Supplemental Information

Table S1. Peptides, transitions, and instrument parameters for GDF11 and MSTN. Related to Figure 1.

Peptide	Parent Mass m/z Da	Product Mass
GDF11		
NLGLDCDEHSSESR	809.8454	969.2779, 1391.5444
YPHTHLVQQANPR	520.9392	713.3695, 812.4346, 925.5221, 1062.5815, 1163.6301
QQIIYGK	425.2451	480.2812, 593.3657, 704.3951
IPGMVVDR	443.7453	619.3232, 676.3447, 773.3978
MSTN		
DFGLDCDEHSTESR	556.5610	703.2864, 1405.5664
ANYCSGECEFVFLQK	926.4057	634.3929, 781.4597, 1070.5354, 1256.6011, 1343.6337, 1503.6647
YPHTHLVHQANPR	523.9399	722.3685, 821.4362, 934.5202, 1071.5791, 1172.6278, 1309.6855
EQIIYGK	425.7377	480.2812, 593.3657, 704.3951
IPAMVVDR	443.7453	394.2099, 787.4123

Table S2. Inter-assay precision of GDF11 quantification. Six replicate measures of recombinant GDF11 at four concentrations diluted in 5% bovine serum albumin in phosphate buffered saline and pooled human serum sample were analyzed. Related to Figure 1.

GDF11 Peptide	IPGMVVDR	YPHTHLVQQANPR
0.777ng/ml		
Mean	0.826	0.897
SD	0.087	0.113
CV	10.5	12.6
2.33ng/ml		
Mean	2.36	2.35
SD	0.331	0.333
CV	14.0	14.1
4.67ng/ml		
Mean	4.59	4.82
SD	0.670	0.540
CV	14.6	11.2
9.33ng/ml		
Mean	8.42	9.42
SD	1.30	1.73
CV	15.5	18.4
Pooled Human Serum		
Mean	0.680	0.699
SD	0.080	0.067
CV	11.7	9.56

Table S3. Intra-assay precision of GDF11 quantification. Five replicate measures of recombinant GDF11 at three concentrations diluted in 5% bovine serum albumin in phosphate buffered saline and pooled human serum sample were analyzed. Related to Figure 1.

GDF11 Peptide	IPGMVVDR
0.777ng/ml	
Mean	0.836
SD	0.022
CV	2.69
4.67ng/ml	
Mean	4.951
SD	0.073
CV	1.47
9.33ng/ml	
Mean	10.2
SD	0.889
CV	8.69
Pooled Human Serum	
Mean	0.512
SD	0.054
CV	10.6

Table S4. Percent recovery of GDF11. A human serum pool was spiked at four increasing concentrations and the recovery was determined relative to the calculated value of the endogenous level plus the spike in concentration. Data was obtained from the YPHTHLVQQANPR peptide sequence. Related to Figure 1.

Spike Concentration (*ng/ml*)	**Measured Concentration (*ng/ml*)**	**%Recovery**
Neat Serum	0.522	-
0.777	1.02	64.0%
1.55	1.87	86.4%
3.11	2.96	78.8%
6.22	6.17	90.8%
12.4	9.55	72.6%

Table S5. Comparison of cardiac parameters to GDF11 levels. Related to Table 1.

	GDF11 Level			
	220-400 pg/ml (n=35)	**401-500 pg/ml (n=33)**	**501-841 ng/ml (n=28)**	
Cardiac parameter	**Mean (±SD)**			**p-value**
Ejection fraction	57.9 (13.3)	59.1 (12.9)	57.3 (12.0)	0.845[1]
Mean gradient	51.0 (11.6)	47.5 (11.0)	48.6 (9.8)	0.394[1]
Aortic valve velocity	4.5 (0.5)	4.4 (0.5)	4.4 (0.4)	0.765[1]
Valve area	0.9 (0.2)	0.8 (0.2)	0.8 (0.2)	0.339[1]
Valve area index	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.978[1]
Left ventricular mass index	129.0 (30.3)	114.2 (30.7)	124.6 (25.9)	0.110[1]

[1]ANOVA F-test

Table S6. Association between GDF11 and frailty, rehospitalization, and multiple adverse events after adjusting for potential confounding variables. Related to Table 1.

