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Research article

Physician preferences for treatment of low-density lipoprotein cholesterol among patients with atherosclerotic cardiovascular disease (ASCVD)–A discrete choice experiment

Marlon Graf [a,*], Amit V. Khera [b,c], Suepattra G. May [a], Sukyung Chung [a], Laetitia N'dri [d], Joaquim Cristino [e], Batul Electricwala [e]

[a] Precision AQ, Bethesda, MD, USA
[b] Division of Cardiology, Brigham and Women's Hospital, Boston, MA, USA
[c] Verve Therapeutics, Cambridge, MA, USA
[d] Bristol Myers Squibb, Princeton, NJ, USA
[e] Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

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ABSTRACT

Objective: Approximately 80 % of patients with atherosclerotic cardiovascular disease (ASCVD) do not achieve the guideline-based target for low-density lipoprotein (LDL-C) levels in current clinical practice, particularly the 95 % of ASCVD patients receiving oral statin monotherapy. The objective was to determine physician prescribing preferences for LDL-C lowering therapies beyond statins for patients with ASCVD.

Methods: A discrete choice experiment (DCE) survey was administered to cardiologists and primary care physicians in the United States, presenting a series of treatment choices systematically varied across 8 treatment attributes: % LDL-C reduction, myalgias, other side effects, route and frequency of administration, time to prior authorization, patient monthly out-of-pocket cost (mOOP), and adherence. Data were analyzed using logistic regression to estimate preference weights for each attribute.

Results: A total of 200 cardiologists and 50 primary care physicians (PCPs) completed the survey. Both exhibited similar prescribing preferences, highly valuing efficacy in reducing LDL-C levels and minimization of patients OOP cost. Each additional 10 % reduction in LDL-C was associated with a 69 % relative increase in physician preference. By contrast, a 10 % relative decrease in preference was observed for each $10 additional monthly mOOP. Compared to PCPs, cardiologists tended to place more emphasis on LDL-C reduction, being more willing to accept higher mOOP or side effects. Although oral therapies were preferred, injectable therapies, like the PCSK9 siRNA-like drug, administered less frequently that allowed for greater LDL-C reduction were seen as having considerable utility, especially among patients with a history of medication nonadherence.

Conclusion: These results document considerable preference similarities among cardiologist and PCP prescribers of LDL-C lowering therapies for ASCVD. Broad availability of several therapies with varying administration frequencies and product profiles are likely of great value to prescribing physicians aiming to achieve target LDL-C concentrations. Considering all aspects of treatment, most participants preferred a PCSK9 siRNA-like drug.

* Corresponding author.2 Bethesda Metro Center, Suite 850, Bethesda, MD, 20814, USA.
E-mail address: marlon.graf@precisionaq.com (M. Graf).

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1. Introduction

In the United States (US), it has been estimated that approximately 80 % of patients prescribed statins do not attain recommended LDL-C goals, a key risk factor for developing atherosclerotic cardiovascular disease (ASCVD) [1–4]. The disease confers a substantial individual and societal economic burden [5,6], accounting for over 30 % of total US health expenditures for individuals over the age of 40 [7].

Current US guidelines recommend statin or combination statin and non-statin therapies (i.e., ezetimibe and monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) [3]. The US Food and Drug Administration (FDA) recently approved the small interfering RNA (siRNA) inclisiran and bempedoic acid, which demonstrated success in reducing LDL-C, in patients with ASCVD who had elevated LDL-C levels despite maximally tolerated lipid-lowering therapy [8,9].

While these conventional therapies show promise in reducing LDL-C, variations in efficacy, side effects, and administration frequency exist [3,10–12]. In current practice, the majority of patients with ASCVD do not achieve the target LDL-C recommended to reduce the risk of recurrent events and require add-on therapy [13–17]. To maximize treatment effectiveness and adherence and to discern any key differences in approaches and treatment philosophies, particularly for newer treatments [18], it is essential to understand considerations from cardiologists and primary care physicians (PCPs).

