Title: Associations of angiopoietins with heart failure incidence and severity.

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Supplemental Methods

MESA Covariates. Age (continuous) and gender (categorical) were self-reported. Race/ethnicity was categorized as non-Hispanic white, African American (black), Hispanic, and Asian (predominantly Chinese American). Height (cm) and weight (kg) were included as continuous variables. Study site was included as a categorical variable. Highest level of education attained was included as a three-level categorical variable: 1) less than a high school diploma or general equivalency diploma, 2) high school diploma or general equivalency diploma and some college without a degree, 3) college degree including technical school, associate, bachelor, or graduate/professional school. Blood pressure was included through diagnosis of hypertension (categorical) and SBP (continuous). Tobacco use was included by smoking status categorized as never, former, or current smoker, and by duration of smoking in pack-years (continuous). Diabetes and total cholesterol level (mg/dl) were included as categorical and continuous variables, respectively. GFR (ml/min) and BNP level (pg/ml) were included as continuous variables. Medication use was included as categorical variables: beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and non-steroidal anti-inflammatory drugs. All covariates were measured as part of the baseline MESA evaluation.

Heart Failure Cohort Covariates. Ang1 and Ang2 were modeled as continuous variables. Dependent variables were modeled as continuous variables and included right atrial pressure (mmHg), mean pulmonary artery pressure (mmHg), pulmonary artery wedge pressure (mmHg), pulmonary vascular resistance (Wood units), cardiac index by thermodilution ($L/min/m^2$), and SBP (mmHg). Covariates in adjusted models included age (years, continuous), gender (categorical), and race/ethnicity,

categorized as white and non-white in the PAH cohort, and black and non-black in the LHD cohort. The etiologies of PAH (idiopathic, connective tissue disease, toxin mediated, congenital, and portopulmonary) and LHD (ischemic vs non-ischemic) were included as categorical variables.

Supplemental Tables

Supplemental e-Table 1. Additional multivariable linear regression models estimating associations between Ang1, Ang2 and cardiac structure and function in the MESA-Angiogenesis cohort (N=1,358)

		Ang1			Ang2		
Parameter	**Model**	**Coefficient**	**(95% CI)**	***P*-value**	**Coefficient**	**(95% CI)**	***P*-value**
RVEDM (g)	GFR	0.0	(-0.2, 0.2)	0.99	0.0	(-0.1, 0.2)	0.75
	BNP*	0.0	(-0.2, 0.2)	0.84	-0.1	(-0.3, 0.1)	0.42
	Medications	0.0	(-0.2, 0.1)	0.96	0.0	(-0.2, 0.2)	0.91
RVEDV (ml)	GFR	-0.2	(-1.1, 0.7)	0.61	0.2	(-1.0, 1.3)	0.77
	BNP*	-0.4	(-1.5, 0.7)	0.48	-0.6	(-1.9, 0.6)	0.33
	Medications	-0.3	(-1.2, 0.6)	0.55	0.0	(-1.1, 1.2)	0.97
RVSV (ml)	GFR	-0.4	(-1.1, 0.3)	0.24	0.3	(-0.5, 1.2)	0.44
	BNP*	-0.5	(-1.3, 0.3)	0.23	-0.4	(-1.4, 0.6)	0.43
	Medications	-0.4	(-1.1, 0.2)	0.21	0.2	(-0.6, 1.1)	0.60
RVEF (%)	GFR	-0.2	(-0.5, 0.1)	0.17	0.2	(-0.1, 0.5)	0.24
	BNP*	-0.2	(-0.5, 0.2)	0.39	0.1	(-0.3, 0.4)	0.80
	Medications	-0.2	(-0.5, 0.1)	0.19	0.2	(-0.1, 0.5)	0.26
LVEDM (g)	GFR	-0.3	(-1.2, 0.6)	0.53	-0.1	(-1.4, 1.2)	0.90
	BNP*	-0.4	(-1.5, 0.7)	0.52	**-1.7**	**(-3.1, -0.2)**	**0.02**
	Medications	-0.3	(-1.2, 0.6)	0.55	-0.1	(-1.4, 1.2)	0.87
LVEDV (ml)	GFR	-0.6	(-1.7, 0.5)	0.27	1.1	(-0.2, 2.3)	0.09
	BNP*	-0.8	(-2.1, 0.6)	0.26	-0.5	(-1.9, 0.9)	0.47
	Medications	-0.6	(-1.7, 0.5)	0.27	1.1	(-0.2, 2.3)	0.10
LVSV (ml)	GFR	0.1	(-0.6, 0.9)	0.71	0.6	(-0.3, 1.4)	0.22
	BNP*	0.1	(-0.7, 1.0)	0.76	-0.3	(-1.3, 0.7)	0.58
	Medications	0.1	(-0.6, 0.8)	0.74	0.4	(-0.4, 1.3)	0.33
LVEF (%)	GFR	**0.4**	**(0.1, 0.6)**	**0.01**	0.0	(-0.4, 0.4)	0.95
	BNP*	**0.4**	**(0.1, 0.7)**	**0.008**	0.0	(-0.5, 0.5)	1.00
	Medications	**0.3**	**(0.1, 0.6)**	**0.01**	-0.1	(-0.5, 0.3)	0.63

Supplemental e-Table 1. All results presented per standard deviation increase in Ang1 (1.67 ng/ml) or Ang2 (2.59 ng/ml). Ventricular measurements were obtained from cardiac magnetic resonance imaging. Ang1=angiopoietin-1, Ang2=angiopoietin-2, CI=confidence interval, RV=right ventricle, LV=left ventricle, EDM=end-diastolic mass, EDV=end-diastolic volume, SV=stroke volume, EF=ejection fraction, GFR=glomerular filtration rate (continuous, ml/min), BNP=brain natriuretic peptide (continuous, pg/ml). Medication models were adjusted for use of beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and non-steroidal anti-inflammatory drugs (categorical). All models were also adjusted for age, gender, race/ethnicity, height, weight, study site, education level, hypertension, systolic blood pressure, smoking status, pack-years smoking history, diabetes, and total cholesterol. *For BNP models, n=1,129 due to missing data.

Supplemental e-Table 2. Hemodynamic measurements during right heart catheterization procedures in pulmonary arterial hypertension (N=73) and left heart disease (N=56) cohorts

Measurement	PAH Cohort	LHD Cohort
RAP (mmHg)	8.9 ± 5.8	8.5 ± 4.8
mPAP (mmHg)	47.4 ± 12.5	28.4 ± 11.8
PAWP (mmHg)	11.5 ± 4.8	14.8 ± 7.1
PVR (Wood units)	8.6 ± 4.7	2.5 ± 1.4
CI ($L/min/m^2$)	2.6 ± 0.8	2.7 ± 0.9
SBP (mmHg)	116 ± 16	131 ± 22

Supplemental e-Table 2. All results presented as mean ± standard deviation. Hemodynamic measurements were obtained during right heart catheterizations. PAH=pulmonary arterial hypertension, LHD=left heart disease, RAP=right atrial pressure, mPAP=mean pulmonary artery pressure, PAWP=pulmonary artery wedge pressure, PVR=pulmonary vascular resistance, CI=cardiac index by thermodilution, SBP=systolic blood pressure.