

pretation is not accurate, since this number needed to treat does not represent patients, but rather patient-years. Indeed, 94 patients treated for 2 years is not necessarily the same as 188 patient-years: the former implies 94 distinct patients treated for 2 years, whereas the latter can equally imply 188 patients treated for 1 year or 47 patients treated for 4 years. The study in fact provided the Kaplan–Meier curves for the cumulative incidence of stroke, which resulted in a 2-year cumulative incidence of stroke of around 2.2% for active treatment and 3.8% for placebo. These values correspond to a more accurate number needed to treat of 63 patients needing to be treated for 2 years to prevent 1 stroke, rather than the reported 94 patients.

Although the number needed to treat is a simple and intuitively appealing measure of the effect of a treatment, its computation must be performed with care in trials with varying follow-up times.

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## Muscle Glycogenesis Due to Phosphoglucomutase 1 Deficiency

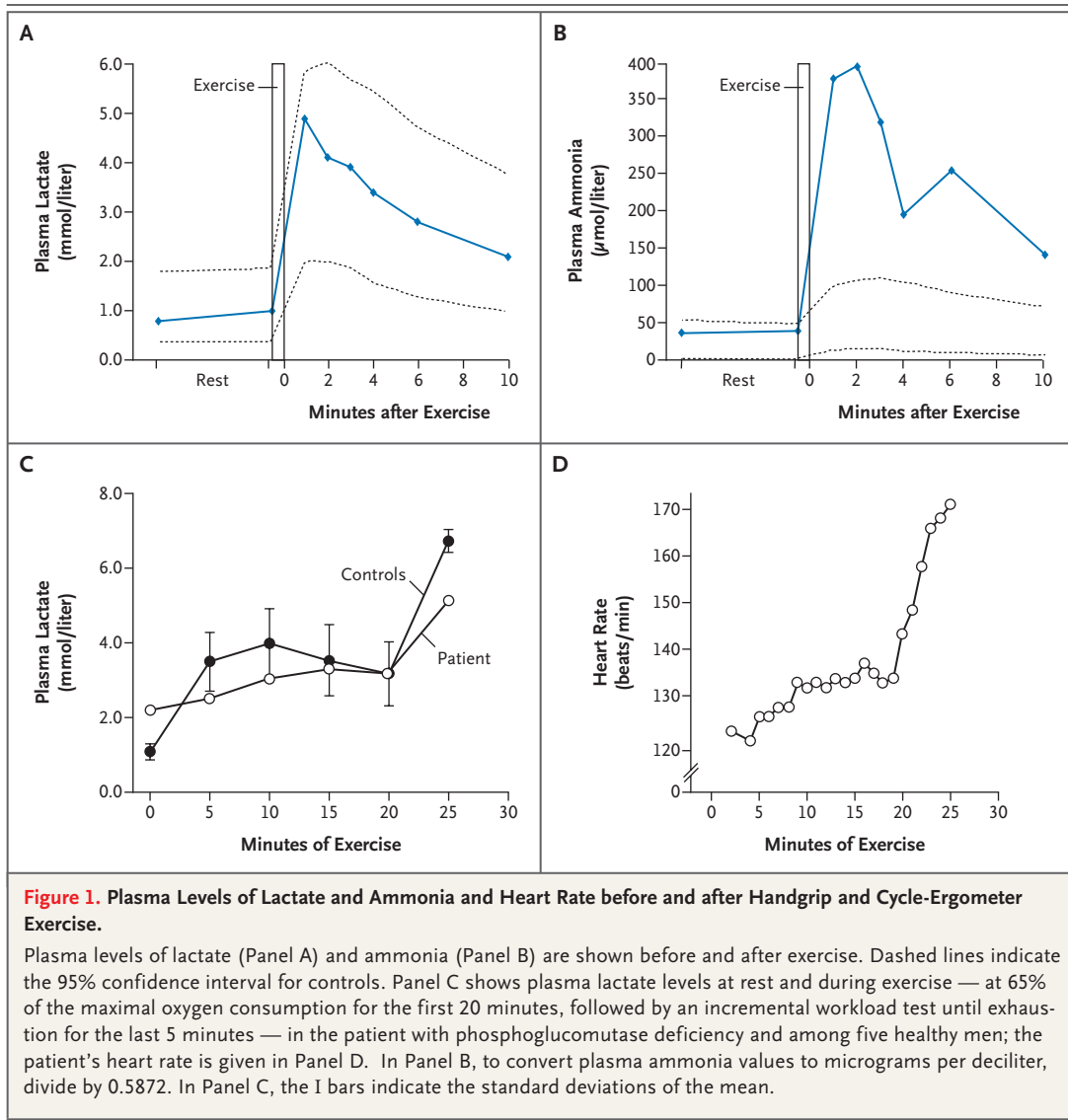
**TO THE EDITOR:** Muscle glycogen storage diseases are rare inborn diseases caused by errors of metabolism associated with either dynamic, exercise-related symptoms or permanent muscle weakness. The most common glycogen storage disease, McArdle's disease (glycogen storage disease type V), is caused by myophosphorylase deficiency and characterized by cramps and muscle pain elicited by sudden vigorous exercise, which may lead to rhabdomyolysis and myoglobinuria. Diagnosis can be suggested by the absence or blunting of the increase in lactate level and the exaggeration of the ammonia response in venous effluent blood in the forearm of a person who is exercising. One exception is that lactate and ammonia responses may be normal in patients with phosphorylase *b* kinase deficiency (glycogen storage diseases type VIII).<sup>1</sup>

