SUPPLEMENTAL MATERIALS

CXCL16 - Novel, independent predictor of cardiovascular death and morbidity in acute coronary syndrome

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Contents of the supplementary material

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Major Resources Tables

Animals (in vivo studies)

Species	Vendor or Source	Background Strain	Sex
NA			

Animal breeding

	Species	Vendor or Source	Background Strain	Other Information
Parent - Male	NA			
Parent - Female	NA			

Antibodies

Target antigen	Vendor or Source	Catalog #	Working concentration	Lot # (preferred but not required)
CXCL16	R&D Systems	DY1164		

Cultured Cells

Name	Vendor or Source	Sex (F, M, or unknown)
NA		

Supplementary figure I: Admission CXCL16 level by statin use at inclusion

CXCL16 levels at admission, by statin use

Median 5.20
(4.48-6.09)

Median 5.43
(4.61-6.40)

CXCL-16 (ng/mL)

Statins on Day of Rand.   ☐ Yes ☐ No
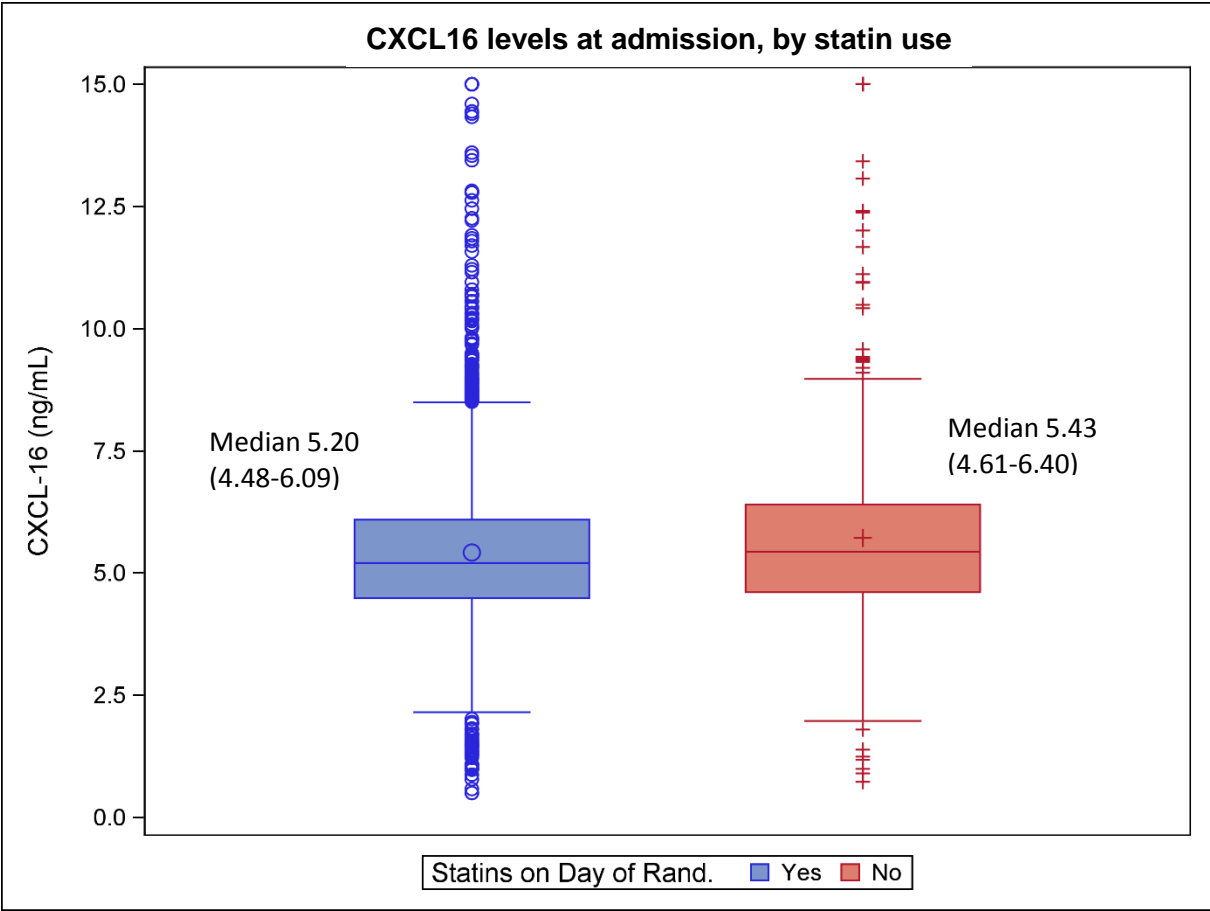
P-value < 0.0001 (from Mann-Whitney U Test)