Our study employed a discrete choice experiment (DCE) to understand physician preferences for attributes of LDL-C lowering therapies used as an adjunct to maximally-dosed statin and lifestyle management. DCEs are used in health economics to measure stakeholder preferences for key treatment attributes, willingness to tradeoff between attributes, and preference shares for particular treatment profiles [19]. Previous DCE studies have elicited patient preferences regarding cardiovascular health, however few have elicited physician preferences. [20–24] Our DCE aims to understand physician perspectives on ASCVD treatments.

2. Methods

A survey study of cardiologists and prPCPs designed to elicit preferences for attributes of treatment for secondary prevention of ASCVD and attainment of recommended LDL-C levels was conducted. The survey included four modules: an eligibility screener, a DCE module to assess preferences for attributes associated with treatment, a module to capture data on patient panel and practice characteristics, and a module to elicit data on participant socio-demographics. The full survey instrument is provided in the supplementary appendix of this manuscript. A convenience sample of cardiologists and PCPs who report currently treating a substantial volume of patients with ASCVD were recruited to participate in the study. We arrived at a target sample of 250 physicians based on previously described guidance for minimum sample size [25].

We performed the study in three phases: a qualitative data collection phase comprising semi-structured in-depth interviews with cardiologists (n = 16) and PCPs (n = 8), a pilot testing phase conducted between October–November 2021, and a primary data

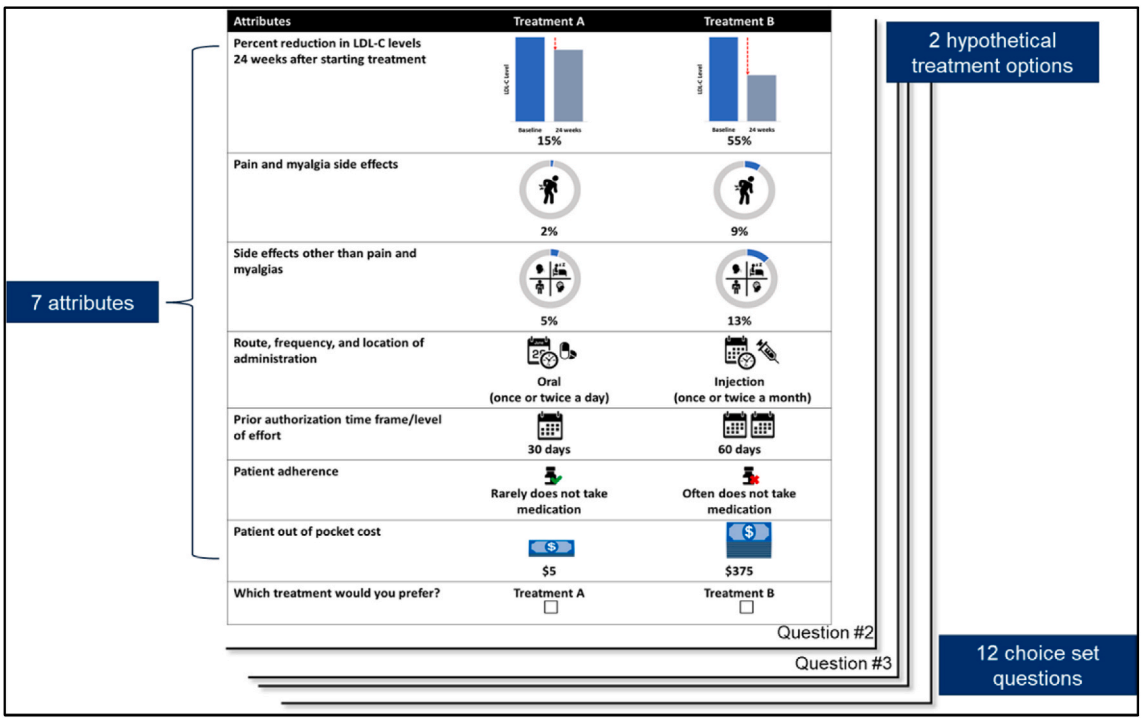

Fig. 1. Dce choice set example Figure.

