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Do the benefits of statins outweigh their drawbacks? Assessing patients' trade-off preferences with conjoint analysis ☆☆☆

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Efficacious lowering of low-density lipoprotein cholesterol through prolonged statin therapy has become a major strategy for primary and secondary prevention of cardiovascular disease. From the perspective of patients, however, the prophylactic efficacy may be difficult to comprehend. It refers to prospective disease prevention at the population level and an uncertain risk reduction for individual patients. At the same time, actual side effects may occur and treatment entails a lifelong regimen.

It is therefore not surprising that a large meta-analysis demonstrated that only 54% of patients showed good adherence to statins [1]. We therefore examined patients' trade-offs between the efficacy, side effects and other drawbacks of statins using a conjoint analysis choice task (see www.sawtoothsoftware.com, 'Technical Papers' in 'Support' menu). Subsequently, we examined associations between trade-offs and non-adherence.

Previously, we and others have used conjoint analysis choice tasks to assess patients' trade-offs with regard to treatment of rheumatoid arthritis, endocrine therapy for breast cancer, and antidepressants [2], [3] and [4]. These tasks are realistic in two respects. First, they do not assess mere preferences but rather *trade-off* preferences, which are inevitable because there is no such thing as a perfect treatment. Second, these tasks *directly* assess patients' trade-offs rather than assessing the benefits and drawbacks with independent questions. In a conjoint analysis choice task, patients are asked to choose between pairs of hypothetical treatment alternatives (presented left and right). Each time, the left alternative is *more* favorable than the right alternative for one characteristic (e.g. cholesterol lowering) but *less* favorable than the right alternative for another characteristic (e.g. muscle pain as a side effect). Using so-called adaptive conjoint analysis (ACA), the fifteen most informative pairs

of treatment alternatives were presented to each individual patient. ACA achieves this by means of a computerized tailoring of pairs of treatment alternatives on the basis of a patient's previous trade-off choices.

Based on the literature and focus groups, we selected the following 7 treatment characteristics: 'prevention of myocardial infarction' and 'cholesterol lowering' (benefits), the side effects of 'muscle and joint pain', 'feeling nauseous and stomach cramps or diarrhea', and 'severe side effects requiring hospital admission e.g. rhabdomyolysis', as well as 'regimen duration', and 'restrictions on alcohol consumption' (drawbacks). To elicit trade-off choosing, every characteristic was described at favorable and less favorable levels (e.g. 'a bit muscle pain' versus 'moderate to severe muscle pain').

From patients' trade-off preferences, we calculated, for each individual patient, a utility for each level of every treatment characteristic on a scale ranging from -2.5 to $+2.5$. The higher the utility, the higher the attractiveness of a level of a treatment characteristic for a patient (e.g. 'a bit muscle pain' was expected to receive a higher utility than 'moderate to severe muscle pain'). Based on the utility estimates, a relative importance score for each treatment characteristic was calculated as well as a benefit/drawback ratio between the importance of the characteristics reflecting benefits and the characteristics reflecting drawbacks in the way as described elsewhere [3] and [4]. Non-adherence was measured with two self-report instruments [5] and [6]. Factor analysis revealed 2 dimensions with sufficient internal consistency: unintentional non-adherence (alpha 0.77, 3 items, range 0–3) and intentional non-adherence (alpha 0.75, 5 items, range 0–5). In addition, non-adherence was also calculated from pharmacy refill data as a combination of adherence measures improves accuracy [7]. The medical ethical committee approved the study. All participants provided informed consent.

Two-hundred-twenty-nine patients who were recruited through pharmacies participated (see Table 1 for demographic and clinical characteristics). Analyses showed that the highest average importance scores were seen for 'muscle and joint pain' as well as for 'feeling nauseous and stomach cramps or diarrhea' (see Table 2). 'Prevention of myocardial infarction' was on average somewhat less but still substantially important. 'Cholesterol lowering' and 'severe side effects requiring hospital admission, e.g. rhabdomyolysis' were on average of intermediate importance. 'Restrictions on alcohol consumption' and 'regimen duration' were on average least important. The benefit/drawback ratio showed that $\sim 40\%$ of the patients valued efficacy equal to or lower than side effects and other drawbacks. After adjusting for relevant demographic and clinical characteristics, a higher benefit/drawback ratio was not associated with decreased unintentional non-adherence (OR 0.3, 95% CI: 0.1–1.2, Wald = 3.0, $p = 0.08$), but was associated with decreased intentional non-adherence (OR 0.1, 95% CI: 0.03–0.40, Wald = 10.0, $p < 0.005$). No such association was found between the benefit/drawback ratio and non-adherence inferred from the pharmacy refill data (OR 1.1, 95% CI: 0.23–5.2 Wald = 0.01, $p = 0.92$). These findings make sense because unintentional non-adherence or a mere forgetting or lack of understanding of the regimen is not likely to reflect trade-

off choosing, whereas intentional non-adherence is, and non-adherence inferred from pharmacy refill data is likely to reflect both forms of non-adherence.