Supplementary table I: Spearman correlation of admission levels of CXCL16 with other biomarkers

Variable	R	p	n
ln CRP	0.25475	<.0001	4719
ln WBC	0.00972	0.4987	4851
ln GDF-15	0.26255	<.0001	5033
ln hs-TnT	0.10791	<.0001	5032
ln NT-proBNP	0.21054	<.0001	5053
ln cystatin C	0.30472	<.0001	4718
ln D-Dimer	0.20851	<.0001	5055
ln IL6	0.20069	<.0001	5055
ln IL18	0.10056	<.0001	5008
ln OxLDL	-0.02800	0.0465	5055
ln ApoA1	-0.08250	<.0001	4718
ln ApoB	0.08544	<.0001	4718

Abbreviations: CRP: C-Reactive Protein, WBC: White Blood Cell Count, GDF-15: Growth Differentiation Factor 15, TnT: Troponin T, NTproBNP: N-Terminal ProBrain Natriuretic Peptide, IL6: Interleukin 6, IL18: Interleukin 18, OxLDL: Oxidized Low-Density Lipoprotein, ApoA1: Apolipoprotein A1, ApoB: Apolipoprotein B

Supplementary table II: Multivariable Cox-regression analyses of the association between admission levels of CXCL-16 and outcome

Outcome	Model*	No of events	No of patients	Event rate (%)	HR (95% CI)†	P-value‡
CV-death / Spontaneous MI / Stroke	Model 0	434	5142	8.4	1.64 (1.44-1.88)	<.0001
	Model 1	432	5130	8.4	1.51 (1.32-1.74)	<.0001
	Model 2	373	4443	8.4	1.45 (1.24-1.70)	<.0001
	Model 3	373	4442	8.4	1.35 (1.15-1.59)	0.0002
	Model 4	371	4418	8.4	1.32 (1.12-1.55)	0.0008
	Model 5	371	4418	8.4	1.25 (1.06-1.47)	0.0065
	Model 6	364	4379	8.3	1.25 (1.06-1.48)	0.0070
	Model 7	363	4355	8.3	1.23 (1.05-1.45)	0.0126
CV-death / Spontaneous MI	Model 0	388	5142	7.5	1.65 (1.43-1.90)	<.0001
	Model 1	386	5130	7.5	1.51 (1.30-1.75)	<.0001
	Model 2	335	4443	7.5	1.44 (1.22-1.70)	<.0001
	Model 3	335	4442	7.5	1.34 (1.13-1.58)	0.0008
	Model 4	333	4418	7.5	1.30 (1.09-1.54)	0.0027
	Model 5	333	4418	7.5	1.23 (1.04-1.46)	0.0165
	Model 6	326	4379	7.4	1.23 (1.03-1.46)	0.0195
	Model 7	325	4355	7.5	1.20 (1.01-1.43)	0.0360
CV-death	Model 0	191	5142	3.7	2.42 (2.01-2.90)	<.0001
	Model 1	189	5130	3.7	2.23 (1.83-2.71)	<.0001
	Model 2	168	4443	3.8	1.93 (1.54-2.41)	<.0001
	Model 3	168	4442	3.8	1.73 (1.37-2.19)	<.0001
	Model 4	168	4418	3.8	1.66 (1.31-2.10)	<.0001
	Model 5	168	4418	3.8	1.57 (1.24-2.00)	0.0002
	Model 6	162	4379	3.7	1.57 (1.22-2.00)	0.0003
	Model 7	161	4355	3.7	1.50 (1.17-1.92)	0.0014
Spontaneous MI	Model 0	243	5142	4.7	1.21 (1.01-1.45)	0.0394
	Model 1	243	5130	4.7	1.10 (0.92-1.33)	0.3012
	Model 2	209	4443	4.7	1.11 (0.90-1.36)	0.3172
	Model 3	209	4442	4.7	1.06 (0.86-1.31)	0.5656
	Model 4	207	4418	4.7	1.04 (0.85-1.28)	0.6994
	Model 5	207	4418	4.7	1.01 (0.82-1.24)	0.9400
	Model 6	206	4379	4.7	1.01 (0.82-1.25)	0.9180
	Model 7	206	4355	4.7	1.01 (0.82-1.25)	0.8980
Stroke	Model 0	62	5142	1.2	1.46 (1.02-2.10)	0.0404
	Model 1	62	5130	1.2	1.37 (0.94-1.98)	0.0977
	Model 2	51	4443	1.1	1.31 (0.86-1.98)	0.2105
	Model 3	51	4442	1.1	1.19 (0.78-1.81)	0.4269
	Model 4	51	4418	1.2	1.20 (0.78-1.83)	0.4027
	Model 5	51	4418	1.2	1.18 (0.77-1.80)	0.4525
	Model 6	51	4379	1.2	1.19 (0.77-1.82)	0.4341
	Model 7	51	4355	1.2	1.18 (0.77-1.80)	0.4530

