



Sildenafil or Revatio® REVERSE-DBMD Trial

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9th International
Annual Conference



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DBMD and the heart

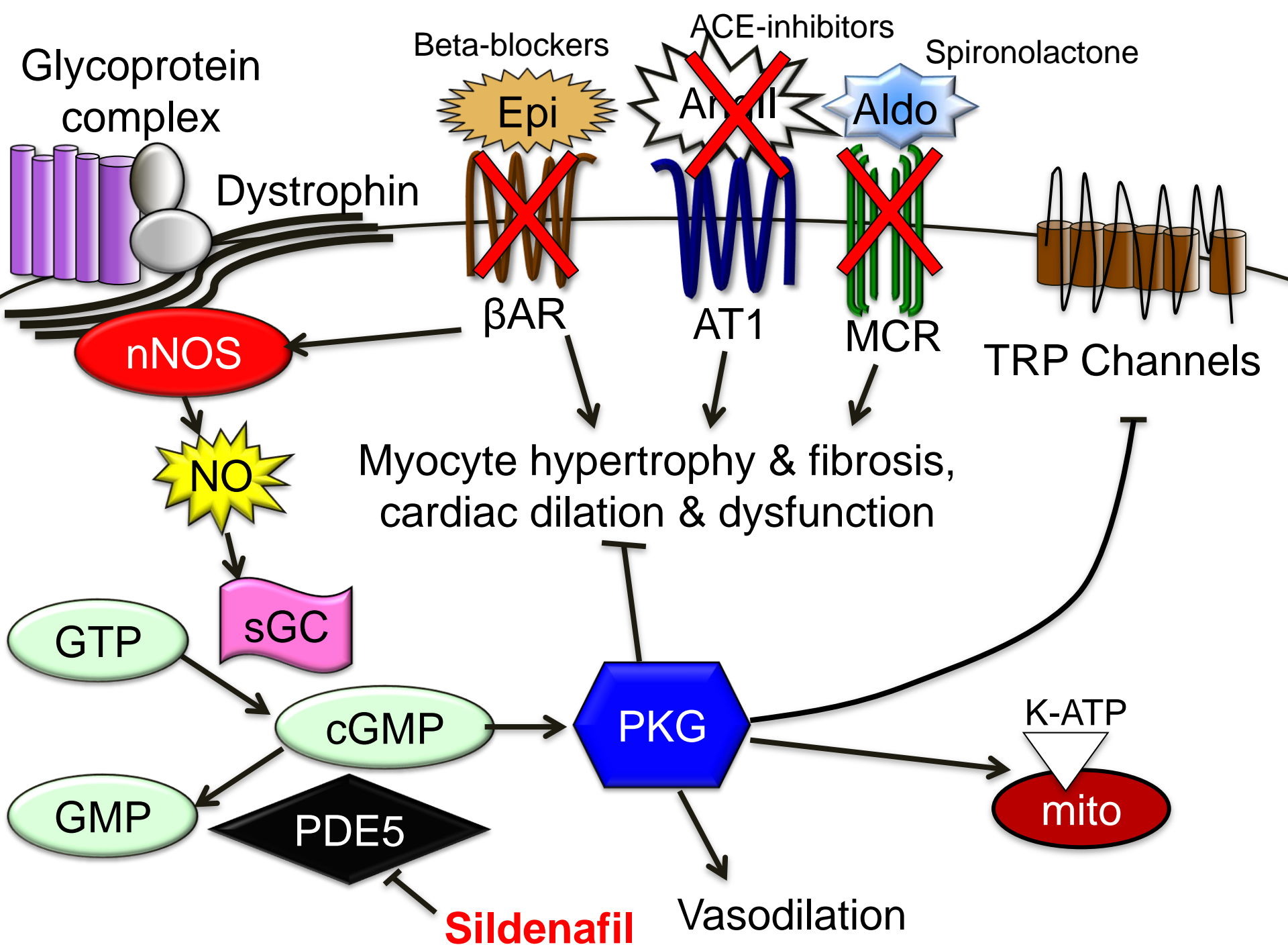
- DBMD typically causes dilation and decreased strength of the heart.
- Improvements in pulmonary and neuromuscular care often leave heart failure and cardiomyopathy behind as major life-threatening aspects of DBMD.
- In contrast with other muscles in the body, the heart must continue to function, beating ~ 100,000 times in one day and about 35 million times in a year.

