhabitants), were drawn at random. Second, from each of the selected communities, subjects were drawn at random, proportional to the population size of each community and stratified by age and gender. Only individuals with German citizenship and main residency in the study area were included. Finally, 7,008 subjects were sampled, with 292 persons of each gender in each of the twelve five-year age strata. In order to minimize drop-outs by migration or death, subjects were selected in two waves. The net sample (without migrated or deceased persons) comprised 6,267 eligible subjects. Selected persons received a maximum of three written invitations. In case of non-response, letters were followed by a phone call or by home visits if contact by phone was not possible. The SHIP population finally comprised 4,308 participants (corresponding to a final response of 68.8%). Nonfasting blood samples were drawn from the cubital vein in the supine position. The samples were taken between 07:00 AM and 04:00 PM, and serum aliquots were prepared for immediate analysis and for storage at -80 °C in the Integrated Research Biobank (Liconic, Liechtenstein). The SHIP samples were genotyped using the Affymetrix Genome-Wide Human SNP Array 6.0 whereas 4070 samples were available for subsequent analysis after QC.

For these analyses heart failure was defined according to a modified Rotterdam definition. Prevalent HF cases in SHIP were defined as having history of HF (either chest pain during exercise, bypass, heart transplant, atrial flutter or fibrillation, LV hypertrophy in individuals aged 45 or older, known MI) and HF symptoms (dyspnea at exercise or swollen legs at evening) that were not related to bronchitis (bronchitis that occurred recently or during the last 12 months). The medical ethics committee of the University of Greifswald approved the

study protocol, and oral and written informed consents were obtained from each of the study participants.

SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania, and the network 'Greifswald Approach to Individualized Medicine (GANI\_MED)' funded by the Federal Ministry of Education and Research (grant 03IS2061A). Genome-wide data have been supported by the Federal Ministry of Education and Research (grant no. 03ZIK012) and a joint grant from Siemens Healthineers, Erlangen, Germany and the Federal State of Mecklenburg- West Pomerania. The University of Greifswald is a member of the Caché Campus program of the InterSystems GmbH.

## **TwinGene**

*Reference PMID: 23137839*

TwinGene is a population-based cohort within the Swedish Twin Registry. TwinGene participants were born between 1911 and 1958, they had previously participated in the Screening Across the Lifespan Twin (SALT) study, a computer-assisted telephone interview conducted between 1998 and 2002. During 2004 and 2008, ~12000 TwinGene participants donated their blood at the local health care facility after overnight fasting, and their height, weight, hip and waist circumference, as well as their blood pressures were measured. The zygosity was identified by self-reported childhood resemblance and DNA markers. Both twins within a pair had to be alive and consent for future participation. We define heart failure (HF) by using the international classification of diseases (ICD) code as below: ICD10: I50, and ICD8, ICD9: 428. Ethical permits for TwinGene project had been approved in 2007 (Dnr: 2007/644-3) and amended in 2012 (Dnr: 2012/257-32).

TwinGene received funding from the Swedish Research Council (M-2005-1112), GenomEUtwin (EU/QLRT-2001-01254; QLG2-CT-2002-01254), NIH DK U01-066134, The Swedish Foundation for Strategic Research (SSF) and the Heart and Lung foundation no. 20070481. TwinGene is part of the Swedish Twin Registry which is managed by Karolinska Institutet and receives funding through the Swedish Research Council (2017–00641).

### **UK Biobank**

*Reference PMID: 25826379, 30305743*

The UK Biobank is a large, population-based prospective cohort with extensive genetic and phenotypic data collected on approximately 500,000 individuals aged 40–69 years recruited from across the UK between 2006 and 2010. Collected information include socio-demographics, lifestyle, and health-related factors, physical measures, biological samples (blood, urine, and saliva) for genomics and biochemical markers assessments, linked electronic health records, disease registers, and death register, with a planned repeat assessments and multi-modal imaging. The UK Biobank genetic data contains genotypes for 488,377 participants assayed using two very similar genotyping arrays with extensive phasing and genotype imputation.

### **Uppsala Longitudinal Study of Adult Men (ULSAM)**

*Reference PMID: 1216390, 23555974*

The ULSAM study (Uppsala Longitudinal Study of Adult Men): Longitudinal community based cohort study of 50 year old men that started in 1970 (n=2322). All 50 year old men in Uppsala were invited to participate. Subjects were reinvestigated at the ages of 60, 70, 77, 82 and 88 years. GWAS data is available in approximately half of the study sample. Untargeted metabolomics and proteomics data is available both in serum and urine in subsamples of the cohort. A large number of cardiovascular events and mortality data is available with more than 20 years of follow-up. Heart failure was defined as in PIVUS. The study was approved by the ethical committee of Uppsala University.

## **Women's Genome Health Study (WGHS)**

*Reference PMID: 18070814*

The Women's Genome Health Study (WGHS) is a prospective cohort of initially healthy, female North American health care professionals at least 45 years old at baseline representing participants in the Women's Health Study (WHS) who provided a blood sample at baseline and consent for blood-based analyses. The WHS was a 2x2 trial beginning in 1992-1994 of vitamin E and low dose aspirin in prevention of cancer and cardiovascular disease with about 10 years of follow-up. Since the end of the trial, follow-up has continued in observational mode. Additional information related to health and lifestyle were collected by questionnaire throughout the WHS trial and continuing observational follow-up. WGHS genetic data are currently not publically accessible. Genetic analysis in the WGHS has been approved by the IRB of Brigham and Women's Hospital.

Heart failure cases were ascertained by cardiologists from medical records. Cases of incident nonfatal HF were confirmed if either the Framingham Heart Study (mainly physical examination and radiographic data) or Cardiovascular Health Study criteria (predominantly based on the treating physician's diagnosis and use of specific therapy) were met. Fatal HF cases included those not identified as a case of HF prior to death and classified into "Definite" or "Probable" fatal HF based on medical records and death certificate with next-of-kin or physician confirmation.

Information on left ventricular ejection fraction (LVEF) within 3 months of the diagnosis of incident HF was collected from medical record review and based on diagnostic tests performed closest to the date of diagnosis of incident HF derived from echocardiography or left ventriculography. Data were collected primarily as continuous variables, and, if the report described ejection fraction as a range, the midpoint value was used. If the degree of impairment of systolic function was described qualitatively, we classified "none" or "mild" left



ventricular dysfunction as having LVEF  $\geq 50\%$  and “moderate” or “severe” systolic dysfunction as having LVEF  $< 50\%$ . We defined systolic HF as incident HF occurring in the setting of LVEF  $< 50\%$  and HF with normal ejection fraction (or “diastolic” HF) as incident HF occurring in the setting of LVEF  $\geq 50\%$ .

The WGHS is supported by the National Heart, Lung, and Blood Institute (HL043851 and HL080467, HL099355) and the National Cancer Institute (CA047988 and UM1CA182913), with collaborative scientific support and funding for genotyping provided by Amgen.

### **DiscovEHR**

*Reference PMID: 26866580, 28008009*

DiscovEHR is a collaboration between Regeneron Genetics Center and Geisinger Health System. The population is derived from patients who have previously consented to participate in the Geisinger MyCode Community Health Initiative. MyCode is an IRB-approved research study, and all participants have provided informed consent for broad use of samples for research. Participants are broadly recruited to MyCode from both primary and specialty care clinics across the Geisinger system. Heart failure was defined from ICD-10 codes of I50 and all child terms. All other participants were used as controls.

