

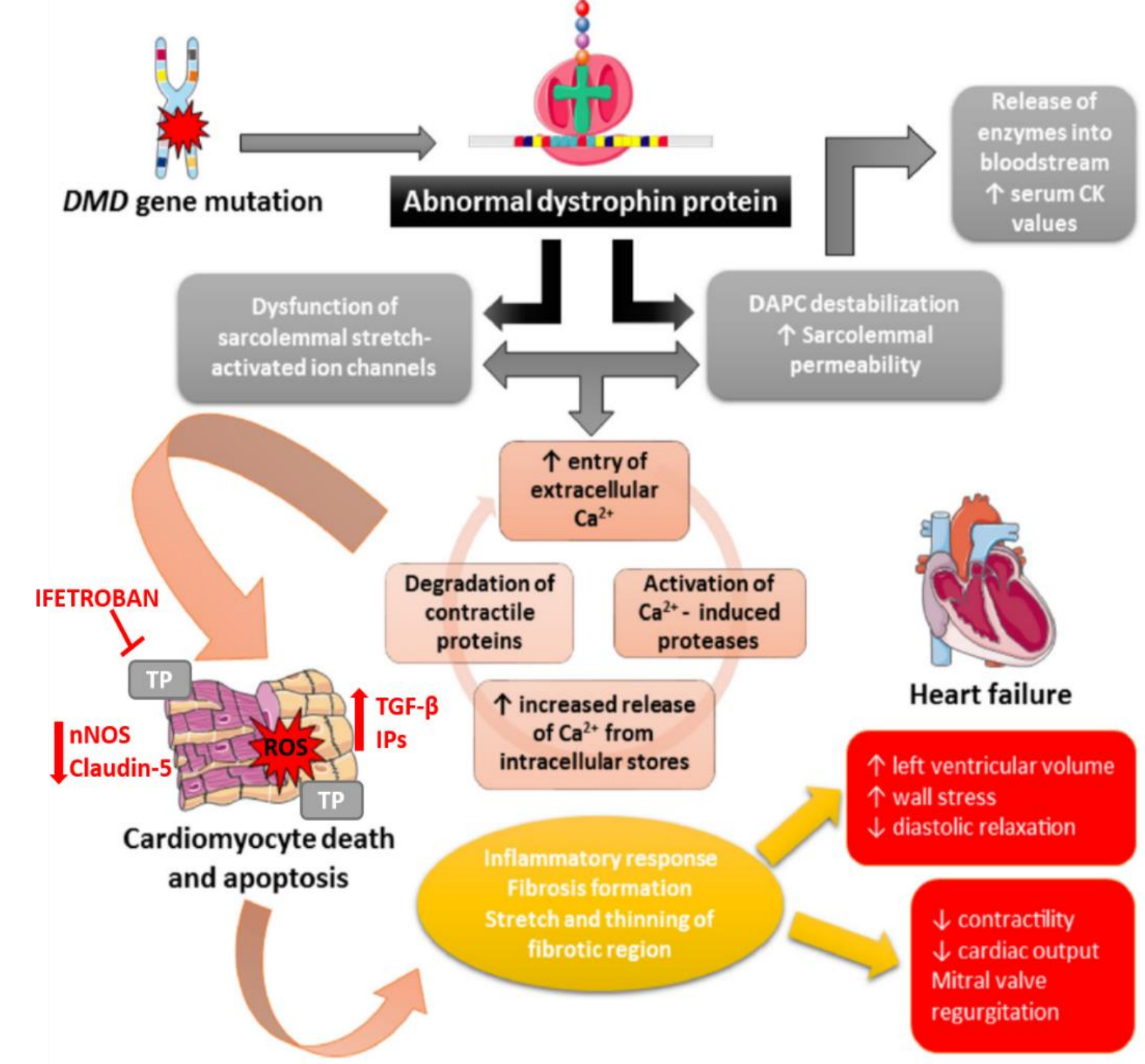


# Preventing Duchenne Muscular Dystrophy Cardiomyopathy Through Antagonism of the Thromboxane Prostanoid Receptor: An FDA Funded Phase 2 Clinical Trial

