drug-eluting stent. However, no stent thrombosis was observed in 6 patients who received an everolimus-eluting stent.

CAA as CL was independently associated with death + recurrent MI (hazard ratio: 2.24; 95% confidence interval: 1.02 to 5.39; $p = 0.04$) and with stent thrombosis (hazard ratio: 6.29; 95% confidence interval: 2.32 to 17.05; $p < 0.001$). Our study indicates high 1-year risk of MI primarily driven by stent thrombosis, mostly occurring within 30 days in patients undergoing PPCI of CL involving CAA. The high definite stent thrombosis rate observed in CAA patients (16.5% at 1 year) might have been secondary to stent malapposition, residual thrombus, or disturbed flow through a metallic-jailed CAA. Self-apposing stents, new-generation stent grafts, or micro-mesh stents and intravascular imaging guidance (4) reduce stent malapposition, improve lesion coverage, and may be useful in this setting. The absence of stent thrombosis in the small number of everolimus-eluting stents is interesting but needs confirmation in larger series. We found that aggressive dual antiplatelet therapy with ticagrelor did not effectively prevent stent thrombosis; therefore, the possibility of adding an oral anticoagulant should be considered, possibly limited to a short period after PPCI.

The low prevalence of CAA is likely caused by inclusion of only cases with CL within the CAA. The lack of standardized anticoagulant, antiplatelet therapy and of routine intravascular imaging is a potential limitation, but reflects real life. Additional limitations include the retrospective nature of this observational study and the small number of observed events.

In conclusion, PPCI-treated patients with STEMI caused by CAA show unacceptable rates of early stent thrombosis causing recurrent MIs. Tailored strategies, including self-apposing stents, intravascular imaging and additional short-term anticoagulation should be considered.

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Lafora Disease Is an Inherited Metabolic Cardiomyopathy

Inherited metabolic storage cardiomyopathies, often clinically misdiagnosed, compose a small, but important, fraction of patients genotyped with clinical suspicion of hypertrophic cardiomyopathy (HCM, ≤1%). Overall, glycogen metabolism disorders affect energy homeostasis, primarily in skeletal muscle, heart, liver, and, less frequently, the central nervous system. These rare diseases are quite variable regarding age of onset, symptoms, morbidity, and mortality. Typical pathologic vacuoles containing glycogen or intermediary metabolites altering cardiac structure and function are usually described in Pompe, Danon, and Fabry diseases as well as in patients with mutations in *PRKAG2*, the regulatory γ subunit of AMP-activated protein kinase. In affected patients, these multisystem disorders may cause left ventricular hypertrophy that could accompany neuromuscular deficits, liver and/or kidney dysfunction, and abnormalities of the peripheral central nervous system (1,2).

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TABLE 1 Cardiac Parameters in WT Mice Compared With Laforin and Malin Knockout Mice

	8-10 Months of Age			14-16 Months of Age		
	WT	***Epm2a*$^{-/-}$**	***Epm2b*$^{-/-}$**	**WT**	***Epm2a*$^{-/-}$**	***Epm2b*$^{-/-}$**
2D echocardiography data						
LAX 2D LVVold, μl	68 ± 20	78 ± 12	61 ± 20	70 ± 19	84 ± 16	75 ± 16
LAX 2D LVEF, %	59 ± 6	53 ± 9	55 ± 6	58 ± 12	**47 ± 7***	**43 ± 8**†
SAX MM LV mass, mg	104 ± 20	128 ± 19	104 ± 14	105 ± 20	**164 ± 25**‡§	**152 ± 32**‡‖
N	5	6	6	11	12	12
Gravimetric, ELISA, and histological analyses						
HW/TLength, mg/mm				0.9 ± 0.0	**1.1 ± 0.1**†	**1.1 ± 0.1**†
BNP expression (fold induction)				1.0 ± 0.2	**2.33 ± 0.6**‡	**2.28 ± 1.0**‡
Cardiomyocytes area, μm^2				419 ± 129	**675 ± 255**‡	**521 ± 174**‡
PAS positive				–	+++	+++
N				7	8	8

Values are mean ± SD. Values in **bold** are statistically significant. *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ *Epm2a*$^{-/-}$ versus WT and *Epm2b*$^{-/-}$ versus WT; §$p < 0.05$; ‖$p < 0.01$ *Epm2a*$^{-/-}$ and *Epm2b*$^{-/-}$ 8 to 10 months versus *Epm2a*$^{-/-}$ and *Epm2b*$^{-/-}$ 14 to 16 months, respectively, using a 2-way analysis of variance test with Bonferroni correction, or a Student *t* test for HW/TLength, cardiomyocyte area, and BNP expression.