We acknowledge and thank all participants in Geisinger’s MyCode Community Health Initiative for their support and permission to use their health and genomic information in the DiscovEHR collaboration. This work was supported by the Regeneron Genetics Center and Geisinger.

### **Bio-SHiFT**

*Reference PMID: 29421013, 30760105, 29191357*

The ‘Serial Biomarker Measurements and New Echocardiographic Techniques in Chronic Heart Failure Patients Result in Tailored Prediction of Prognosis’ (Bio-SHiFT) study is a prospective, observational study of 398 stable outpatients with chronic heart failure (CHF)

conducted in Erasmus MC, Rotterdam, the Netherlands, and Northwest Clinics, Alkmaar, the Netherlands. Patients were recruited during their regular outpatient visits and were in clinically stable condition. In brief, patients were eligible if CHF (including HF with preserved ejection fraction) was diagnosed  $\geq 3$  months ago according to the guidelines of the European Society of Cardiology. This study was approved by the medical ethics committee of the Erasmus MC, Rotterdam, the Netherlands, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. The study is registered in ClinicalTrials.gov, number NCT01851538.

During follow-up, hospitalizations for HF, myocardial infarction (MI), percutaneous coronary interventions (PCIs), coronary artery bypass grafting (CABG), arrhythmias, and cerebrovascular accidents (CVAs), as well as cardiac transplantation, left ventricular assist device (LVAD) implantation, and mortality, were recorded in the electronic case report form by trained research physicians, and associated hospital records and discharge letters were collected. Subsequently, hospital records and discharge letters were reviewed by a clinical event committee blinded to the biomarker results, and primary and secondary end points were adjudicated. The primary end point comprised the composite of cardiac death, cardiac transplantation, LVAD implantation, and hospitalization for HF, whichever occurred first in time. Secondary end points included individual components of the primary end point and also MI, PCI, CABG, CVA, and all-cause mortality. The study was supported by the Jaap Schouten Foundation and the Foreest Medical School. Funding for genotyping was provided by Servier as part of the IMI BigData@Heart program.

### **Henry Ford Pharmacogenomic Registry (HFPGR)**

*Reference PMID: 29739794*

The Henry Ford Heart Failure Pharmacogenomic Registry (HFPGR) was approved by the Institutional Review Board at the Henry Ford Health System, and all patients gave written informed consent prior to participation. This registry study of heart failure (HF) patients was created with the overall goal of discovering novel ways to better predict prognosis and

response to HF treatments. Enrollment in the registry started in October 2007 and completed in March 2015 at the Henry Ford Health System, which is a vertically integrated health system serving the primary and specialty health care needs of individuals in southeastern Michigan, USA. Patients were invited into study if they were 18 years of age or older, insured, and met the definition for HF as defined by the Framingham Heart Study. Patients were excluded from the registry if they were receiving dialysis or chronically dependent on supplemental oxygen. Detailed phenotypic information (e.g., demographics, physical examination, past medical history, laboratory values, functional status, medications) and blood samples were collected upon enrollment into the HF registry. Patient deaths were collected from the Social Security Administration Death Master File, Michigan State Division of Vital Records, and the Henry Ford Health System administrative data. Overall the registry enrolled 1760 patients who met inclusion and exclusion criteria, of whom 860 self-identified as white/European ancestry. Among these patients 523 had left ventricular ejection fraction <50% (assessed by any modality). The study was funded in part by the Fund for Henry Ford Hospital and a grant from the National Institutes of Health (R01HL103871, Lanfear).

## **TRIUMPH**

*Reference PMID: 29096809, 29187387*

TRIUMPH was designed as a translational bench-to-bedside study program encompassing the entire spectrum of biomarker discovery to clinical validation. The clinical validation study was an observational prospective study enrolling patients admitted with acute HF in 14 hospitals in the Netherlands between September 2009 and December 2013. This cohort study was designed to validate the clinical value of biomarkers successfully passing the bioinformatics and early validation stages of TRIUMPH, as well as to evaluate more established biomarkers of HF further. There was a particular interest in the change in biomarker levels over time, as well as in the analyses and prognostic significance of repeated biomarker sampling during the follow-up of patients with HF. The study was approved by the medical ethics committees at all participating centers.

Patients  $\geq 18$  years of age were eligible for enrollment if they were hospitalized with decompensation of known chronic HF or newly diagnosed HF. Furthermore, 3 other criteria had to be met: 1) natriuretic peptide levels had to be elevated to  $\geq 3$  times the upper limit of normal; 2) there had to be evidence of sustained systolic or diastolic left ventricular dysfunction; and 3) patients had to be treated with intravenous diuretics. Patients with HF that was precipitated by a noncardiac condition, by severe valvular dysfunction without sustained left ventricular dysfunction, or by an acute ST-segment elevation myocardial infarction were excluded. Furthermore, patients scheduled for a coronary revascularization procedure, on a waiting list for heart transplantation, with severe renal failure for which dialysis was needed, or with a coexisting condition with a life expectancy  $< 1$  year could not participate. All study participants provided written informed consent.

Information on vital status and hospital readmissions was obtained until at least 9 months with a maximum of 400 days after the index hospitalization. We approached the civil registry, screened all medical records, and asked patients for information during their follow-up visits.

The primary endpoint was the composite of all-cause mortality and readmission for HF.

Readmission for HF was defined as an unplanned rehospitalization resulting from decompensation of HF, with at least 2 of the following 3 criteria being present: elevated natriuretic peptide levels  $\geq 3$  times the upper limit of normal; symptoms of cardiac decompensation (rales, edema, or elevated central venous pressure); and treatment with intravenous diuretics. Secondary endpoints included the individual components of the primary endpoint and cardiovascular mortality. An event adjudication committee, blinded to biomarker information, was established for reviewing and adjudication of endpoints.

This work received support from the Center for Translational Molecular Medicine, project TRIUMPH (grant 01C-103). Funding for genotyping was provided by Servier as part of the IMI BigData@Heart program.

**A systems BIOlogy Study to TAIlored Treatment in Chronic Heart Failure (BIOSTAT-CHF)**

*Reference PMID: 28329163, 27126231*

BIOSTAT-CHF was a multicentre, multinational, prospective, observational study. The validation cohort consisted of 1,738 patients recruited from 6 hospitals in Scotland from 2010-2014. Heart failure cases were 18 years or older, had previously been diagnosed with heart failure, had a previous documented admission with heart failure requiring diuretic treatment, and were treated with a furosemide dose of at least 20 mg per day or equivalent. Controls were only available within the validation cohort, and consisted of non-diabetic individuals who had never undergone echocardiography and never had a loop diuretic prescription. Moreover, non-HF controls had never been admitted in hospital for HF. The study was approved by the ethics committees of the local sites. This project was funded by a grant from the European Commission (FP7-242209-BIOSTAT-CHF; EudraCT 2010–020808–29).

### **The Copenhagen Cardiovascular Genetic study (COGEN)**

*Reference PMID: -*

The Copenhagen Cardiovascular Genetic study (COGEN) is a biobank that has collected superfluous whole blood from patients admitted to six cardiology departments in the Capital region of Copenhagen from 2010-2017. Inclusion criteria for cases: patients  $\geq 18$  years, LVEF  $< 40\%$  or symptoms of clinical HF assessed by a physician including NYHA  $> 1$ .

Exclusion criteria: patients with cardiac valvular pathology (e.g. aortic stenosis), HTx, PAH or other structural heart disease.

