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BRIEF REPORT

Homozygous Familial Hypercholesterolemia Is a Life-Limiting Condition

Medical Life-Trajectories in the Post-2010 Era

Janneke W.C.M. Mulder, MD,[a,*] M. Doortje Reijman, MD, PhD,[b,*] D. Meeike Kusters, MD, PhD,[b] Eric Boersma, PhD,[c] Fahad Alnouri, MD,[d] Dirk J. Blom, MD, PhD,[e] Alberico L. Catapano, MD, PhD,[f] Marina Cuchel, MD, PhD,[g] Eldad J. Dann, MD, PhD,[h] Tomas Freiberger, MD, PhD,[i] Urh Groselj, MD, PhD,[j] Mariko Harada-Shiba, MD, PhD,[k] G. Kees Hovingh, MD, PhD,[l] Iulia Iatan, MD, PhD,[m] Daiana Ibarretxe, MD, PhD,[n] Meral Kayikcioglu, MD, PhD,[o] Ngoc-Thanh Kim, MD,[p] Reinhard Klingel, MD, PhD,[q,r] Frederick J. Raal, MD, PhD,[s] Laurens F. Reeskamp, MD, PhD,[l] Fouzia Sadiq, PhD,[t] Willemijn A.M. Schonck, MD,[l] Tycho R. Tromp, MD, PhD,[l] Thanh-Huong Truong, MD, PhD,[u] Albert Wiegman, MD, PhD,[b,†] Jeanine E. Roeters van Lennep, MD, PhD,[a,†] the Homozygous Familial Hypercholesterolemia International Clinical Collaborators[‡]

Homozygous familial hypercholesterolemia (HoFH) is a rare (~1:360,000) genetic disorder characterized by extremely high low-density lipoprotein cholesterol (LDL-C) levels, leading to premature atherosclerotic cardiovascular disease (ASCVD) and early death.[1] HoFH is typically caused by bi-allelic pathogenic variants in low-density lipoprotein receptor (*LDLR), APOB*, and/or *PCSK9* genes via a semidominant inheritance pattern, while *LDLRAP1* pathogenic variants cause a rare recessive form. Phenotypic severity is generally correlated with residual LDLR function.[1] Lipid-lowering treatment (LLT) is initiated with a combination of high-intensity statin and ezetimibe, followed by a trial of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor therapy, which is continued if LDL-C reduction is >15%. If LDL-C goals remain unmet, LDLR-independent drugs, apheresis, or rarely liver transplantation are pursued.[1] Despite combination LLT, most patients with HoFH do not reach guideline-recommended LDL-C goals.[2] Data on life-courses largely stem from older case reports and case series when more recent LLT were not

What is the clinical question being addressed?
What are the characteristics and medical life-trajectories of HoFH patients treated in contemporary health care?

What is the main finding?
This analysis of HoFH patients highlights the young age at death, mostly from cardiovascular causes, and the low attainment of LDL-C goals despite treatment advances, underscoring the need for earlier diagnosis and better treatment.

From the [a]Department of Internal Medicine, Erasmus MC Cardiovascular Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands; [b]Department of Pediatrics, Amsterdam University Medical Centers, Location Academic Medical Center, Amsterdam, the Netherlands; [c]Department of Cardiology, Erasmus MC Cardiovascular Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands; [d]Cardiovascular Prevention Unit, Department of Adult Cardiology, Prince Sultan Cardiac Centre, Riyadh, Saudi Arabia; [e]Department of Medicine, Division of Lipidology and Cape Heart Institute, University of Cape Town, Cape Town, South Africa; [f]IRCCS MultiMedica, Sesto San Giovanni (MI), and Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy; [g]Department of Medicine, Division of Translational Medicine and Human Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [h]Blood Bank and Apheresis Unit, Rambam Health Care Campus, and The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel; [i]Centre for Cardiovascular Surgery and Transplantation, and Medical Faculty, Masaryk University, Brno, Czech Republic; [j]University of Ljubljana, Faculty of Medicine and UMC-University Children's Hospital Ljubljana, Ljubljana, Slovenia; [k]Cardiovascular Center, Osaka Medical and Pharmaceutical University, Takatsuki, Japan; [l]Department of Vascular Medicine, Amsterdam University Medical Centers, Location Academic Medical Center, Amsterdam, the Netherlands; [m]Centre for Heart Lung

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available.[3,4] We describe characteristics and clinical courses of HoFH patients under contemporary care, with particular focus on deceased patients.

