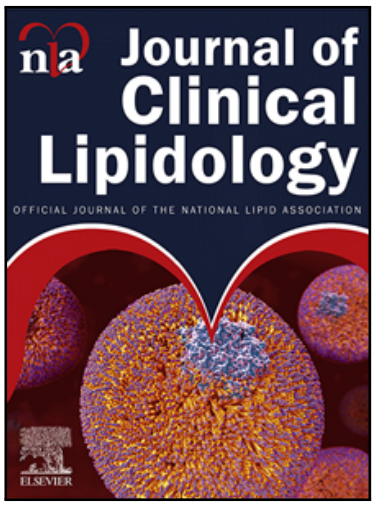

Global Disparities in Access to Lipid-lowering Therapies for Patients with Homozygous Familial Hypercholesterolemia – A Physician Survey

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Highlights:

- Significant disparities exist in LLT registration, reimbursement, and access between high-income and non-high-income countries.
- Public reimbursement and access to LLTs were significantly less common in non-high income countries.
- Improving LLT availability and accessibility is crucial for better HoFH outcomes.

Global Disparities in Access to Lipid-lowering Therapies for Patients with Homozygous Familial Hypercholesterolemia – A Physician Survey

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Abstract

Background Lipid levels and atherosclerotic cardiovascular disease (ASCVD) outcomes have been shown to differ globally in patients with Homozygous Familial Hypercholesterolemia (HoFH), which may be related to availability and accessibility of lipid-lowering therapy (LLT).

Objective In the current study, we investigated global disparities in availability and accessibility of LLTs for patients with HoFH.

Methods Physicians participating in the HoFH International Clinical Collaborators (HICC, NCT04815005) were invited to complete an online survey on registration status, reimbursement, and access to various LLTs. Responses were compared between high-income and non-high-income countries.

Results Responses were received from 87 physicians (64.4% from high-income countries). Physicians from high-income countries reported significantly higher registration rates for PCSK9 mAbs (96.4% vs 51.6%), lomitapide (83.6% vs 9.7%), evinacumab (69.1% vs 0.0%), colesevelam (50.% vs 3.2%), and lipoprotein-apheresis (96.4% vs 45.2%). Public sector reimbursement was also more common in high-income countries for PCSK9 mAbs (90.9% vs 24.1%), lomitapide (74.5% vs 3.4%), evinacumab (60.0% vs 0.0%), colesevelam (40.0% vs 3.4%), and lipoprotein-apheresis (94.% vs 37.9%). Access to LLTs was also higher in high-income countries for statins (91.% vs 61.3%), ezetimibe (87.% vs 38.7%), PCSK9 mAbs (53.6% vs 6.5%), lomitapide (32.% vs 0.0%), evinacumab (32.1 vs 3.2%), colesevelam (39.3% vs 3.2%), and lipoprotein-apheresis (57.1% vs 3.2%).

Conclusion Our results confirm significant global disparities in LLT registration, reimbursement, and access between high-income and non-high-income countries. Improving

LLT availability and accessibility, particularly in non-high-income countries, is essential to improve outcomes in patients with HoFH.

Keywords homozygous familial hypercholesterolemia; lipid-lowering treatment; access; reimbursement; registration; global disparities

Introduction

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder characterized by extremely high levels of low-density lipoprotein cholesterol (LDL-C) and a very high risk of atherosclerotic cardiovascular disease.[1,2] This risk can be mitigated by intensive LDL-C lowering with a combination of lipid-lowering therapies (LLTs).[3,4] However, even with combination therapy, most patients with HoFH still fail to attain guideline-recommended LDL-C goals.[3,5] Recent studies have identified significant global disparities in on-treatment LDL-C levels and cardiovascular outcomes among patients with HoFH.[5] For example, patients with HoFH in non-high-income countries are less likely to receive combination therapy that includes novel expensive LLTs, resulting in a cardiovascular event-free survival period shortened by approximately a decade compared to patients with HoFH residing in high-income countries.[5] These discrepancies are likely, at least in part, attributable to global differences in registration, reimbursement, and availability of LLTs across different countries. Nevertheless, a comprehensive analysis of these global inequalities is currently lacking.

The primary objective of this study is to provide a comprehensive overview of the global availability of and accessibility to LLTs for patients with HoFH as perceived by healthcare professionals (HCPs) with the aim to explore and quantify availability of these therapies and understand factors contributing to disparities across different country income levels.

Material and methods

Participating centres and healthcare provider selection

The HoFH International Clinical Collaborators (HICC, NCT04815005) is a global consortium of clinicians and researchers dedicated to the care of patients with HoFH.[5] This consortium provides a robust foundation for the study, enabling the inclusion of a diverse and representative sample of HCPs from various geographical and healthcare settings. All HCPs directly involved in the care of patients with HoFH were eligible to participate in this study. Eligible HCPs were identified through their affiliation with the HICC registry. In addition, HICC collaborators were asked to distribute the survey to colleagues outside of the HICC consortium who treat patients with HoFH. To be included, HCPs needed to have personal experience in treating patients with HoFH, see these patients regularly, and be currently involved in the care of one or more patient(s) with HoFH. The current study complied with the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (329/2024).

Study design and data collection

To identify patterns and disparities in the management of HoFH across diverse healthcare settings, the authors constructed an online survey. This survey collected data on several key aspects, including the registration, reimbursement, and availability of LLTs across different regions, to assess global disparities in access to these therapies. The survey also collected data on possible factors that may be associated with disparities, including economic, regional, and healthcare system variables. A copy of the survey can be found in **Supplementary Table S1**. The online survey was distributed via email with an open link on 25 May 2024 and was also disseminated at a HICC collaborators meeting on 28 May 2024. HCPs could choose to participate anonymously or to provide their contact details at the beginning of the survey.

Answers were captured using CastorEDC version 2024.2.4.1 between May 25 and August 20, 2024.