Inclusion criteria for controls: patients  $\geq 18$  years, LVEF  $\geq 50\%$ . Exclusion criteria for controls: symptoms of clinical HF assessed by a physician including NYHA  $> 1$ , patients with cardiac valvular pathology (e.g. aortic stenosis), HTx, PAH or other structural heart disease. All data were de-identified prior to analyses. The ethics committee of Region North Jutland (N-20140048) approved the project and COGEN has permission from the Data Protection Agency (00916 GEH-2010-001). The COGEN was funded by the Gentofte Hospital, Denmark.

## **Genetics of Diabetes Audit and Research Tayside Scotland (GoDARTS)**

*Reference PMID: 29025058, 9329309*

GoDARTS is a cohort study of 18,306 participants, 10,149 with type 2 diabetes and 8157 healthy controls at baseline recruited from 1996 to 2009 in Tayside, Scotland. Genetic data are available for 8,564 T2D cases and 4,586 controls. Overall, 53.33% of the cohort are male. The majority of the cohort are Caucasian (99.70%) and the median age at recruitment was 64 years. Patients consented to electronic health record linkage to allow follow-up on mortality, hospitalisations and investigations including echocardiography. HF cases met at least one of the below criteria: 1. Echocardiographic evidence of left ventricular systolic impairment and diuretic prescription, 2. Admission to hospital with HF and receipt of a loop diuretic prescription. Patients with Type 2 Diabetes were identified from the demographic database according to data within the 'diabetes type' field. Patients who were never prescribed a loop diuretic were not classified as HF cases. Date of HF diagnosis was taken as either the date of the earliest echocardiogram or the date of the earliest admission to hospital for HF. Non-HF controls were defined as individuals with T2DM who had never undergone echocardiography and never had loop diuretic prescription. Moreover, non-HF controls had never admitted in hospital for HF. The study was approved by the East of Scotland Research Ethics Committee.

The Wellcome Trust United Kingdom Type 2 Diabetes Case Control Collection (supporting GoDARTS) was funded by the Wellcome Trust (072960/Z/03/Z, 084726/Z/08/Z, 084727/Z/08/Z, 085475/Z/08/Z, 085475/B/08/Z) and as part of the EU IMI-SUMMIT programme. We acknowledge the support of the Health Informatics Centre, University of Dundee, for managing and supplying the anonymized data and NHS Tayside, the original data owner.

## **The Genetic Risk Assessment of Defibrillator Events (GRADE)**

*Reference PMID: 22004663, 29892015*

GRADE (The Genetic Risk Assessment of Defibrillator Events) study, designed to identify genetic modifiers of arrhythmic risk. Inclusion criteria were: patients who were  $\geq 18$  years of age with a diagnosis of at least moderate systolic left ventricular dysfunction ( $EF \leq 30\%$ ), and who had an ICD at the University of Pittsburgh Medical Center, Emory University Medical Center, Massachusetts General Hospital, Ohio State University Medical Center, Mid-Ohio Cardiology or the Pittsburgh Veterans Affairs Medical Center. Subjects were excluded if they had intractable Class IV heart failure, and conditions (other than HF) that were expected to limit survival to less than 6 months. The institutional review boards of participating medical centers approved the study and each patient gave written informed consent prior to participation. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and the trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT 02045043). Controls were European ancestry AF-free controls from the Broad AF study with no diagnosis of heart failure. GRADE was funded by NIH-NHLBI R01 HL77398 (Genetic Modulators of Sudden Death).

### **The Ludwigshafen Risk and Cardiovascular Health (LURIC) study (LURIC)**

*Reference PMID: 11258203*

The Ludwigshafen Risk and Cardiovascular Health (LURIC) study is a monocentric hospital based prospective study including 3316 individuals referred for coronary angiography recruited in the Ludwigshafen Cardiac Center, southwestern Germany from 1997 – 2000. Clinical indications for angiography were chest pain or a positive non-invasive stress test suggestive of myocardial ischemia. To limit clinical heterogeneity, individuals suffering from acute illnesses other than acute coronary syndrome, chronic non-cardiac diseases and a history of malignancy within the five past years were excluded. All participants were completed a detailed questionnaire which gathered information on medical history, clinical, and lifestyle factors. Fasting blood samples were obtained by venipuncture in the early morning and stored for later analyses. Samples were genotyped on an Affymetrix 6.0 array. Variants with a call rate less than 0.98, Hardy-Weinberg Equilibrium  $P < 5 \times 10^{-4}$ , and MAF  $<$

0.01 were removed. Imputation was performed using the 1000 Genomes Project reference panel with IMPUTE 2.

A clinical diagnosis of (left) heart failure was defined by the combined presence of symptoms of dyspnea on exertion and cardiac disease with impaired left ventricular function. Left ventricular dysfunction or impaired left ventricular function was defined by imaging techniques, such as echocardiography and left ventricular angiography, and graded semi-quantitatively into normal, minimal, moderate and severe impairment of left ventricular pump function. Based on the underlying cardiac disease, heart failure/left ventricular dysfunction was either of ischaemic (in case of CAD) or of non-ischaemic origin (dilated cardiomyopathy being the most frequent non-CAD disease). Mis- or underreporting of heart failure and/or left ventricular dysfunction was avoided in LURIC since virtually all LURIC participants, except for family members without coronary angiography, underwent echocardiography and left ventricular angiography. HF with preserved ejection fraction was defined as symptoms and signs of HF, a preserved left ventricular function with an ejection fraction >45% (echocardiographic or invasive) and the presence of diastolic HF according to the definition published by Paulus et al. (How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;28:2539–2550). In particular, diastolic dysfunction was diagnosed in 388 patients (85%) based on haemodynamic criteria (mean pulmonary capillary wedge pressure >12mmHg or a left ventricular end-diastolic pressure >16 mmHg). In the remaining 71 patients (15%) diastolic dysfunction was identified by an elevated NT-proBNP concentration (>220 pg/mL) and electrocardiographic evidence of atrial fibrillation

Study protocols were approved by the ethics committee of the "Landesärztekammer Rheinland-Pfalz" and the study was conducted in accordance with the "Declaration of Helsinki". Informed written consent was obtained from all participants.



## **Penn Heart Failure Study**

*Reference PMID: 29540468, 21248228*

A case-control genome-wide association study comparing patients with prevalent heart failure referred for evaluation and treatment at a heart failure specialty center. Prevalent heart failure diagnosed by a heart failure cardiologist based on clinical evaluation and cardiac imaging. Controls were patients from the same referral center with no reported diagnosis of Heart Failure (ICD-9 of 428.xx or ICD10 of I50.xx). Local ethics approval was obtained. Funded by the NIH (NIH R01L088577, NIH R01H105993).

## **dal-OUTCOMES**

*Reference PMID: 23126252*

The dal-OUTCOMES study was a phase 3 randomized, double-blind comparison of dalcetrapib, a cholesteryl ester transfer protein inhibitor, to placebo in 15 871 patients with recent ACS. Trial design and principal results have been described previously (23126252; 19958854) The trial was performed between April 2008 and September 2012 at 935 sites in 27 countries. Qualifying patients were randomly assigned to receive dalcetrapib, 600 mg daily, or matching placebo, beginning 4 to 12 weeks after an index ACS event, when they were clinically stable and had completed all planned coronary revascularization procedures. Major exclusion criteria included New York Heart Association class III or IV symptoms of heart failure or class II symptoms if the left ventricular ejection fraction was found to be 40% or less, uncontrolled hypertension, a triglyceride level higher than 400 mg/dL, hemoglobin A1c >10%, liver disease, or creatine phosphokinase levels >3 times the ULN. Evidence-based treatments, including statins, were encouraged for all patients. Hospitalization for congestive heart failure was determined from the case report file adverse events and verified for non-overlap with a primary composite event date. The institutional review board of each site approved the trial. There were 6338 participants to the pharmacogenomics study, recruited from April 2008 through July 2010 at 461 sites in 14 countries. All participants

provided written informed consent to participate to the genetic study of the dal-OUTCOMES trial. The trial and the genomic study were funded by Hoffmann–La Roche.