Data were collected from the 'HoFH International Clinical Collaborators' (HICC) registry (NCT04815005), including patients from 41 countries with clinically or genetically diagnosed HoFH, alive in 2010 or later.[2] Ethics approval was obtained by individual contributors according to standards set by their Institutional Review Board. This study was conducted according to International Standards of Good Clinical Practice.

Collaborators supplied clinical data. *LDLR* variants were categorized by residual LDLR activity as absent ("null") or impaired ('defective').[5] Pathogenic variants in *APOB* and *PCSK9* genes were classified as defective.[6] *LDLRAP1* variants remained a separate category. LDL-C goal achievement was adjudicated according to the 2023 European Atherosclerosis Society HoFH consensus statement: <70 mg/dL without ASCVD, <55 mg/dL with ASCVD or an additional risk factor, and <115 mg/dL in children and adolescents.[1]

We analyzed HICC registry data of patients who died during January 2011 to May 2024, and provide a descriptive comparison with data from living patients from the cohort previously published.[2] Continuous data are presented as median (Q1-Q3) and categorical data as percentage.

In total, 66 patients from 20 countries died at a median age of 37 years (Q1-Q3: 20-50 years). Their age at diagnosis was 12 years (Q1-Q3: 5-24 years) and 89% presented with xanthomas. Of the deceased patients with genetic data (88%), 36% carried 2 *LDLR* null variants, 17% 1 null and 1 defective variant, 45% 2 defective variants, and 1 patient (2%) had 2 pathogenic *LDLRAP1* variants. Deceased patients, compared with living patients,[2] were older (37 years [Q1-Q3: 20-50 years] vs 28 years [Q1-Q3: 15-42 years]), had higher untreated LDL-C levels (623 mg/dL [Q1-Q3: 507-753 mg/dL] vs 566 mg/dL [Q1-Q3: 448-700 mg/dL]), and more frequently carried ≥1 *LDLR* null variant (**Table 1**).

At last clinical follow-up, deceased patients had a higher prevalence of other cardiovascular risk factors compared with living patients, with a higher prevalence of a history of smoking (40% vs 18%) and hypertension (26% vs 15%). Most recent median LDL-C was 346 mg/dL (Q1-Q3: 235-490 mg/dL) in the deceased patients, which was higher than in living patients (293 mg/dL [Q1-Q3: 178-443 mg/dL]). Most deceased were treated with statins (83%), ezetimibe (68%), and lipoprotein apheresis (24%). The number of LLTs ranged from none (14%) to 4 (8%), with 65% on 0 to 2 LLTs (middle-income countries 82% vs high-income countries 47%), comparable with living patients (62%). Similarly, only 5% of the deceased (3 of 58) and 4% of the living patients (21 of 523) achieved guideline-recommended LDL-C goals.

Overall age at death was 37 years (Q1-Q3: 20-50 years), with ASCVD being the cause in 80%, occurring at 36 years (Q1-Q3: 17-48 years). The majority experienced (recurrent) ASCVD before death. Common ASCVD diagnoses in deceased patients were as follows: aortic stenosis (48%), angina pectoris (32%), myocardial infarction (27%), and interventions: CABG (26%) and aortic valve replacement (23%). Two patients received liver transplantation at ages 3 and 24 years, but unfortunately died shortly after. ASCVD was present in 42% of living patients.

