

## Original Investigation

# The Effect of Information Presentation on Beliefs About the Benefits of Elective Percutaneous Coronary Intervention

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**IMPORTANCE** For stable angina, the benefits of percutaneous coronary intervention (PCI) are limited to symptom relief, but patients often believe that PCI prevents myocardial infarction (MI). Whether presenting accurate information about the benefits of PCI would dispel these beliefs remains unknown. We hypothesized that explanatory information would be more effective for influencing volunteers' beliefs.

**OBJECTIVE** To assess the effect of explicit and explanatory information on participants' beliefs about PCI and their willingness to choose it.

**DESIGN, SETTING, AND PARTICIPANTS** We conducted a randomized trial in 2012 among adults older than 50 years living in the general community. We recruited participants using the Internet.

**INTERVENTIONS** Participants read 1 of 3 scenarios in which they experienced class I angina and were referred to a cardiologist. The cardiologist provided no information about the effects of PCI on MI risk, a specific statement that PCI does not reduce MI risk, or an explanation of why PCI does not reduce MI risk.

**MAIN OUTCOMES AND MEASURES** Participants' beliefs about the benefit of PCI and choice of PCI and medication.

**RESULTS** A total of 1257 participants (90.0%) completed the survey; 54.5% chose PCI. Compared with those receiving explicit and explanatory information, those receiving no information were most likely to believe that PCI prevents MI (71.0% vs 38.7% vs 30.6%, respectively;  $P < .001$ ), most likely to choose PCI (69.4% vs 48.7% vs 45.7%, respectively;  $P < .001$ ), and least likely to agree to medication therapy (83.1% vs 87.4% vs 92.3%, respectively;  $P < .001$ ). Across the entire sample, the decision to have PCI was strongly correlated with the belief that PCI would prevent MI (odds ratio, 5.82 [95% CI, 4.13-8.26]) and that the participant would feel less worried (odds ratio, 5.36 [95% CI, 3.87-7.45]), but was not associated with how much participants were limited by symptoms.

**CONCLUSIONS AND RELEVANCE** In the setting of mild, stable angina, most people assume PCI prevents MI and are likely to choose it. Explicit information can partially overcome that bias and influence decision making. Explanatory information was the most effective intervention in overcoming this bias.

*JAMA Intern Med.* 2014;174(10):1623-1629. doi:10.1001/jamainternmed.2014.3331  
Published online August 25, 2014.

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Percutaneous coronary intervention (PCI) is a common procedure for opening coronary artery stenoses. Approximately 1 million PCIs were performed in the United States in 2010,<sup>1</sup> many of these for patients with stable coronary disease. Numerous randomized trials have demonstrated that for patients with stable coronary disease, PCI does not reduce the risk for death or myocardial infarction (MI) when added to optimal medical therapy (OMT).<sup>2,3</sup> When compared with OMT alone, some studies show that the addition of PCI provides more rapid improvement of anginal symptoms; however, this difference wanes over time.<sup>2-4</sup>

Several studies<sup>5-9</sup> of patients undergoing elective PCI have assessed patients' perceptions of the benefits of PCI. These studies have demonstrated that most patients with stable coronary disease believe that PCI will reduce their risk for MI or death. The publication of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial,<sup>2</sup> a high-profile randomized trial that was covered extensively in the popular press,<sup>10,11</sup> appears to have done little to correct this misperception among patients undergoing PCI.<sup>7</sup>

The reasons that patients overestimate the benefit of PCI are unknown. They might receive no information from their physicians and simply assume the benefits.<sup>8</sup> In that context, explicit information, provided through an informed consent document<sup>12</sup> or a decision aid,<sup>13</sup> may improve patient knowledge and affect patients' decision making. An alternative hypothesis suggests that patients are focused on an outdated model of heart disease in which the disease process is presented primarily as a plumbing problem; in this model, narrowing in the vessel leads to lack of blood flow and eventually infarction.<sup>14</sup> Public health campaigns focusing on acute coronary syndromes and linking chest pain with a life-threatening emergency may serve to reinforce this image. In that case, a more detailed explanation of the pathophysiology of coronary disease may be necessary.

