event, and those with medically managed acute coronary syndrome were excluded.

Despite the diagnostic value of PFT, over the past decade, RCTs have failed to show its role in guiding the choice of antiplatelet therapy. In turn, PFT has struggled to find a space in routine clinical practice. The experience from previous studies led to the design of the TROPICAL-ACS trial, the results of which now provide additional insights on how to use PFT to help select a $P2Y_{12}$ inhibitor, thus suggesting a potential resurgence of a nearly abandoned instrument. Future research should build upon TROPICAL-ACS to help to define antiplatelet treatment approaches associated with optimal safety and efficacy performance profiles for the individual patient.

Dominick J Angiolillo
University of Florida College of Medicine-Jacksonville, Jacksonville, FL 32209, USA
dominick.angiolillo@jax.ufl.edu

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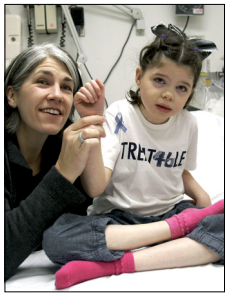
1 Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. *Nat Rev Cardiol* 2015; **12:** 30–47.
2 Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol* 2013; **62:** 2261–73.
3 Franchi F, Rollini F, Cho JR, Ferrante E, Angiolillo DJ. Platelet function testing in contemporary clinical and interventional practice. *Curr Treat Options Cardiovasc Med* 2014; **16:** 300.
4 Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 2011; **305:** 1097–105.
5 Trenk D, Stone GW, Gawaz M, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (testing platelet reactivity in patients undergoing elective stent placement on clopidogrel to guide alternative therapy with prasugrel) study. *J Am Coll Cardiol* 2012; **59:** 2159–64.
6 Collet JP, Cuisset T, Range G, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 2012; **367:** 2100–09.
7 Cayla G, Cuisset T, Silvain J, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open label, blinded-endpoint, randomised controlled superiority trial. *Lancet* 2016; **388:** 2015–22.
8 Sibbing D, Aradi D, Jacobshagen C, et al, on behalf of the TROPICAL-ACS Investigators. Guided De-Escalation of Antiplatelet Treatment in Acute Coronary Syndrome Patients Undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet* 2017; published online Aug 27. http://dx.doi.org/10.1016/S0140-6736(17)32155-4.
9 Cuisset T, Deharo P, Quilici J, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. *Eur Heart J* 2017; published online May 16. DOI:10.1093/eurheartj/ehx175.
10 De Luca L, D'Ascenzo F, Musumeci G, et al. Incidence and outcome of switching of oral platelet p2y12 receptor inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention: the SCOPE registry. *EuroIntervention* 2017; **13:** 459–66.
11 Rollini F, Franchi F, Angiolillo DJ. Switching P2Y12-receptor inhibitors in patients with coronary artery disease. *Nat Rev Cardiol* 2016; **13:** 11–27.
12 Moon JY, Franchi F, Rollini F, et al. Role of genetic testing in patients undergoing percutaneous coronary intervention. *Expert Rev Clin Pharmacol* 2017; published online July 10. DOI:10.1080/17512433.2017.1353909.

A hopeful therapy for Niemann-Pick C diseases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Niemann-Pick C1 disease (NPC1) is a rare autosomal recessive lysosomal storage disease, which was separated from the sphinomyelinase-deficient NPCA and NPCB when cholesterol was found to be stored.[1] No drugs for the disease are currently approved in the USA, although miglustat is approved in Europe. In *The Lancet*, Daniel Ory and colleagues[2] report strong evidence that intrathecal delivery of hydroxypropyl-beta-cyclodextrin (HPBCD) slows the progression of NPC1.

In this non-randomised, open-label, dose-escalation phase 1/2a study, 14 neurologically affected NPC1 patients were given monthly intrathecal HPBCD doses ranging from 50 mg to 1200 mg. Three additional patients were treated every 2 weeks for 18 months. Ory and colleagues[2] reported no major adverse events, and treated patients showed improved neurological severity scores compared with a historical cohort of 21 NPC1 participants of similar age range, suggesting slowed disease progression. This rate of progression decreased as measured by a multimodal scale, especially for cognition and speech.

Cyclodextrins are used to move cholesterol in or out of cell membranes.[3] In 2001, Camargo and colleagues[4] reported a small but significant effect of HPBCD on slowing neurodegeneration in a mouse model of NPC1. When treatment was started earlier and at higher doses, HPBCD was found to be efficacious in extending survival.[5] Intrathecal delivery to mouse and cat brains was shown to be quite effective in ameliorating the symptoms of the disease.[2] Ory and

colleagues' work extends these studies to human beings.

The findings from Ory and colleagues' study[2] raise many questions. First, is the benefit only from desequestering cholesterol in the cell, allowing more normal cholesterol metabolism, or removal of excess cholesterol? Second, are there particular cells for which the therapy is most important? NPC has been termed juvenile Alzheimer's, another disorder in which cholesterol metabolism is important and in which treatment with HPBCD in animal models has been beneficial.[6] Both diseases share defects of autophagy and activation of microglia. Correction of cholesterol storage in these cells may attenuate the microglial activation, which seems to be a major initiator of autophagic and other destructive pathways causing neurodegeneration in NPC disease.[7]

Third, what is the fate of the cholesterol-laden HPBCD? In one study,[8] the HPBCD-cholesterol complex was slowly cleared while free HPBCD appeared in urine within 24 h. Liu and colleagues[5] found of nearly 2 times increase in acidic sterol (ie, bile acids) output in faeces with HPBCD treatment. Would the cholesterol-laden HPBCD increase lung storage of cholesterol as it passes through the pulmonary capillary bed? This could be important as, in mouse models, systemic delivery of HPBCD did not decrease cholesterol storage in the lung[5,9] and might have made it worse. Pulmonary complications contribute to patient deaths, especially in patients with NPC2.