Patients who died at age <37 years (median age of death) differed from those who died at ≥37 years: HoFH was diagnosed earlier in life (7 years [Q1-Q3: 4-13 years] vs 23 years [Q1-Q3: 9-36 years]), more frequently presented with xanthomas (94% vs 85%), more frequently carried *LDLR* null/null or defective/null variants (75% vs 33%), and they more often resided in non-high-income countries (58% vs 45%). Additionally, patients who died at age <37 years were more commonly untreated (18% vs 9%), and

Innovation, Department of Medicine, St Paul's Hospital, Providence Health Care, University of British Columbia, Vancouver, British Columbia, Canada; [n]Unitat de Medicina Vascular i Metabolisme, Hospital Universitari Sant Joan, IISPV, CIBERDEM, Universitat Rovira i Virgili, Reus, Spain; [o]Ege University Medical Faculty, Department of Cardiology, Bornova, Izmir, Turkey; [p]Department of Cardiology, Hanoi Medical University, Hanoi, Vietnam; [q]Apheresis Research Institute, Cologne, Germany; [r]First Department of Internal Medicine, University of Mainz, Mainz, Germany; [s]Carbohydrate and Lipid Metabolism Research Unit, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; [t]Directorate of Research, Shifa Tameer-e-Millat University, Islamabad, Pakistan; and the [u]Faculty of Medicine, Phenikaa University, and Vietnam Atherosclerosis Society, Hanoi City, Vietnam. *These authors contributed equally to this work. †These authors contributed equally to this work. ‡For a full list of the Homozygous Familial Hypercholesterolemia International Clinical Collaborators, please see the Supplemental Appendix.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Characteristics and Cardiovascular Outcomes of Patients With HoFH in the HICC Registry

	Alive	Deceased		
	Total Alive (n = 700)	Total Deceased (n = 66)	Age of Death <37 y (n = 33)	Age of Death ≥37 y (n = 33)
Women	365 (52.1)	32 (48.5)	16 (48.5)	16 (48.5)
Residing in high-income country	376 (53.7)	32 (48.5)	14 (42.4)	18 (54.5)
Latest age, n (%)	676 (96.6)	66 (100)	33 (100)	33 (100)
Latest age, y	28 (15-42)	37 (20-50)	20 (13-26)	51 (44-57)
LDL-C levels				
Untreated, n (%)	481 (68.7)	48 (72.7)	27 (81.8)	21 (63.6)
mg/dL	566 (448-700)	623 (507-753)	660 (589-801)	562 (436-638)
mmol/L	14.6 (11.6-18.1)	16.1 (13.1-19.5)	17.1 (15.3-20.8)	14.6 (11.3-16.5)
Last reported[a], n (%)	538 (76.9)	58 (87.9)	27 (81.8)	31 (93.9)
mg/dL	293 (178-443)	346 (235-490)	386 (272-507)	293 (165-427)
mmol/L	7.6 (4.6-11.4)	9.0 (6.1-12.7)	10.0 (7.0-13.1)	7.6 (4.3-11.1)
Genetic information available	519 (74.1)	58 (87.9)	28 (84.8)	30 (90.9)
Genetic variants classified according to residual LDLR activity	469 (67.0)	58 (87.9)	28 (84.8)	30 (90.9)
Null/null	92/469 (19.6)	21/58 (36.2)	12/28 (42.9)	9/30 (30.0)
Null/defective	70/469 (14.9)	10/58 (17.2)	9/28 (32.1)	1/30 (3.3)
Defective/defective	266/469 (56.7)	26/58 (44.8)	7/28 (25.0)	19/30 (63.3)
Other, being:				
LDLRAP1	27/469 (5.8)	1/58 (1.7)	0	1/30 (3.3)
Miscellaneous[b]	14/469 (3.0)	0	0	0
Last clinical follow-up				
BMI, n (%)	349 (49.9)	50 (75.8)	22 (66.7)	28 (84.8)
BMI, kg/m^2	23.3 (19.8-27.0)	23.4 (20.8-28.0)	21.8 (17.8-25.2)	24.0 (21.4-29.1)
History of smoking	77/439 (17.5)	23/58 (39.7)	3/29 (10.3)	20/29 (69.0)
Hypertension	81/546 (14.8)	15/57 (26.3)	2/28 (7.1)	13/29 (44.8)
Diabetes mellitus	21/558 (3.8)	2/58 (3.4)	0	2/30 (6.7)
Chronic kidney disease	5/386 (1.3)	2/48 (4.2)	0	2/23 (8.7)
LLT at last follow-up				
Statin	441/489 (90.2)	55 (83.3)	26 (78.8)	29 (87.9)
High intensity	287/441 (65.1)	38/55 (69.1)	16/26 (61.5)	22/29 (75.9)
Moderate intensity	55/441 (12.5)	4/55 (7.3)	2/26 (7.7)	2/29 (6.9)
Low intensity	6/441 (1.4)	13/55 (23.6)	8/26 (30.8)	5/29 (17.2)
Unknown dose	93/441 (21.1)	0	0	0
Ezetimibe	302/489 (61.8)	45 (68.2)	23 (69.7)	22 (66.7)
Lipoprotein apheresis	222/576 (38.5)	16 (24.2)	8 (24.2)	8 (24.2)
PCSK9 inhibitor	105/489 (21.5)	9 (13.6)	4 (12.1)	5 (15.2)
Lomitapide	37/489 (7.6)	7 (10.6)	3 (9.1)	4 (12.1)
Liver transplantation	5 (0.7)	2 (3.0)	2 (6.1)	0
Mipomersen	0	1 (1.5)	0	1 (3.0)
Evinacumab	13/489 (2.7)	0	0	0
Mortality cause				
Cardiovascular		53 (80.3)	28 (84.8)	25 (75.8)
Noncardiovascular		10 (15.2)	4 (12.1)	6 (18.2)
Unknown		3 (4.5)	1 (3.0)	2 (6.1)
Cardiovascular disease				
Angina pectoris	77 (11.0)	21 (31.8)	6 (18.2)	15 (45.5)
Myocardial infarction	77 (11.0)	18 (27.3)	6 (18.2)	12 (36.4)
PCI	83 (11.9)	11 (16.7)	3 (9.1)	8 (24.2)
CABG	107 (15.3)	17 (25.8)	5 (15.2)	12 (36.4)
Ischemic stroke or TIA	11 (1.6)	5 (7.6)	1 (3.0)	4 (12.1)
Carotid intervention[c]	11 (1.6)	5 (7.6)	3 (9.1)	2 (6.1)
PAD	40/596 (6.7)	5 (7.6)	2 (6.1)	3 (9.1)