Data analysis

In the current study we describe the global disparities in the availability and accessibility of LLTs. For the comparison between high-income and non-high-income regions of the world, countries were categorized according to the 2024 World Bank definition of income categories: high income, upper-middle income, lower-middle income, and low-income.[6] The upper-middle income, lower-middle income, and low-income countries were combined into a single "non-high-income" category. The countries were also grouped into continental regions according to the United Nations geoscheme.[7]

Endpoints

The objective of the study was to evaluate the registration, reimbursement, and accessibility of LLTs for patients with HoFH based on HCPs data. Registration was defined as the official approval and availability of LLTs in each country. HCPs were asked to indicate whether each listed LLT is registered in their country, and to specify whether the registration of each therapy includes its use for adult patients, paediatric patients of 12-18 years, and/or paediatric patients of 0-11 years. For each LLT with a positive registration status, HCPs were asked to specify which reimbursement options applied for their patients with HoFH. The reimbursement options included full payment by the public sector, such as government healthcare; full coverage by private insurance; partial coverage requiring a co-payment by patients, either through private or public means; scenarios where patients must fully fund the therapy themselves; and access through compassionate use or early access programs funded by the pharmaceutical industry. HCPs were also able to indicate any other forms of reimbursement available. Accessibility was defined as the extent to which patients with

HoFH can obtain LLTs in their country. All HCPs were asked to indicate, for each type of LLT, the level of access their patients with HoFH have. The options ranged from full access without significant hurdles, to restricted access where fewer than 50% of patients can use the therapy, to scenarios where no patients could access the therapy. If any access was reported, HCPs were further asked to specify how LLTs are funded for the majority of their patients, whether fully funded by the public sector or private insurance, partially funded requiring a co-payment, not funded with full patient cost, or accessed through compassionate use programs. To assess the prescribing patterns for LLT among patients with HoFH, HCPs were asked to indicate the approximate percentage of their HoFH patients for whom they prescribe each type of LLT, using the following categories: 0%, <10%, 10-25%, 25-50%, 50-75%, and 75-100%. Additionally, opinions on liver transplantation as a treatment option and the use of prophylactic antiplatelet therapy in the management of HoFH were collected. We collected data on statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 monoclonal antibodies (PCSK9 mAbs) (alirocumab or evolocumab), proprotein convertase subtilisin/kexin type 9 small interfering RNA (PCSK9 siRNA) (inclisiran), microsomal triglyceride transfer protein (MTTP) inhibitor (lomitapide), Angiopoietin-like protein 3 (ANGPTL3) monoclonal antibody (evinacumab), bile acid sequestrant (colesevelam), ATP-citrate lyase (ACL) inhibitor (bempedoic acid), lipoprotein apheresis, and liver transplantation. We included LLTs with no published data from trials on patients with HoFH in the survey to account for possible off-label use.

Statistical analysis

Only the data from HCPs who had completed more than 95% of the survey were included in the analyses. Continuous data are reported as mean and standard deviation or as median and interquartile ranges, for normally and non-normally distributed data, respectively. Categorical data are presented as frequencies and percentages. Differences in categorical data between

country-income level subgroups were analysed with a Chi-squared test or Fischer's exact test. All statistical analyses were performed using R, version 4.3.2 (R Foundation, Vienna, Austria). Statistical significance was set at 0.05 (2-sided).

Results

Demographic characteristics

87 HCPs from 48 countries worldwide (**Figure 1 and Supplemental Table S2**) completed the survey. The demographic characteristics of HCPs are shown in **Table 1**. Among the HCPs, 34 (39.1%) were women and 56 (64.4%) were from high-income countries. Of the non-high-income countries, the majority were from upper middle-income countries (54.8%) or lower middle-income countries (32.3%), and only 12.9% from low-income countries **(Supplemental Table S2).** Five (5.8%) HCPs practiced in African countries, 24 (27.6%) in Asian countries, 41 (47.1%) in European Countries, 16 (18.4%) in American countries, and one (1.2%) in Oceania **(Supplemental Table S3 and S4)**. When multiple responses were received from the same country, the within-country responses were found to be highly consistent. In terms of specialty, most (29 [33.3%]) were lipidologists, followed by cardiologists (26 [29.9%]), internists (12 [13.8%]), paediatricians (9 [10.3%]), endocrinologists (5 [5.8%]), and other specialties (6 [6.9%]) (**Table 1**). Generally, HCPs treated a median of 6 [3 - 10] patients with HoFH annually, with a median of 3 [2 - 6] female patients and 3 [1 - 5] male patients.

Registration status of lipid-lowering therapies

The overall registration rates of LLTs, as reported by HCPs, stratified by patient age group, and by country income status, are summarized in **Figure 2A, Figure 2B and Supplemental Table S5.** We observed significant differences between high-income and non-high-income countries in the registration of certain LLTs. For example, the registration of PCSK9 mAbs was significantly higher in high-income countries (54 [96.4%] vs 16 [51.6%], p<0.001), as was the registration of lomitapide (47 [83.9%] vs 3 [9.7%], p<0.001), evinacumab (39 [69.6%] vs 0 [0.0%], p<0.001), colesevelam (28 [50.0%] vs 1 [3.2%], p<0.001), and

lipoprotein apheresis (54 [96.4%] vs 14 [45.2%], p<0.001). HCPs from some countries indicated that their country did not have a registration status specifically for HoFH, but noted, for example, having a registration status for the use in heterozygous FH.

Significant differences by age group were also noted. For paediatric patients aged 0-11 years, registration rates for statins were significantly higher in high-income countries (35 [62.5%] vs 7 [22.6%], p=0.001). Lomitapide registration was significantly higher for adults and paediatric patients aged 12-18 years in high-income countries (47 [83.9%] vs 3 [9.7%] for adults, p<0.001; 12 [21.4%] vs 0 [0.0%] for paediatric patients aged 12-18 years, p=0.02). PCSK9 mAbs, colesevelam, and lipoprotein apheresis all showed significant differences in registration across all age groups, with higher rates in high-income countries (PCSK9 mAbs and lipoprotein apheresis: all p<0.01; colesevelam: all p<0.05). In contrast, some LLTs, such as ezetimibe, PCSK9 siRNA therapy and bempedoic acid, did not show significant differences in registration rates between high-income and non-high-income countries overall and across all age groups.

Reimbursement of lipid lowering therapies

Significant differences in reimbursement rates for various LLTs were observed between high-income and non-high-income countries (**Figure 3 and Supplemental Table S6**). While reimbursement rates for statins were generally similar between the two groups, a significantly greater proportion of patients in non-high-income countries were required to pay the full costs themselves (3 [5.5%] vs 11 [37.9%]; p<0.001). The same holds for ezetimibe (3 [5.5%] vs 10 [34.5%]; p=0.001) and PCSK9 siRNA (1 [1.8%] vs 5 [17.2%]; p=0.03). A similar trend was seen for PCSK9 mAbs (5 [9.1%] vs 8 [27.6%]; p=0.06).

Reimbursement rates by the public sector were significantly higher in high-income countries compared with non-high-income countries for PCSK9 mAbs (50 [90.9%] vs 7 [24.1%];

p<0.001), PCSK9 siRNA (24 [43.6%] vs 3 [10.3%]; p=0.004), lomitapide (41 [74.5%] vs 1 [3.4%]; p<0.001), evinacumab (33 [60.0%] vs 0 [0.0%]; p<0.001), colesevelam (22 [40.0%] vs 1 [3.4%]; p=0.001), and lipoprotein apheresis (52 [94.5%] vs 11 [37.9%]; p<0.001).