Variables	Odds Ratio	95% CI	p-value
	Frailty		
Age/10 yr	5.78	2.35 – 17.3	<0.001
Sex – Female	4.79	1.29 – 21.5	0.026
Cardiac Com.	9.12	2.50 – 42.1	0.002
BMI/5 pts	1.64	0.95 – 3.1	0.092
GDF11			**0.003**
	Rehospitalization		
Atrial fibrillation or flutter	11.67	2.82 – 61.37	0.001
Stroke	26.20	2.53 – 416.5	0.010
Pulmonary Disease	0.26	0.05 – 1.06	0.076
BMI/ 5pts	2.40	1.36 – 4.85	0.006
GDF11			**0.044**
	Multiple Adverse Events		
Diabetes	3.17	1.01 – 10.12	0.047
GDF11			**0.041**

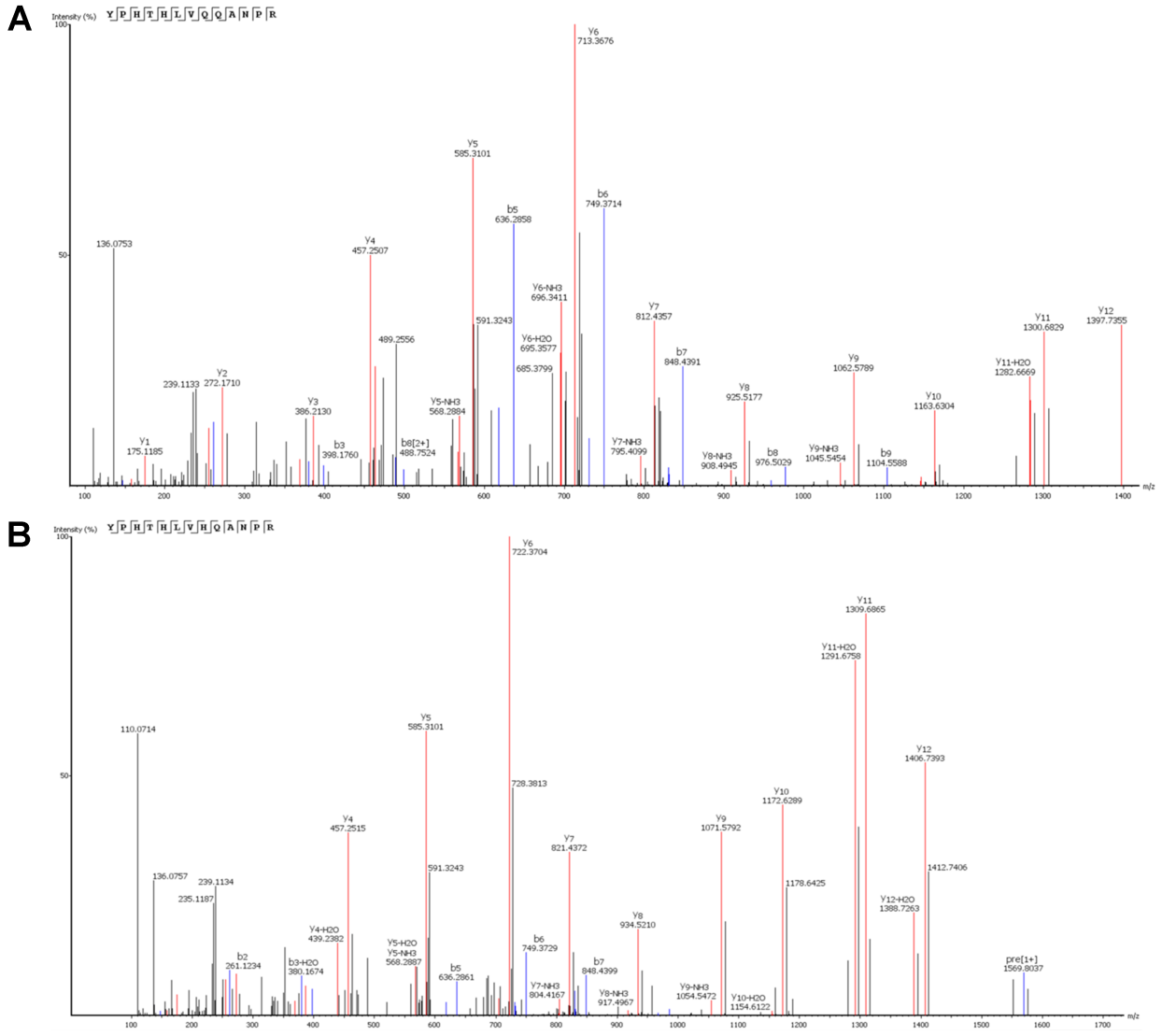

Figure S1. Comparative MS/MS peptide spectra for GDF11 (A) and MSTN (B). Related to Figure 1.