2D = 2-dimensional; BNP = B-type natriuretic peptide; HW = heart weight; LAX = long axis view; LV = left ventricular; LVEF = left ventricular ejection fraction; LVVold = end-diastolic left ventricular volume; MM = motion-mode; PAS = periodic acid-Schiff staining in heart sections; SAX = short axis view; TLength = tibial length; WT = wild type.

Lafora disease (LD) is a rare neurodegenerative disease (<5/1,000,000) mainly present in Mediterranean countries and consanguineous regions, although its exact prevalence is unknown. It manifests during adolescence with neurological symptoms that eventually lead patients to a vegetative state and premature death. There is no treatment available, apart from antiepileptic drugs and palliative support. LD is caused by mutations in laforin (*EPM2A*) or malin (*EPM2B*), which are key regulators of glycogen metabolism. Patients with LD show abnormal glycogen deposits called Lafora bodies, in brain, skeletal muscle, skin, liver, and the heart. The accumulation of Lafora bodies as a result of laforin or malin deficiency has recently led some authors to consider LD as a new member of the family of glycogen storage diseases (3). Although rhythm disturbances and heart failure have been reported in some patients with LD (4), the consequences of laforin or malin loss for cardiac function over time have not been explored.

To address this question, we blindly assessed cardiac function and remodeling in 2 previously described mouse models of LD, lacking either laforin (*Epm2a*$^{-/-}$) or malin (*Epm2b*$^{-/-}$), which show evident neurological abnormalities beginning at 8 to 10 months of age (5). Experiments were conducted in accordance with the guidelines of the Institutional Animal Welfare Committee. Echocardiography analysis, performed in 2 separate groups of mice at 8 to 10 months of age and at 14 to 16 months of age under light anesthesia, revealed that laforin and malin knockout mice develop cardiac hypertrophy and marked systolic dysfunction by 14 to 16 months of age, as indicated by an increased end-diastolic left ventricular wall thickness and normalized cardiac mass, and a decreased left ventricular ejection fraction (Table 1). Histological assessment showed abundant glycogen aggregates inside the cardiomyocytes, including typical Lafora bodies, and increased cardiomyocytes area in both LD mouse lines. In addition, LD mice showed increased normalized cardiac weight (heart weight to tibial length ratio) and B-type natriuretic peptide expression, confirming the presence of cardiac hypertrophy and dysfunction (Table 1).

These pathological features resemble the inherited metabolic cardiomyopathies of human multisystem glycogen-storage disorders caused by mutations in genes regulating glycogen metabolism. Overall, our results strongly suggest that cardiac studies should be systematically performed in patients with LD, that laforin and malin deficiency should be considered part of the genetic spectrum of metabolic HCM, and that HCM patients with an unknown underlying genetic cause might benefit from genetic screening of laforin and malin genes, especially if neurological symptoms are also present.

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Directly Observed Therapy

A Possible Tool to Tackle Medication Nonadherence in the CVD Epidemic

The recent paper by Ferdinand et al. (1) highlights the morbidity and economic burden of medication nonadherence for cardiovascular disease (CVD). Several barriers to medication compliance exist, of which prescription complexity and pill burden are substantial factors. The polypill, a fixed-dose combination of common antihypertensives, aspirin, and a statin, was suggested in the paper as a tool to reduce nonadherence in high-risk populations (2). Taking a single pill daily rather than multiple pills improves compliance.

However, the pharmaceutical ingenuity of the polypill may not be enough to ensure compliance. We suggest that it may be worth it to consider directly observed therapy (DOT), a strategy of watching patients take their pill or pills daily in an ambulatory care setting, as a tool to reduce CVD-related morbidity and mortality. This method has had a resounding success for other disease epidemics such as tuberculosis (3). Several drugs with proven mortality-reducing benefits in secondary prevention for CVD such as aspirin, beta-blockers, statins, and angiotensin-converting enzyme inhibitors lend themselves to once-a-day doses and are, thus, amenable to DOT. Hameed et al. (4) implemented a DOT clinic in the ambulatory setting and obtained promising results with a resolution of 50% of previously classified resistant hypertension.

Given the epidemic of CVD and the numerous facets that interplay in nonadherence to the appropriate regimen, investing in the infrastructure for DOT in addition to the polypill strategy may lead to improved cardiovascular disease-related outcomes.

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REPLY: Directly Observed Therapy

A Possible Tool to Tackle Medication Nonadherence in the CVD Epidemic

We appreciate Drs. Mezue and Rangaswami's interest in our State-of-the-Art Review paper (1) and would like to respond by making the following 4 points. First, we agree there is good evidence of directly