Patient access to lipid lowering therapies

Full patient access was significantly higher in high-income countries compared to non-high-income countries for statins (51 [91.1%] vs 19 [61.3%]; p=0.003), ezetimibe (49 [87.5%] vs 12 [38.7%]; p<0.001), PCSK9 mAbs (30 [53.6%] vs 2 [6.5%]; p<0.001), PCSK9 siRNA (19 [33.9%] vs 2 [6.5%]; p=0.002), lomitapide (18 [32.1%] vs 0 [0.0%]; p<0.001), evinacumab (18 [32.1%] vs 1 [3.2%]; p<0.001), colesevelam (22 [39.3%] vs 1 [3.2%]; p<0.001) and lipoprotein apheresis (32 [57.1%] vs 1 [3.2%]; p<0.001) (**Figure 4 & Supplemental Table S7)**. Additionally, no patient access was significantly lower in high-income countries compared with non-high-income countries for PCSK9 mAbs (1 [1.8%] vs 14 [45.2%]; p<0.001), PCSK9 siRNA (16 [28.6%] vs 18 [58.1%]; p=0.02), lomitapide (10 [17.9%] vs 24 [77.4%]; p<0.001), evinacumab (13 [23.2%] vs 25 [80.6%]; p<0.001), colesevelam (28 [50.0%] vs 27 [87.1%]; p<0.001) and lipoprotein apheresis (3 [5.%] vs 18 [59.1%]; p<0.001). No significant differences were identified with respect to access to bempedoic acid (p = 0.10) and liver transplantation (p = 0.18) between high-income and non-high-income countries.

Also, significant disparities in methods of accessibility between high-income and non-high-income countries were observed **(Supplemental Table S8 and Supplemental Figure S1).** Full funding, either by public sector healthcare or private insurance, was significantly higher in high-income countries compared to non-high-income countries for ezetimibe (44 [78.6%] vs 12 [42.9%]; p=0.002), PCSK9 mAbs (47 [85.5%] vs 5 [29.4%]; p<0.001), siRNA (28 [70.0%] vs 1 [7.7%]; p<0.001), lomitapide (32 [69.6%] vs 0 [0.0%]; p=0.002), lipoprotein apheresis (45 [84.9%] vs 3 [23.1%]; p<0.001) and liver transplantation (30 [85.7%] vs 5

[33.3%]; p=0.001). Concurrently, the non-funding of LLT was significantly lower in high-income countries compared to non-high-income countries for statins (1 [1.8%] vs 12 [38.7%]; p<0.001), ezetimibe (1 [1.8%] vs 13 [46.4%]; p<0.001), PCSK9 mAbs (1 [1.8%] vs 8 [47.1%]; p<0.001), PCSK9 siRNA (2 [5.0%] vs 8 [61.5%]; p<0.001), colesevelam (0 [0.0%] vs 4 [100%]; p<0.001), bempedoic acid (3 [12.0%] vs 5 [71.4%]; p=0.007), lipoprotein apheresis (1 [1.9%] vs 3 [23.1%]; p=0.03) and liver transplantation (1 [2.9%] vs 5 [33.3%]; p=0.01).

Prescription rates of lipid-lowering therapies

Most HCPs (83 [96.6%]) frequently (75%-100%) prescribed statins, with no significant difference between high-income and non-high-income countries (55 [98.2%] vs 29 [93.5%], p=0.36) (Supplemental Table S9). Ezetimibe was also frequently prescribed by 75 (86.2%) of HCPs, with significantly higher prescription rates in high-income countries compared to non-high-income countries (54 [96.4%] vs 21 [67.7%], p=0.01). PCSK9 mAbs were prescribed frequently by 25 (28.7%) of HCPs, with significantly higher frequently prescription rates (21 [37.5%] vs 4 [12.9%]) and lower non-prescription (0.0%) rates (3 [5.4%] vs 14 [45.2%]) rates in high-income countries (p<0.001). Non-prescription rates for lomitapide, evinacumab, and lipoprotein apheresis were significantly lower in high-income countries compared to non-high-income countries (18 [32.1%] vs 24 [77.4%], p=0.003; 24 [42.9%] vs 27 [87.1%], p=0.004; 14 [25.0%] vs 19 [61.3%], p=0.008, respectively). Overall, high non-prescription rates were noted for PCSK9 siRNA (57 [65.5%]), colesevelam (72 [82.8%]), bempedoic acid (70 [80.5%]), and liver transplantation (69 [79.3%]), with no significant differences between high-income and non-high-income countries.

The reasons for non-prescription of LLTs varied significantly between high-income and non-high-income countries for all therapies except bempedoic acid **(**all p<0.05, **Supplemental**

Table S10 and Supplemental Figure S2). Reimbursement and access concerns were significantly more common reasons for non-prescription in non-high-income countries, reflecting the financial and systemic barriers faced in these regions. In contrast, reasons such as patient preference were more frequently cited in high-income countries.

Opinions about liver transplantation and prophylactic antiplatelet therapy

Twenty-one (24.1%) HCPs would consider or have considered liver transplantation as a treatment for their patients. No significant differences were found based on country income status **(Supplemental Table S11**), but opinions regarding liver transplantation varied significantly by world region, with higher proportions among HCPs from the Americas (8 [50.0%]), Africa (2 [40.0%]), and Oceania (1 [100%]) considering this option compared to those from Europe (7 [17.1%]) and Asia (3 [12.5%]; p=0.013). About half (42 [48.3]) of the HCPs held the opinion that liver transplantation should be reserved for selected cases, while 24 (27.6%) selected that "the risks of liver transplantation never justify the potential benefit" and 12 (13.8%) that it should be considered only in conjunction with heart transplantation.

More than half (52 [59.8%]) of the HCPs would consider or have considered prescribing prophylactic antiplatelet therapy in patients with HoFH who have not experienced a cardiovascular event. No significant subgroup differences were observed based on country income level **(Supplemental Table S12).** Factors influencing the consideration of prophylactic antiplatelet therapy included information from vascular imaging (43 [49.4%]), the presence of other ASCVD risk factors (36 [41.4%]), and the patient's age (21 [24.1%]). A lower proportion of HCPs from high-income countries selected patient age as an influencing factor compared to those from non-high-income countries (9 [16.1%] vs 12 [38.7%]; p=0.04).