Sildenafil

- Phosphodiesterase type-5 (PDE5) inhibitor that was initially developed to treat blockages of coronary arteries; didn't help.
- Initial testing was in people with coronary artery disease, many of whom had erectile dysfunction.
- Volunteers in these studies reported normalization of erectile function, leading to its initial FDA approval (Viagra).

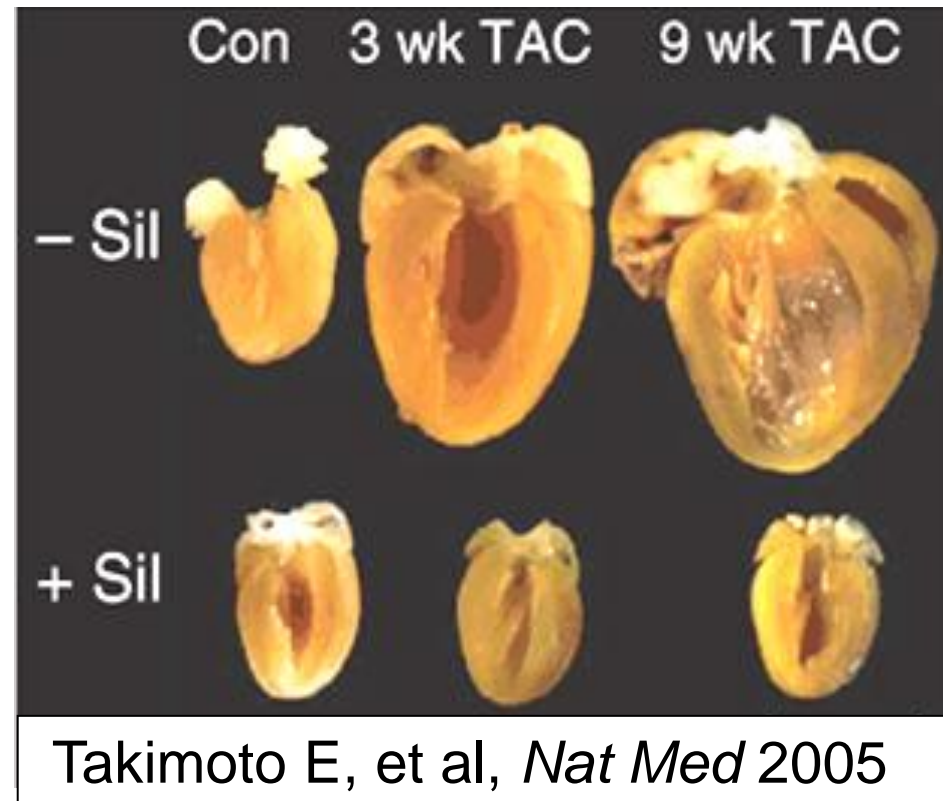
Revatio (sildenafil)

- Because there is a lot of PDE5 in the lung's blood vessels, and because PDE5 inhibition can dilate these blood vessels, sildenafil was tested in pulmonary hypertension.
- Approved for treatment of pulmonary hypertension.
- Several studies in children, some in infants; approved for use in children (EU), and under review for use in children by the US FDA.



Sildenafil in the heart

- Sildenafil has no significant effect on normal, unstressed hearts.
- Work by Dr. David Kass at JHU focused on the role of PDE5 in remodeling of the heart in response to high pressures.
- Sildenafil was very beneficial...in mice.



Several other important sildenafil reports in mdx mice:

Sildenafil and cardiomyocyte-specific cGMP signaling prevent cardiomyopathic changes associated with dystrophin deficiency

2008

M. Khairallah^{*†}, R. J. Khairallah^{*}, M. E. Young[‡], B. G. Allen^{*}, M. A. Gillis^{*}, G. Danialou[†], C. F. Deschepper[§], B. J. Petrof[†], and C. Des Rosiers^{*¶}

Sildenafil reverses cardiac dysfunction in the *mdx* mouse model of Duchenne muscular dystrophy

2010

Candace M. Adamo^a, Dao-Fu Dai^{b,1}, Justin M. Percival^{c,1}, Elina Minami^d, Monte S. Willis^e, Enrico Patrucco^a, Stanley C. Froehner^{c,2}, and Joseph A. Beavo^{a,2}

Departments of ^aPharmacology, ^bPathology, ^cPhysiology and Biophysics, and ^dMedicine, University of Washington, Seattle, WA 98195; and ^eDepartment of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, NC 27599

Contributed by Joseph A. Beavo, September 10, 2010 (sent for review August 9, 2010)

Am J Physiol Heart Circ Physiol 300: H144–H153, 2011.

