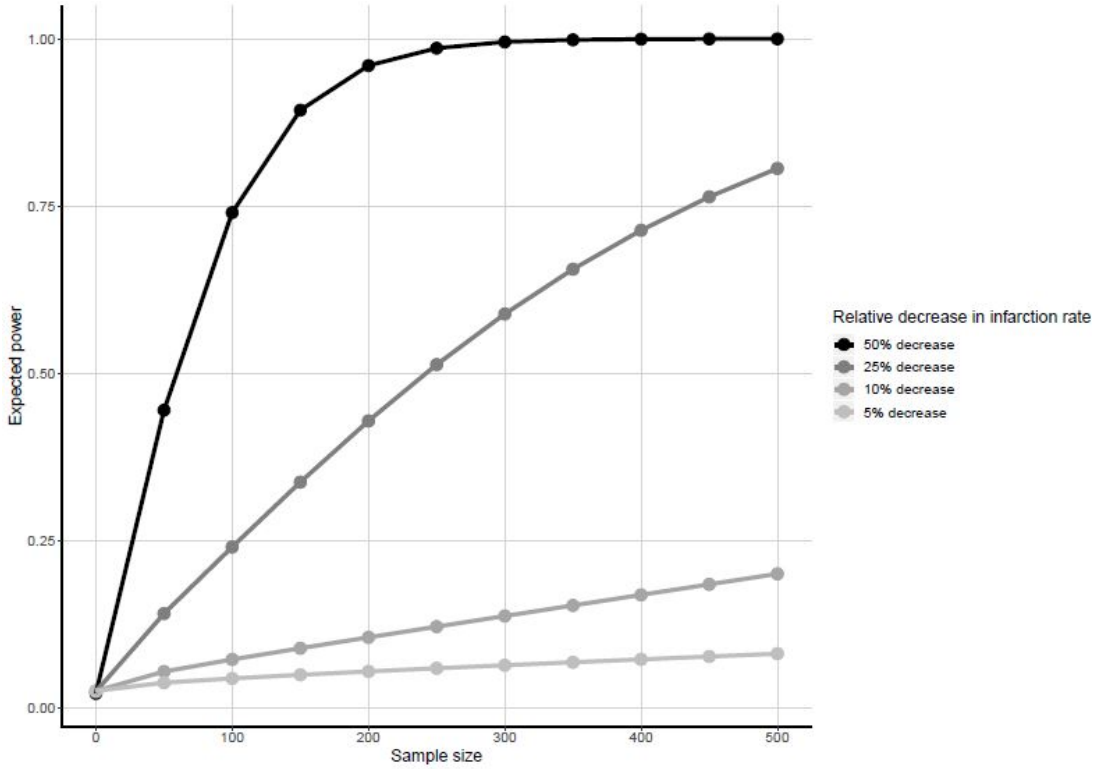
Supplemental discussion

Power calculation

We used the Fazekas and infarction data within men with classical FD since progression risk was highest in this group. Effect of enzyme replacement therapy was regarded as negligible so we included all patients (treated and untreated). We calculated sample sizes needed for trials looking to decrease the infarction rate or to stabilize the Fazekas score, with the outcomes categorized as binary[1] and ordinal[1 2], respectively.

Infarctions on MRI were present in 0% of men with classical disease at 20 years old and in 50% at ~45 years old (**Figure 1**). Hypothetically, a new treatment might relatively reduce the infarction rate with 50%, 25%, 10% or 5%, resulting in an absolute infarction rate reduction at 45 years of age of 25% (50% of 50%), 12.5% (25% of 50%), 5.0% (10% of 50%), and 2.5% (5% of 50%), respectively.