Little is known about how the presentation of the potential benefits and risks of PCI and OMT influences patients' beliefs or decision making. In this study, we aimed to explore participants' beliefs and willingness to accept hypothetical elective PCI in addition to OMT under the following 3 different scenarios: (1) participants receive no information about the effects of PCI on MI; (2) participants are told specifically that PCI will not reduce the risk for MI; and (3) participants are told why PCI does not reduce the risk for MI. We hypothesized that, in the absence of information, participants would be more likely to believe that PCI prevents MI and would be more likely to choose it. We further hypothesized that explanatory information would have the greatest effect on participants' beliefs and choices.

## Methods

### Study Design

We used an experimental study design in which volunteer participants were randomized to read 1 of the 3 descriptions of the risks and benefits of PCI for patients with stable angina. Participants were English-speaking members of the general pub-

lic who were recruited by Survey Sampling International, a private survey company. Survey Sampling International maintains a panel of more than 1 million individuals nationwide who have agreed to receive solicitations via e-mail to participate in online surveys. Participants were invited by means of e-mail with an embedded link and were entered into lotteries for modest cash prizes in exchange for completing the 15-minute survey. Participants were told only that "the purpose of this survey is to investigate how individuals make decisions about undergoing a medical intervention for heart disease based on the information provided to them." They were given no more specific information about the content of the survey. Participation was voluntary and all answers were anonymous. The study was approved by the institutional review boards of Baystate Medical Center and the University of Michigan. Participants were presented with a written description of the study and gave electronic consent by clicking "agree."

The inclusion criterion (age >50 years) was designed to identify participants at risk for coronary disease. We purposefully chose to draw a sample that was demographically balanced to be representative of the US population in terms of race/ethnicity and to have 50% of the respondents be 60 years or older. We excluded participants who had undergone catheterization or PCI in the past, to minimize the influence of information they may have received from their physicians.

All study participants read the same hypothetical scenario (eBox in the Supplement), in which they were asked to imagine seeing a cardiologist about chest pain. The scenario was drawn from our own experience and a review of recorded discussions between cardiologists and patients. The scenario was revised after feedback from a group of interventional cardiologists and underwent pilot testing for clarity with several adults in the target age range. The scenario depicted a patient with stable Canadian Cardiovascular Society class I angina (pain with strenuous physical activity), a condition that could be treated with medication or PCI, but for which PCI would not be expected to yield a benefit in reduction of MI risk. Next, participants were randomized to 1 of the 3 scenarios. In the first scenario (no information), the hypothetical cardiologist said nothing about the effects of PCI on MI. The second scenario was identical to the first except that participants were told explicitly that PCI does not reduce the risk for MI (explicit information). The final scenario was identical to the second, except that in addition to the explicit information, the participant received a detailed explanation of why PCI does not reduce the risk for future MI (explanatory information).

All participants received the same information about the technical aspects and risks of the procedure and information about the risks and benefits of medication therapy. They were all told that they should take medication and that the medications would reduce the risk for an MI whether or not they underwent PCI.

After reading the scenario, each participant was asked to complete a questionnaire containing 38 questions (eAppendix in the Supplement). Participants' beliefs about the benefits of PCI, our primary outcome, were assessed by asking directly whether PCI could prevent an MI. We also asked participants to indicate on a Likert scale what their risk for MI

Table 1. Characteristics of Study Participants by Randomization Groups<sup>a</sup>