Discussion

Our survey study performed among HCPs who treat patients with HoFH highlights significant global disparities in the registration, reimbursement, and accessibility to LLTs between high-income and non-high-income countries. The availability of certain costly, novel, and more effective medications vary significantly based on a country's income level. High-income countries reported higher rates of registration and reimbursement for newer and more expensive LLTs such as PCSK9 mAbs, lomitapide, evinacumab, and lipoprotein apheresis. Furthermore, patient accessibility of these LLTs was notably higher in high-income countries. This difference may be explained by costs associated with therapy, where more expensive drugs may not be available in non-high-income countries. These disparities may have profound implications for patient outcomes, as patients in high-income countries generally benefit from better access to the more effective LLTs, while those in non-high-income countries face substantial barriers. These data are intended to inform the development of targeted interventions and policy recommendations with the aim of improving the standard of care for patients with HoFH worldwide.

An online survey study in 2021 from the World Heart Federation with participants from 38 countries investigated the general availability, free prescription, and insurance coverage of high-intensity statins, ezetimibe, statin/ezetimibe combinations, and PCSK9 inhibitors.[8] The investigators also found a substantial difference between country income groups, with required full or large co-payments by patients for LLT being most common in low-income countries. Notably, the availability and insurance coverage for PCSK9 inhibitors were highest in the high-income countries. Additionally, other studies also observed significant global disparities in availability, reimbursement, and/or accessibility of treatments across different country income levels, such as for secondary cardiovascular prevention[9] and diabetes[10,11].

These previous findings align with our results, demonstrating that both older and newer generation LLTs are more accessible in high-income countries for patients with HoFH, while patients in non-high-income countries often face challenges due to unavailability and high costs. These global discrepancies highlight the complexity of current access to healthcare for patients. A remarkable finding is that even statins, which are inexpensive, were not easily accessible for patients from non-high-income countries. These findings highlight the need for improving access to fundamental treatments, such as statins, in non-high-income countries to improve global health inequalities for patients with HoFH. In addition to financial barriers, disparities in access to LLTs may also be influenced by variations in healthcare provider awareness of HoFH and national guideline availability. Limited knowledge and acceptability of new treatment options among both providers and patients, as well as differences in prescribing confidence, have been identified as significant barriers to optimal lipid management, particularly in low- and middle-income countries[12]. However, we believe lack of physician knowledge likely does not explain the disparities we identified, as the physicians who completed our survey all have a special interest in the condition and treat multiple patients with HoFH.

Although colesevelam, or other bile acid sequestrants, could potentially be added to statin + ezetimibe based therapy at a lower cost that some of the novel LLTs its usage generally remains low for many reasons. Firstly, access to colesevelam remains limited in many regions despite its lower cost compared to novel LLTs, mainly because colesevelam is not marketed in many non-high-income countries because of lack of profitability. Additionally, healthcare systems formularies often prioritize access to first-line LLTs like statins and ezetimibe. Furthermore, bile acid sequestrants as a class have limited efficacy in HoFH and in addition to poor gastrointestinal tolerability may also interfere with the absorption of other drugs.

Several factors likely contribute to these geographic disparities, including economic constraints on medical resources, healthcare policies, drug availability, agreements between governments and the pharmaceutical industry, variations in healthcare infrastructure, and geographic challenges.[13,14] For example, living farther from specialized HoFH centres may present a barrier, particularly for patients requiring lipoprotein apheresis treatment and access to intravenous medication. A qualitative study in 24 French patients with HoFH on apheresis treatment observed a mean travel distance of 184 km (range 4-500km), while a Turkish study found that 34.8% of 69 HoFH patients travelled more than 50 km to reach the lipoprotein apheresis centre.[15,16] In the French study, patients had full coverage of their treatment and travel costs[15], but in countries where such coverage is lacking or where travel distances are even greater, access to treatment may be substantially hindered.

Limited access to LLTs results in suboptimal management of LDL-C levels, and this increases the risk of atherosclerotic cardiovascular events and morbidity and mortality among patients with HoFH.[17] Previous contemporary clinical data from the largest HoFH registry showed a median (IQR) treated LDL-C of 4.9 (3.0-7.5) mmol/L in high-income countries, compared to 10.1 (7.4-13.2) mmol/L in patients from non-high-income countries.[5] Patients from non-high-income countries were also observed to receive fewer and less combination LLT and were found to have a cardiovascular event-free survival duration that was a decade shorter than that of patients from high-income countries.

The results from this HCP survey suggest that the inequalities in the registration, reimbursement of, and access to LLTs play a key role in the observed differences in patient outcomes and prognosis. Addressing the underlying causes of these global treatment disparities is essential for improving access to LLTs and health outcomes for patients with

HoFH worldwide. The development of LDL-receptor-independent LDL-C lowering drugs like lomitapide and evinacumab holds significant promise for improving the survival of HoFH patients, with evinacumab potentially increasing median survival by 12 years.[18] Nevertheless, our study reveals significant discrepancies in the accessibility of advanced LLTs between high-income and non-high-income countries, giving rise to concerns that these advancements may not be equally advantageous to all patients with HoFH on a global scale. Future implementation research should focus on identifying and mitigating barriers to treatment registration and access.[19] Additionally, the registration status for each LLT should specifically include patients with HoFH in each country to ensure appropriate use in this population. Global health initiatives should advocate for equitable access to both established and novel LLTs for all patients with HoFH. In addition, studies should investigate underlying factors for between and within country differences between patients in access to LLT. National policymakers should actively implement evidence-based changes to improve patient care. In non-high-income countries, national policymakers should investigate avenues to improve patient access and reduce patient costs for LLT. Furthermore, research is needed to assess how these treatment disparities impact patients, including patient reported outcomes such as quality of life across various treatment modalities.

A limitation of this study is that 87 HCPs from 48 countries were included and as such precludes us from drawing firm conclusions for countries that did not participate. Due to the underrepresentation of regions such as Africa (5.8%) and Oceania (1.2%), the survey findings may predominantly reflect practices from regions with higher representation, being Europe (47.1%), Asia (27.6%), and the Americas (18.4%). However, given the rarity of HoFH and thus the limited number of HCPs treating this condition, the inclusion of 87 HCPs from 48 countries represents the largest global study thus far. Especially since the inclusion criteria

required HCPs to actively treat at least one patient with HoFH annually, providing valuable insights into current HoFH care.

The cross-sectional study design does not allow for the assessment of changes in LLT access and availability, but it offers a contemporary baseline for future comparisons as new treatments emerge and guidelines evolve. This baseline may also help identify current trends and highlight areas where further education, guideline development or policy adjustments are needed.