collection phase, conducted between November–December 2021. Eligible providers included physicians board certified in cardiology, internal medicine, or family medicine and who reported seeing on average > 10 patients with ASCVD per month who are not below the recommended LDL-C threshold and not well controlled on statin therapy. In addition, eligible respondents needed to report prescribing 1) ≥20 % of ASCVD patients low/moderate intensity statins or ≥25 % high intensity statins 2) ≥10 % cholesterol absorption inhibitors, and 3) ≥5 % PCSK9i monoclonal antibody for secondary prevention of ASCVD. Prior to participating in any of the study phases, informed consent was obtained from participants, after presenting them with an information statement detailing study objectives, compensation as well as participant rights and responsibilities. For the semi-structured interviews, informed consent was obtained verbally by the interviewer after walking participants through the study information statement and for the survey, participants were presented with the information statement and then asked to consent by selecting the "Yes, I consent to participate in this survey" option from among the "yes" and "no" options provided to them, which then allowed them to proceed to the actual survey.

Sixteen cardiologists and eight PCPs participated in 60-min interviews during phase 1 of this study and were asked about 1) patient diagnosis and treatment decision making, 2) initial treatment regimen, 3) subsequent treatment regimen, 4) evidence gaps and unmet needs, as well as 5) potential impact of COVID-19 on their clinical practice. Subsequently, eight respondents participated in pilot testing and debriefing interviews to further hone the survey instrument and assess respondent comprehension of the background content and survey questions. This testing included ensuring that patients understood the definitions for the various attributes, as well as the iconography used to represent the attributes in the study design. Results from the pilot testing and consultation with clinical experts informed revisions to the final versions of the survey, which was administered to respondents on a web-based survey platform.

The Advarra Institutional Review Board, an independent organization accredited by the Office for Human Research Protections (OHRP) and the Association for the Accreditation of Human Research Protection Programs (AAHRPP) reviewed study procedures and exempted the study from full review due to minimal risk to study participants.

Using information from publicly available sources, including clinical trials and published literature, we constructed stylized treatment profiles from our mix of attributes and levels to calibrate study results to real world treatment preferences, including newer generation treatment options for LDL-C. To gain insight into provider treatment preferences, twelve choice set questions (Fig. 1)

Table 1
Provider characteristics.

Characteristic	Cardiologists (N = 200)		PCPs (N = 50)	
	Mean or N	SD or %	Mean or N	SD or %
Age (Mean, SD)	51.4	10.8	52.4	9.5
Gender				
Male	174	87 %	38	76 %
Female	24	12 %	12	24 %
Prefer not to say	2	1 %	0	0 %
Primary Specialty[a]				
Cardiology	200	100 %	N/A	
Internal Medicine	12	6 %	31	62 %
Family Medicine	0	0 %	20	40 %
Years in Practice				
2–5 years	14	7 %	0	0 %
6–10 years	31	16 %	5	10 %
11–15 years	38	19 %	6	12 %
16–20 years	41	21 %	14	28 %
More than 20 years	76	38 %	25	50 %
Practice Type[a]				
Solo Practice	18	9 %	7	14 %
Partnership Practice	36	18 %	14	28 %
Group Model Health Maintenance Organization (e.g., Kaiser Permanente)	3	2 %	0	0 %
Government (e.g., VA, military, public health)	3	2 %	0	0 %
University/Academic Medical Center	51	26 %	3	6 %
National Cancer Institute (NCI) Designated Cancer Center	0	0 %	0	0 %
Specialty Group Practice	60	30 %	7	14 %
Multi-Specialty Group Practice	23	12 %	19	38 %
Hospital-Based Practice	36	18 %	3	6 %
ASCVD patients with elevated LDL-C levels seen monthly				
11-20	2	1 %	0	0 %
21-35	9	5 %	1	2 %
36-50	36	18 %	11	22 %
51-100	65	33 %	23	46 %
More than 100 patients	88	44 %	15	30 %
ASCVD patients not well-controlled on statins & require add-on therapy				
11-20	42	21 %	7	14 %
21-35	45	23 %	9	18 %
36-50	48	24 %	14	28 %
51-100	38	19 %	15	30 %
More than 100 patients	27	14 %	5	10 %

[a] Providers could select more than one answer choice.

comparing two hypothetical treatment plans varying on seven key attributes were presented to survey participants. The attributes included in the survey were generated from a review of the literature and from the qualitative data collection component of this study. The survey design was developed in accordance with the ISPOR Conjoint Analysis Good Research Practices Task Force for Pharmacoeconomic Research [26].