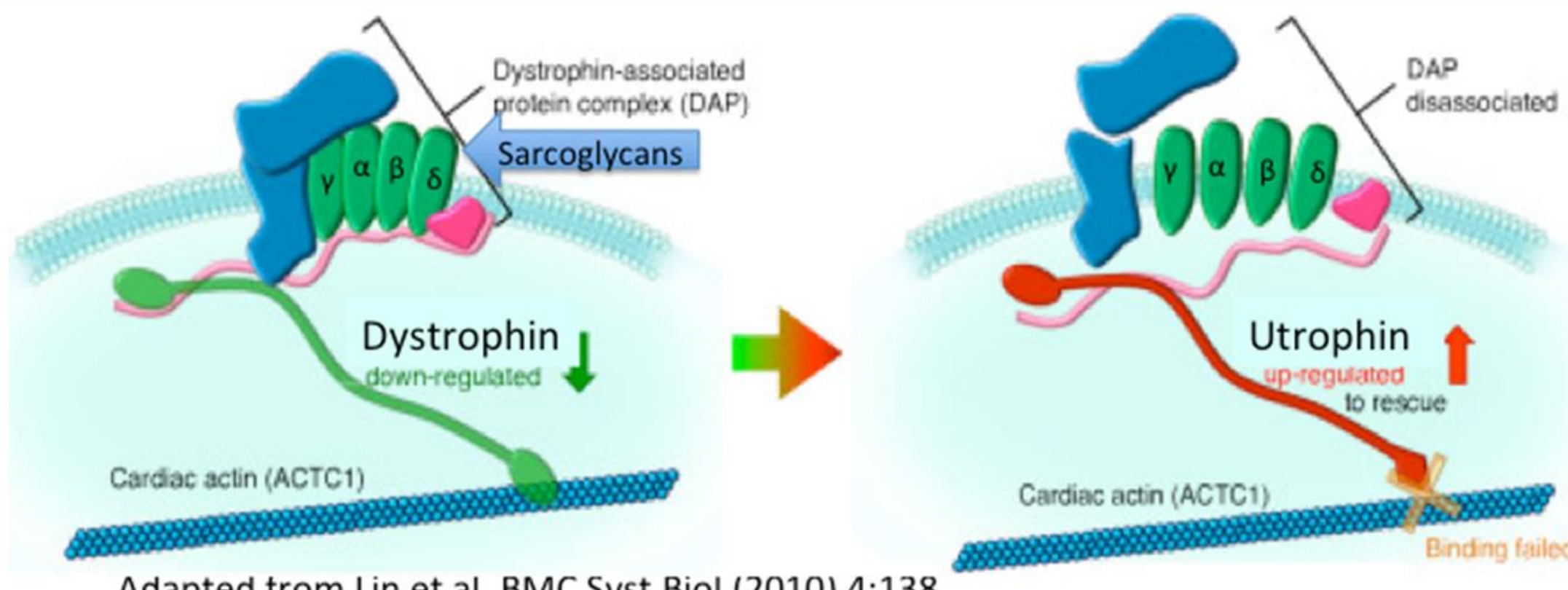
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## BACKGROUND

- Muscular dystrophy (MD) is associated with mechanical damage and increased membrane permeability of muscle cells. In the heart, this causes progressive weakness and cardiac fibrosis in Duchenne (DMD).
- Isoprostanes, products of oxidative stress, are increased in DMD and can signal through the thromboxane-prostanoid receptor (TPr) to cause fibrosis. TPr activation increases calcium levels inside the heart muscle cells and could contribute to arrhythmia or heart damage in DMD.
- We thus hypothesized that TPr activation contributes to the cardiac phenotype of DMD, and that blocking the TPr would be cardioprotective in mouse models of MD.