Outcome	Model*	No of events	No of patients	Event rate (%)	HR (95% CI)†	P-value‡
CV-death / All MI / Stroke	Model 0	508	5142	9.9	1.58 (1.40-1.79)	<.0001
	Model 1	505	5130	9.8	1.48 (1.30-1.69)	<.0001
	Model 2	440	4443	9.9	1.45 (1.25-1.67)	<.0001
	Model 3	440	4442	9.9	1.37 (1.18-1.59)	<.0001
	Model 4	438	4418	9.9	1.34 (1.16-1.56)	0.0001
	Model 5	438	4418	9.9	1.28 (1.10-1.49)	0.0011
	Model 6	431	4379	9.8	1.27 (1.09-1.47)	0.0022
	Model 7	430	4355	9.9	1.25 (1.07-1.45)	0.0043

* Models include:

Model 0: CXCL16 at admission, adjusted for randomized treatment

Model 1: Model 0 + age, gender, body mass index, diabetes, dyslipidemia, hypertension, chronic renal disease, congestive heart failure, ST-elevation Myocardial Infarction (MI)/non-ST-elevation acute coronary syndrome (ACS) at randomization, smoking, type of ACS, randomized treatment, aspirin at entry and previous (MI/Peripheral artery disease/coronary artery bypass grafting/percutaneous coronary intervention/non-hemorrhagic stroke)

Model 2: Model 1 + hsCRP and white blood cells

Model 3: Model 2 + cystatin C

Model 4: Model 3 + NT-ProBNP and Troponin T

Model 5: Model 4 + GDF-15

Model 6: Model 5 + Apo-A1 and IL-6

Model 7: Model 6 + D-dimer, IL-18, oxLDL and Apo-B

† Hazard ratio is per 50% increase in CXCL16

‡P-value is for effect of CXCL16

Supplementary Table III: Prediction performance of models with and without CXCL16 at admission.

Outcome	C-index (95% CI) Model* without CXCL-16	C-index (95% CI) Model* with CXCL-16	L-R test p-value
CV-death/sMI/Stroke	0.703 (0.675-0.731)	0.706 (0.679-0.734)	0.0115
CV-death/sMI	0.711 (0.682-0.741)	0.714 (0.685-0.743)	0.0338
CV-death	0.798 (0.760-0.836)	0.808 (0.771-0.845)	0.0013
sMI	0.688 (0.651-0.726)	0.688 (0.651-0.726)	0.8978
Stroke	0.739 (0.678-0.800)	0.741 (0.680-0.801)	0.4469
CV-death/All MI/Stroke	0.679 (0.653-0.704)	0.682 (0.656-0.708)	0.0037