A list of potential attributes and levels for the DCE was generated from a review of the literature, in consultation with cardiologists, and based on findings from a series of in-depth interviews with cardiologists and PCPs completed during the earlier qualitative study phase. In order to arrive at an appropriate and feasible number of attributes for the DCE, several factors were considered in attribute selection: 1) relevance of the attribute to available treatment options as well as availability of data on a given attribute for each treatment option; 2) ease of quantifying the attribute and communicating the description of the attribute in a survey; 3) potential for overlap or correlation with other attributes; 4) relevance to the objectives of the study; and 5) variation in the attribute across currently and potentially available treatments for ASCVD [19]. The final set of attributes and levels is summarized in the supplementary appendix.

Using the DCE design, attributes included in the choice sets were the following: 1) % LDL-C reduction, 2) % risk for muscle, joint, back, extremity pain and myalgia side effects, 3) % risk for side effects other than muscle, joint, back, extremity pain and myalgia, 4) route, frequency and location of treatment administration, 5) time required to obtain prior authorization, 6) patient out of pocket cost (OOP), and 7) adherence. Other study measurements collected included practice characteristics and socio-demographics. We queried respondents about their practice setting (e.g., academic center, multi-specialty, or solo private practice, etc.) and the average number and presenting characteristics of ASCVD patients treated each month. The socio-demographic questions elicited data about respondent age, gender, race, and medical training.

We first generated descriptive statistics on the study sample, including key information on provider demographic and health characteristics. Where possible, final results were stratified by the demographic and patients' health covariates presented in the scenarios collected in the survey. We then analyzed responses to the treatment attribute choice scenarios estimated provider preferences for changes in attribute levels, for example reduce risk of pain and myalgia, using a random coefficients logit model. Based on these regression estimates, we then proceeded to calculate trade-offs between relevant treatment attributes, denoted as the marginal rate of substitution (MRS) between two attributes or the ratio of the two attributes' coefficients [26].

3. Results

Of 982 respondents who responded to the study invitation, 617 (63 %) met initial study eligibility criteria, 365 (37 %) were excluded for not meeting eligible criteria or for reporting insufficient patient or prescribing volume, and 250 (41 %) completed the survey. We closed the survey when the accrual target of 250 for the sample population was achieved. Hence, the completed analytic sample included data for 200 cardiologists and 50 PCPs. Respondent demographic characteristics are presented in Table 1. Additional detail on the study population and the patient population they served is presented below in Table 1.

This study determined respondent preferences across the attributes of efficacy, cost, method and route of administration, safety/tolerability, and adherence for ASCVD management. The relative importance of treatment attributes derived from the results of providers' responses to the DCE module are shown in Figs. 2 and 3. Respondents placed the most weight on LDL-C reduction (OR = 1.69, 95 % CI: [1.446,1.976], $p < 0.001$) and monthly out of pocket costs (OR = 0.90, 95 % CI [0.874,0.929], $p < 0.001$). The risk of side effects, other than pain and myalgias, were negatively perceived by providers (OR = 0.96, 95 % CI: [0.938,0.978], $p < 0.001$). Respondents were 35 % more likely to prefer an oral (once or twice daily) route of administration compared to the combination of oral

