Patient Preference Weights for Benefit-Risk Analysis: A Statin Case Study

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BACKGROUND

- New pharmaceuticals often offer significant improvements in efficacy, but also may increase the risk of serious side effects.
- The Food and Drug Administration's (FDA) 2007 reauthorization legislation requires the agency to evaluate strategies for comparing the benefits and risks of pharmaceuticals.
- Patients benefit from new treatments, but also bear treatment-related side effects.
- Patients' benefit-risk tradeoff preferences may be useful in informing regulatory decision making.

OBJECTIVE

- Obtain valid patient preference weights and risk-tolerance estimates to support benefit-risk analysis of antihypercholesterolemia treatments.

METHODS

Subjects

- Inclusion criteria
  - Aged 18 years or older
  - United States (US) resident
  - Self-reported physician diagnosis of hypercholesterolemia
- Recruitment
  - Knowledge Networks nationally representative Web panel
  - All subjects provided online informed consent
  - Final sample was 637:
    - 327 subjects completed the survey in the usual way (no-time- to-think [NTTT] sample)
    - 310 subjects received information about attributes and choice tasks and were instructed to think about that material for 24 to 48 hours before returning to complete the choice tasks (time-to- think [TTT] sample).

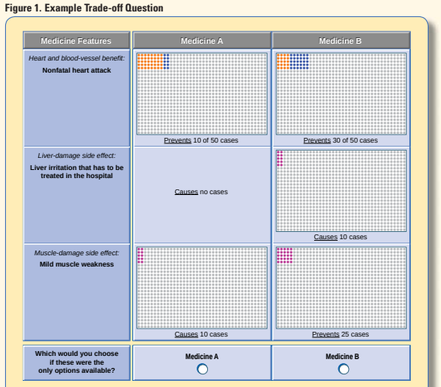
Survey Instrument

- Web-enabled survey instrument
- Discrete-choice experiment (choice-format conjoint or stated-choice survey)[1,2,3,4]
- 10 trade-off questions
- Medication attributes (Table 1):
  - Cardiovascular events:
    - Lower chance of angina that requires minor surgery in a hospital
    - Lower chance of nonfatal heart attack or stroke
    - Lower chance of death from heart attack
  - Hepatoxicity side effects:
    - Chance of short-term hepatitis without hospitalization
    - Chance of hepatitis that has to be treated at the hospital
    - Death from liver failure
  - Nephrotoxicity side effects:
    - Chance of mild muscle damage (myopathy)
    - Chance of severe muscle damage (rhabdomyolysis)
    - Muscle damage that leads to kidney failure
- Subjects chose the option they would prefer if these were the only options available (Figure 1)
- Experimental design:
  - Statistically efficient subject to varying only one attribute in each of the three categories[5,6,7]
  - Blocked into 9 versions
- Internal-validity tests:
  - Repeated test-retest question
  - Transitivity test
  - Across-set monotonicity test
  - Dominance test
- Standard demographic information and subjects' experience with hypercholesterolemia treatments

Table 1. Treatment Attributes and Levels

Attribute Category	Attribute	Levels
Cardiovascular events	Lower chance of chest pain (angina) that requires minor surgery in a hospital	100 out of 1,000 people
		50 out of 1,000 people
		0 out of 1,000 people
	Lower chance of nonfatal heart attack or stroke	40 out of 1,000 people
		30 out of 1,000 people
		20 out of 1,000 people
		0 out of 1,000 people
	Lower chance of death from heart attack	20 out of 1,000 people
		10 out of 1,000 people
		0 out of 1,000 people
Hepatoxicity outcomes	Chance of a bad liver test result with no damage	50 out of 1,000 people
		25 out of 1,000 people
		0 out of 1,000 people
	Chance of short-term liver irritation (hepatitis) without hospitalization	20 out of 1,000 people
		10 out of 1,000 people
		0 out of 1,000 people
	Chance of liver irritation (hepatitis) that has to be treated at the hospital	20 out of 1,000 people
		10 out of 1,000 people
		0 out of 1,000 people
	Death from liver failure	10 out of 1,000 people
		5 out of 1,000 people
		0 out of 1,000 people
Nephrotoxicity outcomes	Chance of mild muscle weakness (myopathy)	50 out of 1,000 people
		25 out of 1,000 people
		0 out of 1,000 people
	Chance of severe muscle weakness (rhabdomyolysis)	20 out of 1,000 people
		10 out of 1,000 people
		0 out of 1,000 people
	Muscle weakness that leads to kidney failure requiring transplant	10 out of 1,000 people
		5 out of 1,000 people
		0 out of 1,000 people

Figure 1. Example Trade-off Question



Analysis

- Preference-weight estimation using multivariate, random-parameters, or mixed-logit estimation[8,9]
- Maximum acceptable risk (MAR):
  - MAR is a measure of risk tolerance—the mean maximum level of treatment-related risk that subjects are willing to accept for a given improvement in cardiovascular symptoms or outcomes
  - Treatment risk at which odds ratio equals 1 (Figure 4)

RESULTS

Demographic Characteristics (N = 637)