### **ENGAGE AF-TIMI48**

*Reference PMID: 24251359*

A 3-arm randomized, double-blind, double-dummy trial comparing two doses of edoxaban to placebo. All patients in the trial had atrial fibrillation requiring anticoagulation. Co-morbidities include diabetes (38%), stroke/TIA (28%), and congestive heart failure (57%).

### **Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)**

*Reference PMID: 12668699*

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) was a randomized, placebo-controlled clinical trial of eplerenone that enrolled a total of 6,642 patients in 37 countries between 1999 and 2001 (Pitt et al., 2003).

Participants were randomized within 3-14 days following a documented acute myocardial infarction with left ventricular dysfunction, demonstrated by left ventricular ejection fraction  $\leq$  40% and clinical evidence of heart failure. Participants were followed up an average of 16 months. Eplerenone was developed by Pharmacia, which was later acquired by Pfizer, and eplerenone is marketed as Inspra. EPHESUS cases from the placebo arm of the trial with informed consent for genetic studies were genotyped on the Illumina Omni Express+Exome array. The controls (A9011027) were recruited in a multi-site, cross-sectional, non-treatment prospective trial to collect data, including DNA, from elderly subjects in the US who were cognitively normal and free of psychiatric diseases or clinically significant cardiovascular disease. Controls were genotyped on the Illumina Quad 660. Eighty-six controls were re-genotyped on the Illumina Omni Express+Exome array for the purpose of extensive SNP quality control comparing arrays. After sample QC, 1091 heart failure cases and 886 controls were used in GWAS analysis adjusting for sex and principle components. Due to

the older age of the control group, age was not associated with heart failure and not included in the GWAS model.

Patients in whom the following criteria were met were eligible for randomization 3 to 14 days after acute myocardial infarction: acute myocardial infarction as documented according to standard criteria; left ventricular dysfunction as documented by a left ventricular ejection fraction of 40 percent or lower on echocardiography, radionuclide angiography, or angiography of the left ventricle after the index acute myocardial infarction and before randomization; and heart failure as documented by the presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound. In patients with diabetes who met the criteria for left ventricular dysfunction after acute myocardial infarction, symptoms of heart failure did not have to be demonstrated, since such patients have an increased risk of cardiovascular events similar to that of nondiabetic patients with symptoms of heart failure.

## **IDEAL**

*Reference PMID: 16287954*

The Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) was a prospective, randomized, open, blinded end-points design comparing simvastatin 20 to 40 mg/day (n = 4,449) with atorvastatin 80 mg/day (n = 4,439) in men and women  $\leq 80$  years of age and with a history of definite myocardial infarction (MI). The study was carried out in 190 centers in the Nordic countries and The Netherlands, recruitment and randomization were carried out from March 1999 to March 2001, and patients were followed-up until March 2005. History of HF and other co-morbid conditions was established from patient records and patients did not undergo specific assessment of cardiac function as part of the baseline evaluation. Patients had to qualify for statin therapy according to national guidelines at time of recruitment. Patients previously treated with statins were eligible if they were using a dose no higher than an equivalent of simvastatin 20 mg/day. Exclusion criteria included HF with

New York Heart Association (NYHA) classification IIIb or IV and hemodynamically important valvular heart disease. Hospitalization with a primary diagnosis of HF was prespecified as a secondary study outcome. Objective evidence of HF had to be assessed by echocardiography, chest x-ray, angiography, or radionuclide angiography as diagnosed before or during hospitalization. Those symptoms and signs had to lead to acute hospitalization for >24 hours and with a requirement of intravenous treatment for HF or an increase >50% of any medication currently being administered to treat HF. The institutional review board at each participating center approved the study, and all patients gave written informed consent. The genomic study was approved by the research ethics committee of the Montreal Heart Institute. The TNT trial was funded by Pfizer. The genomic study was funded in part by grants from Genome Quebec, Genome Canada, The Quebec Government (Ministère de l'économie et de l'innovation) and the Canadian Institutes of Health Research to the Montreal Heart Institute.

#### **PEGASUS-TIMI54**

*Reference PMID: 24655690, 25773268*

A multinational, randomized, double-blind, placebo-controlled trial of the efficacy of ticagrelor in stable ischemic heart disease among patients with prior MI. Co-morbidities included smoking (17%), hypertension (78%), diabetes (32%), prior PCI (83%), and prior CABG (60%).

#### **PROspective Study of Pravastatin in the Elderly at Risk for vascular disease (PROSPER)**

*Reference PMID: 10569329, 12457784, 21977987*

All data come from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). A detailed description of the study has been published elsewhere. PROSPER was a prospective multicenter randomized placebo-controlled trial to assess whether treatment with pravastatin diminishes the risk of major vascular events in elderly. Between December 1997

and May 1999, we screened and enrolled subjects in Scotland (Glasgow), Ireland (Cork), and the Netherlands (Leiden). Men and women aged 70-82 years were recruited if they had pre-existing vascular disease or increased risk of such disease because of smoking, hypertension, or diabetes. A total number of 5,804 subjects were randomly assigned to pravastatin or placebo. A large number of prospective tests were performed including Biobank tests and cognitive function measurements.

We examined incident heart failure hospitalization and cardiovascular mortality as previously defined. Heart failure hospitalizations were defined based on a combination of symptoms (e.g. shortness of breath) and signs, including chest radiograph with fluid congestion or echocardiogram with severely diminished LV function. All outcomes were adjudicated by an expert committee blinded to randomized study medication and using pre-defined criteria.

The study was approved by the institutional ethics review boards of centres of Cork University (Ireland), Glasgow University (Scotland) and Leiden University Medical Center (the Netherlands) and all participants gave written informed consent.

The PROSPER study was supported by an investigator initiated grant obtained from Bristol-Myers Squibb. Support for genotyping was provided by the seventh framework program of the European commission (grant 223004) and by the Netherlands Genomics Initiative (Netherlands Consortium for Healthy Aging grant 050-060-810).

### **SAVOR-TIMI53**

*Reference PMID: 22093196, 23992601*

A multi-national, randomized, double-blind, placebo-controlled trial randomizing saxagliptin to placebo in diabetics. Co-morbidities include atherosclerosis (78%), HTN (81%), and heart failure (13%).

### **Stabilization of Plaque using Darapladib-Thrombolysis in Myocardial Infarction 52**

#### **(SOLID-TIMI52)**

*Reference PMID: -*

The SOLID-TIMI 52 was a multinational, double-blind trial that enrolled 13,026 participants who had been hospitalized with an acute coronary syndrome event in the past 30 days and randomized them to once daily darapladib or placebo for a median follow-up of 2.5 years (7). The primary endpoint was CHD death, MI or urgent coronary revascularization. In each country, the study was approved by national regulatory authorities and by local ethics committees or institutional review boards, according to local regulations. This study did not meet its primary endpoint (PMID: 25173516). Clinical and genetic data can be requested from GSK (<https://www.clinicalstudydatarequest.com/>).