Abbreviations: CV - Cardiovascular; sMI - Spontaneous myocardial infarction;
* Multivariable Cox regression analysis adjusted for clinical variables and all analyzed biomarkers, e.g. fully adjusted model 7

Supplementary Table IV: CXCL16 levels according to randomized treatment and time point of measurement

Visit	Treatment	n	Mean (SD)	Geometric mean	Ratio of geometric means (95% CI)	P-value*
Discharge	Ticagrelor	2271	6.074 (1.768)	5.813	0.984 (0.971-0.997)	0.0146
	Clopidogrel	2305	6.145 (1.825)	5.910		
Month 1	Ticagrelor	2113	5.517 (1.435)	5.316	0.999 (0.987-1.012)	0.9000
	Clopidogrel	2143	5.499 (1.496)	5.320		
Month 6	Ticagrelor	1522	5.285 (1.233)	5.148	1.003 (0.990-1.016)	0.6576
	Clopidogrel	1578	5.263 (1.244)	5.133		

*P-values derived from an analysis of covariance (ANCOVA) model with ln CXCL-16 as dependent variable and ln admission CXCL-16 and randomized treatment (Ticagrelor, Clopidogrel) as independent variables.

Supplementary table V: Multivariable Cox-regression analyses of the association between 1-month levels of CXCL-16 and outcome

Outcome	Model*	No of events	No of patients	Event rate (%)	HR (95% CI)[†]	P-value[‡]
CV-death / Spontaneous MI / Stroke	Model 0	240	4234	5.7	1.53 (1.25-1.86)	<.0001
	Model 1	240	4227	5.7	1.37 (1.11-1.68)	0.0027
	Model 2	220	3760	5.9	1.30 (1.05-1.61)	0.0144
	Model 3	220	3759	5.9	1.22 (0.99-1.52)	0.0682
	Model 4	218	3739	5.8	1.21 (0.98-1.51)	0.0808
	Model 5	218	3739	5.8	1.20 (0.96-1.48)	0.1022
	Model 6	217	3724	5.8	1.19 (0.96-1.48)	0.1059
	Model 7	217	3703	5.9	1.19 (0.96-1.48)	0.1056
CV-death / Spontaneous MI	Model 0	215	4234	5.1	1.55 (1.26-1.91)	<.0001
	Model 1	215	4227	5.1	1.37 (1.10-1.70)	0.0046
	Model 2	197	3760	5.2	1.30 (1.04-1.63)	0.0215
	Model 3	197	3759	5.2	1.21 (0.96-1.52)	0.1003
	Model 4	195	3739	5.2	1.20 (0.96-1.51)	0.1145
	Model 5	195	3739	5.2	1.19 (0.95-1.49)	0.1403
	Model 6	194	3724	5.2	1.19 (0.94-1.49)	0.1409
	Model 7	194	3703	5.2	1.19 (0.94-1.49)	0.1424
CV-death	Model 0	85	4234	2.0	1.74 (1.25-2.43)	0.0010
	Model 1	85	4227	2.0	1.44 (1.02-2.03)	0.0389
	Model 2	81	3760	2.2	1.32 (0.93-1.87)	0.1163
	Model 3	81	3759	2.2	1.17 (0.83-1.65)	0.3814
	Model 4	81	3739	2.2	1.14 (0.80-1.61)	0.4682
	Model 5	81	3739	2.2	1.13 (0.80-1.59)	0.5006
	Model 6	80	3724	2.1	1.15 (0.81-1.64)	0.4227
	Model 7	80	3703	2.2	1.15 (0.81-1.64)	0.4311
Spontaneous MI	Model 0	154	4234	3.6	1.45 (1.13-1.87)	0.0034
	Model 1	154	4227	3.6	1.32 (1.02-1.70)	0.0352
	Model 2	140	3760	3.7	1.29 (0.99-1.69)	0.0621
	Model 3	140	3759	3.7	1.23 (0.94-1.62)	0.1333
	Model 4	138	3739	3.7	1.23 (0.93-1.62)	0.1429
	Model 5	138	3739	3.7	1.22 (0.93-1.60)	0.1599
	Model 6	138	3724	3.7	1.20 (0.91-1.58)	0.1893
	Model 7	138	3703	3.7	1.21 (0.92-1.59)	0.1753
Stroke	Model 0	36	4234	0.9	1.28 (0.76-2.14)	0.3556
	Model 1	36	4227	0.9	1.17 (0.70-1.95)	0.5491
	Model 2	34	3760	0.9	1.14 (0.68-1.93)	0.6189
	Model 3	34	3759	0.9	1.06 (0.63-1.78)	0.8226
	Model 4	34	3739	0.9	1.05 (0.63-1.77)	0.8403
	Model 5	34	3739	0.9	1.05 (0.63-1.77)	0.8456
	Model 6	34	3724	0.9	1.04 (0.63-1.73)	0.8835
	Model 7	34	3703	0.9	1.04 (0.63-1.72)	0.8713

