Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure with Preserved Ejection Fraction (RELAX):

A Randomized Clinical Trial

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on behalf of the
NHLBI Heart Failure Clinical Research Network

U.S. Department of Health and Human Services
National Institutes of Health

National Heart Lung and Blood Institute
People Science Health

Background

- Phosphodiesterase type-5 (PDE-5) metabolizes cGMP, the intracellular 2nd messenger for nitric oxide (NO) and the natriuretic peptides (NP)
- If PDE-5 activated in HF; may limit beneficial effects of NO and NP in the heart, vasculature and kidney
- PDE-5 Inhibitor therapy approved for
  - *Erectile dysfunction*
  - *Group I pulmonary arterial hypertension (PAH*)
- Role in heart failure (HF) with reduced (HFrEF) or preserved (HFpEF) ejection fraction unclear

Background

- **Experimental HF:** PDE-5 inhibition
  - *Reversed cardiac remodeling and dysfunction*
  - *Improved vascular and renal function*
- **Small Clinical Studies:** PDE-5 inhibition (sildenafil)
  - *HFrEF*

    Improved maximal exercise capacity
  - *HFpEF + PAH + RV dysfunction*

    Improved hemodynamics, lung function, RV function and LV remodeling

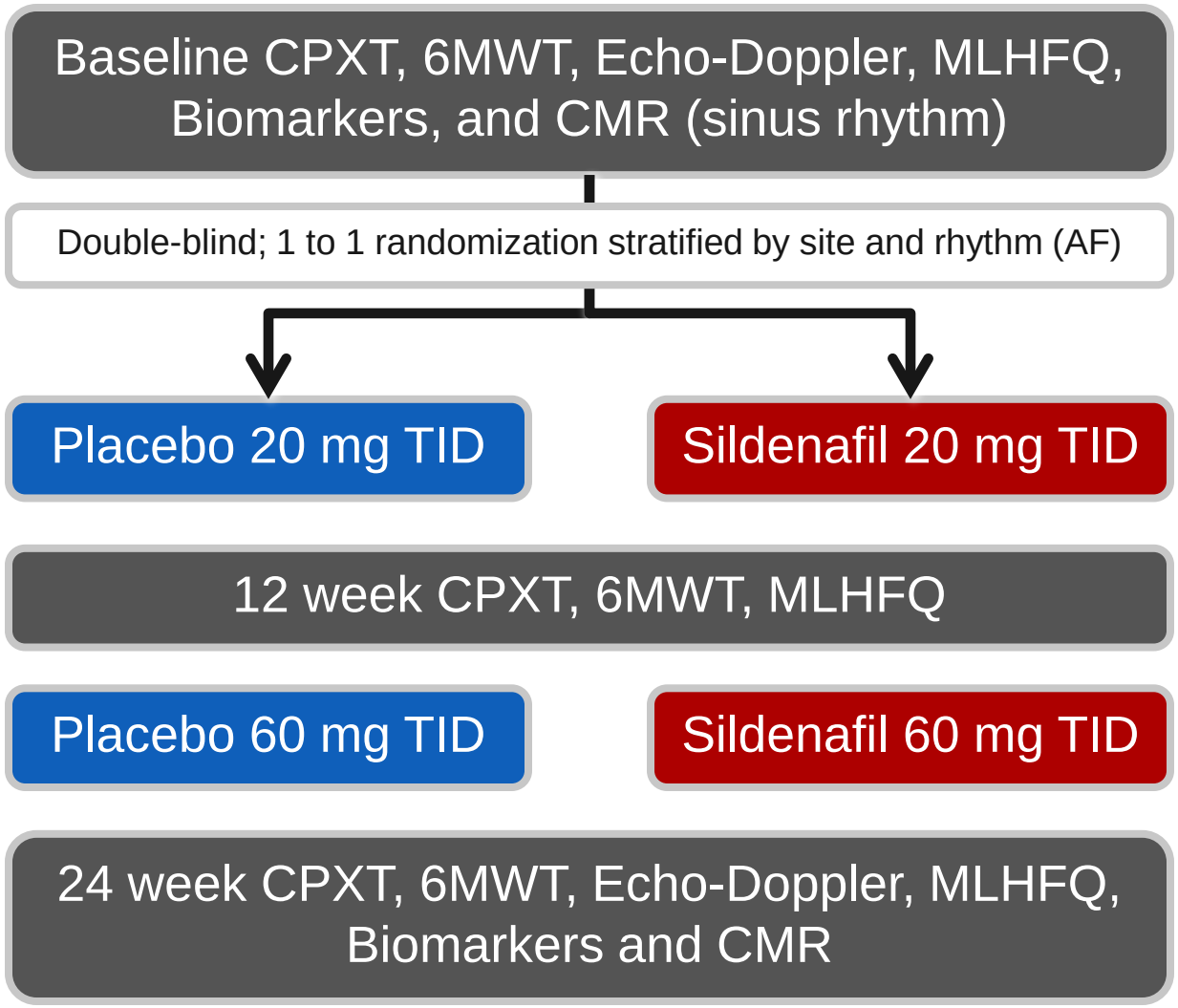
Hypothesis

In comparison to placebo, chronic (24 weeks) therapy with the PDE-5 inhibitor sildenafil will improve exercise capacity (peak VO_2) and clinical status in HFpEF.

Study population

- NYHA class II-IV HF symptoms
- EF ≥ 50%
- Objective evidence of HF (at least one)
  - *HF hospitalization*
  - *Elevated PCWP at catheterization for dyspnea*
  - *Left atrial enlargement + chronic diuretic for HF*
- At study entry (both)