A 35-year-old man was referred for investigation of recurrent cramps provoked by exercise. He was the second child of nonconsanguineous, healthy parents who had no family history of a muscle disease. He had two episodes of dark-brown urine after strenuous exercise, suggesting rhabdomyolysis. No second wind occurred dur-

ing exercise. Neurologic examination showed mild weakness of the pelvic-girdle muscles. The creatine kinase level at rest was 300 U per liter, but it increased by a factor of 10 to 20 after strenuous exercise. Needle electromyography showed a myopathic pattern in the vastus medialis. A standardized forearm-exercise test<sup>2</sup> showed that the patient was able to perform isometric, nonischemic exercise at 70% of the maximum voluntary contraction force for 30 seconds. The increase in plasma lactate level was normal, but ammonia release was four times the expected increase (Fig. 1A and 1B).

<sup>13</sup>C-magnetic resonance spectroscopy of the gastrocnemius muscle revealed a normal glycogen-to-creatine ratio. After performing 160 seconds of aerobic plantar flexion, producing 1680 joules, muscle acidification was normal.<sup>3</sup> During recovery, the myoglobin reoxygenation rate was normal, as was the perfusion profile.

The patient performed a constant workload test for 20 minutes, followed by an incremental exercise test until exhaustion on a cycle ergometer (Tunturi Oy); normal increases in the plasma lactate level during submaximal and maximal



exercise were observed, as compared with the levels in five healthy age-matched men (Fig. 1C and 1D).

A muscle biopsy revealed abnormal subsarcolemmal and sarcoplasmic accumulations of normally structured, free glycogen (Fig. 2A through D in the Supplementary Appendix, available with the full text of this letter at NEJM.org). An *in vitro* muscle study of anaerobic glycogenolysis and glycolysis showed a metabolic block after formation of glucose-1-phosphate and before formation of glucose-6-phosphate, indicating phosphoglucomutase deficiency, which is responsible for this enzymatic step (Fig. 2E in the Supplemen-

tary Appendix). Biochemical investigation of muscle revealed a reduction of phosphoglucomutase activity to 1% of the value among controls (with values in the patient of 1.5 U per gram, vs. the control range of 115 to 130 U per gram),<sup>4</sup> whereas total and active phosphorylase activities and phosphofructokinase activity were within the control range. Molecular analysis of the phosphoglucomutase 1 (*PGM1*) gene<sup>5</sup> revealed two heterozygous mutations: a c.343A→G mutation inherited from the father, resulting in a change from threonine to alanine at position 115, affecting a highly conserved amino acid residue, and a c.1145-1G→C in an intron 7–8 splicing donor site,

inherited from the mother. These mutations were absent in 65 controls of the same ethnic group as the patient.

Thus, this patient had biochemically and genetically proven phosphoglucomutase deficiency. This myopathy is characterized by exercise-induced intolerance with episodes of rhabdomyolysis, normal elevation of lactate, and hyperammonemia on a forearm-exercise test. Our findings suggest that phosphoglucomutase deficiency should be added to the list of rare glycolytic disorders and designated glycogenosis type XIV.

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