[TABLE 1] [TABLE 2]

Our findings suggest that many patients do not consider the prospective efficacy of statins to outweigh their side effects and other drawbacks. Furthermore patients' trade-offs may help physicians to identify patients at risk for intentional non-adherence for whom a more persuasive explanation of the efficacy of statins or resolution of negative perceptions of side effects might be fruitful. On the other hand, the finding that many patients seemed to value the efficacy equally or less important than the side effects and other drawbacks could also suggest that there is overprescribing from a patient's perspective. Particularly for these patients, alternative prevention strategies aimed at changing modifiable lifestyle risk factors should be discussed between a physician and a patient. Considering patients' trade-offs is all the more important because the American College of Cardiology and the American Heart Association recently liberalized the boundary for statin therapy initiation but also acknowledged that decisions to initiate statins should not be solely based on passing a certain atherosclerotic cardiovascular disease risk threshold, but should be based on a shared decision making process in which physicians and patients weigh the potential benefits against the side effects and practical inconveniences [8]. The assessment of patients' trade-off preferences about cardiovascular drugs in larger-scale longitudinal studies and clinical practice is therefore strongly encouraged.

Conflicts of interest

LVD has received two unrestricted grants (BMS and Astra Zeneca). ECGVG is currently employed at the Dutch Kidney Foundation (Nierstichting). PCS has received unrestricted funding from the private–public funded Top-Institute PHARMA (www.tipharma.nl) and the EU Innovative Medicines Initiative (IMI). The other authors report no relationships that could be construed as a conflict of interest.

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TABLES

Table 1. Demographic and clinical characteristics of the participants.

Variables	Statistic
N participants	229
<i>Demographic characteristics</i>	
N (%) men	146 (64)
mean age (SD) in years	63.9 (10.2)
N (%) married or living together	185 (81)
N (%) higher educated (vs. low to intermediate)	105 (46)
<i>Clinical characteristics</i>	
Status of use	
N (%) starters (< 3 months)	21 (9)
N (%) users (> 3 months)	189 (83)
N (%) discontinued	19 (8)
Duration of use (only users)	
N (%) 0–1 years	23 (12)
N (%) 1–4 years	64 (34)
N (%) 4 years or longer	102 (54)
Name of statin treatment	
N (%) atorvastatin	41 (18)
N (%) fluvastatin	2 (1)
N (%) pravastatin	19 (8)
N (%) rosuvastatin	27 (12)
N (%) simvastatin	140 (61)
<i>Primary vs. secondary prevention</i>	
Primary prevention	
N (%) elevated cholesterol	117 (51)
N (%) diabetes	37 (16)
Secondary prevention	
N (%) MI/AP/TIA/Stroke/IC	81 (35)
N (%) PCI	31 (14)
N (%) CBAG	12 (5)

Abbreviations: MI, Myocardial Infarction; AP, Angina Pectoris; TIA, Transient Ischemic Attack; IC, Intermittent Claudication, PCI, Percutaneous Coronary Intervention; CBAG, Coronary Bypass Artery Grafting.

Table 2. Mean and SD of utilities of treatment attribute levels and relative importance of treatment attributes.

Treatment attributes and their levels	Utilities [□]		Average importance % [†]	
	M	SD	M	SD
<i>Efficacy</i>				
Prevention of myocardial infarction			17.2	4.3
In 2/10 people (a fifth)	- 0.49	0.47		
In 5/10 people (half)	+ 0.56	0.45		
Cholesterol lowering			14.0	2.9
But above target level	- 0.37	0.36		
At target level	+ 0.44	0.34		
<i>Side effects</i>				
Muscle and joint pain			19.1	3.2
A bit	+ 0.59	0.44		
Moderate to severe	- 0.52	0.47		
Feeling nauseous and stomach cramps or diarrhea			20.5	2.7
A bit	+ 0.64	0.48		
Moderate to severe	- 0.57	0.50		
Severe side effects requiring hospital admission e.g. rhabdomyolysis			12.4	2.1
1/1000 people	+ 0.40	0.30		
2/1000 people	- 0.33	0.33		
<i>Practical aspects</i>				
Regimen duration			6.7	1.7
5 years treatment	+ 0.23	0.18		
Lifelong treatment	- 0.16	0.21		
Restrictions on alcohol consumption			10.1	3.9
Preferably not	-	0.31		

Treatment attributes and their levels	Utilities [□]		Average importance % [†]	
	M	SD	M	SD
	0.26			
2–3 daily units allowed	+ 0.33	0.30		

□ Utilities estimated on a scale ranging from ~ -2.5 to $+2.5$; the higher the estimated utility value of an attribute level, the more that attribute level is preferred, e.g. 5 years of treatment versus lifelong treatment.

† The relative importance of each attribute is calculated as follows: for each attribute the difference between the utilities of its levels is divided by the sum of the differences between the utilities for all of the attributes and multiplied by 100.