  - *Peak VO_2 < 60% age/sex nl value + RER ≥ 1.0*
  - *NT-proBNP*
    - *≥ 400 pg/ml **or***
    - *< 400 pg/ml with documented ↑ PCWP ≤ two weeks of NT-proBNP < 400*

Study Design



Study Endpoints

- **Primary Endpoint**
  - *Change in peak VO_2 after 24 weeks of therapy*
- **Secondary Endpoints**
  - *Change in 6MWD after 24 weeks of therapy*
  - *Hierarchical composite clinical rank score*
- **Other Endpoints**
  - *Change in CV structure and function (24 weeks)*
    Echo-Doppler
    Cardiac magnetic resonance imaging (CMR)
  - *Change in biomarkers (24 weeks)*

Hierarchical composite clinical rank score

HEART FAILURE NETWORK

At 24 weeks, all patients ranked

1	**FIRST** Death
X	**LAST** Death

Hierarchical composite clinical rank score

HEART FAILURE NETWORK

At 24 weeks, all patients ranked

1	**FIRST** Death
X	**LAST** Death
X+1	Alive with **FIRST** CV or renal hospitalization
Y	Alive with **LAST** CV or renal hospitalization

Hierarchical composite clinical rank score

HEART FAILURE NETWORK

At 24 weeks, all patients ranked

1	**FIRST** Death
X	**LAST** Death
X+1	Alive with **FIRST** CV or renal hospitalization
Y	Alive with **LAST** CV or renal hospitalization
Y+1	**LEAST** favorable change in MLHFQ
Z	**MOST** favorable change in MLHFQ

Mean rank score (lower worse) compared between treatment groups
Anchor value (no treatment effect) = Z / 2

Baseline Features

Characteristic	Placebo (N = 103)	Sildenafil (N = 113)
Age (years)	69	68
Female	53%	43%
White race	92%	90%
BMI (kg/m^2)	33	33
NYHA class II/III	45% / 55%	49% / 51%
HF hospitalization in past year	39%	35%
Hx hypertension	90%	80%*
Hx of coronary artery disease	36%	42%
Diabetes	44%	42%
Hx of atrial fibrillation	50%	52%