Characteristics	All Participants (N = 1257)	Information Group			P Value
		None (n = 415)	Explicit (n = 423)	Explanatory (n = 419)	
Age, mean (SD), y <sup>b</sup>	60.83 (7.65)	60.79 (7.93)	60.74 (7.54)	60.96 (7.5)	.91
Sex					
Male	621 (49.4)	209 (50.4)	205 (48.5)	207 (49.4)	.75
Female	631 (50.2)	205 (49.4)	217 (51.3)	209 (49.9)	
Not reported	5 (0.4)	1 (0.2)	1 (0.2)	3 (0.7)	
Race <sup>c</sup>					
White	1004 (79.9)	326 (78.6)	334 (79.0)	344 (82.1)	.78
African American	186 (14.8)	64 (15.4)	65 (15.4)	57 (13.6)	.74
Native American	15 (1.2)	6 (1.4)	3 (0.7)	6 (1.4)	.55
Asian	48 (3.8)	16 (3.9)	20 (4.7)	12 (2.9)	.37
Pacific Islander	3 (0.2)	2 (0.5)	1 (0.2)	0	.37
Other/mixed race	20 (1.6)	8 (1.9)	6 (1.4)	6 (1.4)	.82
Ethnicity (any race)					
Hispanic	68 (5.4)	16 (3.9)	28 (6.6)	24 (5.7)	.43
Arabic	16 (1.3)	7 (1.7)	3 (0.7)	6 (1.4)	.20
Educational level					
High school diploma or less	242 (19.3)	84 (20.2)	81 (19.1)	77 (18.4)	.51
Some college/trade school	398 (31.7)	129 (31.1)	123 (29.1)	146 (34.8)	
Bachelor's or associate's degree	451 (35.9)	151 (36.4)	152 (35.9)	148 (35.3)	
Master's degree or more	159 (12.6)	49 (11.8)	63 (14.9)	47 (11.2)	
Not reported	7 (0.6)	2 (0.5)	4 (0.9)	1 (0.2)	
Experience in a medical field					
None	1012 (80.5)	326 (78.6)	342 (80.9)	344 (82.1)	.19
Experience	205 (16.3)	77 (18.6)	71 (16.8)	57 (13.6)	
Not reported	40 (3.2)	12 (2.9)	10 (2.4)	18 (4.3)	
Feel limited by symptoms	956 (76.1)	315 (75.9)	317 (74.9)	324 (77.3)	.74

<sup>a</sup> Unless otherwise indicated, data are expressed as number (percentage) of participants.

<sup>b</sup> Ages for all participants ranged from 50 to 91 years.

<sup>c</sup> Some respondents indicated more than 1 race.

would be with or without PCI and whether OMT or PCI was more effective in reducing the risk for MI. To assess whether participants would choose PCI, we asked: "If this scenario actually happened to you, would you choose to get the stenting procedure or not?" Additional questions assessed participants' beliefs about the benefits of medications, whether they would agree to take medications, what the physician had said, how much the symptoms would limit their activities, and how worried they would be about the symptoms. We asked 3 true-false knowledge questions to assess comprehension, 3 questions to assess general beliefs about approaches to heart disease, and 7 demographic questions. Because participants are likely to have different levels of baseline physical activity, their feelings about the burden of class I angina are likely to differ. Angina burden was therefore assessed by asking: "Given your current level of activity, if you actually experienced these chest pain symptoms, how much would they limit what you could do?" Answers, provided on a 10-point scale, were dichotomized at 5.

### Statistical Analysis

Continuous variables were summarized as mean (SD) and categorical variables were summarized as percentages and frequencies. Analysis of variance and the  $\chi^2$  test were used to compare each variable between the randomization groups.

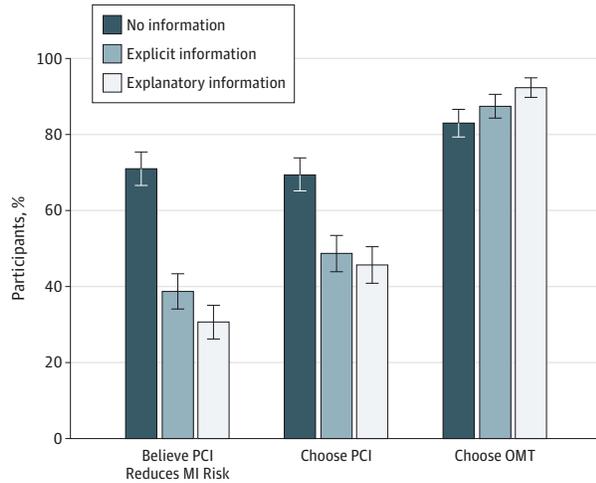
We used contingency tables to summarize predictors and outcomes by the randomization groups and the  $\chi^2$  test to examine the distribution differences among the 3 groups. We used logistic regression to relate the choice of PCI to the various predictors. The multivariate model was selected using a backward selection criterion with an entry *P* value of .05 and a retention *P* value of .10, and the randomization group was included in all candidate models. All *P* values were 2 sided and not adjusted for multiple comparisons. All analyses were conducted using commercially available software (SAS, version 9.2 [SAS Institute Inc] and R, version 3.0.0 [http://www.r-project.org]).