Heart failure status at enrolment was identified from medical record with no specific definition. I HF hospitalizations adjudicated during follow up were defined as admission to hospital or attendance at an acute health care facility for administration of intravenous diuretic treatment, escalation of diuretic doses, and/or inotropes. Confirmation of heart failure diagnosis was obtained by chest imaging demonstrating pulmonary congestion or edema, or, in patients without available chest imaging, at least one of the following: Pulmonary edema, (i.e. rales >1/3 up the lung fields thought to be of cardiac causes), pulmonary capillary wedge pressure >18 mmHg or BNP >500 pg/ml (or NT-terminal prohormone BNP >2500 pg/ml).

## **TNT**

*Reference PMID: 15755765*

The Treating to New Targets (TNT) trial included 10 001 patients with stable coronary heart disease (CHD) and LDL-C levels <130 mg/dL (3.4 mmol/L) randomly assigned to receive either 10 or 80 mg of atorvastatin per day and were followed up for a median of 4.9 years. Eligible patients were men and women 35 to 75 years of age with clinically evident CHD, defined as previous MI, prior or current angina with objective evidence of CHD, or a history of coronary revascularization. Major exclusion criteria included significant liver disease, uncontrolled diabetes, hypothyroidism, or hypertension, unexplained creatine phosphokinase levels >6 times the upper limit of normal, or an acute coronary syndrome within 1 month of

screening. History of HF was determined through questionnaires administered at the time of study enrollment. Patients with New York Heart Association class IIIb or IV HF or with a left ventricular ejection fraction known to be <30% were excluded. Patients did not undergo an assessment of left ventricular function as part of their baseline evaluation for the trial.

Hospitalization for a primary diagnosis of HF was a predefined secondary efficacy outcome of the study and was defined based on hospital admission for diagnosis of HF for which the cause of HF was related to impaired left ventricular emptying or filling characteristics and not temporally related to an acute MI. The institutional review board at each participating center approved the study, and all patients gave written informed consent. After approval by the institutional review committee, informed consent for genetic analysis was sought on and 5966 DNA samples were obtained from consenting individuals. The TNT trial was funded by Pfizer. The genomic study was funded in part by grants from Genome Quebec, Genome Canada, The Quebec Government (Ministère de l'économie et de l'innovation) and the Canadian Institutes of Health Research to the Montreal Heart Institute.

## **ACTION-HF**

*Reference PMID: 22560018*

The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study was a randomized clinical trial that took place at 82 centers within the United States, Canada, and France from April 2003 through February 2007, enrolling a total of 2331 patients. The primary objective of the trial was to compare usual HFrEF care to usual HFrEF care plus exercise training, but it included a genetic sub-study. The trial included adult HFrEF patients with LVEF  $\leq$  35% and NYHA class II to IV symptoms despite optimal heart failure therapy for at least 6 weeks. In primary analysis, exercise training resulted in non-significant reductions in the primary end point of all-cause mortality or hospitalizations although in the prespecified adjusted analysis, the exercise intervention significantly reduced the composite primary outcome. The institutional review boards of participating medical centers approved the study and each patient gave written informed consent prior to

participation. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and the trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT00047437). The HF-ACTION trial was funded by the National Institutes of Health and the National Heart, Lung, and Blood Institute, Bethesda, MD. There was a genetic sub-study which included 1018 of the participants, of which 966 had high quality genome-wide array data generated. Participants self-identified as European ancestry/white with full data were included in the current survival analysis (n=584).

### **ATHENA-HF**

*Reference PMID: 28700781, 27522631*

ATHENA-HF was a multicentre, randomized, placebo-controlled trial that tested if a high-dose of spironolactone given early during an episode of acute HF can improve NT-proBNP levels at 96 hours among patients hospitalized for decompensated HF, in addition to standard care (NCT02235077). Individuals not taking spironolactone prior to the hospitalisation were randomized to 100 mg spironolactone or placebo, while patients taking low-dose spironolactone (12.5-25 mg/day; patients receiving > 25 mg were excluded) before the hospital admission were randomized to 100 mg or 25 mg per day in the usual care arm. The study drug was given for up to 96 hours. Secondary endpoints included a clinical congestion score, dyspnea relief, daily cumulative net urine output for up to 96 hours (or discharge, whichever came first), net weight change from baseline to 96 hours (or discharge, whichever came first), the development of in-hospital worsening HF. Exploratory end points included a day-30 postrandomization composite of rates of all-cause mortality, all-cause readmission, or outpatient worsening HF.

Briefly, patients were eligible to participate in the study if they had a clinical diagnosis of HF with at least 1 sign and 1 symptom of AHF and with a NT-proBNP level  $\geq 1000$  pg/mL or BNP level  $\geq 250$  pg/mL, regardless of LVEF, measured within 24 hours of randomization. Other



key inclusion criteria included having a serum potassium  $\leq 5.0$  mmol/L, an estimated glomerular filtration rate  $\geq 30$  mL/min/1.73m<sup>2</sup> and a systolic blood pressure  $>90$  mm Hg.

The ATHENA-HF study was approved by all local IRBs and all patients provided a written consent to participate in the study. Moreover, in centers electing to participate in the genomics/pharmacogenomics sub-study of the HFN clinical trials, the sub-study was approved by the IRB at each site. Patients taking part in the ATHENA-HF trial in these participating centers were offered the possibility to participate in the genetics sub-study. All participants willing to participate in the substudy provided written informed consent.

This study was conducted by the Heart Failure Clinical Research Network. It was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award U10 HL084904 (for the Coordinating Center) and awards U10 HL110297, U10 HL110342, U10 HL110309, U10 HL110262, U10 HL110338, U10 HL110312, U10 HL110302, U10 HL110336, and U10 HL110337 (for Regional Clinical Centers).

## **CARRESS-HF**

*Reference PMID: 23131078*

CARRESS-HF was a multicentre, randomized trial that compared ultrafiltration with a strategy of diuretic-based stepped pharmacologic therapy on a bivariate change from baseline in serum creatinine and body weight at 96 hours after randomization (primary endpoint; NCT00608491). Secondary endpoints included the rate of clinical decongestion and measures of global well-being and dyspnea, changes in renal function and electrolytes, net fluid loss from randomization changes in biomarkers, death or rehospitalization at 60 days.

Briefly, patients were eligible to participate in the study if they were hospitalized with a primary diagnosis of acute decompensated HF, irrespective of LVEF. All patients had

worsened renal function (increase in serum creatinine  $\geq 0.3$  mg/dL [ $26.5 \mu\text{mol/L}$ ]) within 12 weeks before or 10 days after the HF admission.

The CARRESS-HF study was approved by all local IRBs and all patients provided a written consent to participate in the study. Moreover, in centers electing to participate in the genomics/pharmacogenomics sub-study of the HFN clinical trials, the sub-study was approved by the IRB at each side. Patients taking part in the CARRESS-HF trial in these participating centers were offered the possibility to participate in the genetics sub-study. All participants willing to participate in the substudy provided written informed consent.

This study was conducted by the Heart Failure Clinical Research Network. It was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award U10 HL084904 (for the Coordinating Center) and awards U10HL084861, U10HL084875, U10HL084877, U10HL084889, U10HL084890, U10HL084891, U10HL084899, U10HL084907, and U10HL084931 (for Regional Clinical Centers).