First published October 22, 2010; doi:10.1152/ajpheart.00522.2010.

Stress-induced opening of the permeability transition pore in the dystrophin-deficient heart is attenuated by acute treatment with sildenafil

2011

Alexis Ascah,² Maya Khairallah,^{1,3} Frédéric Daussin,² Céline Bourcier-Lucas,² Richard Godin,² Bruce G. Allen,^{1,4} Basil J. Petrof,⁵ Christine Des Rosiers,^{1,3} and Yan Burelle²

REVERSE-DBMD trial

- Title: REvatio for hEaRt diseaSE in Duchenne & Becker Muscular Dystrophy
- Hypothesis: Sildenafil will improve both cardiac and vascular properties of the enrolled participants compared to placebo.
- Design: 6 months randomized, double-blinded, placebo-controlled therapy with sildenafil (Revatio 20 mg 3x/day), followed by 6 months of open-label treatment with sildenafil 20 mg 3x/day. **Currently Enrolling!**

REVERSE-DBMD trial

- Primary endpoint: The difference between the change in cardiac left ventricular end-systolic volume (LVESV) as determined by cardiac MRI between baseline and after 6 months of treatment in those treated with oral sildenafil compared with those treated with placebo.
- Each person acts as their own “control.”
- Enrollment will be 30 participants.

REVERSE-DBMD trial

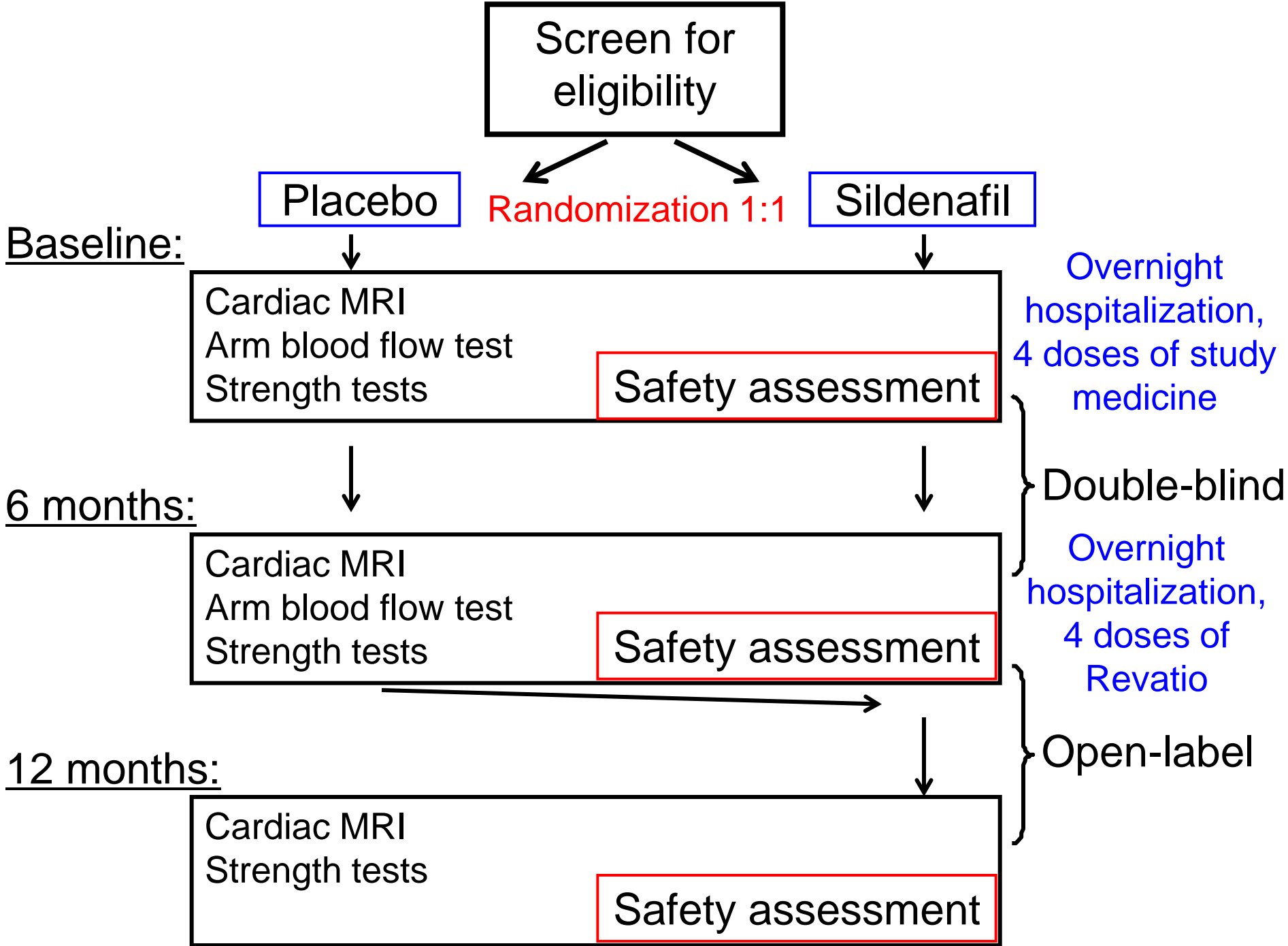
- Secondary endpoints: other measures of cardiac function (systolic and diastolic) and size by MRI at 6 months;
- Difference in LVESV at 6 vs. 12 months
- Non-cardiac effects: difference in function of arteries by flow-mediated vasodilation, difference in diaphragm function and grip strength, difference in quality of life.
- Determine the safety and tolerability of sildenafil administered at a dose of 20 mg three times daily in the context of DBMD with cardiac dysfunction.