## Results

### Participants

Of 1396 adults who met the inclusion criteria and began the survey, 1257 (90.0%) completed it; sex and age were similar for the final sample and those who dropped out (mean age, 60.8 and 62.0 years, respectively; sex, 49.4% and 52.6% male, respectively). The dropout rate was similar across the 3 experimental conditions (9%-11%). Characteristics of the participants appear in Table 1. Overall, 956 participants (76.1%) thought the symptoms described in the hypothetical sce-

**Figure 1. Patient Beliefs Concerning Percutaneous Coronary Intervention (PCI) and Medication**



Participants were asked if they believe PCI will prevent a myocardial infarction (MI), if they would choose to have PCI, and if they would choose to take optimal medical therapy (OMT). Responses are stratified by information group. Error bars indicate 95% confidence intervals.

nario would limit their activity at least somewhat (>5 of 10 points on the Likert scale). The percentage did not differ by presentation of the information.

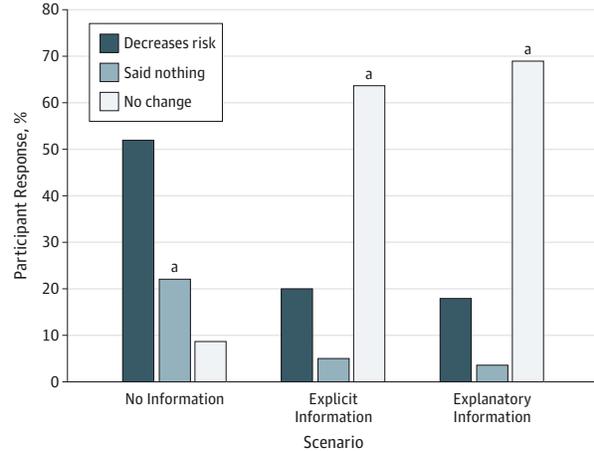
**Effects of Information on Participant Beliefs**

Information affected participants' beliefs about PCI (Figure 1). With no information, 71.0% of participants incorrectly believed that PCI would reduce their risk for an MI. This percentage dropped to 38.7% with presentation of explicit information and 30.6% with explanatory information ( $P < .001$  for no vs explicit information;  $P = .01$  for explanatory vs explicit information). We saw a similar pattern regarding worry about an MI. With no information, 64.6% of participants said they would be less worried if they had PCI. This percentage dropped to 40.2% with explicit information and 34.6% with explanatory information ( $P < .001$  for no vs explicit information;  $P = .10$  for explanatory vs explicit information). The experimental factors had no effect on answers to the other 2 knowledge questions. The percentage of participants who correctly stated that the stent procedure itself carries a risk for MI in the groups with no information, explicit information, and explanatory information were 94.7%, 93.3%, and 94.3%, respectively, and the percentages who correctly identified that stents do not eliminate symptoms of angina in all patients were 79.0%, 79.9%, and 79.9%, respectively.

**Decision to Undergo PCI and Take Medications**

Overall, 54.5% of respondents chose to have PCI performed (Figure 1). Those who received no information about the relationship between PCI and MI were more likely to choose PCI than those who were told explicitly that PCI would not reduce the risk for MI (69.4% vs 48.7%;  $P < .001$ ). Explanatory information did not affect the decision to undergo PCI relative to explicit information alone (45.7% vs 48.7%;  $P = .38$ ).