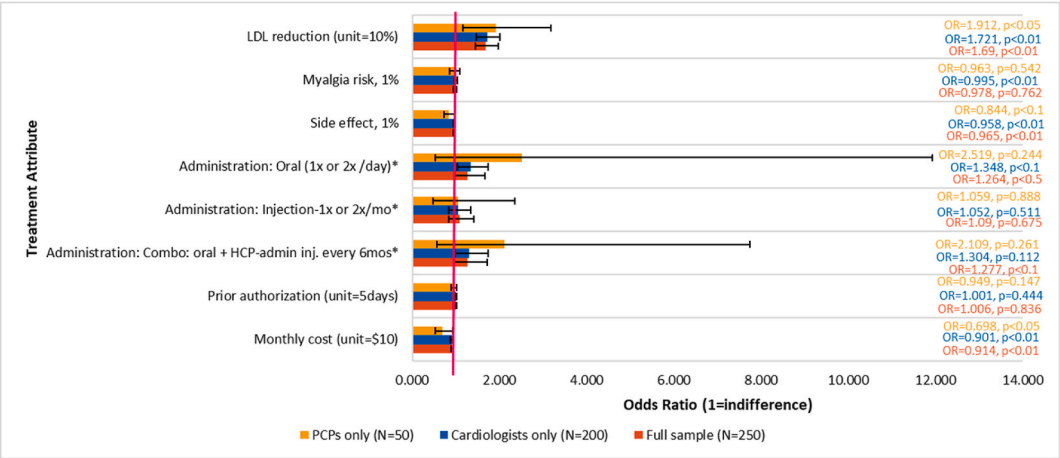

Fig. 2. Relative importance of treatment attributes (baseline models)
* Reference category = Combo: oral + at home inj. 1x or 2x/mo
OR>1 means treatment with a particular attribute is preferred; OR<1 means treatment with a particular attribute is less preferred.

and at home injections once or twice monthly (OR = 1.35, 95 % CI: [1.043,1.742], p < 0.05). Respondents were 30 % more likely to prefer a combination therapy with injections once every 6 months administered by a healthcare provider (HCP) compared to combination therapy with at home injections once or twice a month (OR = 1.30, 95 % CI: [0.976,1.743], p < 0.1). Preferences of cardiologists and PCPs were similar, but cardiologists expressed stronger preferences for greater reduction of LDL-C levels (OR = 1.72, 95 % CI: [1.472,2.011], p < 0.001) while PCP respondents expressed stronger preferences for minimizing both side effects (OR = 0.84, 95 % CI: [0.726,0.982], p < 0.05) and patient out of pocket costs (OR = 0.70, 95 % CI: [0.524,0.930], p < 0.05).

For non-adherent patients, respondents showed a strong aversion of oral medication only compared to combination therapy with oral and injections (OR = 0.33, 95 % CI: [0.160,0.671], p < 0.01). Providers slightly preferred a less frequent injection administered by an HCP compared to more frequent injections at home (Fig. 3). When looking at cardiologists only, preferences were similar to the full sample, but, for non-adherent patients, they showed a strong preference for injection only compared to the combination of oral and injection once or twice a month at home (OR = 2.45, 95 % CI: [1.152,5.200], p < 0.05). Results of this model are not presented for PCPs, as the sample size did not allow for use of the interaction terms required to estimate preferences for specific modes of administration in non-adherent patients.

The tradeoffs respondents were willing to make between treatment attributes were shown through MRSs. Fig. 4a shows the MRS between monthly out of pocket costs and LDL-C reduction and Fig. 4b shows the MRS between side effects and LDL-C reduction across subgroups. Overall, respondents were willing to prescribe a drug with $50 higher mOOP for an additional 10 % reduction in LDL-C levels. Cardiologists and PCPs showed substantial differences such that, for a drug that provides an additional 10 % reduction in LDL-C levels, cardiologists were willing to accept $61 higher mOOP whereas PCPs are only willing to accept $18 higher mOOP. Further for non-adherent patients, cardiologists were willing to accept even higher costs ($71 mOOP) for an additional 10 % reduction in LDL-C levels.

When assessing the trade-offs between side effects and LDL-C reduction, respondents overall were willing to accept a 12 % increase in the risk of side effects for a drug with an additional 10 % reduction in LDL-C levels. Cardiologists were willing to accept a larger increase in side effects for LDL-C reduction than PCPs. Cardiologists were willing to accept 15 % additional risk of side effects for a drug that provides an additional 10 % reduction in LDL-C levels, compared to 4 % for PCPs. For non-adherent patients, cardiologists were willing to accept up to 52 % additional risk of side effects for an additional 10 % reduction in LDL-C.

Using the treatment profile calibration (e.g., each therapy's individual attribute levels) and stated preferences from the DCE module, preference shares across subgroups for ezetimibe-like, PCSK9i monoclonal antibody-like, and PCSK9 siRNA-like drugs were calculated and are depicted below in Fig. 5. Overall, the majority of provider respondents would prefer an siRNA-like drug (52.7 %), while about one third would prefer an ezetimibe-like drug (34.8 %). When looking at respondent subgroups, cardiologists show an even stronger preference towards an siRNA-like drug (57.5 %), especially for patients who are non-adherent (61 %). Conversely, PCPs are much more likely to choose an ezetimibe-like drug (97.2 %) and very few would prefer a PCSK9-like (<1 %) or siRNA-like drug (2.8 %).