Continued on the next page

TABLE 1 Continued

	Alive	Deceased		
	Total Alive (n = 700)	Total Deceased (n = 66)	Age of Death <37 y (n = 33)	Age of Death ≥37 y (n = 33)
Aortic valve disease				
Aortic stenosis	146 (20.9)	32 (48.5)	14 (42.4)	18 (54.5)
Aortic valve replacement	41 (5.9)	15 (22.7)	7 (21.2)	8 (24.2)
Any ASCVD before death, n (%)	297 (42.4)	47 (71.2)	20 (60.6)	27 (81.8)
Age ASCVD onset before death, n (%)	239/297 (80.5)	45/47 (95.7)	18/20 (90.0)	27/27 (100)
Age ASCVD onset before death, y	29 (17-41)	27 (16-36)	18 (8-22)	31 (27-39)
Any ASCVD including CVD death, n (%)		59 (89.4)	29 (87.9)	30 (90.9)
Age ASCVD incl CVD death onset, n (%)		59/59 (100)	29/29 (100)	30 (100)
Age ASCVD incl CVD death onset, y		23 (13-34)	16 (11-20)	34 (27-40)

Values are n (%), median (Q1-Q3), or n/N (%). [a]For the patients with preapheresis and postapheresis low-density lipoprotein cholesterol (LDL-C) levels, time-averaged LDL-C values were calculated according to the formula by Kroon with a coefficient of 0.65.[11,12] [b]Other possibilities are that genetic testing revealed no, 1, or 3 pathogenic variants in combination with a clinical phenotype consistent with HoFH. [c]Carotid intervention contains carotid endarterectomy and carotid stenting.

