

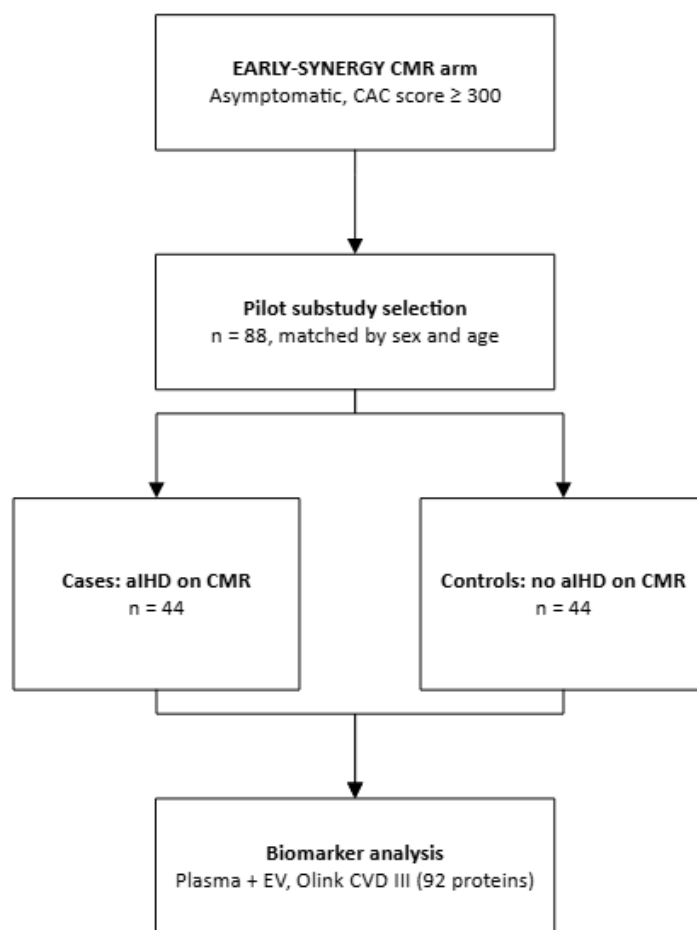


Figure S1 Overview of population selection.