Additionally, as with any survey-based study, we had to rely on self-reported data which introduces potential biases, including participation, response, recall, and social desirability biases. HCPs from all but one country from those participating in HICC completed the survey, which minimizes the risk of participation bias. In addition, HCPs from 6 non-HICC countries completed the survey. To address potential reporting biases, the survey was carefully designed with the option to participate anonymously to mitigate these biases and encourage honest responses. The HCPs' specialized expertise in HoFH plus professional responsibility likely contributed to more accurate and reflective responses, even in self-reported data. The survey's specific questions focused on current practices to minimize recall bias. Finally, in countries with multiple HCPs, we observed no significant within-country differences in responses.

Conclusions

Our findings highlight significant global disparities in the registration, reimbursement, and accessibility to LLTs between high-income and non-high-income countries. It is of the utmost importance to bridge this gap to expand treatment options in all countries, particularly non-high-income countries. If these disparities persist, differences in prognosis are likely to become even more pronounced, especially with the introduction of new, more effective but costly LLTs. It is imperative that these inequities be addressed to ensure fair and universal

access to healthcare, thereby maximizing patient outcomes and enhancing cardiovascular health for patients with HoFH worldwide.

Declaration of interests

Dr Reeskamp is co-founder of Lipid Tools and reports lecture fees from Novartis, Ultragenyx, and Daiichi Sankyo. **Dr Hovingh** reports research grants from the Netherlands Organization for Scientific Research (vidi 016.156.445), CardioVascular Research Initiative, European Union and the Klinkerpad fonds, institutional research support from Aegerion, Amgen, AstraZeneca, Eli Lilly, Genzyme, Ionis, Kowa, Pfizer, Regeneron, Roche, Sanofi, and The Medicines Company; speaker's bureau and consulting fees from Amgen, Aegerion, Sanofi, and Regeneron until April 2019 (fees paid to the academic institution); GKH is part-time employment at Novo Nordisk and has stock in Novo Nordisk, Denmark. **Dr Roeters van Lennep** reports that a research grant from Novartis was received by the department. **Dr Blom** reports research grants from Amgen, Amryt, AstraZeneca, Sanofi, and Regeneron; lecture fees and personal fees from Amgen, Amryt, MSD, Sanofi-Aventis and Novartis; participation in advisory board for Amryt (Chair of the LOWER study steering committee); and being a member of the executive committee of the Lipid and Atherosclerosis Society of South Africa and the International Atherosclerosis Society. The other authors **WAMS, JM,** and **TT** do not have disclosures for this manuscript.

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Author Contribution Statement

Conceptualization: WAMS, JM, TT, LFR, GKH, JRvL, DJB; Data curation: WAMS, JM; Formal analysis: WAMS, JM, JRvL, DJB; Investigation: WAMS, JM, TT, LFR, GKH, JRvL, DJB; Methodology: WAMS, JM, TT, LFR, GKH, JRvL, DJB; Supervision: DJB; Writing - original draft: WAMS, JM; Writing – review and editing of the manuscript: WAMS, JM, TT, LFR, GKH, JRvL, DJB. All authors had full access to the data and had the final responsibility to submit for publication.

Use of AI and AI-assisted Technologies

Artificial intelligence was not used in the writing of the text nor in the creation of the figures.

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Ethical statement

The current study complied with the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (329/2024).

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Figure legend.

Figure 1. Map of countries of the participating healthcare professionals.

Figure 2. (A) Worldwide registration of lipid-lowering therapies overall and for different ages. (**B)** Medication registration by country income status.

Figure 3. Reimbursement of lipid-lowering therapies by country income status.

Figure 4. Perceived patient access by healthcare professionals by country income status

Graphical Abstract. Global Disparities in Access to Lipid-lowering Therapies for Patients with HoFH

Table legend.

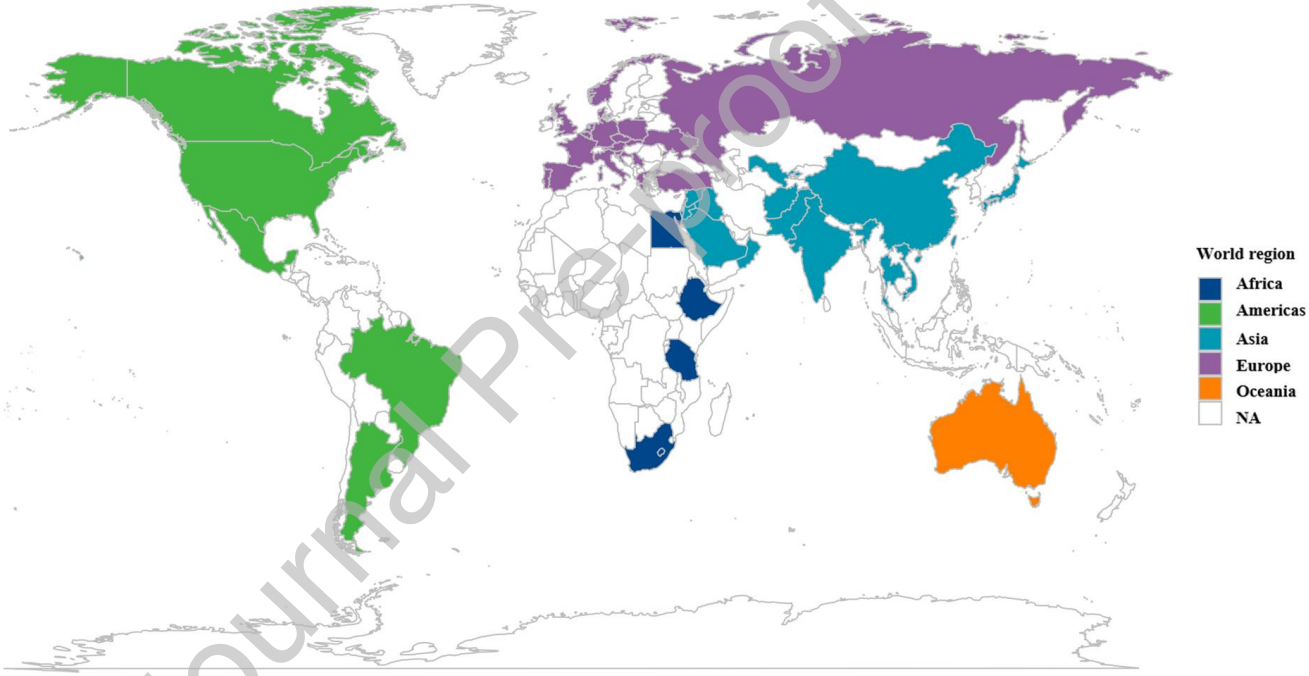
Table 1. Participant characteristics.