- Mean age: 62 (SD = 11.4)
- White: 86%
- Female: 46%
- Married: 61%
- Some college education or higher: 55%

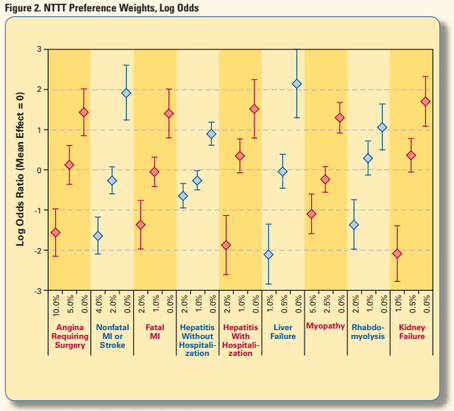
Hypercholesterolemia Treatment Experience (N = 637)

- Diagnosed with hypercholesterolemia within the past three years 84%
- Had taken at least two different medications to treat hypercholesterolemia: 55%
- Exercise regularly to lower cholesterol levels: 45%

Preference Weights (Figure 2, Figure 3)

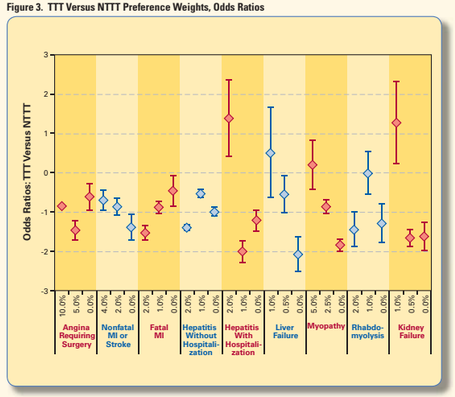
- Preference weights naturally ordered (Figure 2):
  - For the same attribute, higher risk levels have lower preference weights
  - For same risk level, more serious outcomes have lower preference weights
- Comparison between NTTT and TTT samples (Figure 3):
  - Preferences similar between two samples
  - 21 out of 27 estimates are significantly different

Figure 2. NTTT Preference Weights, Log Odds



Note: Vertical bars denote 95% confidence intervals..

Figure 3. TTT Versus NTTT Preference Weights, Odds Ratios



Maximum Acceptable Risk for 1% Reduction in Fatal MI Risk (Figure 4, Table 2)

- The odds ratio between 1% and 0% fatal MI risk with no side-effect risk is 4.25.
- Increasing the side-effect risk for kidney failure, moderate hepatitis, and myopathy decreases the odds ratio for treatments that reduce MI risk.
- MAR is the level of side-effect risk that reduces the odds ratio to 1.

Maximum Acceptable Risk for 1% Reduction in Fatal MI Risk (Figure 4, Table 2)

- MARs are larger for less serious side effects
- MARs for liver failure and kidney failure are less than 1%, indicating relatively smaller risk aversion for MI risk
- Subjects in the TTT sample had higher MARs for five of the six side-effect risks, but none of the differences is statistically significant.

Figure 4. Odds Ratios: 1% Fatal MI Risk with No Treatment Versus 0% Fatal MI Risk with Side-Effect Risk, (NTTT)

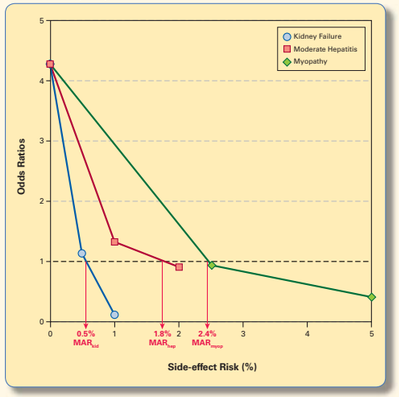


Table 2. Maximum Acceptable Side-Effect Risk for 1% Reduction in Chance of Fatal MI (1%-0%)

	Side Effect	Mean Maximum Acceptable Risk	
		NTTT Sample	TTT Sample
LIVER TOXICITY	Hepatitis without hospitalization	1.75% (-1.77%–9.45%)	1.83% (0.78%–3.89%)
	Hepatitis with hospitalization	1.13% (0.46%–1.68%)	0.93% (0.42%–2.60%)
	Death from liver failure	0.33% (0.15%–0.61%)	0.62% (0.28%–0.89%)
KIDNEY TOXICITY	Myopathy	2.37% (1.05%—5.80%)	6.38% (-16.41%–33.47%)
	Rhabdomyolysis	1.41% (0.70%–2.19%)	1.61% (1.18%–2.06%)
	Kidney failure	0.52% (0.22%–0.73%)	0.61% (0.26%–0.97%)

Numbers in parentheses denote 95% confidence intervals.

CONCLUSIONS

- Obtaining evidence on patients' tolerance for clinically relevant therapeutic risks is empirically feasible.
- Patients' benefit-risk tradeoff preferences are well-defined and correctly ordered.
- Such empirical estimates of patients' benefit-risk tradeoff preferences may help inform regulatory decision making.

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DISCLOSURE

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