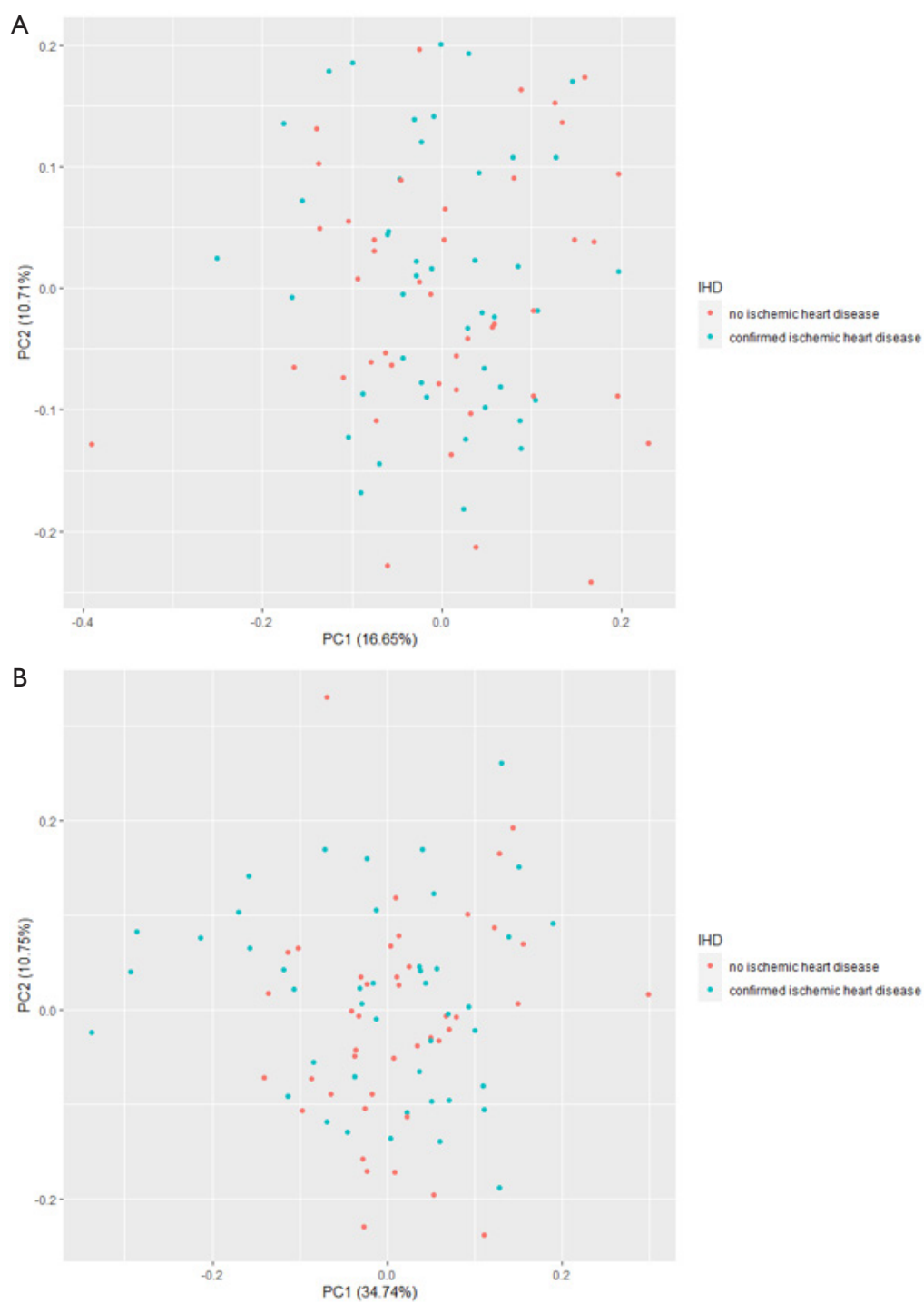


Figure S2 Principal component analysis plots for (A) plasma and (B) EVs.

Plasma and EV concentrations

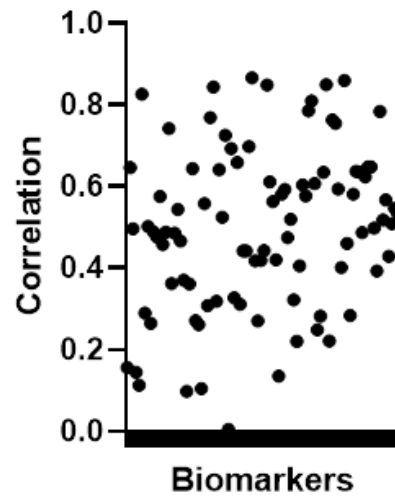


Figure S3 Pearson's r coefficients for all biomarker concentrations.