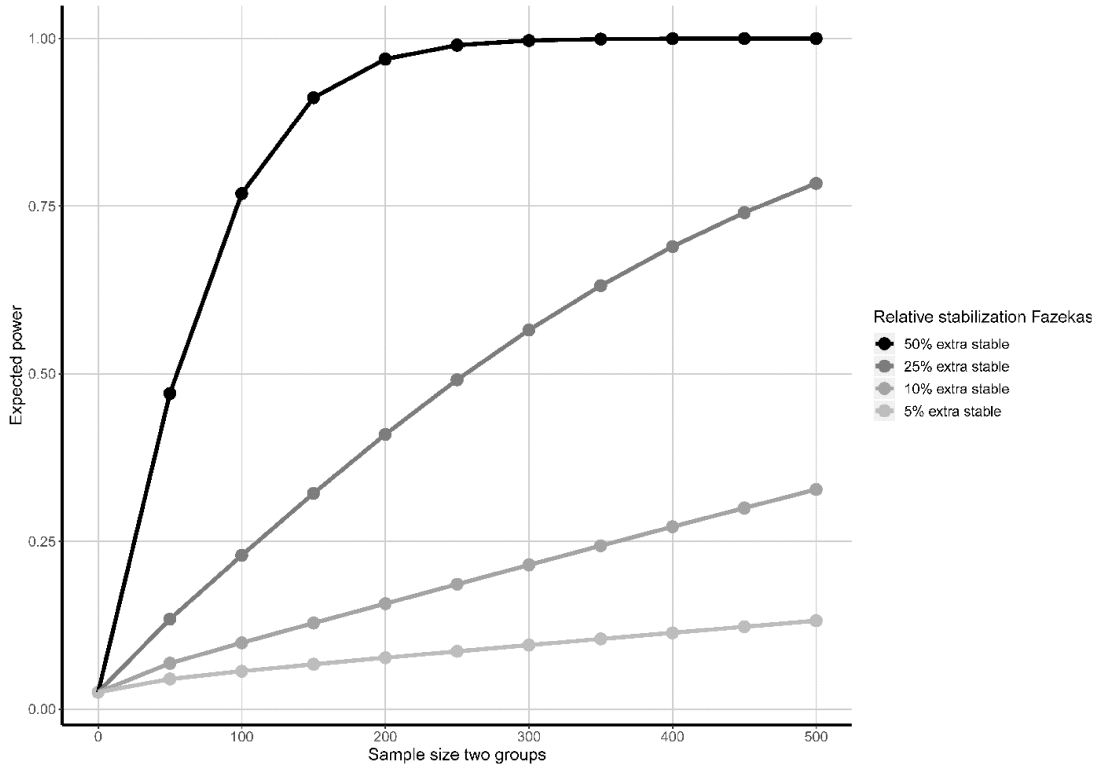


Supplemental figure 4 *Power calculation for a relative reduction of the infarction rate of 50%, 25%, 10% and 5% in 0 to 500 men with classical disease.*

If a new treatment would result in a relative infarction reduction of 50%, a group of 116 men with classical disease (58 per treatment arm) should be followed for ~25 years (start treatment at 20 years and stop trial at 45 years), for a power of 0.8 and significance level of 0.05 (**Supplemental figure 4**). If a new treatment would result in a relative infarction reduction of only 5%, a group of 12548 men

with classical disease (6274 per treatment arm) should be followed for ~25 years for a power of 0.8 and significance level of 0.05.

The Fazekas score started to increase from 20 years old (coded as Fazekas score 0: n=45) and increased until the end of follow-up at a median of 45 years old (data from study Fazekas score 0: n=19, 1: n=7, 2: n=4, 3: n=2, 4: n=4, 5 and 6: n=9). A total of 26 patients had a Fazekas score >0. Hypothetically, a new treatment might stabilize the Fazekas score in 50%, 25%, 10% or 5% of patients. Using a random number generator we randomly selected an additional 50% (n=13), 25% (n=5), 10% (n=3), or 5% (n=1) of patients that had a Fazekas score >0 and recoded them as 0. The new Fazekas score was then compared to the old score.



Supplemental figure 5 *Power calculation for a relative reduction of the infarction rate of 50%, 25%, 10% and 5% in zero to 500 men with classical disease.*

If a new treatment would result in a stabilization of 50% of men with classical disease at a Fazekas score of 0, a group of 106 men with classical disease (53 per treatment arm) should be followed for ~25 years (start treatment at 20 years and stop trial at 45 years), for a power of 0.8 and significance level of 0.05 (**Supplemental figure 5**). If a new treatment would result in a relative infarction reduction of only 5%, a group of 5518 men with classical disease (2759 per treatment arm) should be followed for ~25 years for a power of 0.8 and significance level of 0.05.

References

1. Campbell MJ, Julious SA, Altman DG. Estimating sample sizes for binary, ordered categorical, and continuous outcomes in two group comparisons. *Bmj* 1995;311(7013):1145-8. [published Online First: 1995/10/28]
2. Whitehead J. Sample size calculations for ordered categorical data. *Statistics in Medicine* 1993;12(24):2257-71. doi: 10.1002/sim.4780122404