4. Discussion

Our study sample was fairly representative as the overall composition of cardiologists was similar in age, gender, and racial distribution to data reported by Association of American Medical Colleges (AAMC) [27,28], while the composition of our PCP study population skewed slightly more male and Asian than recent data from both AAMC and the American Academy of Family Physicians

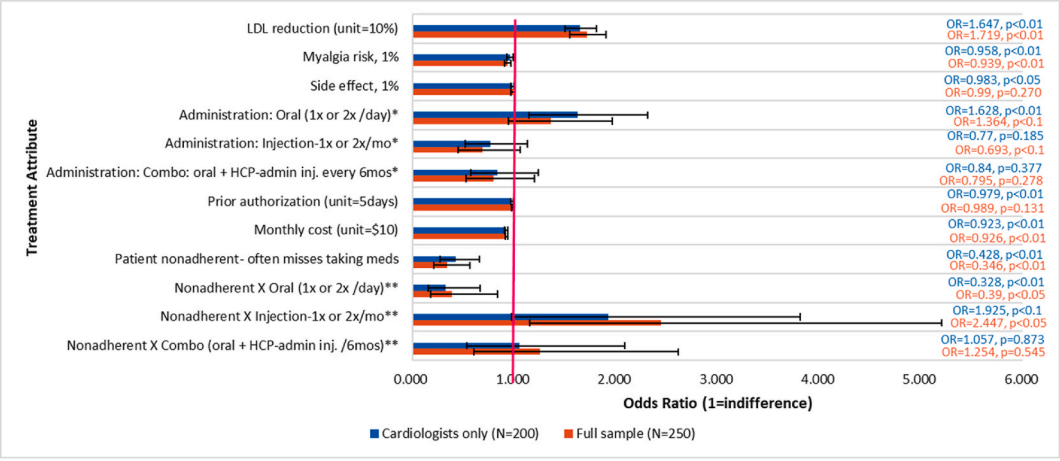

Fig. 3. Relative importance of treatment attributes (adherence models)
* Reference category = Combo: oral + at home inj. 1x or 2x/mo
** Reference category = Nonadherent X Combo (oral + at home inj. 1x or 2x/mo)
OR>1 means treatment with a particular attribute is preferred; OR<1 means treatment with a particular attribute is less preferred.