**Figure 2. Patient Recollection of Cardiologist Statements About the Effect of Percutaneous Coronary Intervention (PCI)**



Respondents in each information group are stratified by those who recalled the cardiologist stating that PCI decreases the risk for myocardial infarction, stating nothing, and stating that the risk would not change.

<sup>a</sup> Correct answer.

The decision to take medications was also influenced by the information about PCI (Figure 1). Those receiving no information were least likely (83.1%) and those receiving explanatory information were most likely (92.3%) to agree to use medications. Explanatory information significantly increased uptake of medications relative to explicit information (92.3% vs 87.4%;  $P = .02$ ).

**Knowledge Recall**

When asked to recall what the physician had said about the effect of PCI on the risk for MI, 22.1% of group with no information, 63.6% of the group with explicit information, and 69.0% of the group with explanatory information were able to recall correctly (no information vs the other groups,  $P < .001$ ) (Figure 2). In addition, in the group with no information, 51.9% of participants falsely remembered that the physician had told them that PCI would reduce their risk for an MI compared with 20.0% in the explicit information and 17.9% in the explanatory information groups ( $P < .001$  for no information vs the other groups). Participants generally believed what they remembered the physician saying. The percentage of participants who believed that PCI would reduce the risk for MI was 80.4% among those who remembered the physician saying the risk would be reduced, 59.1% among those who remembered the physician saying nothing, and 21.8% among those who remembered the physician saying that the risk would remain the same ( $P < .001$  for all comparisons).

**Predictors of the Decision to Undergo PCI**

To better understand the extent to which beliefs and symptoms affected the decision, we created a multivariate model to predict the choice to undergo PCI in the entire sample (Table 2). The strongest predictor of decisions was belief that PCI would reduce the risk for an MI (odds ratio [OR], 5.82 [95%

Table 2. Univariate and Multivariate Analysis of Predictors of the Decision to Undergo PCI<sup>a</sup>

Predictor	Choose PCI, Unadjusted No. (%)	OR (95% CI)	P Value
Educational level			
Some college or more	551 (54.8)	1.51 (1.02-2.23)	.04
High school diploma or less	132 (53.2)	1 [Reference]	
Worried about MI			
Yes	652 (57.0)	2.63 (1.42-5.06)	.003
No	22 (22.4)	1 [Reference]	
More worried without PCI			
Yes	461 (81.2)	5.36 (3.87-7.45)	<.001
No	209 (31.8)	1 [Reference]	
Believe PCI will reduce the risk for MI			
True	474 (81.3)	5.82 (4.13-8.26)	<.001
False	208 (31.2)	1 [Reference]	
Perceive greater risk without medication			
Yes	487 (57.5)	0.73 (0.52-1.02)	.07
No	183 (47.8)	1 [Reference]	
Recollection of what the physician said			
Risk will be the same	221 (37.2)	1 [Reference]	<.001
PCI will decrease risk	309 (83.2)	2.60 (1.65-4.13)	
PCI will increase risk	27 (39.1)	0.85 (0.40-1.72)	
Nothing said	79 (63.2)	1.56 (0.88-2.80)	
Do not remember	43 (47.8)	1.10 (0.58-2.08)	

Abbreviations: MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention.

<sup>a</sup> The multivariable model controls for randomization groups.

CI, 4.13-8.26)). Participants were also more likely to choose PCI if they were worried about an MI or believed that they would be less worried about having an MI if they had PCI (an indirect measure of their belief in the benefits of PCI). Participants who correctly believed that medication would reduce the risk for an MI tended to be less likely to opt for PCI (OR, 0.73 [95% CI, 0.52-1.02]). Participants with an educational level higher than a high school diploma were more likely to choose PCI (OR, 1.51 [95% CI, 1.02-2.23]). Finally, participants' memories of what the physician said also affected their choice. Those who mistakenly remembered that the physician said that PCI would reduce the risk for an MI were more likely and those who correctly remembered that the physician said that PCI would not reduce the risk were less likely to choose PCI than those who remembered that the physician did not say anything. Age, sex, and race were not associated with the decision to undergo PCI (all  $P > .15$ ). Most important, the degree to which participants perceived the symptoms to be limiting was not associated with choosing PCI ( $P = .68$ ).