## **CHARM**

*Reference PMID:* (13678868; 13678870; 13678871; 13678869)

The CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) included 7,599 patients with at least 4-week duration of symptomatic HF (New York Heart Association [NYHA] functional class II to IV) receiving standard therapy and which were enrolled into 1 of 3 component clinical trials according to LVEF and angiotensin-converting enzyme inhibitor (ACE-I) treatment: CHARM-Alternative (n = 2,028, LVEF  $\leq 40\%$  and not receiving an ACE-I due to previous intolerance), CHARM-Added (n = 2,548, LVEF  $\leq 40\%$  receiving ACE-I treatment), and the CHARM-Preserved study (n = 3,023, LVEF  $> 40\%$ ). Important exclusion criteria were serum creatinine 3 mg/dl (265  $\mu\text{mol/l}$ ) or more, serum potassium 5.5 mmol/l or more, known bilateral renal artery stenosis, symptomatic hypotension, critical aortic or mitral stenosis, or recent (in the previous 4 weeks) myocardial

infarction, stroke, or heart surgery. Within each of the component trials, patients were randomly allocated to candesartan or matching placebo, initiated at 4 mg or 8 mg (at the discretion of the investigator) once daily at the enrollment visit. The dose was increased toward the target dose (32 mg once daily) in a stepwise fashion. Follow-up ranged between trials and was 38 months in the overall CHARM Program. Heart failure hospitalization was adjudicated endpoints. A hospital for HF was based on signs and symptoms of worsening heart failure and require treatment with intravenous diuretics. Evidence of worsening heart failure had to include at least one of the following items: increasing dyspnoea on exertion, orthopnoea, nocturnal dyspnoea, pulmonary oedema, increasing peripheral oedema, increasing fatigue or decreasing exercise tolerance, renal hypoperfusion (ie, worsening renal function), raised jugular venous pressure, and radiological signs of CHF. A subset of participants had consented genetic studies, and 3270 DNA samples were shared with the Montreal Heart Institute for genomic analysis. The CHARM Program studies complied with the Declaration of Helsinki and were approved by ethics committees in all participating centres and all patients provided informed consent. The genomic study was approved by the Montreal Heart Institute research ethics committee. The CHARM studies were sponsored by AstraZeneca. Support for genotyping was provided by an unrestricted research grant from AstraZeneca to the Montreal Heart Institute.

## **CORONA**

*Reference PMID: 17984166*

The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial tested the hypothesis that rosuvastatin would reduce the primary composite outcome of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke in patients with chronic symptomatic systolic heart failure of ischemic origins. A total of 5,011 patients  $\geq 60$  years of age in New York Heart Association (NYHA) functional class II, III, or IV were randomized to receive either rosuvastatin (10 mg daily) or placebo, in addition to standard therapy. NYHA class was assessed by investigators at each visit. Major exclusion criteria included

decompensated heart failure, myocardial infarction within the past 6 months, unstable angina or stroke, percutaneous coronary intervention (PCI), or coronary-artery bypass grafting (CABG) within the past 3 months, previous or planned heart transplantation, hypertrophic cardiomyopathy. Hospitalization for heart failure required documentation that worsening heart failure was the principal reason for hospitalization, and if competing reasons were judged to be of equal importance, heart failure received preference. A subset of participants had consented to genetic studies and 3214 DNA samples were shared with the Montreal Heart Institute for genomic analysis. The trial complied with the Declaration of Helsinki and was approved by the Ethics Committees of the participating hospitals. The genomic study was approved by the Montreal Heart Institute research ethics committee. All patients provided written informed consent. The CORONA study was sponsored by AstraZeneca. Support for genotyping was provided by an unrestricted research grant from AstraZeneca to the Montreal Heart Institute.

## **DOSE-AHF**

*Reference PMID: 21366472*

DOSE was a multicentre, randomized, double-blind trial that used a 2x2 factorial design to evaluate multiple diuretic strategies in patients with acute decompensated HF. Patients were randomized to receive furosemide administered intravenously either as bolus every 12 hours or continuous infusion and either at a low dose (the patient's previous oral dose) or a high dose (2.5 times the previous oral dose). The study treatment was given for up to 72 hours. The coprimary endpoints were the patients' global assessment of symptoms and the change in the serum creatinine level from baseline to 72 hours. Secondary endpoints included patient-reported dyspnea, changes in weight and net fluid loss, worsening renal function, changes in biomarker levels as well as clinical end points, including the composite of death, rehospitalization, or an emergency room visit within 60 days.

Briefly, patients were eligible to participate in the study if they had presented within the previous 24 hours with acute decompensated HF, diagnosed on the basis of the presence of at least one symptom and one sign of HF, irrespective of ejection fraction. All patient also had a history of chronic HF treated with an oral loop diuretic for at least 1 month before the hospitalization. Patients with systolic blood pressure < 90 mm Hg or a serum creatinine > 3.0 mg/dL were excluded.

The DOSE study was approved by all local IRBs and all patients provided a written consent to participate in the study. Moreover, in centers electing to participate in the genomics/pharmacogenomics sub-study of the HFN clinical trials, the sub-study was approved by the IRB at each side. Patients taking part in the DOSE trial in these participating centers were offered the possibility to participate in the genetics sub-study. All participants willing to participate in the substudy provided written informed consent.

This study was conducted by the Heart Failure Clinical Research Network. It was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award HL084904 (for the Coordinating Center) and awards HL084861, HL084875, HL084877, HL084889, HL084890, HL084891, HL084899, HL084907, and HL084931 (for Regional Clinical Centers).

## **EXACT-HF**

*Reference PMID: 25986447, 23861505*

EXACT-HF was a multicentre, randomized, placebo-controlled trial that tested if a high-dose of allopurinol (target dose: 600 mg) given for 24 weeks could improve the primary composite endpoint of survival, worsening HF, and patient global assessment compared to placebo (NCT00987415). Secondary endpoints included changes in quality of life assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), the 6-minute walk test, multiple

echocardiographic measurements and biomarkers, as well as time to first HF hospitalization and time to all-cause death or hospitalization.

Briefly, patients were eligible to participate in the study if they had symptomatic HF (LVEF  $\leq 40\%$ ) and elevated serum uric acid ( $\geq 9.5$  mg/dL). Patients were required to have at least 1 additional high-risk marker, including an acute HF event (hospitalization or emergency room visit) within 12 months, severe LV dysfunction (LVEF  $\leq 25\%$ ), or natriuretic peptide (BNP  $> 250$  pg/ml or NT-pro-BNP  $> 1500$  pg/ml).

The EXACT-HF study was approved by all local IRBs and all patients provided a written consent to participate in the study. Moreover, in centers electing to participate in the genomics/pharmacogenomics sub-study of the HFN clinical trials, the sub-study was approved by the IRB at each side. Patients taking part in the EXACT-HF trial in these participating centers were offered the possibility to participate in the genetics sub-study. All participants willing to participate in the substudy provided written informed consent.

This study was conducted by the Heart Failure Clinical Research Network. It was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award U10 HL084904 (for the Coordinating Center) and awards U01HL084861, U10HL110312, U109HL110337, U01HL084889, U01HL084890, U01HL084891, U10HL110342, U10HL110262, U01HL084931, U10HL110297, U10HL110302, U10HL110309, U10HL110336, U10HL110338) (for Regional Clinical Centers); The National Center for Advancing Translational Sciences (UL1TR000454, UL1TR000439); and The National Institute on Minority Health and Health Disparities (8 U54 MD007588).