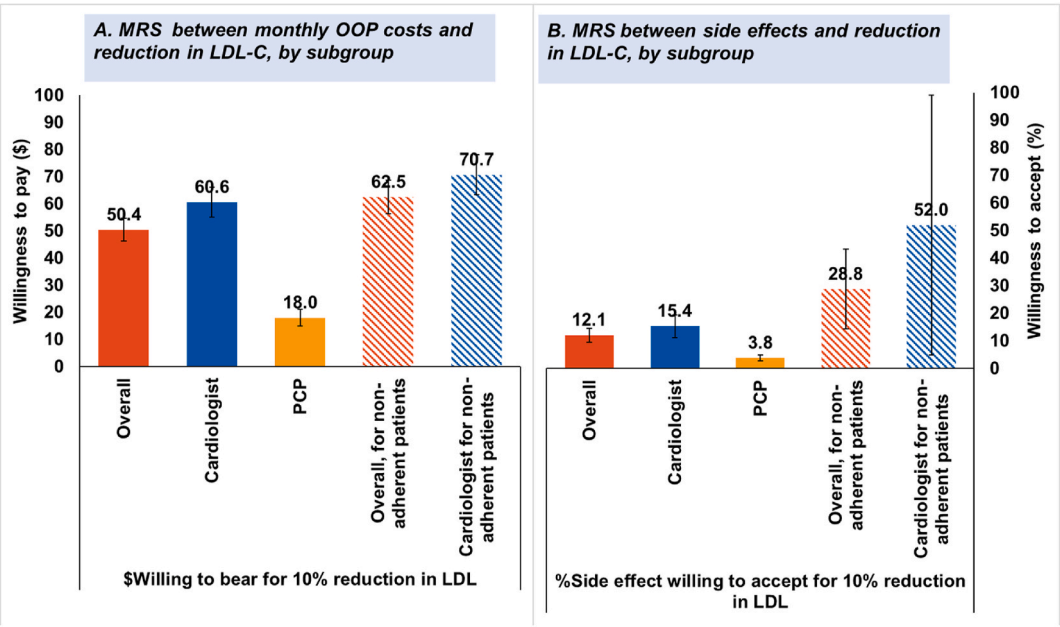

Fig. 4. Marginal Rate of Substitutions (MRS) between monthly OOP costs and reduction in LDL-C/side effect risk, by subgroup.

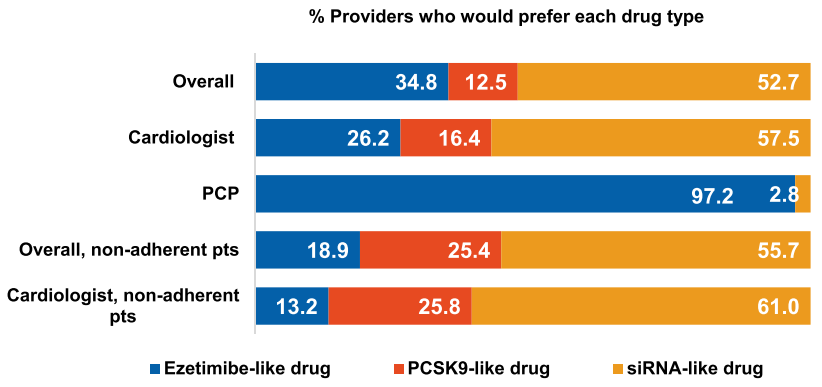

Fig. 5. Preference shares.

(AAFP) [27,29]. Our study of US cardiologists and PCPs demonstrated provider preferences towards attributes of treatment associated with lipid-lowering therapies for patients with ASCVD and whose LDL-C is not well-controlled on statin monotherapy. Our analysis of treatment preferences demonstrates that providers placed the greatest emphasis on LDL-C reduction and patient mOOP, followed by potential side effects. Providers were 35 % more likely to select oral compared to combination therapy with oral and home injections. However, when considering a non-adherent patient, the oral and injection combination therapy was preferred as the potential to improve adherence to lipid lowering medication was found to provide long-term survival benefits [30].

Despite a compelling evidence base and universal endorsement by professional society guidelines, the majority of ASCVD patients in the U.S. fail to achieve adequate LDL-C reduction to protect against recurrent events [2,31,32]. A recent study based on 2019 claims data indicated that, of the estimated 24 million ASCVD patients in the U.S., only 27 % achieved LDL-C <70 mg/dL [2]. Fewer than 4 % of these patients received ezetimibe and fewer than 1 % received a PCSK9i monoclonal antibody. These observations indicate the critical importance of both developing new therapeutic options to address this unmet need as well as understanding physician prescribing preferences to inform optimal access and shared decision-making with their patients.

In this study, both cardiologists and PCPs exhibited similar prescribing preferences for secondary prevention of ASCVD. Both groups highly valued a therapy's ability to effectively reduce LDL-C levels as well as consideration of the monthly OOP cost borne by patients. However, cardiologists were more willing to accept a higher monthly OOP cost than PCPs ($61 versus $18, respectively, per additional 10 % LDL-C lowering). This is also consistent with work recently published by Khera et al. (2020), which found for families of patients with ASCVD, insurance premiums and prescription medications represented between one-third to nearly half of their OOP

healthcare expenditures. Thus, patient adherence may be limited by their ability to consistently pay for medication as 45 % of patients in this study reported difficulty paying their bills over a 12-month period [5]. Although understanding the reasons behind this discrepancy was beyond the scope of the current study, potential reasons may include that 1) PCPs manage a range of therapeutics in their ASCVD patients, each with their own OOP cost, which may allow for a more comprehensive understanding of the financial toxicity of OOP costs, 2) PCPs follow a different set of guidelines, and 3) PCPs exhibit greater familiarity with their patients and/or the cost of specific health care options.