ASCVD = atherosclerotic cardiovascular disease; AVR = aortic valve replacement; BMI = body mass index; CABG = coronary artery bypass grafting; LLT = lipid-lowering therapy; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin-kexin type 9; TIA = transient ischemic attack.

had higher untreated LDL-C levels (660 mg/dL [Q1-Q3: 589-801 mg/dL] vs 562 mg/dL [Q1-Q3: 436-638 mg/dL]) and treated LDL-C levels (386 mg/dL [Q1-Q3: 272-507 mg/dL] vs 293 mg/dL [Q1-Q3: 165-427 mg/dL]). Furthermore, they had fewer modifiable risk factors and their deaths were more often classified as ASCVD-related (85% vs 76%) (Table 1).

This descriptive analysis shows that patients with HoFH still die very young. Nearly all deceased patients (95%) failed to achieve guideline-recommended LDL-C goals, with two-thirds on 0 to 2 LLTs. Although LLT intensity was somewhat higher in living patients, our data underscore the lack of optimal treatment of HoFH. Death occurred earlier in those residing in non-high-income countries, which may relate to LLT access. Although novel LLTs are crucial for improving outcomes, drawbacks such as costs may prevent their availability, especially in non-high-income countries. This could be one reason why PCSK9 inhibitor use was much lower than expected. Additional reasons include limited efficacy of PCSK9 inhibitors in patients with minimal LDLR activity, their later registration for pediatric patients, and no registration in patients age <8 years.

Throughout a lifetime, HoFH exerts a considerable burden, with most patients experiencing (recurrent) cardiovascular events. Modifiable risk factors, like smoking and hypertension, were less prevalent in patients who died younger. Seemingly paradoxical, this likely reflects the phenomenon that these patients did not live long enough to develop age-related cardiovascular risk factors. Instead, cardiovascular risk was primarily driven by the cumulative LDL-C burden because LDL-C levels were considerably higher in this group. No sex differences were observed between age-of-death groups, in line with recent observations.[7]

The mean age of ASCVD death in HoFH patients has increased from 17.5 years (95% CI: 13.0-22.0 years) in the prestatin era to 24.7 years (95% CI: 19.8-29.6 years) in studies after 1990.[8] Our findings suggest that in contemporary care, the age of cardiovascular death further increased to 36 years (Q1-Q3: 17-48 years), which is still extremely premature. The increase in survival likely reflects the advent of novel treatments that have emerged over the past decades. Given the recent development of LDLR-independent LDL-C lowering drugs (ie, lomitapide and evinacumab), survival of HoFH patients is expected to further improve. Modeling studies suggest that lomitapide and evinacumab could extend median survival by ~11 to 12 years in HoFH patients, which we deem a clinically relevant addition in light of the presented data.[9,10]

Study strengths include the HICC registry's specific inclusion criteria, resulting in a large, broad, and more representative contemporary cohort. This allowed for an extensive analysis of deceased HoFH patients, relevant to the current HoFH management. Two limitations should be noted: missing data in key

determinants of (long-term) mortality prevented us from performing multivariable survival analysis, and the deceased patients may over-represent the most severe cases, introducing potential survivorship bias. Therefore, future HoFH studies are needed to provide further insights into the long-term impact of novel LDLR-independent LLT on global life expectancy.

Despite treatment advances, the age of death in patients with HoFH still remains too young. This underscores the importance of even earlier diagnosis, intensified treatment, and better access to combination and novel LLTs to achieve lower LDL-C levels and improve outcomes for patients with HoFH globally.