Table 1. Participant characteristics

Characteristic	HCPs
Total number of HCPs	87
Total number of participating countries	48
Gender, women, N (%)	34 (39.1%)
Demographic region, N (%)	
Africa	5 (5.8%)
Asia	24 (27.6%)
Europe	41 (47.1%)
Americas	16 (18.4%)
Oceania	1 (1.2%)
Specialty, N (%)	
Cardiologist	26 (29.9%)
Internist	12 (13.8%)
Lipidologist	29 (33.3%)
Paediatrician	9 (10.3%)
Endocrinologist	5 (5.8%)
Other #	6 (6.9%)
Number of total annual HoFH patients, median [IQR]	6 [3 - 10]
Female patients	3 [2 - 6]
Male patients	3 [1 - 5]
Number of responders by country income status, N (%)	
High-income countries	56 (64.4%)
Non-high-income countries	31 (35.6%)

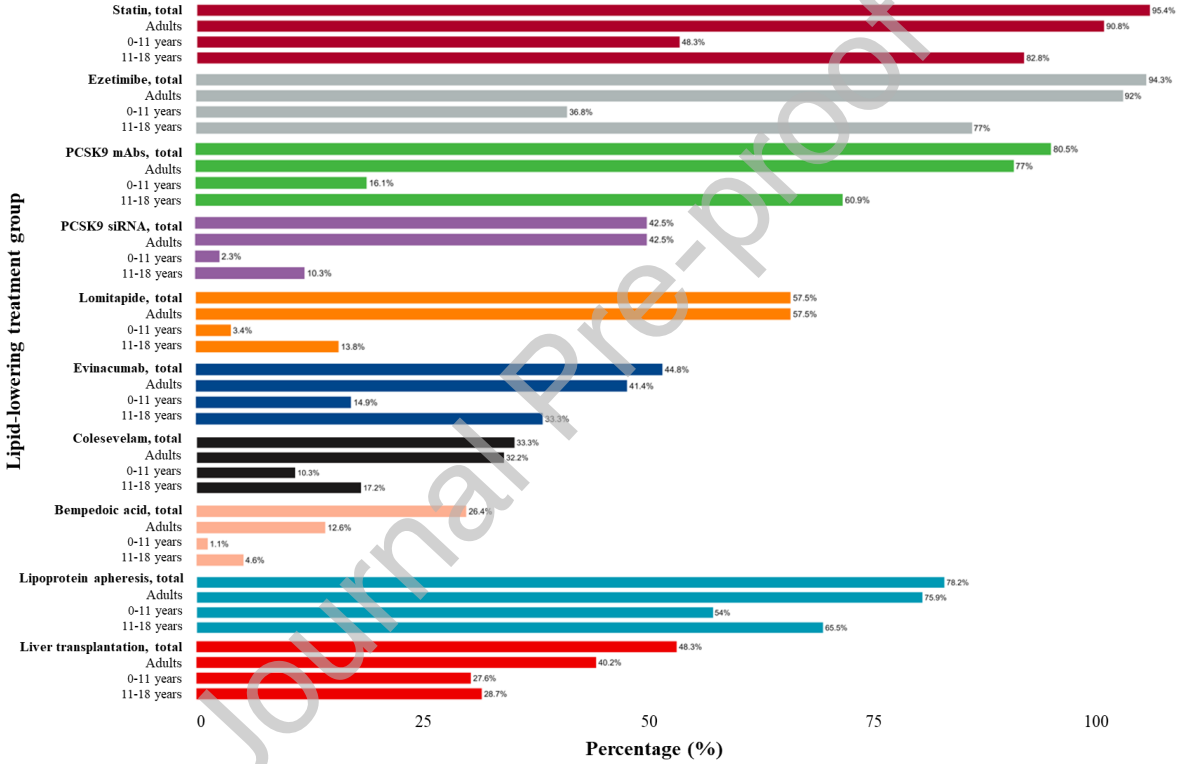
Values are N (%) and median [IQR]. # other specialisms were haematology, medical biochemistry, cardiometabolic medicine, translational medicine. Gender was self-reported by the healthcare professional. HoFH = homozygous familial hypercholesterolemia; HCPs = Healthcare professionals.

Figure 1. Map of countries of the participating healthcare professionals.



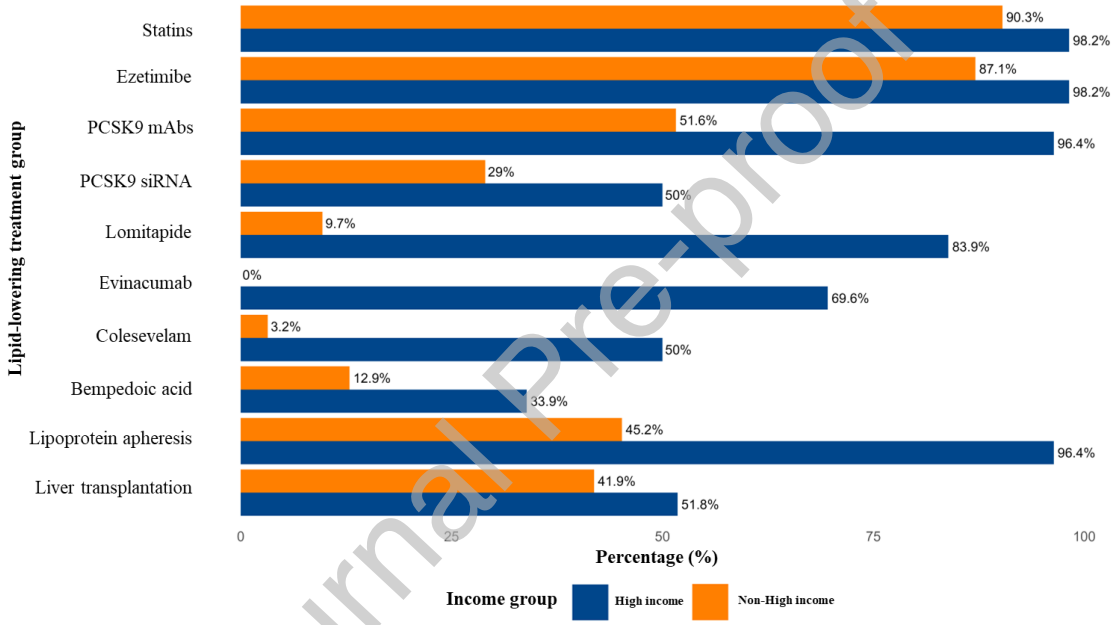
This figure illustrates the countries that participated in this survey, classified by world region.