Inclusion criteria:

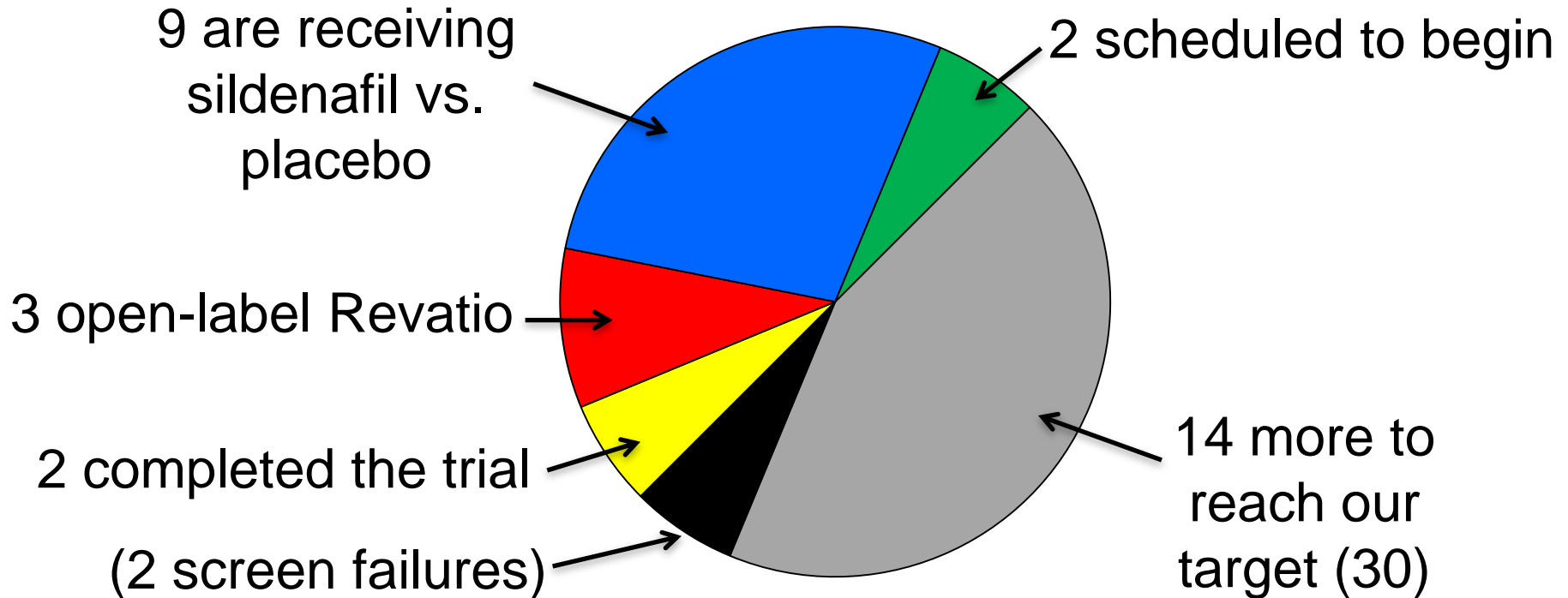
- Duchenne or Becker muscular dystrophy
- Male gender
- Age 15 to 50 years
- Cardiac EF \leq 50%
- Stable dose of ACE-inhibitor or ARB for at least 3 months; beta-blockers and corticosteroids are not required but if used, on a stable dose for at least 3 months.
- Ability to provide informed consent, follow protocol, and adhere with follow-up.