Outcome	Model*	No of events	No of patients	Event rate (%)	HR (95% CI)†	P-value‡
CV-death / All MI / Stroke	Model 0	260	4234	6.1	1.42 (1.17-1.72)	0.0003
	Model 1	260	4227	6.2	1.29 (1.06-1.57)	0.0106
	Model 2	236	3760	6.3	1.27 (1.03-1.55)	0.0240
	Model 3	236	3759	6.3	1.20 (0.97-1.47)	0.0893
	Model 4	234	3739	6.3	1.19 (0.97-1.47)	0.1011
	Model 5	234	3739	6.3	1.18 (0.96-1.45)	0.1224
	Model 6	233	3724	6.3	1.17 (0.95-1.43)	0.1452
	Model 7	233	3703	6.3	1.17 (0.95-1.43)	0.1429

* Models include:

Model 0: CXCL16 at 1 month, adjusted for randomized treatment

Model 1: Model 0 + age, gender, body mass index, diabetes, dyslipidemia, hypertension, chronic renal disease, congestive heart failure, ST-elevation Myocardial Infarction (MI)/non-ST-elevation acute coronary syndrome (ACS) at randomization, smoking, type of ACS, randomized treatment, aspirin at entry and previous (MI/Peripheral artery disease/coronary artery bypass grafting/percutaneous coronary intervention/non-hemorrhagic stroke)

Model 2: Model 1 + hsCRP and white blood cells

Model 3: Model 2 + cystatin C

Model 4: Model 3 + NT-ProBNP and Troponin T

Model 5: Model 4 + GDF-15

Model 6: Model 5 + Apo-A1 and IL-6

Model 7: Model 6 + D-dimer, IL-18, oxLDL and Apo-B

† Hazard ratio is per 50% increase in CXCL16

‡P-value is for effect of CXCL16

Supplementary table VI: Multivariable Cox-regression analyses of the association between change in CXCL16 from admission to 1 month and outcome