Median values or % shown

****p-value < 0.05***

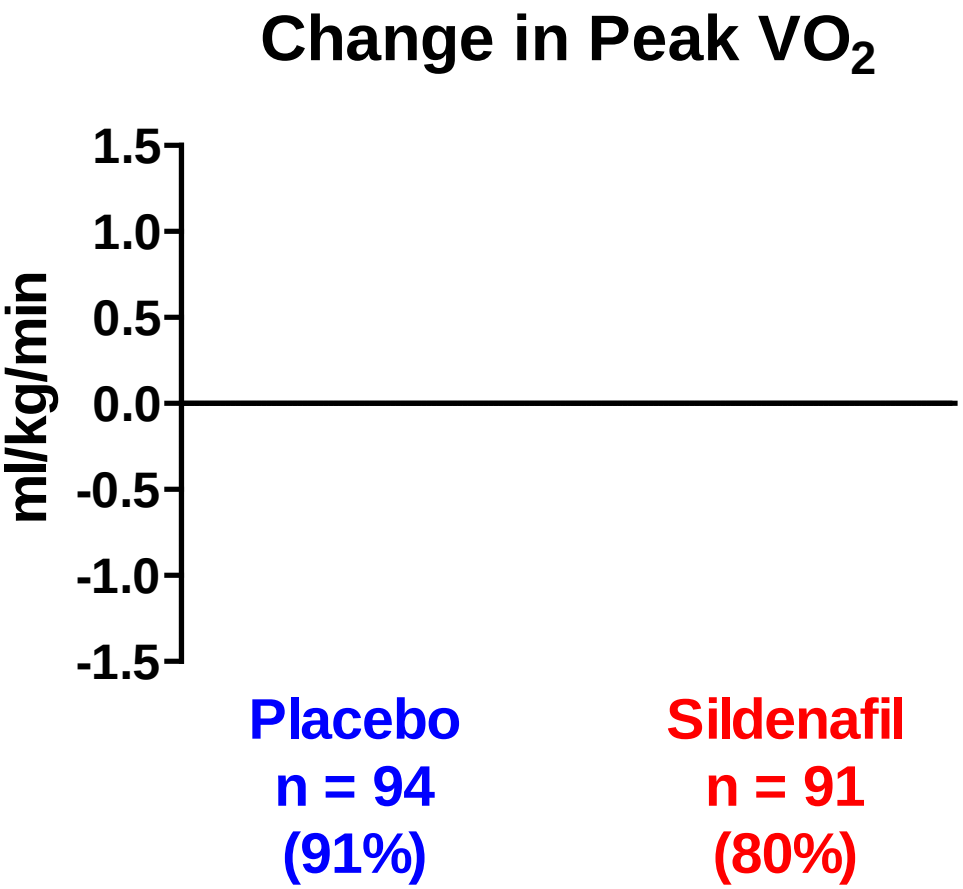
Baseline Features

Characteristic	Placebo (N = 103)	Sildenafil (N = 113)
Ejection fraction (%)	60	60
NT-proBNP (pg/ml)	648	757
Peak VO2 (ml/kg/min) (% predicted)	11.9 (41%)	11.7 (41%)
Chronotropic incompetence present	78%	76%
6MWD (m) (% predicted)	305 (68%)	308 (70%)
Cardiac index (L/min/m^2) - *(normal > 2.5)*	2.48	2.47
Relative Wall Thickness ≥ 0.42	44%	48%
E/e' - *(normal ≤ 8)*	17	15
LA volume index (ml/m^2) - *(normal < 29)*	43	44
PASP (mmHg) - *(normal < 30)*	41	41