Lastly, it is well documented that many ASCVD patients have trouble adhering to medications for a wide range of reasons, including broad healthcare disparities due to socioeconomic status and other demographic characteristics, treatment cost, limited access to healthcare, side effect burden of lipid-lowering therapies, overall health literacy, presence of comorbid conditions that may limit adherence, and many others. For those patients, providers in our survey tended to prefer therapies with less-frequent administration, in order to minimize risk of non-adherence and treatment impact [33].

This study has several limitations and future research would benefit from a deeper exploration of the tradeoffs observed, particularly between specialties. First, this study examined preferences of cardiologists and PCPs in the U.S. only. Additional studies of non-U.S. prescribers as well as non-physicians who play an important role in prescribing lipid-lowering therapies, such as nurse practitioners or physician assistants, are likely to be of interest. Second, the survey was conducted using a web-based format and may therefore have excluded physicians without online access. Third, our PCP sample is relatively small ($n = 50$), and respondents may be different from physicians who did not respond to the survey along other demographic and practice-related characteristics. However, respondent characteristics were comparable to aggregate profiles of cardiologists and PCPs in the US, as reported by their respective membership organizations, and thus we believe the reported results are largely generalizable. Fourth, it is possible that some combinations of the treatment attributes in the DCE do not resemble existing drugs or drug combinations, which might introduce statistical noise or inconsistencies in responses. For example, one of the attributes referred to an injectable therapy only; such a treatment regimen is typically only used for patients with statin intolerance and is not the norm for LDL-C reduction. Results of the study stem from a stated, rather than a revealed preference survey design. The actual treatment cardiologists and PCPs choose may depend on other factors not included in the survey, such as a treatment's cardiovascular outcomes, care team advice, availability of a given therapy on formulary, and other factors.

5. Conclusion

Prescribing providers have a range of treatment options available to lower LDL-C in patients with ASCVD. Researchers and clinicians often presume that the value of a therapy is primarily around a singular endpoint, in this case LDL-C reduction. While the results from this survey of US providers suggests that LDL-C lowering efficacy is indeed a primary driver of physician prescribing preferences it is not the only one and preferences vary by stakeholder type as well as patient group. PCPs tended to be more cautious in their approach to managing LDL-C levels, paying closer attention to side effect profiles and potential drug interactions, in addition to placing greater consideration on patient out-of-pocket costs. Cardiologists showed a slightly higher willingness to accept side effects in exchange for greater reductions in LDL-C levels. For patients perceived to be non-adherent to treatment, physicians preferred injectable medications.

These findings are well aligned with recent lipid clinical guidelines, which increasingly emphasize shared decision making based on individualized preference to guide selection of lipid-lowering therapies beyond non-statin therapies, including factors such as out of pocket payments, risk of side effects, and likelihood of adherence. Moreover, differences in perceptions between PCPs and cardiologists indicate a potential need for targeted education efforts (e.g., education around the importance of LDL-C lowering to achieved guideline-based targets among primary care physicians and the need to consider monthly OOP for cardiologists).

Data availability statement

Data for this study will be made available upon reasonable request to the authors.

Funding statement

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CRediT authorship contribution statement

Marlon Graf: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Amit V. Khera:** Writing – review & editing, Validation, Methodology, Investigation. **Suepattra G. May:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Sukyung Chung:** Writing – review & editing, Visualization, Validation, Software, Methodology, Formal analysis. **Laetitia N'dri:** Writing – review & editing, Resources, Project administration, Methodology, Investigation. **Joaquim Cristino:** Writing – review & editing, Resources, Project administration, Methodology, Conceptualization. **Batul Electricwala:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

This study was funded by Novartis Pharmaceuticals Corporation. Marlon Graf is employed by Precision AQ, a company awarded a contract by Novartis to conduct this work. Suepattra G. May and Sukyung Chung are former employees of Precision AQ. Suepattra G. May owns equity interest in Precision AQ's parent company, Precision Medicine Group. Batul Electricwala is a current employee of Novartis and may hold Novartis stock. Joaquim Cristino and Laetitia N'dri are former employees of Novartis and may hold Novartis stock. Amit V. Khera served as a scientific advisor on this study and receives consulting fees from Novartis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35990.

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