## Discussion

In a review of 145 000 elective PCIs from the National Cardiovascular Data Registry,<sup>15</sup> approximately half of the procedures were classified as appropriate. Most of the inappropriate PCIs were performed for patients with no angina (54%) or low-risk ischemia (72%). Consequently, the National Summit on Overuse,<sup>16(p26-27)</sup> convened jointly by the American Medical Association and the Joint Commission, cited elective PCI as 1 of 5 overused interventions and emphasized the need to

“focus on informed consent and promote patient knowledge/understanding of the benefits/risks of PCI.”

In this experimental study, we found that presenting factual information affected participants' beliefs and decisions regarding PCI for stable coronary disease. When participants received no information about whether PCI would prevent MI, 71.0% believed that the procedure would do so. Simply stating that PCI would not prevent MI reduced this percentage to 38.7%. Explaining why PCI would not prevent MI was even more effective. However, despite the more detailed explanation, 30.6% continued to believe that PCI would prevent an MI. We also found that the belief that PCI could prevent MI was the strongest predictor of participants choosing to have PCI and that feeling less worried about an MI after PCI was almost as strong. Conversely, symptoms did not appear to influence respondents' decisions. The impact of the information presented is particularly striking, given that it was limited to a few lines of text and that no opportunity existed to ask clarifying questions.

This study is the first of which we are aware to compare the effect of explicit information on beliefs about the benefits of PCI. Although patients have been demonstrated consistently to believe that PCI will prevent MIs in stable coronary disease, less is known about why they believe this, what can be done to improve their knowledge, and whether improved knowledge will influence their choice of PCI vs OMT. In our study, in the absence of information, the percentage of participants choosing PCI who perceived that PCI would prevent MI was 84.6%, almost identical to the percentage of real patients undergoing PCI who were observed to hold this belief in 2008.<sup>7</sup> This finding suggests that physicians should state

explicitly that PCI will not prevent MI. Otherwise patients will assume that it will. This finding mirrors that of another observational study in which patients who had undergone PCI believed that the procedure would improve their survival despite reporting that the physician had not told them of such a benefit.<sup>8</sup>

Several strategies have been proposed to improve patient understanding, including a standardized consent template that specifically states that the procedure will not prevent an MI<sup>12</sup> and decision aids that express the benefits shown in clinical trials.<sup>13,17,18</sup> The effect of the consent template on knowledge does not appear to have been tested, and decision aids for stable angina are currently in the trial phase.<sup>13</sup> Our results imply that even the small amount of information provided in this study, if read and attended to by patients, has the potential for a marked effect on their beliefs and decisions. Our information was presented at the point of decision making, whereas consent documents are often signed immediately before the procedure,<sup>7</sup> when such information may be less likely to influence decision making.

Our study also suggests that not all patients' misconceptions can be overcome easily. Many participants continued to believe that PCI prevents MI, even when given a detailed explanation about why it does not. Some appeared to misremember what the cardiologist had told them. Indeed, after real discussions between patients and their cardiologists, patients often report that the physician described a mortality benefit to them, when the physician denied communicating such a benefit.<sup>8</sup> Another group correctly remembered what the cardiologist said, but nevertheless disagreed. These statements exemplify how deeply ingrained this belief is after years of educational campaigns about acute coronary syndromes. Cardiologists may mistakenly believe they are successfully communicating with patients, and thus self-assessment of delivery of this message could be an important quality improvement initiative based on the data from this study and others.<sup>7,8</sup>

Providing specific information about the benefits of PCI also affected participants' choice of PCI and OMT. A belief that PCI could prevent MI was the strongest predictor of choosing PCI, and participants who received explicit or explanatory information chose PCI 20% less often than those given no information. This finding follows the evidence from the studies of decision aids.<sup>13,17,19</sup> Given that approximately 300 000 PCIs are performed annually in the United States for stable angina,<sup>1</sup> a 20% absolute reduction in patients choosing PCI could translate into 60 000 procedures. At a mean procedural cost of \$14 400, this reduction represents a potential savings of \$864 million.<sup>20</sup>