Median values or % shown

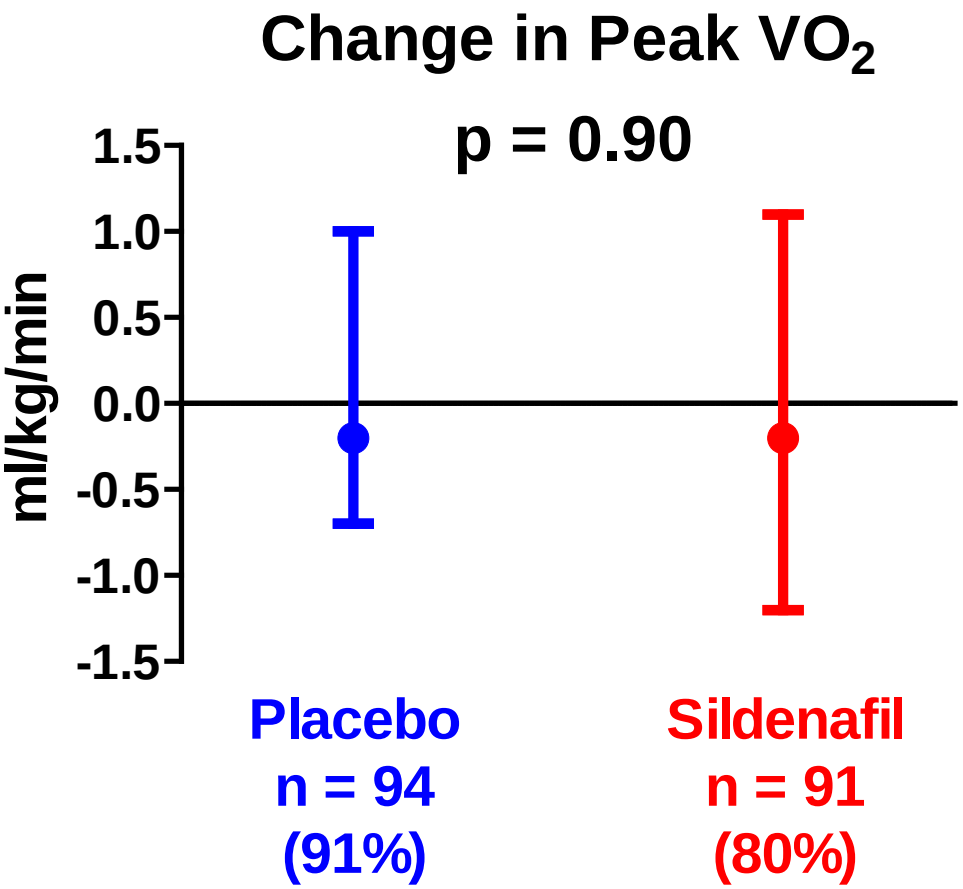
All p > 0.05

Results: Primary Endpoint



Withdrew consent (n=14), death (n=3), unwilling (n=3) or unable (n=9) to complete CPXT, inadequate peak VO_2 data (n=2)