Exclusion criteria:

- Nitrates or alpha-adrenergic receptor blockers
- Allergy to sildenafil, or history of severe allergy
- Eye disease: retinitis pigmentosa
- History of priapism, sickle cell anemia, multiple myeloma, or leukemia
- Bleeding disorders
- Active tobacco use
- Atrial fibrillation
- Unable to tolerate MRI (ICD or cannot fit in MRI)
- Systolic blood pressure ≤ 85 mmHg
- Chronic kidney disease stages 4 and 5
- Current use of sildenafil.



Status of Enrollment:



Several more have had adjustment in medications to be compliant with inclusion or exclusion criteria, and will have cardiac function assessed 3 months later.

Additional issues:

1. Safety – “Adverse Events”:
 - One participant with a history of GI troubles (gastroparesis, swallowing air with BiPAP) was hospitalized with the same; he had complete resolution after an NG tube.
 - One participant had fecal impaction and was evaluated in an outside Accident/ER.
 - One participant was hospitalized due to power outage and need for BiPAP.
 - One participant developed viral gastroenteritis during initial study hospitalization, which resolved in 12 hours.

Additional issues:

1. Safety

- No major problems to date.

2. Non-cardiac effects

- No problems or complaints.

3. Blood pressure

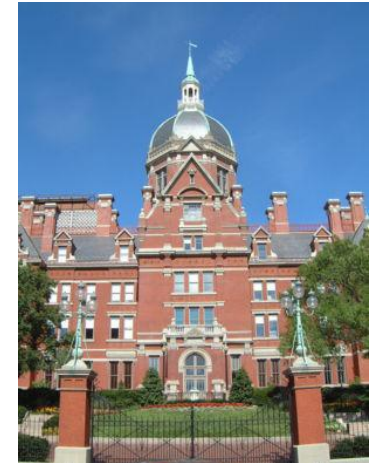
- Generally low for this group, but OK so far.

4. Dosing

- Based on approved dose for pulmonary hypertension.

Others on the Study Team:

- Kathryn Wagner, MD, PhD (co-PI with me)
- David Kass, MD
- Geni Bibat, MD
- Reid Thompson, MD
- Stuart Russell, MD
- Doris Leung, MD
- Al Lardo, PhD
- Mary Corretti, MD
- Clinical Trials.gov ID: NCT01168908



Kennedy Krieger Institute

<http://www.clinicaltrials.gov/ct2/show/NCT01168908>

Should I start using sildenafil?

- Research studies are done with careful analysis for both risks and benefits.
- Many treatments that seem to be good are not proven safe/effective in trials.

Hurt By Avandia?
Now Is The
Time To Act



Get Help Now

**IMPORTANT
DRUG
WARNING**

Please take the time to read the following important information regarding Trasylol (aprotinin injection)

MEDIATOR
150 mg

Combien de morts ?

Representing Victims of
Ketek Side Effects



ADHD Drugs Linked
to Teen Sudden Death



Jun 16, 2009 1:22 AM CDT

Vioxx Side Effects

Heart Attack, Stroke,
Kidney Failure?



Summary:

- Cardiomyopathy and heart failure are a common, life-threatening problem in DMD.
- Sildenafil looks promising for the treatment of these conditions, based on the molecular defect in DMD.
- Our trial is about half-way finished, and we expect to share good news soon about this medication in DMD.

Acknowledgements:

- Funding:
 - [Pilot Trials Now](#): Charley's Fund, Nash Avery Foundation, Cure Duchenne, [Action Duchenne](#), Hope for Javier, Zubin's Wish
- Pfizer, Inc.
 - IIR Grant to supply Revatio and placebo for the trial
- Kennedy Krieger Institute's Kirby Research Center
 - MRI's are donated
- PPMD/DuchenneConnect
 - Recruitment & Motivation