In addition, when we provided more explanation about the limits of PCI to reduce the risk for MI, the participants were more likely to agree to take medications. This point is important, because unlike PCI, medications can reduce the risk for MI and death. A common misconception is that patients can choose between OMT and PCI, when in fact this dichotomy is false. Patients choose between PCI and no PCI; OMT is recommended regardless of whether or not a patient receives a stent.<sup>21</sup>

Our study has a number of limitations. First, participants read a hypothetical scenario and did not engage in a discus-

sion with a cardiologist. We did this to maintain tight experimental control over the information presented to determine what kind of information influences beliefs and decisions. We tried to make the scenario realistic, but the choices the participants made may be different from what they would do had they actually confronted the decision or had the opportunity to ask questions. In practice, many consent discussions are one-sided presentations in which patients passively receive incomplete information, without acknowledgment that a choice needs to be made or elicitation of values or preferences.<sup>13,22</sup> Second, we chose to describe a case of mild (class I) angina to limit the effect of symptoms on the decision to proceed to PCI. The results of our regression model suggest that this strategy succeeded. However, faced with more severe symptoms, participants may have reacted differently. Based on interviews with patients, those with more severe angina are even more likely to believe that PCI prevents MI and are more likely to choose it.<sup>13</sup> However, more than 25% of patients who undergo PCI in the United States have mild or no symptoms.<sup>15</sup> Third, the cardiologist in the scenarios made no treatment recommendation. In practice, patients frequently follow physician recommendations, although at least 1 study of a video decision aid for ischemic heart disease found that patients who viewed the decision aid were less likely than control subjects to accept an angiographer's recommendation for revascularization.<sup>17</sup> Last, the study sample consisted entirely of people willing to take surveys over the Internet and is likely not representative of the nation as a whole. Again, we were using an experimental design, not attempting to assess general beliefs in the population. We enrolled a broad demographic, including various educational levels, and findings were consistent across all of these. We are also reassured that the percentage of participants in the scenario with no information who believed that PCI could prevent MI was almost identical to that seen in studies of real patients.<sup>5,7-9</sup>

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## Conclusions

As health care reform moves forward, appreciation is growing that shared decision making can improve the value of care delivered by helping patients to choose treatments that meet their personal needs and preferences.<sup>23</sup> In the case of PCI for stable angina, communicating the benefits of PCI remains challenging, yet essential to an informed decision. Our study demonstrates that with relatively little effort—as little as 2 lines of text—a change in patients' perceptions and decisions may be possible. Including an additional paragraph of text explaining why the benefits were limited to angina relief was even more powerful. Although we did not intend for these scenarios to be used as scripts, the modest amount of information included in them may be realistically incorporated into a clinic visit, without requiring patients to watch lengthy videos or requiring physicians to spend more than a few extra minutes. Clinically based studies should now be undertaken to assess the effect of brief interventions on patients' misconceptions regarding the benefit of PCI for stable angina.

## ARTICLE INFORMATION

**Accepted for Publication:** March 25, 2014.

**Published Online:** August 25, 2014.  
doi:10.1001/jamainternmed.2014.3331.

**Author Contributions:** Dr Rothberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Rothberg, Scherer, Kashef, Coylewright, Zikmund-Fisher.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Rothberg, Scherer, Kashef.

**Critical revision of the manuscript for important intellectual content:** Scherer, Coylewright, Ting, Hu, Zikmund-Fisher.

**Statistical analysis:** Rothberg, Scherer, Hu.

**Obtained funding:** Rothberg.

**Administrative, technical, or material support:** Scherer, Kashef.

**Conflict of Interest Disclosures:** None reported.

**Funding/Support:** This study was supported by the Department of Medicine, Baystate Medical Center.

**Role of the Sponsor:** The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Previous Presentation:** This paper was presented at the 36th Annual Meeting of the Society of General Internal Medicine; April 26, 2013; Denver, Colorado.

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