## **FIGHT**

*Reference PMID: 27483064*

FIGHT was a multicentre, randomized, placebo-controlled trial that tested the effect of the glucagon-like peptide 1 (GLP-1) agonist liraglutide (1.8 mg/day) on the primary end point which was a global rank score based on time to death, time to rehospitalization for HF, and time-averaged proportional change in NT-proBNP from baseline to 180 days (NCT01800968). Secondary and exploratory endpoints included all-cause mortality, rehospitalization for HF, changes in multiple echocardiographic measures from baseline to 180 days, 6-minute walk distances at 30, 90, and 180 days, and changes in the KCCQ clinical summary score.

Briefly, patients were eligible to participate in the study if they had an established diagnosis of HF and a LVEF  $\leq 40\%$ . Moreover, patients had a recent (within 14 days) hospitalization for HF despite already receiving evidence-based therapies and a preadmission oral diuretic dose  $\geq 40$  mg of furosemide (or an equivalent).

The FIGHT study was approved by all local IRBs and all patients provided a written consent to participate in the study. Moreover, in centers electing to participate in the genomics/pharmacogenomics sub-study of the HFN clinical trials, the sub-study was approved by the IRB at each site. Patients taking part in the FIGHT trial in these participating centers were offered the possibility to participate in the genetics sub-study. All participants willing to participate in the substudy provided written informed consent.

This research was supported by grants U10 HL084904 (awarded to the coordinating center) and U01 HL084861, U10 HL110312, U10 HL110337, U10 HL110342, U10 HL110262, U10 HL110297, U10 HL110302, U10 HL110309, U10 HL110336, and U10 HL110338 (awarded to the regional clinical centers) from the National Heart, Lung, and Blood Institute (NHLBI). The study drug (liraglutide) and matching placebo injections were supplied by NovoNordisk Inc.

## **INDIE-HFPEF**

*Reference PMID: 28476756, 30398602*

INDIE-HFpEF was a multicentre, randomized, placebo-controlled trial, crossover trial that evaluated the effects of inorganic nitrite or placebo administered via micronebulizer device. (NCT02742129). The primary end point was peak oxygen consumption. Secondary end points included the Kansas City Cardiomyopathy Questionnaire NYHA functional class, multiple echocardiographic measurements, NT-proBNP and other biomarkers and clinical outcomes.

Briefly, patients aged  $\geq 40$  were eligible to participate in the study if they had a diagnosis of HF, a LVEF  $\geq 50\%$  and objective evidence of HF together with chronic treatment with a loop diuretic. Key exclusion criteria included a systolic blood pressure  $< 115$  mm Hg seated or  $< 90$  mm Hg while standing.

The INDIE-HFpEF study was approved by all local IRBs and all patients provided a written consent to participate in the study. Moreover, in centers electing to participate in the genomics/pharmacogenomics sub-study of the HFN clinical trials, the sub-study was approved by the IRB at each site. Patients taking part in the INDIE-HFpEF trial in these participating centers were offered the possibility to participate in the genetics sub-study. All participants willing to participate in the substudy provided written informed consent.

This study was conducted by the Heart Failure Clinical Research Network. It was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award U10 HL084904 (for the Coordinating Center) U10 HL110312, U10 HL110337, U10 HL110342, U10 HL110262, U10 HL110297, U10 HL110302, U10 HL110309, U10 HL110336, and U10 HL110338 (for the regional clinical centers) and Savara Therapeutics.

## **IRONOUT**



*Reference PMID: 28510680*

IRONOUT was a multicentre, randomized, placebo-controlled trial that tested if oral iron polysaccharide (150 mg twice daily) improves peak exercise capacity in patients with HF. ([NCT02188784](#)). The study drug was given for 16 weeks. The primary endpoint of the study was peak oxygen uptake (peak  $\dot{V}O_2$ ) after 16 weeks of therapy. Secondary end points included multiple exercise-related assessments, 6-minute walk distance, concentrations of NT-proBNP and multiple other biomarker and the KCCQ. Exploratory objectives also included time to death and time to HF hospitalization.

Briefly, patients with stable HF were eligible to participate in the study if they presented a LVEF $\leq$ 40% and NYHA functional class II-IV symptoms, had evidence of iron deficiency (ferritin 15-100 ng/mL or between 100-299 ng/mL with a transferrin saturation <20%) and hemoglobin levels between 9 to 15 g/dL (men) or 9 to 13.5 g/dL (women).

The IRON-OUT study was approved by all local IRBs and all patients provided a written consent to participate in the study. Moreover, in centers electing to participate in the genomics/pharmacogenomics sub-study of the HFN clinical trials, the sub-study was approved by the IRB at each side. Patients taking part in the IRONOUT trial in these participating centers were offered the possibility to participate in the genetics sub-study. All participants willing to participate in the sub-study provided written informed consent.

This study was conducted by the Heart Failure Clinical Research Network. This research was supported by the following NHLBI grants U10 HL084904 (awarded to the coordinating center) and U10HL110337, U10HL110302, U10HL110312, U10HL110262, U10HL110297, U10HL110342, U10 HL110309, U10 HL110336, and U10 HL110338 (awarded to the regional clinical centers).

## **NEAT-HFpEF**

*Reference PMID: 26549714*

NEAT-HFpEF was a multicentre, randomized, placebo-controlled, crossover trial that tested if isorbide mononitrate improved the daily activity level of patients compared to placebo as assessed by patient-worn accelerometers(NCT02053493). Secondary endpoints included additional accelerometer-derived parameters, the 6-minute walk distance, the KCCQ and the Minnesota Living with HF Questionnaire, and NT-proBNP levels. Serious adverse events were also collected.

Briefly, patients with HF were eligible to participate in the study if they were  $\geq 50$  years of age, were receiving stable medical therapy, had an LVEF  $\geq 50\%$  and objective evidence of HF. Key exclusion criteria included a systolic blood pressure  $< 110$  mm Hg or  $> 180$  mm Hg.

The NEAT-HFpEF study was approved by all local IRBs and all patients provided a written consent to participate in the study. Moreover, in centers electing to participate in the genomics/pharmacogenomics sub-study of the HFN clinical trials, the sub-study was approved by the IRB at each side. Patients taking part in the NEAT-HFpEF trial in these participating centers were offered the possibility to participate in the genetics sub-study. All participants willing to participate in the substudy provided written informed consent.

This study was conducted by the Heart Failure Clinical Research Network. The trial was supported by the NHLBI: coordinating center: U10 HL084904; regional clinical centers: U01 HL084861, U10 HL110312, U109 HL110337, U01 HL084889, U01 HL084890, U01 HL084891, U10 HL110342, U10 HL110262, U01 HL084931, U10 HL110297, U10 HL110302, U10 HL110309, U10 HL110336 and U10 HL110338.

**Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF)**

*Reference PMID: 25176015, 23563576*

Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial is a multicenter (1,043 centers in 47 countries), prospective, randomized, comparative trial. A total of 8,399 patients with HFrEF (LVEF  $\leq 40\%$  and  $\leq 35\%$  were used at different points in the trial) and NYHA class II-IV symptoms were randomized to either the ARNI LCZ696 (sacubitril/ valsartan) 200 mg PO BID or enalapril 10 mg PO BID (the goal dose from SOLVD), during 2009-2012. Exclusion criteria include: symptomatic hypotension, SBP  $< 100$  mmHg at screening or  $< 95$  mmHg at randomization, eGFR  $< 30$  mL/min/1.73 m<sup>2</sup>, reduction in eGFR  $> 25\%$  from screening to randomization (amended to  $> 35\%$ ), potassium  $> 5.2$  mmol/L at screening or  $> 5.4$  mmol/L at randomization, history of angioedema, and "Unacceptable side effects" with ACE-inhibitors or ARBs. Doses were adjusted for tolerability. With a median follow-up of 27 months, the trial was stopped following a positive interval efficacy analysis. The ARNI group had a reduction in the primary outcome of CV mortality or HF hospitalization (21.8% vs. 26.5%; NNT 21) as well as each of the individual components. Importantly, the ARNI had a significant reduction in all-cause mortality (17.0% vs. 19.8%; NNT 36). The ARNI was generally well tolerated except for a higher rate of symptomatic hypotension, though not to an increased rate of discontinuation of the therapy due to hypotension. There was no difference in the rates of angioedema. The protocol was approved by the Ethics Committee/Institutional Review Board affiliated to each investigative site. Informed consent was obtained for all participants. PARADIGM-HF trial and sample analysis were supported by Novartis.

Heart failure cases were at least 18 years of age, had New York Heart Association (NYHA) class II, III, or IV symptoms, and an ejection fraction of 40% or less (which was changed to 35% or less by an amendment to the protocol on December 15, 2010). Patients were required to have a plasma B-type natriuretic peptide (BNP) level of at least 150 pg per milliliter (or an N-terminal pro-BNP [NT-proBNP] level  $\geq 600$  pg per milliliter) or, if they had been hospitalized for heart failure within the previous 12 months, a BNP of at least 100 pg per milliliter (or an NT-proBNP  $\geq 400$  pg per milliliter).

## **RELAX**

*Reference PMID: 23478662*

RELAX was a multicentre, randomized, placebo-controlled trial that tested if phosphodiesterase (PDE)-5 inhibition with sildenafil (Target dose: 60 mg 3 times daily) improves exercise capacity in patients compared to placebo (NCT00763867). The study drug was administered for 24 weeks. The primary endpoint of the study was peak oxygen consumption at 24 weeks. Secondary endpoints included 6-minute walk distance at 24 weeks and change in peak oxygen consumption and 6-minute walk distance walked, concentrations of multiple biomarkers including NT-proBNP, and multiple measurements related to LV structure and vascular function. Time to death and cause-specific hospitalisations were also collected.

Briefly, stable patients with HF were eligible to participate in the study if they presented NYHA functional class II to IV, an LVEF  $\geq 50\%$  and had objective evidence of HF. Moreover, a age- and sex-specific reduced peak oxygen consumption and either elevated natriuretic peptides or elevated LV filling were required for study entry.

The RELAX trial was approved by all local IRBs and all patients provided a written consent to participate in the study. Moreover, in centers electing to participate in the genomics/pharmacogenomics sub-study of the HFN clinical trials, the sub-study was approved by the IRB at each side. Patients taking part in the RELAX trial in these participating centers were offered the possibility to participate in the genetics sub-study. All participants willing to participate in the substudy provided written informed consent.

This study was conducted by the Heart Failure Clinical Research Network. The trial was funded by the NHLBI through grants by grants U10HL084904 (for the data coordinating center), and U10HL084861, U10HL084875, U10HL084877, U10HL084889, U10HL084890,

U10HL084891, U10HL084899, U10HL084907, and U10HL084931 (for the clinical centers). This work is also supported by grant UL1TR000454 from the National Center for Advancing Translational Sciences and grant 8 U54 MD007588 from the National Institute on Minority Health and Health Disparities. Pfizer provided study drug (sildenafil and matched placebo).

## **ROSE-AHF**

*Reference PMID: 24046475*

ROSE-AHF was a multicentre, randomized, placebo-controlled trial if low-dose nesiritide or low-dose dopamine could enhance decongestion and preserve renal function compared to placebo in patients with acute decompensated HF. The study drug was administered for 72 hours. The coprimary endpoints of the study were cumulative urine volume and changes in cystatin C at 72 hours (NCT01132846). Secondary endpoints included changes in multiple endpoints from randomization to 72 hr in serum creatinine, dyspnea assessment by assessment by visual analogue scale, persistent or worsening HF, adverse events, NT-proBNP and several other biomarkers, and days alive and free from HF hospitalization during the 60 days following.

Briefly, patients were eligible to participate in the study if they were hospitalized for acute HF and presented had renal dysfunction (estimated glomerular filtration rate of 15-60 mL/min/1.73 m<sup>2</sup>) at admission and were enrolled within 24 hours of admission. The diagnosis of acute HF was based on at least 1 symptom and 1 sign of HF, irrespective of LVEF.

The ROSE-AHF study was approved by all local IRBs and all patients provided a written consent to participate in the study. Moreover, in centers electing to participate in the genomics/pharmacogenomics sub-study of the HFN clinical trials, the sub-study was approved by the IRB at each side. Patients taking part in the ROSE-AHF trial in these

participating centers were offered the possibility to participate in the genetics sub-study. All participants willing to participate in the substudy provided written informed consent.

This study was conducted by the Heart Failure Clinical Research Network. It was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award (coordinating center: U10 HL084904; regional clinical centers: U01 HL084861, U10 HL110312, U109 HL110337, U01 HL084889, U01 HL084890, U01 HL084891, U10 HL110342, U10 HL110262, U01 HL084931, U10 HL110297, U10 HL110302, U10 HL110309, U10 HL110336, U10 HL110338). It was also supported by the National Center for Advancing Translational Sciences (UL1TR000454, UL1TR000135, UL1RR025008, UL1TR000439) and the National Institute on Minority Health and Health Disparities (8 U54 MD007588).

## **TIME-CHF**

*Reference PMID: 19176440*

The randomized controlled multicenter Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) enrolled a total of 622 patients aged 60 years or older, New York Heart Association (NYHA) class of II or greater, prior hospitalization for heart failure within 1 year, and N-terminal BNP level of 2 or more times the upper limit of normal into a randomized study of biomarker guided intensification of treatment for HF vs. standard care. All participants were of European ancestry. The study had an 18-month follow-up and it was conducted at 15 outpatient centers in Switzerland and Germany between January 2003 and June 2008. For HERMES participation, only patients that consented and donated genetic material for later study were included (N=546). Among these, 442 had ejection fraction <50%. The original clinical trial was sponsored by the Horten Research Foundation (Lugano, Switzerland; 55% of the study's budget), as well as by smaller unrestricted grants from AstraZeneca Pharma, Novartis Pharma, Menarini Pharma, Pfizer Pharma, Servier, Roche Diagnostics, Roche Pharma, and Merck Pharma.

## **Val-HeFT**

*Reference PMID: 11759645*

Val-HeFT (Valsartan Heart Failure Trial) is a randomized trial of the addition of the angiotensin-receptor blocker valsartan to standard therapy for heart failure with follow-up for morbidity and mortality (Cohn et al., 2001). The trial followed 5010 patients with heart failure of New York Heart Association (NYHA) class II, III, or IV who were randomly assigned to receive 160 mg of valsartan or placebo twice daily. The primary outcomes were mortality and the combined end point of mortality and morbidity, defined as the incidence of cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for at least four hours. Valsartan was found to significantly reduce the combined end point of mortality and morbidity and improved clinical signs and symptoms in patients with heart failure, when added to prescribed therapy. The genotyped sample consists of 1025 Val-HeFT participants of European descent with DNA and informed consent for genetic studies.