Outcome	Model*	No of events	No of patients	Event rate (%)	HR (95% CI)†	P-value‡
CV-death / Sp. MI / Stroke	Model 0	239	4191	5.7	1.27 (0.97-1.67)	0.0843
	Model 1	239	4184	5.7	1.15 (0.88-1.51)	0.3019
	Model 2	219	3746	5.8	1.14 (0.86-1.50)	0.3612
	Model 3	219	3745	5.8	1.10 (0.83-1.44)	0.5184
	Model 4	217	3725	5.8	1.10 (0.83-1.45)	0.5142
	Model 5	217	3725	5.8	1.11 (0.84-1.47)	0.4557
	Model 6	216	3710	5.8	1.12 (0.85-1.48)	0.4151
	Model 7	216	3689	5.9	1.12 (0.85-1.47)	0.4338
CV-death / Sp. MI	Model 0	214	4191	5.1	1.25 (0.94-1.67)	0.1311
	Model 1	214	4184	5.1	1.13 (0.85-1.50)	0.4149
	Model 2	196	3746	5.2	1.11 (0.83-1.49)	0.4748
	Model 3	196	3745	5.2	1.07 (0.80-1.43)	0.6666
	Model 4	194	3725	5.2	1.07 (0.80-1.44)	0.6472
	Model 5	194	3725	5.2	1.09 (0.81-1.45)	0.5823
	Model 6	193	3710	5.2	1.10 (0.82-1.47)	0.5342
	Model 7	193	3689	5.2	1.09 (0.82-1.47)	0.5515
CV-death	Model 0	84	4191	2.0	1.14 (0.72-1.79)	0.5872
	Model 1	84	4184	2.0	1.00 (0.65-1.55)	0.9955
	Model 2	80	3746	2.1	1.11 (0.71-1.73)	0.6570
	Model 3	80	3745	2.1	1.03 (0.67-1.60)	0.8908
	Model 4	80	3725	2.1	1.03 (0.66-1.61)	0.8983
	Model 5	80	3725	2.1	1.04 (0.67-1.63)	0.8467
	Model 6	79	3710	2.1	1.10 (0.70-1.73)	0.6744
	Model 7	79	3689	2.1	1.09 (0.69-1.72)	0.7036
Spontaneous MI	Model 0	154	4191	3.7	1.30 (0.93-1.82)	0.1294
	Model 1	154	4184	3.7	1.20 (0.86-1.69)	0.2909
	Model 2	140	3746	3.7	1.17 (0.82-1.67)	0.3864
	Model 3	140	3745	3.7	1.14 (0.80-1.62)	0.4778
	Model 4	138	3725	3.7	1.14 (0.80-1.64)	0.4635
	Model 5	138	3725	3.7	1.15 (0.81-1.65)	0.4275
	Model 6	138	3710	3.7	1.14 (0.80-1.62)	0.4848
	Model 7	138	3689	3.7	1.14 (0.80-1.62)	0.4784
Stroke	Model 0	36	4191	0.9	1.20 (0.60-2.40)	0.5979
	Model 1	36	4184	0.9	1.07 (0.55-2.08)	0.8422
	Model 2	34	3746	0.9	1.08 (0.55-2.12)	0.8341
	Model 3	34	3745	0.9	1.03 (0.53-2.02)	0.9202
	Model 4	34	3725	0.9	1.01 (0.52-1.96)	0.9771
	Model 5	34	3725	0.9	1.01 (0.52-1.96)	0.9734
	Model 6	34	3710	0.9	1.01 (0.52-1.95)	0.9751
	Model 7	34	3689	0.9	1.01 (0.52-1.94)	0.9846

Outcome	Model*	No of events	No of patients	Event rate (%)	HR (95% CI)†	P-value‡
CV-death / All MI / Stroke	Model 0	259	4191	6.2	1.21 (0.93-1.57)	0.1592
	Model 1	259	4184	6.2	1.10 (0.85-1.43)	0.4487
	Model 2	235	3746	6.3	1.12 (0.86-1.46)	0.4067
	Model 3	235	3745	6.3	1.08 (0.83-1.41)	0.5507
	Model 4	233	3725	6.3	1.09 (0.83-1.43)	0.5254
	Model 5	233	3725	6.3	1.10 (0.84-1.44)	0.4717
	Model 6	232	3710	6.3	1.11 (0.85-1.45)	0.4288
	Model 7	232	3689	6.3	1.11 (0.85-1.45)	0.4390

* Models include:

Model 0: Change in CXCL16 from admission to 1 month, adjusted for CXCL16 at admission and randomized treatment

Model 1: Model 0 + age, gender, body mass index, diabetes, dyslipidemia, hypertension, chronic renal disease, congestive heart failure, ST-elevation Myocardial Infarction (MI)/non-ST-elevation acute coronary syndrome (ACS) at randomization, smoking, type of ACS, randomized treatment, aspirin at entry and previous (MI/Peripheral artery disease/coronary artery bypass grafting/percutaneous coronary intervention/non-hemorrhagic stroke)

Model 2: Model 1 + hsCRP and white blood cells

Model 3: Model 2 + cystatin C

Model 4: Model 3 + NT-ProBNP and Troponin T

Model 5: Model 4 + GDF-15

Model 6: Model 5 + Apo-A1 and IL-6

Model 7: Model 6 + D-dimer, IL-18, oxLDL and Apo-B

† Hazard ratio is per 50% increase in CXCL16

‡P-value is for effect of CXCL16