Table S1 Differential expression analysis in EVs

Protein	logFC	P.Value	adj.P.Val	UniProt
AP-N	0,142123	0,018127	0,534135	P15144
TFF3	0,18235	0,028091	0,534135	Q07654
IL2-RA	0,109233	0,036509	0,534135	P01589
SELE	0,26181	0,040742	0,534135	P16581
CXCL16	0,14285	0,04321	0,534135	Q9H2A7
RARRES2	0,341017	0,043903	0,534135	Q99969
t-PA	0,164323	0,044845	0,534135	P00750
TNFSF13B	0,136287	0,046446	0,534135	Q9Y275
vWF	0,159989	0,059063	0,534682	P04275
FABP4	0,152422	0,067905	0,534682	P15090
IL-6RA	0,210344	0,081072	0,534682	P08887
TR-AP	0,10916	0,082398	0,534682	P13686
JAM-A	0,23178	0,087176	0,534682	Q9Y624
PECAM-1	0,093601	0,053319	0,534682	P16284
GP6	0,093061	0,080806	0,534682	Q9HCN6
CNTN1	0,058387	0,108688	0,562451	Q12860
LDL receptor	0,120541	0,108917	0,562451	P01130
TNFRSF10C	-0,11405	0,111223	0,562451	O14798
TFPI	0,189984	0,116177	0,562451	P10646
GRN	0,122508	0,130569	0,562451	P28799
PRTN3	0,143795	0,131984	0,562451	P24158
PSP-D	0,101018	0,134499	0,562451	P35247
KLK6	0,087527	0,146691	0,586765	Q92876
SELP	0,19965	0,156143	0,592333	P16109
TIMP4	0,186453	0,170768	0,592333	Q99727
MMP-9	0,137807	0,17109	0,592333	P14780
MCP-1	0,122148	0,173837	0,592333	P13500
MB	0,130158	0,180662	0,593603	P02144
FAS	0,136349	0,208051	0,609261	P25445
NT-proBNP	0,069768	0,214829	0,609261	P16860
MMP-3	0,130276	0,21982	0,609261	P08254
CASP-3	0,310734	0,224642	0,609261	P42574
CCL16	0,179321	0,225016	0,609261	O15467
SPON1	0,083379	0,242236	0,609261	Q9HCB6
PCSK9	0,112893	0,24782	0,609261	Q8NBP7
OPN	-0,15614	0,259806	0,609261	P10451
Gal-3	0,077757	0,26313	0,609261	P17931
ALCAM	0,079012	0,263867	0,609261	Q13740
EGFR	0,0368	0,268322	0,609261	P00533
IL-17RA	0,076768	0,271509	0,609261	Q96F46
BLM hydrolase	0,118074	0,271518	0,609261	Q13867
MPO	0,053846	0,304762	0,655836	P05164
uPA	0,092551	0,306532	0,655836	P00749
CHI3L1	-0,18102	0,329668	0,689306	P36222
PI3	0,063384	0,345996	0,701724	P19957
PDGF subunit A	0,070481	0,356636	0,701724	P04085
PAI	0,135044	0,370308	0,701724	P05121
ICAM-2	0,058301	0,387703	0,701724	P13598
IL-1RT2	0,058166	0,395286	0,701724	P27930
MEPE	0,062353	0,40176	0,701724	Q9NQ76
GDF-15	0,09727	0,407342	0,701724	Q99988
CD163	0,082577	0,407549	0,701724	Q86VB7
TNFRSF14	0,054732	0,413891	0,701724	Q92956
MMP-2	0,026348	0,420761	0,701724	P08253
CSTB	0,059951	0,4247	0,701724	P04080
OPG	0,047525	0,431709	0,701724	O00300
CD93	0,07971	0,440827	0,701724	Q9NPY3
TNF-R1	0,051152	0,442391	0,701724	P19438
U-PAR	0,047482	0,461785	0,71069	Q03405
AXL	0,054934	0,469485	0,71069	P30530
LTBR	0,041321	0,471219	0,71069	P36941
EPHB4	0,036558	0,483917	0,711506	P54760
IGFBP-7	0,08524	0,489538	0,711506	Q16270
TNF-R2	0,056115	0,494961	0,711506	P20333
ST2	0,054725	0,513694	0,722934	Q01638
SHPS-1	0,042881	0,530971	0,722934	P78324
CHIT1	0,098574	0,54493	0,722934	Q13231
PLC	0,080317	0,547217	0,722934	P98160
PGLYRP1	0,088069	0,552681	0,722934	O75594
Notch 3	0,042495	0,561774	0,722934	Q9UM47
CTSD	0,038154	0,564409	0,722934	P07339
SCGB3A2	-0,06338	0,565774	0,722934	Q96PL1
TLT-2	0,035462	0,578775	0,724312	Q5T2D2
COL1A1	-0,01271	0,582598	0,724312	P02452
CDH5	0,041361	0,591202	0,725208	P33151
PON3	-0,02998	0,650404	0,787331	Q15166
CCL24	-0,06936	0,686765	0,818553	O00175
AZU1	0,024686	0,69399	0,818553	P20160
CCL15	0,035919	0,754902	0,879126	Q16663
IL-1RT1	0,021695	0,775544	0,891876	P14778
IGFBP-2	0,047536	0,79511	0,898716	P18065
CTSZ	-0,01208	0,814187	0,898716	Q9UBR2
IL-18BP	0,015586	0,819406	0,898716	Q95998
TR	-0,01933	0,820567	0,898716	P02786
Ep-CAM	0,031778	0,8516	0,921732	P16422
RETN	0,028469	0,865167	0,925528	Q9HD89
CPB1	-0,01958	0,880255	0,930845	P15086
ITGB2	-0,0115	0,915873	0,957504	P05107
Gal-4	-0,00541	0,940808	0,967647	P56470
DLK-1	0,005016	0,953294	0,967647	P80370
CPA1	-0,00449	0,95713	0,967647	P15085
IGFBP-1	-0,00184	0,98803	0,98803	P08833