## MOUSE MODELS

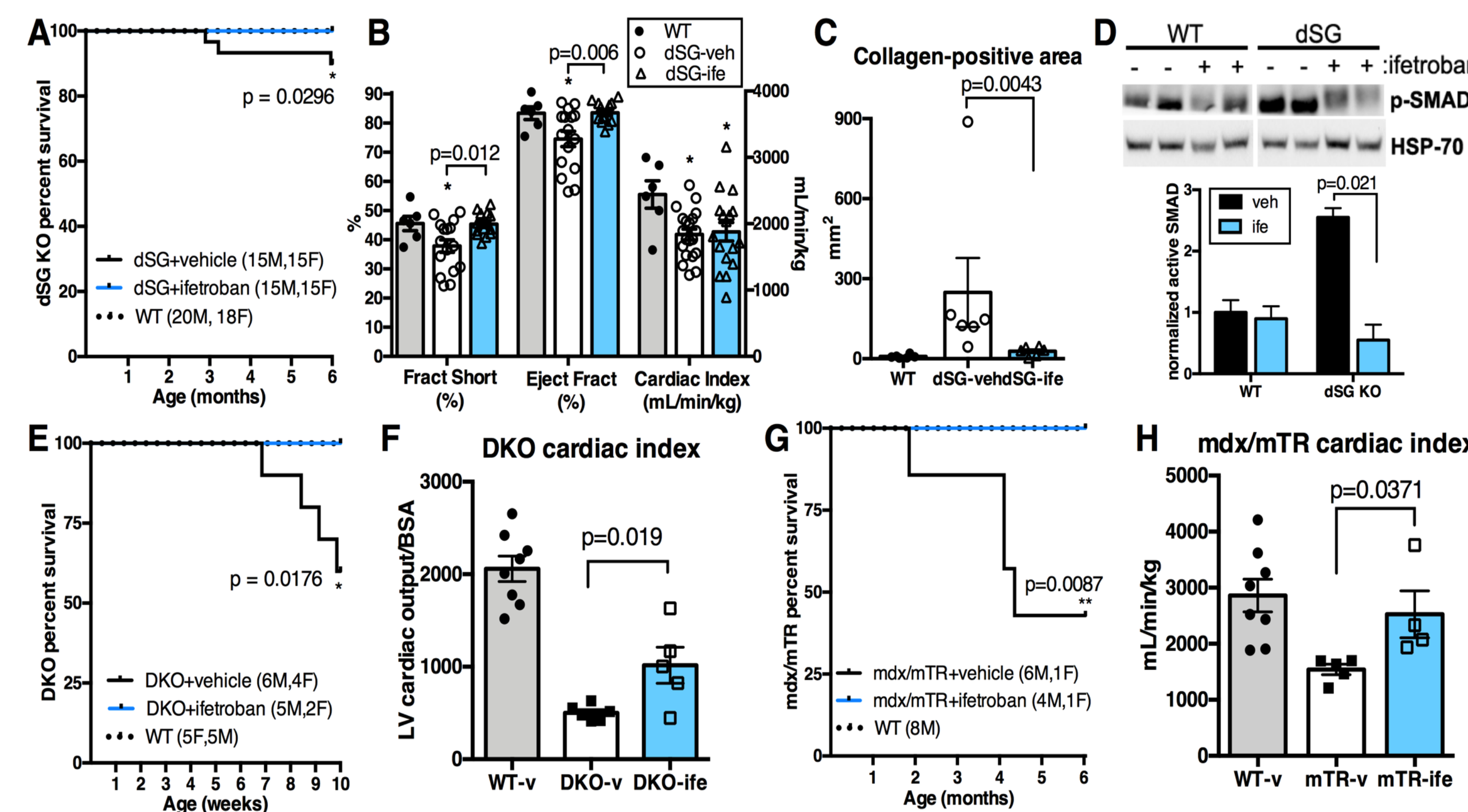


- DMD mouse models:
- Utrophin/dystrophin double knockout (DKO) → Evaluated at 10 weeks of age
  - 2nd generation dystrophin/RNA telomerase component double knockout (mdx/mTR), which has shortened telomeres → Evaluated at 6 months of age, with a midpoint echo at 3 months
  - Limb-girdle muscular dystrophy (LGMD) mouse model: Delta-sarcoglycan knockout (dSG) → Evaluated at 3 and 6 months of age