Better drugs and modes of delivery will certainly be developed. One can envision continuous infusion of HPBCD with a pump as is done with baclofen for spasticity of cerebral origin,[10] and this therapy might also provide increased hope for babies born with NPC1. Whole exome sequencing has become very cheap and could replace biochemical tests for newborn screening, adding NPC1 and NPC2 to the panel. The early diagnosis accompanied by therapy started at pre-symptomatic stages of the disease would be expected to secure better efficacy. This possibility is particularly attractive for cerebellar dysfunction, as it largely anticipates the onset of symptoms. In the mouse, cerebellar morphogenic defects occur near birth and are demonstrated by a small cerebellum at 7 days postnatally. These defects, which are likely to be responsible for the pronounced vulnerability of the cerebellum, are mostly rescued by the HPBCD administration during early post natal life.[11]

Because the full development and functional maturation of the human cerebellum encompasses several years of post natal life, with Purkinje cells reaching adult size only at age 7–9 years,[12] there is a large temporal window for rescuing cholesterol dyshomoeostasis. Of course, the potential toxicity of such early therapy on the developing nervous system would need to be studied, but allowing cholesterol to be more available to many pathways in development might not be dangerous. The study by Ory and colleagues[2] is a major advance in the treatment of this devastating disease and is to be applauded.

Robert P Erickson, Maria Teresa Fiorenza
Department of Pediatrics, University of Arizona School of Medicine, Tucson, AZ, 85724-5073, USA (RPE); Division of Neuroscience, Department of Psychology, Sapienza University, Rome, Italy (MTF); and IRCCS Fondazione Santa Lucia, Rome, Italy (MTF)
erickson@peds.arizona.edu

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1 Pentchev PG, Comly ME, Kruth HS, Patel S, Proestel M, Weintroub H. The cholesterol storage disorder of the mutant BALB/c mouse. A primary genetic lesion closely linked to defective ester- ification of exogenously derived cholesterol and its relationship to human type C Niemann–Pick disease. *J Biol Chem* 1986; **261:** 2772–77.
2 Ory DS, Ottinger EA, Farhat NY, et al. Intrathecal 2-hydroxypropyl-beta-cyclodextrin decreases neurological disease progression in Niemann-Pick Disease, type C1: an ad-hoc analysis of a non-randomized, open-label, phase 1–2 trial. *Lancet*, 2017; published online Aug 10. http://dx.doi.org/10.1016/S0140-6736(17)31465-4.
3 Christian AD, Haynes MP, Phillips MC, Rothblat GH. Use of cyclodextrins for manipulating cellular cholesterol content. *J Lipid Res* 1997; **38:** 2264–72.
4 Camargo F, Erickson RP, Garver WS, et al. Cyclodextrins in the treatment of a mouse model of Niemann-Pick C disease. *Life Sci* 2001; **70:** 131–42.
5 Liu B, Ramirez M, Miller AN, Repa JJ, Turley SD, Dietschy JM. Cyclodextrin overcomes the transport defect in nearly every organ of NPC1 mice leading to excretion of sequestered cholesterol as bile acid. *J Lipid Res* 2010; **51:** 933–44.
6 Yao J, Ho D, Calingasan NY, Pipalia NH, Lin Mt, Beal MF. Neuroprotection by cyclodexrin in cell and mouse models of Alzheimer disease. *J Exp Med* 2012; **209:** 2501–13.
7 Sarkar S, Carroll B,Buganim Y, Maetzel D, et al. Impaired autophagy in the lipid-storage disorder Niemann-Pick type C1 disease. *Cell Rep* 2013; **5:** 1302–15.
8 Pitha J, Gerloczy A, Olivi A. Parenteral Hydroxypropyl Cyclodextrins: Intravenous and Intracerebral Administration of Lipophils. *J Pharm Sci* 1994; **83:** 833–41.
9 Muralidhar A, Borbon IA, Esharif D, et al. Pulmonary function and pathology in hydroxypropyl-beta-cyclodextin-treated and untreated *Npc1*$^{-/-}$ mice. *Mol Genet Metab* 2011; **103:** 142–47.
10 Albright AL, Barron WB, Fasick MP, Polinko P, Nanosky J. Continuous intrathecal baclofen infusion for spasticity of cerebral origin. *JAMA* 1993; **270:** 2475–77.
11 Nusca S, Canterini S, Palladino G, et al. A marked paucity of granule cells in the developing cerebellum of the Npc1(-/-) mouse is corrected by a single injection of hydroxypropyl-β-cyclodextrin. *Neurobiol Dis* 2014; **70:** 117–26.
12 Tsekhmistrenko TA. Quantitative changes in human cerebellar pyriform neurons from birth to the age of 20 years. *Neurosci Behav Physiol* 1999; **29:** 405–09.