Table S2 Differential expression in plasma

Protein	logFC	P.Value	adj.P.Val	UniProt
AP-N	0,119793	0,030553	0,900876	P15144
RARRES2	0,121262	0,038032	0,900876	Q99969
LDL receptor	0,207107	0,045361	0,900876	P01130
SELE	0,208776	0,071402	0,900876	P16581
CHI3L1	-0,32925	0,07121	0,900876	P36222
EGFR	0,075449	0,082987	0,900876	P00533
PSP-D	0,206509	0,106665	0,900876	P35247
PRTN3	0,146341	0,148915	0,900876	P24158
TNFSF13B	0,089981	0,152934	0,900876	Q9Y275
ST2	0,135176	0,163624	0,900876	Q01638
DLK-1	-0,16801	0,181605	0,900876	P80370
SPON1	0,070444	0,188482	0,900876	Q9HCB6
TFPI	0,089407	0,195498	0,900876	P10646
MPO	0,127705	0,220885	0,900876	P05164
IL-17RA	0,123734	0,236696	0,900876	Q96F46
SELP	0,119457	0,253165	0,900876	P16109
PECAM-1	0,067748	0,255554	0,900876	P16284
CCL15	-0,09442	0,25744	0,900876	Q16663
MMP-3	0,124975	0,259284	0,900876	P08254
JAM-A	0,115575	0,268894	0,900876	Q9Y624
PI3	0,11194	0,281793	0,900876	P19957
GP6	0,160077	0,298321	0,900876	Q9HCN6
CCL24	-0,19929	0,30109	0,900876	O00175
CD93	-0,06217	0,319708	0,900876	Q9NPY3
t-PA	0,107573	0,335637	0,900876	P00750
CTSZ	-0,0774	0,347017	0,900876	Q9UBR2
CHIT1	0,268309	0,354601	0,900876	Q13231
RETN	-0,09242	0,364958	0,900876	Q9HD89
GRN	0,062217	0,36602	0,900876	P28799
PON3	-0,11483	0,378291	0,900876	Q15166
TLT-2	-0,06872	0,411711	0,900876	Q5T2D2
TR-AP	0,053615	0,423794	0,900876	P13686
vWF	0,066077	0,425655	0,900876	P04275
CASP-3	0,200049	0,428977	0,900876	P42574
TNF-R2	-0,06239	0,435485	0,900876	P20333
SHPS-1	0,056004	0,438645	0,900876	P78324
MMP-9	0,118566	0,447421	0,900876	P14780
PLC	-0,04637	0,451789	0,900876	P98160
COL1A1	-0,05313	0,453301	0,900876	P02452
CNTN1	0,037475	0,454321	0,900876	Q12860
CSTB	0,090634	0,457377	0,900876	P04080
FAS	0,074063	0,461134	0,900876	P25445
KLK6	0,052084	0,468773	0,900876	Q92876
CPA1	-0,10862	0,469582	0,900876	P15085
EPHB4	-0,04251	0,481453	0,900876	P54760
U-PAR	0,046889	0,482801	0,900876	Q03405
IL-1RT2	-0,0426	0,489914	0,900876	P27930
BLM hydrolase	0,065393	0,5091	0,900876	Q13867
TNFRSF10C	-0,06524	0,522798	0,900876	O14798
CPB1	-0,08994	0,526735	0,900876	P15086
OPN	0,060048	0,532957	0,900876	P10451
IGFBP-2	-0,08331	0,534393	0,900876	P18065
IL-18BP	-0,04626	0,541708	0,900876	O95998
OPG	-0,03985	0,561803	0,900876	O00300
CXCL16	0,030432	0,567493	0,900876	Q9H2A7
ITGB2	-0,04077	0,567627	0,900876	P05107
MEPE	0,045195	0,572041	0,900876	Q9NQ76
SCGB3A2	-0,08937	0,58244	0,900876	Q96PL1
AZU1	0,071963	0,597499	0,900876	P20160
PGLYRP1	-0,05481	0,605702	0,900876	O75594
IL-1RT1	-0,02671	0,611831	0,900876	P14778
TNFRSF14	-0,03476	0,613311	0,900876	Q92956
PCSK9	0,031214	0,616904	0,900876	Q8NBP7
ICAM-2	0,038564	0,627935	0,902657	P13598
LTBR	-0,02925	0,646892	0,904541	P36941
uPA	0,023115	0,656002	0,904541	P00749
CDH5	-0,0303	0,658742	0,904541	P33151
CCL16	0,045658	0,692958	0,908966	O15467
TR	0,049505	0,693234	0,908966	P02786
Notch 3	-0,02796	0,703282	0,908966	Q9UM47
PDGF subunit A	0,057899	0,704149	0,908966	P04085
CTSD	0,030771	0,721076	0,908966	P07339
NT-proBNP	0,053287	0,743186	0,908966	P16860
GDF-15	0,029823	0,765006	0,908966	Q99988
FABP4	-0,04002	0,767377	0,908966	P15090
IL2-RA	-0,02335	0,783869	0,908966	P01589
ALCAM	-0,01306	0,785941	0,908966	Q13740
MMP-2	-0,01547	0,798628	0,908966	P08253
AXL	0,016314	0,799804	0,908966	P30530
IL-6RA	0,016759	0,814396	0,908966	P08887
PAI	0,039222	0,814456	0,908966	P05121
TIMP4	0,022944	0,819151	0,908966	Q99727
Ep-CAM	0,050565	0,820046	0,908966	P16422
CD163	-0,0186	0,848429	0,926425	Q86VB7
TFF3	0,014353	0,856065	0,926425	Q07654
Gal-4	-0,01502	0,877001	0,926425	P56470
Gal-3	0,011959	0,891738	0,926425	P17931
MCP-1	0,011248	0,894149	0,926425	P13500
IGFBP-7	-0,00794	0,904232	0,926425	Q16270
MB	0,013567	0,906285	0,926425	P02144
TNF-R1	-0,00711	0,927459	0,937651	P19438
IGFBP-1	0,009231	0,971141	0,971141	P08833