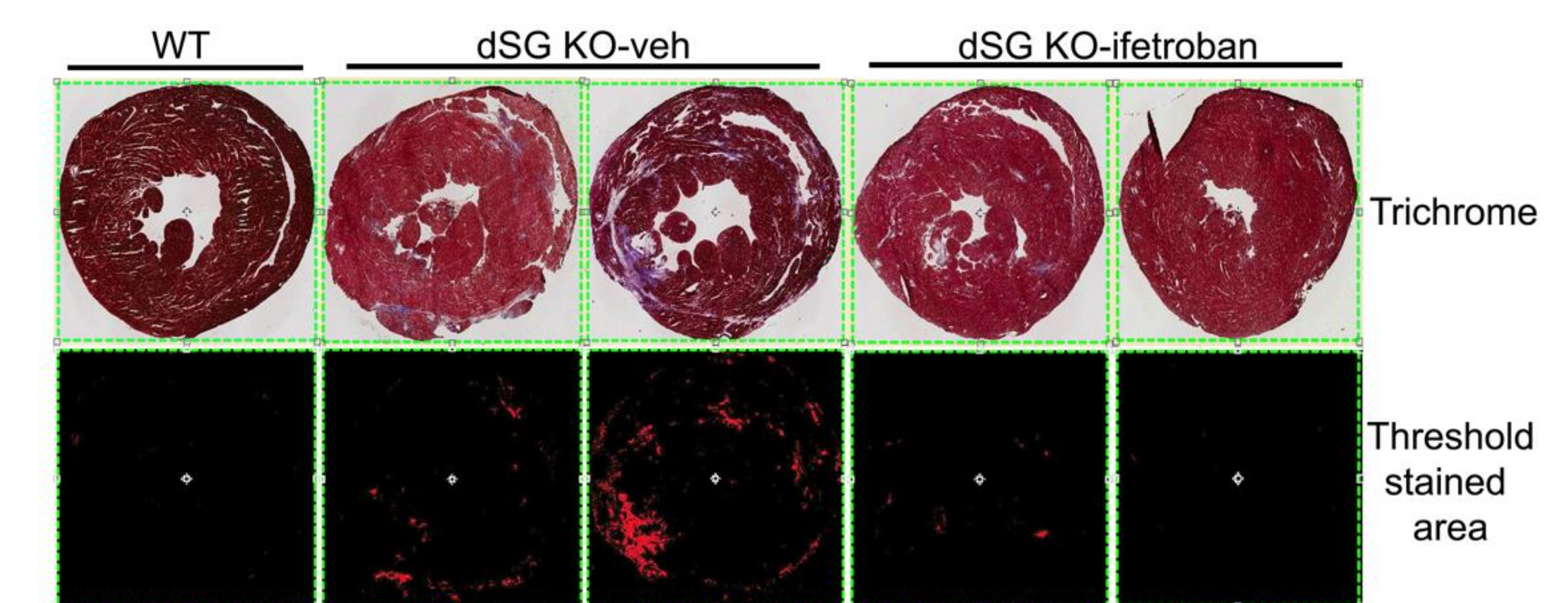
Mice were given either normal drinking water, or water containing 25 mg/kg/day of the TPr antagonist ifetroban, beginning at weaning. Water and drug changed 1x/week.

## PRECLINICAL DATA

### Ifetroban prevents cardiac fibrosis and improves survival in DMD mice



Treatment with the TPr antagonist ifetroban (ife) improves survival (A), normalizes fractional shortening and ejection fraction (B) and decreases epicardial interstitial fibrosis (C; n = 6) in dSG KO LGMD male mice. Fibrotic area was quantified from trichrome-stained whole slices in Leica Image Analysis using the same trichrome-defined image mask for all slides. Ife also decreased phospho-SMAD2/3, a TGFβ signaling molecule (D; n = 2). Comparison by unpaired t-test shown; intervening lanes were removed from blot in D. Utrophin-dystrophin double knockout DMD mice (DKO) and dystrophin KO mice with short telomeres (G2 mdx/mTR) have increased survival (E, G) and improved LV cardiac index with ife treatment (F, H). The results of log-rank test (E, G) or unpaired t-test (F, H) comparisons are shown. (H) is male mice only, due to sex differences of cardiac output in fully grown mice. \*, p < 0.05 by log-rank test. dSG KO = delta-sarcoglycan knockout;