Results: Primary Endpoint

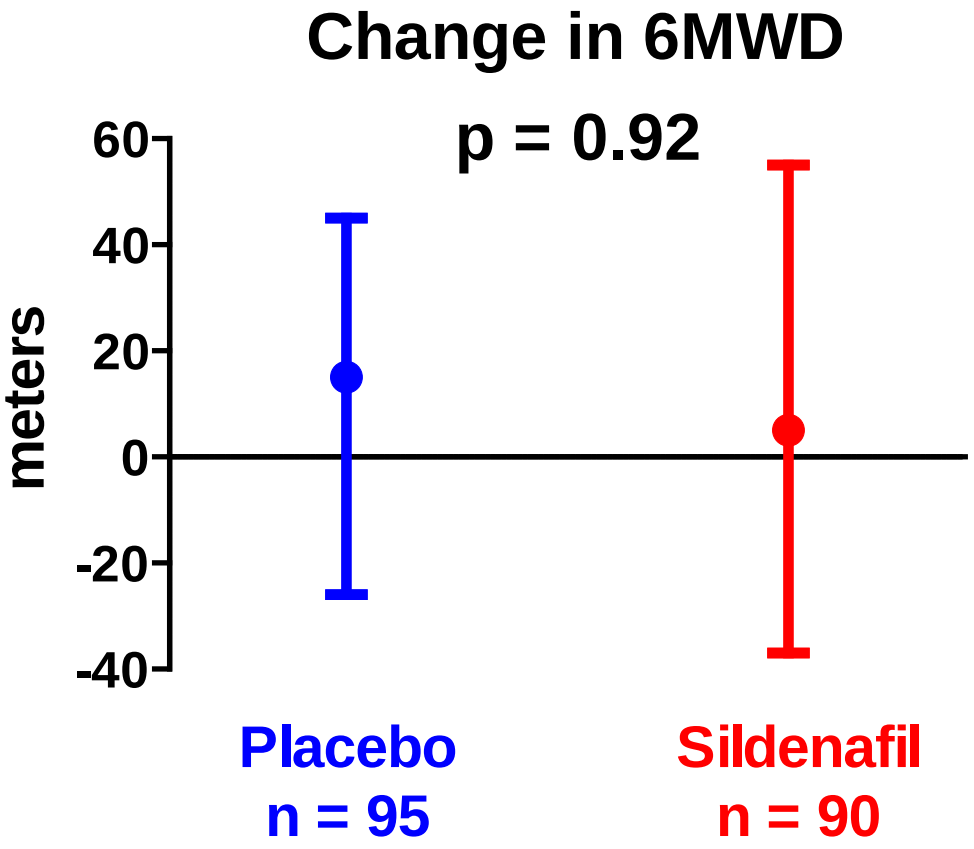


Sensitivity analyses for missing data

Multiple imputation: p = 0.98; LOCF: p = 0.98

Data are median and IQR

Results: Secondary Endpoints



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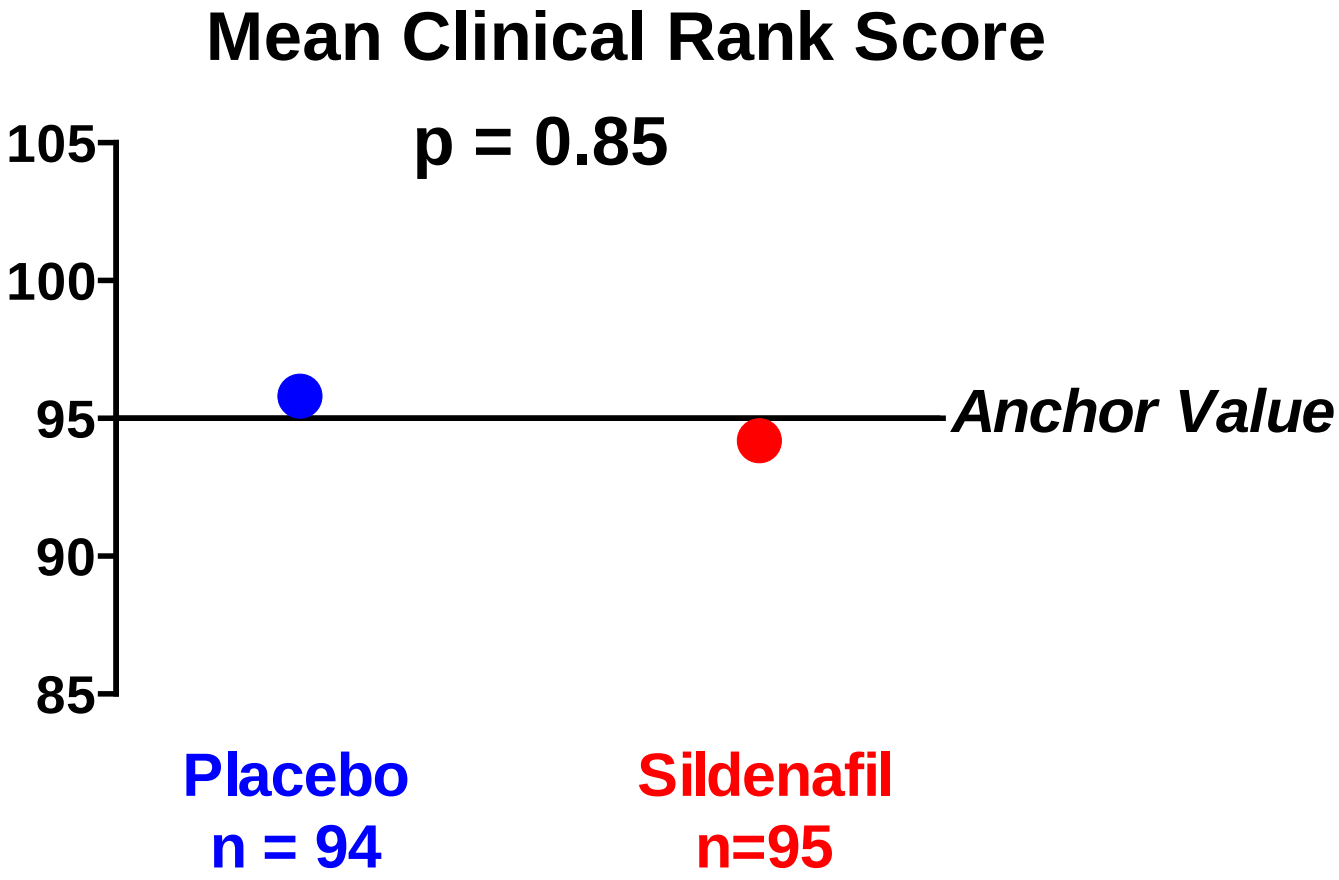
Results: Secondary Endpoints



Results: Safety

Characteristic	Placebo	Sildenafil
Death (%)	0%	3%
CV or cardiorenal hospitalization (%)	13%	13%
Adverse events (%)	76%	80%
Serious adverse events (%)	16%	22%
Withdrew or Unwilling or Unable to complete 24 week CPXT	8%	16%