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In-house funding at each institution was used to cover effort of contributors for data collection and entry. The creation and the maintenance of the REDCap database and support of a study coordinator for bulk data entry was provided in house by Dr Cuchel at the University of Pennsylvania. Support of the registry coordinators (Drs Schonck and Tromp) was provided in house by Dr Hovingh at Amsterdam UMC. The HICC is an investigator-initiated project supported by funding from the academic institutions of the collaborators. The European Atherosclerosis Society provided funding to support a registry coordinator. Dr Blom has received research grants from Amgen, Amryt, AstraZeneca, Sanofi, and Regeneron; has received lecture fees and personal fees from Amgen, Amryt, Merck Sharp & Dohme, Sanofi-Aventis, and Novartis; participation in the advisory board for Amryt (Chair of the LOWER study steering committee); and serves as a member of the executive committee of the Lipid and Atherosclerosis Society of South Africa and the International Atherosclerosis Society. Dr Catapano has received honoraria, lecture fees, or research grants from Aegerion, Akcea Therapeutics, Amarin, Amgen, Amryt Pharma, AstraZeneca, Daiichi-Sankyo, Esperion, Ionis Pharmaceutical, Medscape Education, Menarini, Merck, Mylan, Novartis, PeerVoice, Pfizer, Recordati, Regeneron, Sanofi, The Corpus, and Viatris. Dr Cuchel has received institutional research funding from Regeneron Pharmaceuticals and Regenxbio; and has received honoraria from Chiesi, Regeneron, and Ultragenyx. Dr Freiberger was supported by the project National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, ID Project No. LX22NPO5104)-Funded by the European Union-Next Generation EU; has received honoraria from Novartis, Sanofi, and Amgen; and has served on the advisory board for Sobi and Medison. Dr Groselj has received lecture fees from Novartis, AstraZeneca, and Ultragenyx. Dr Harada-Shiba has received research grants from the Japan Agency for Medical Research and Development; and has received honoraria and lecture fees from Amgen, Novartis, Ultragenyx, MEDPACE, Protocera, Kowa, Kaneka Medics, Boehringer Ingelheim, Sanofi and BML. Dr Hovingh has received research grants from the Netherlands Organization for Scientific Research (vidi 016.156.445), CardioVascular Research Initiative, European Union, and the Klinkerpad fonds; has received institutional research support from Aegerion, Amgen, AstraZeneca, Eli Lilly, Genzyme, Ionis, Kowa, Pfizer, Regeneron, Roche, Sanofi, and The Medicines Company; has received speakers bureau and consulting fees from Amgen, Aegerion, Sanofi, and Regeneron until April 2019 (fees paid to the academic institution); is a part-time employee at Novo Nordisk; and has stock in Novo Nordisk. Dr Iatan has served on advisory boards for Amgen, HLS Therapeutics, and Novartis; and has received honoraria from Novartis and Sanofi-Aventis. Dr Kayikcioglu has received honoraria from Abbott, Abdi Ibrahim, Chiesi, LIB Therapeutics, Novartis, Novo Nordisk, TR-pharma, and Ultragenyx; has received research funding from Amryt Pharma; and has participated in clinical trials with Amgen, Ionis, LIB Therapeutics, Novartis, and Novo Nordisk, during the past 3 years. Dr Klingel has received research funding and consulting fees from Diamed and Asahi Kasei Medical. Dr Raal has received advisory board fees and lecture fees from Amgen, Sanofi-Aventis, Regeneron Pharmaceuticals, Novartis, and LIB Therapeutics. Dr Reeskamp is cofounder of Lipid Tools; and has received lecture fees from Novartis, Ultragenyx, and Daiichi-Sankyo. Dr Wiegman has received lecture fees and research support for pharmaceutical trials of lipid-lowering agents from Amgen, Chiesi, Merck Sharp & Dohme, Esperion, Novartis, Regeneron Pharmaceuticals, Sanofi, Silence Therapeutics, and Ultragenyx, which were received by the department. Dr Roeters van Lennep's department has received a research grant from Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Albert Wiegman, Department of Pediatrics, Amsterdam University Medical Centers, Location Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. E-mail: a.wiegman@amsterdamumc.nl.

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KEY WORDS ASCVD, cardiovascular disease, homozygous familial hypercholesterolemia, LDL-cholesterol, mortality

APPENDIX For a full list of the Homozygous Familial Hypercholesterolemia International Clinical Collaborators on this project, please see the online version of this paper.