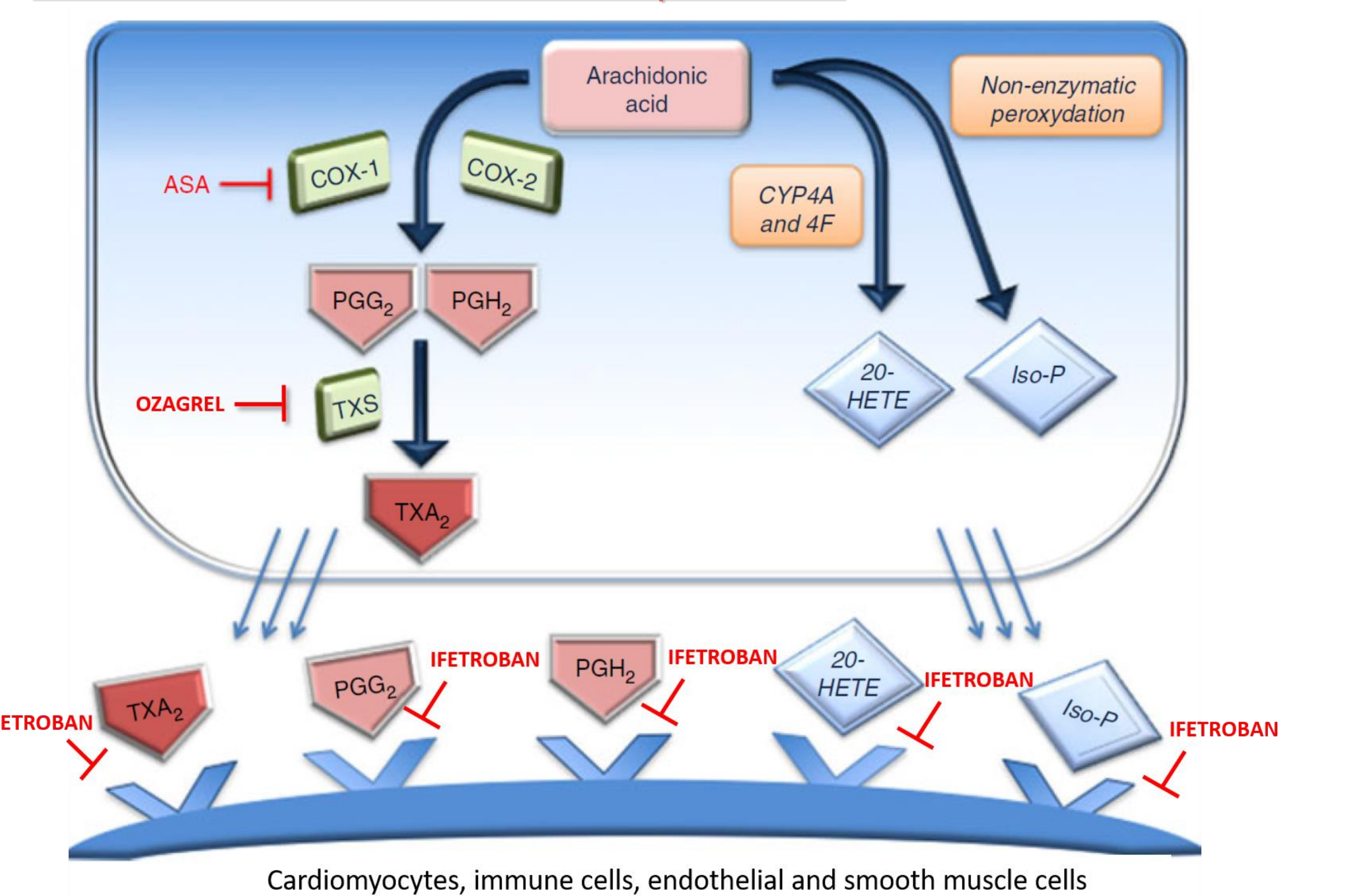


The diffuse myocardial fibrosis characteristic of DMD typically begins in the free wall of the LV, and is seen as blue stain (top) or red mask (bottom). Fibrotic area was quantified from trichrome-stained male frozen heart sections in Leica Image Analysis, using the same trichrome-defined mask for all slides. Ifetroban-treated dSG KO mice had reduced myocardial fibrosis (C), which corresponded with reduced phosphorylation of SMAD2/3, a TGF-β signaling protein (D).

## CENTRAL HYPOTHESIS

Our preclinical studies demonstrate ifetroban is cardioprotective in several muscular dystrophy models of heart disease.

These data have led us to design the proposed randomized, placebo-controlled, multicenter phase 2 trial to test the central hypothesis that **Thromboxane Receptor signaling promotes cardiac inflammation contributing to DMD cardiomyopathy and thus treatment with ifetroban will impact heart muscle disease in DMD patients.**



## THE FIGHT DMD TRIAL

- ★ 48 DMD participants needed ≥ 7 years of age
- ★ 12 Months of treatment
- ★ 3 Office visits