All p > 0.05

Results: Other endpoints

Characteristic	Placebo	Sildenafil
Change in LV mass by CMR (g)	0.6	-1.5
Change in E/e’	-1.6	0.2
Change in PASP (mmHg)	-2	2
Change in creatinine (mg/dl)	0.01	0.05*
Change in cystatin C (mg/L)	0.01	0.05*
Change in NT-proBNP (pg/ml)	-23	15*
Change in endothelin-1 (pg/ml)	-0.01	0.38*
Change in uric acid (mg/dl)	-0.01	0.30*

p-value < 0.05

Median values shown

Conclusions

- Chronic therapy with the PDE-5 inhibitor sildenafil was not associated with clinical benefit in HFpEF
- Continued efforts to identify key pathophysiologic perturbations and novel therapeutic targets in HFpEF are needed

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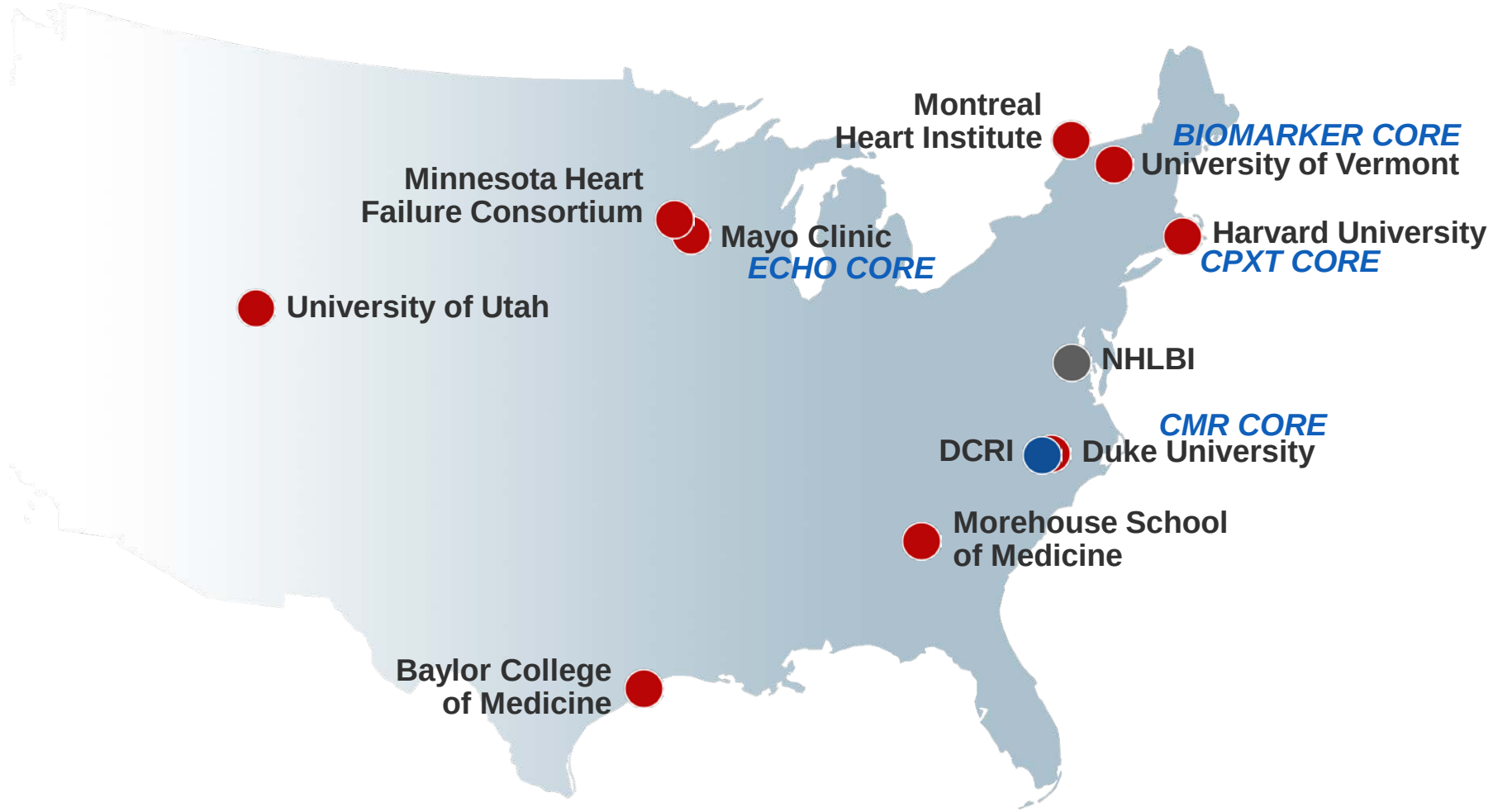

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