Figure 2A. Worldwide registration of lipid-lowering therapies overall and for different ages.



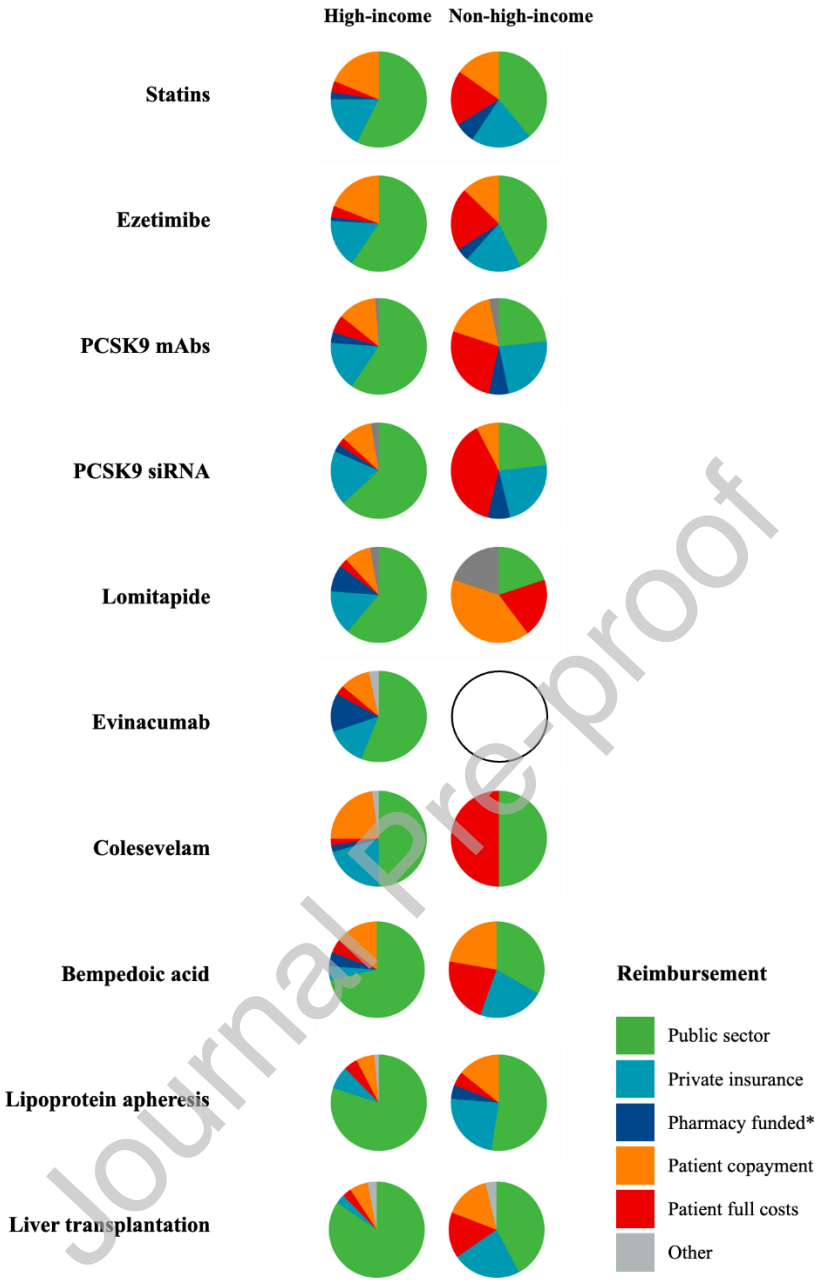
This figure illustrates the global registration of lipid-lowering therapies overall and across different age categories (adults, paediatric patients aged 12-18 years, and paediatric patients aged 0-11 years). PCSK9 mAbs = proprotein convertase subtilisin/kexin type 9 monoclonal antibodies; PCSK9 siRNA = proprotein convertase subtilisin/kexin type 9 small interfering RNA.

Figure 2B. Medication registration by country income status.



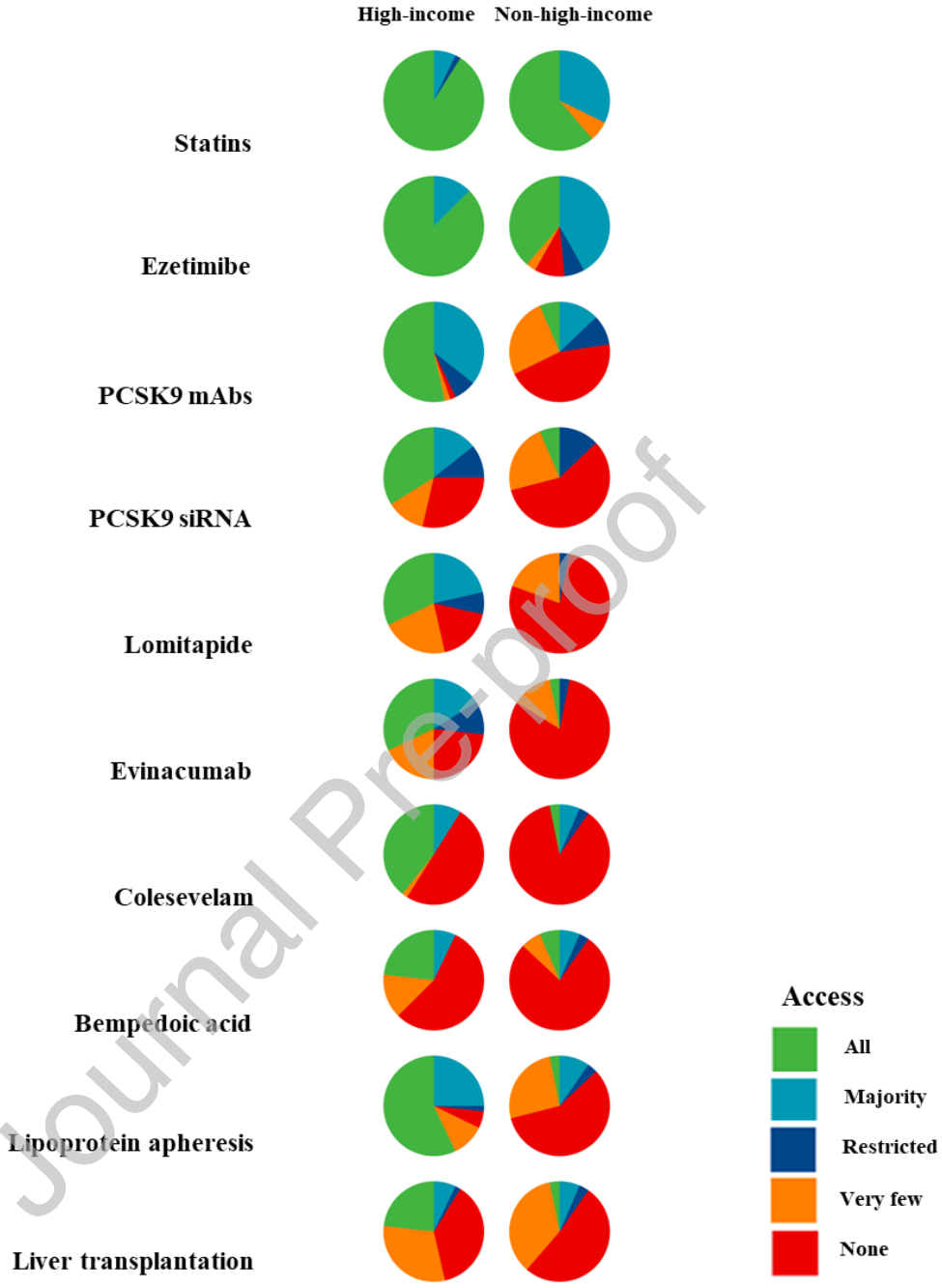
This figure illustrates the global registration of lipid-lowering therapies across high-income countries and non-high-income countries. PCSK9 mAbs = proprotein convertase subtilisin/kexin type 9 monoclonal antibodies; PCSK9 siRNA = proprotein convertase subtilisin/kexin type 9 small interfering RNA.