Appendix 1

CMR acquisition protocol

Adapted from: Ties D, van Dorp P, Pundziute G, et al. Early detection of obstructive coronary artery disease in the asymptomatic high-risk population: objectives and study design of the EARLY-SYNERGY trial. *Am Heart J* 2022;246:166-77 (22).

CMR-MPI was conducted on a 1.5-T clinical MRI system in accordance with a standardized study protocol that permits minor deviations based on local hospital constraints to accommodate limitations in available scanning time and imaging sequences.

Stress perfusion imaging induced by vasodilators was carried out using either adenosine or regadenoson. Regadenoson was utilized in cases where there are contraindications for adenosine (for instance, active bronchoconstrictive or bronchospastic diseases) or if it was the standard practice in the local clinical setting. Hyperemia was achieved through a continuous intravenous infusion of 140 µg/kg/min adenosine over a duration of

4 minutes or via a single intravenous bolus of 400 µg regadenoson. If there was an inadequate hemodynamic response to adenosine, the dose was escalated to a maximum of 210 µg/kg body weight/min at the discretion of the attending physician.

Following standardized axial, coronal, and sagittal localizer and scout imaging, 2D balanced steady-state free precession (bSSFP) cine imaging was performed with retrospective ECG gating of the left ventricular (LV) long-axis views, including 4-chamber, 3-chamber, 2-chamber, and LV outflow tract perspectives. Subsequently, basal, midventricular, and apical short-axis slice positions were established. First-pass 2D saturation-recovery bSSFP perfusion imaging was executed on the 3 short-axis slices either 4 minutes after the initiation of adenosine or 1-2 minutes following regadenoson infusion, by administering 0.1 mmol/kg gadolinium (Dotarem) at a rate of 5 mL/s, followed by a saline flush of 20 mL at 5 mL/s.

For this study, patients were deemed to have ischemia if at least 10% of the left ventricle was ischemic.