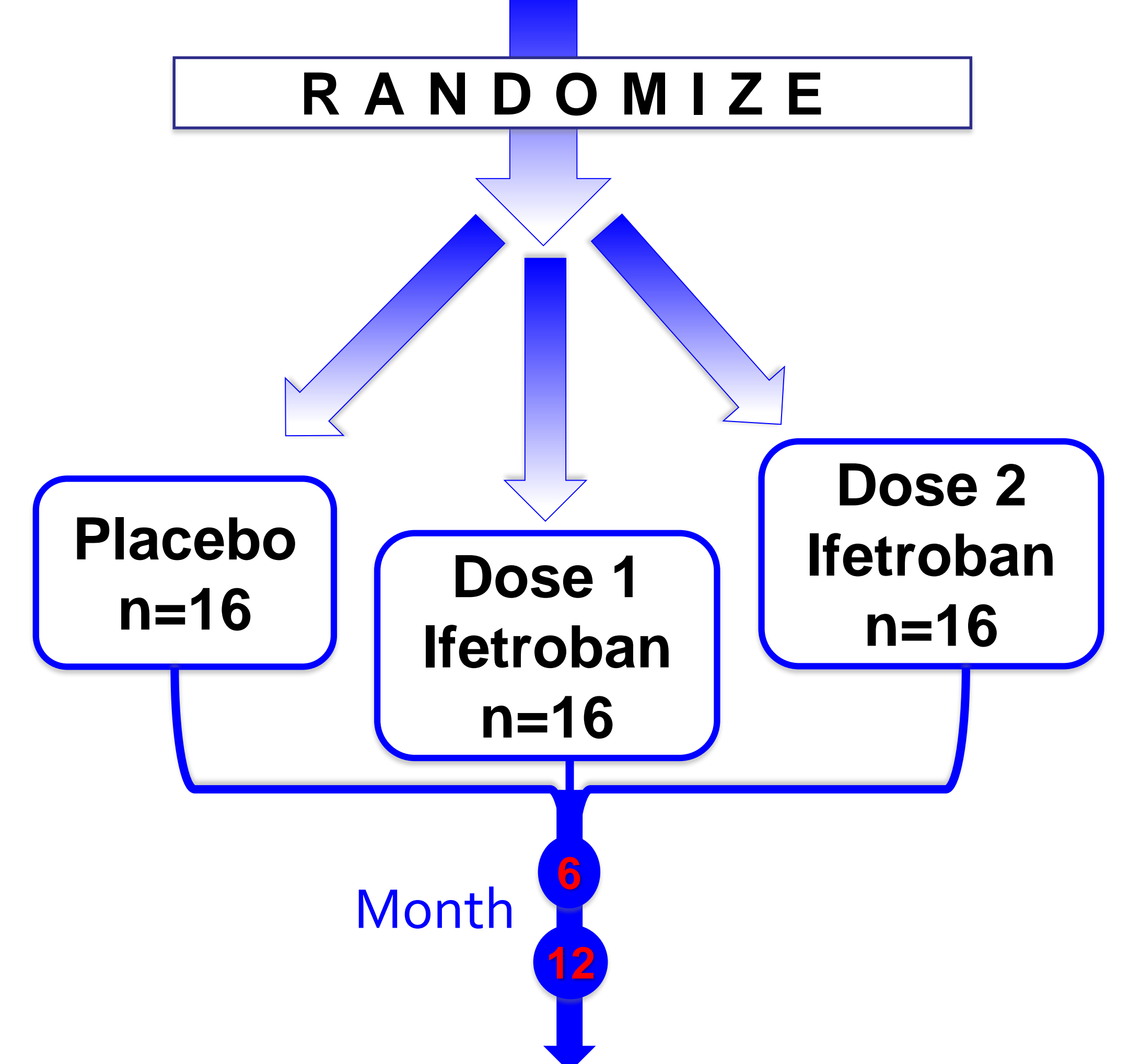
The FIGHT DMD Clinical Trial will determine the safety, pharmacokinetics and efficacy of ifetroban in Duchenne muscular dystrophy.

Ifetroban is being studied as a potential anti-fibrotic medication in several diseases but is not approved for and has never been studied in DMD.

Ifetroban is a treatment thought to impact the heart disease associated with DMD.

## TRIAL DESIGN

- 48 DMD participants**
- ≥ 7 years of age
  - Stable or No steroids allowed
  - EF ≥ 35% by MRI/Echo
  - ACEi, BB & ARB allowed
  - Aldosterone receptor antagonists & exon-skipping agents allowed



- Endpoints**
- Safety
  - Efficacy
    - Cardiac MRI
    - Quality of Life
  - Exploratory
    - Daily life activity
    - Muscle strength

## ACKNOWLEDGEMENTS

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