Figure 3. Reimbursement of lipid-lowering therapies by country income status.



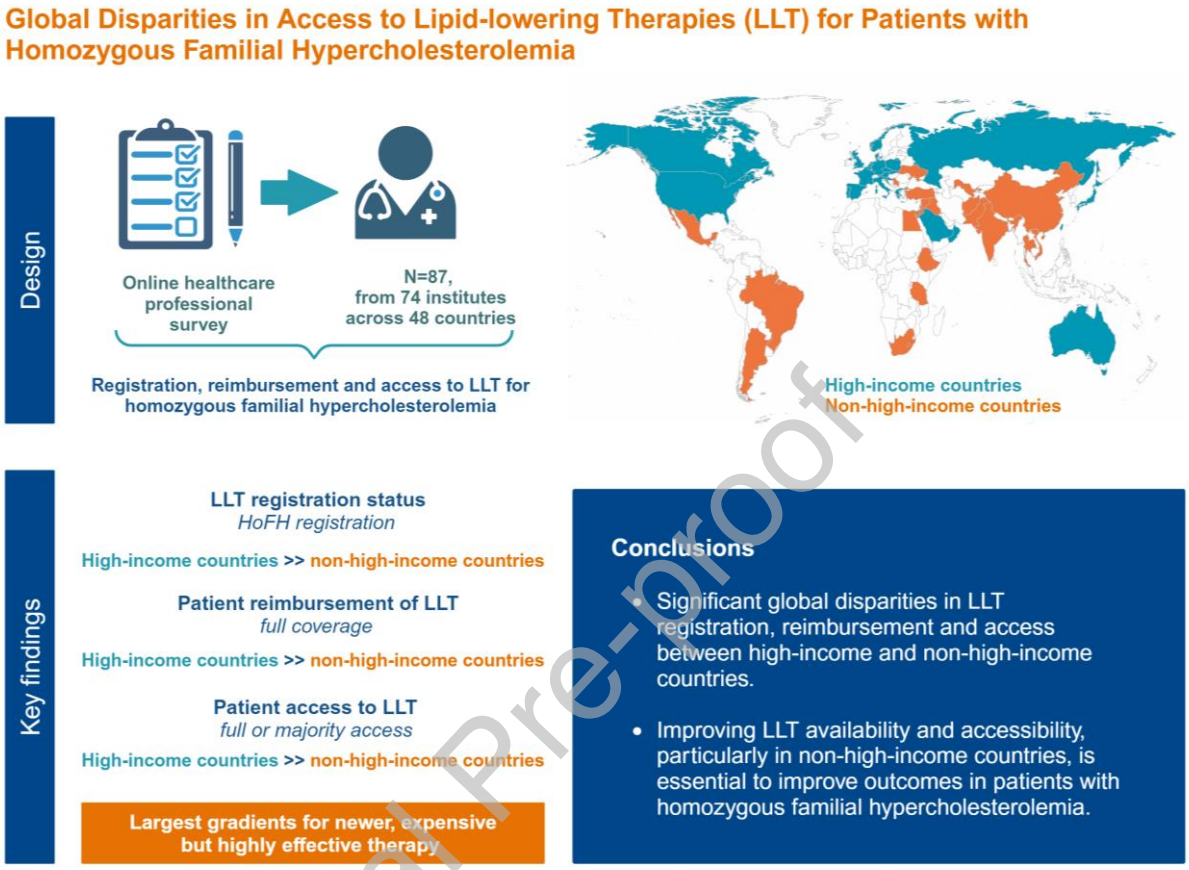
*This figure illustrated the global disparities of the reimbursement of lipid-lowering treatments between high-income and non-high-income countries. *Pharmacy funded includes access through compassionate use or early access programs funded by the pharmaceutical industry. PCSK9 mAbs = proprotein convertase subtilisin/kexin type 9 monoclonal antibodies; PCSK9 siRNA = proprotein convertase subtilisin/kexin type 9 small interfering RNA.*

Figure 4. Perceived patient access by healthcare professionals by country income status



This figure illustrated the global disparities of the accessibility to lipid-lowering therapies across high-income countries and non-high-income countries. Restricted access was defined as less than 50% of the patients have access. PCSK9 mAbs = proprotein convertase subtilisin/kexin type 9 monoclonal antibodies; PCSK9 siRNA = proprotein convertase subtilisin/kexin type 9 small interfering RNA.

Graphical Abstract. Global disparities in access to lipid-lowering therapies for patients with HoFH



This graphical abstract illustrates significant global disparities in the registration, reimbursement, and access to lipid-lowering therapies (LLTs) for patients with homozygous familial hypercholesterolemia. High-income countries have significantly better access, full reimbursement, and registration of LLTs compared to non-high-income countries, especially for newer, expensive but highly effective therapies. Addressing these gaps, particularly in non-high-income countries, is essential to improve health outcomes for HoFH patients worldwide.