

Treatment effect expressed as the novel Delay of Event measure is associated with high willingness to initiate preventive treatment – A randomized survey experiment comparing effect measures



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ABSTRACT

Objectives: This study aimed to investigate patients' willingness to initiate a preventive treatment and compared two established effect measures to the newly developed Delay of Events (DoE) measure that expresses treatment effect as a gain in event-free time.

Methods: In this cross-sectional, randomized survey experiment in the general Swedish population, 1079 respondents (response rate 60.9%) were asked to consider a preventive cardiovascular treatment. Respondents were randomly allocated to one of three effect descriptions: DoE, relative risk reduction (RRR), or absolute risk reduction (ARR). Univariate and multivariate analyses were performed investigating willingness to initiate treatment, views on treatment benefit, motivation and importance to adhere and willingness to pay for treatment.

Results: Eighty-one percent were willing to take the medication when the effect was described as DoE, 83.0% when it was described as RRR and 62.8% when it was described as ARR. DoE and RRR was further associated with positive views on treatment benefit, motivation, importance to adhere and WTP.

Conclusions: Presenting treatment effect as DoE or RRR was associated with a high willingness to initiate treatment.

Practice implications: An approach based on the novel time-based measure DoE may be of value in clinical communication and shared decision making.

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1. Introduction

Patients' understanding of a proposed medication's effectiveness is central to evidence-based medicine and medical decision-making. Informed shared decision-making is possible when a patient has an adequate understanding of their medical situation/increased risk including a sound understanding of the expected benefits from treatment. It is well documented that the way treatment information is presented influences patients' understanding and decisions to initiate and adhere to a proposed treatment [1–3]. This is of special concern in the prevention of chronic diseases, where the treatment goal is to prevent or delay major disease events or premature death. Long-term adherence to such chronic treatments is known to be poor [4]. Insufficient adherence to cardiovascular preventive treatments is associated

with increased morbidity [5–7], and thus nonadherence is considered to be a cardiovascular risk factor [8].

The way a treatment's effect is presented has been shown to influence decisions by patients as well as physicians [1,9]. It is therefore of clinical interest to determine the optimal way of describing treatment effect that increases patients' willingness to initiate and adhere to treatment.

Commonly used measures describing preventive treatment effect include relative risk reduction (RRR), absolute risk reduction (ARR) and number-needed-to-treat (NNT) [10]. These measures compare the proportion of events in relative and absolute terms in two compared trial arms. While these measures are methodologically justified, they may be difficult to use in shared decision-making as people typically have difficulties understanding proportional measures [11–13]. ARR and its inverse, NNT, have the advantage of presenting the effect as absolute figures. However, research has shown that presenting benefit as ARR or NNT is suboptimal when communicating treatment benefits [14,15]. RRR typically comes out as more favorable than ARR and NNT when comparing patients' willingness to initiate treatment

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[1]; however, RRR may be deceptive as the measure is ignorant of the baseline risk. Several authors have proposed that these established effect measures may be complemented by other estimates providing the effect on the time dimension of interest [16–18]. Time-based effect measures of treatment effect are of interest in shared clinical decision-making as such measures seem to be preferable and easier to comprehend for laypeople as well as health care professionals [19,15,20]. Previous studies investigating the role of different effect measures in medical decision-making have used time-based measures based on extrapolation of data [21], which raises questions about the correctness and comparability. With the goal of combining the clinical benefits of time-based measures with the rigor of statistical calculated measures, a relatively new way of demonstrating treatment on a timescale has been proposed [22]. DoE may be estimated modelling survival percentiles with Laplace regression, a statistical method appropriate for censored quantiles and survival distribution [23]. The DoE may be understood as the horizontal difference between a treatment arm and control arm in a Kaplan-Meier curve. Delay of Events is an absolute measure that is conditional on the event, which means that if a patient has the event without treatment during the follow-up period, the DoE depicts the time that event may be delayed by due to treatment. Thus, DoE captures the magnitude of the effect expressed as a gain in disease-free time for treated compared to untreated patients.

The objective of this study is to compare the established proportional effect measures, RRR and ARR, with the novel time-based measure DoE, to determine how the different formats affect

a person's willingness to initiate a preventive medication treatment. A secondary objective is to investigate how the different ways of demonstrating treatment effect affect individuals' views on treatment benefit, motivation to initiate and adhere to treatment, and willingness to pay for treatment [24,25].

2. Methods

2.1. Design and sample

This is a cross-sectional postal questionnaire study in a population-based sample (age 45–75). We randomly selected 1800 people from the Swedish national population registry. The sample was then further randomized into three equally sized groups (A, B and C), which received different treatment effect information about a hypothetical cardiovascular treatment, further described below. The questionnaire was returned by 1079 individuals who gave informed consent to participate. Fourteen questionnaires were returned unopened to the sender by the mail service, as the recipient could not be reached/were no longer living at the address. Thirteen recipients declined to participate, and 694 persons did not answer at all, making the response rate of the distributed questionnaires 60.4% (1079/1786). The response rate in the three groups varied from 56.8% to 65.2%. Data were collected from November 2013 to February 2014. Fig. 1 presents a flow chart of the study. Those who declined to participate did that either by sending us a letter or email or thru telephone.

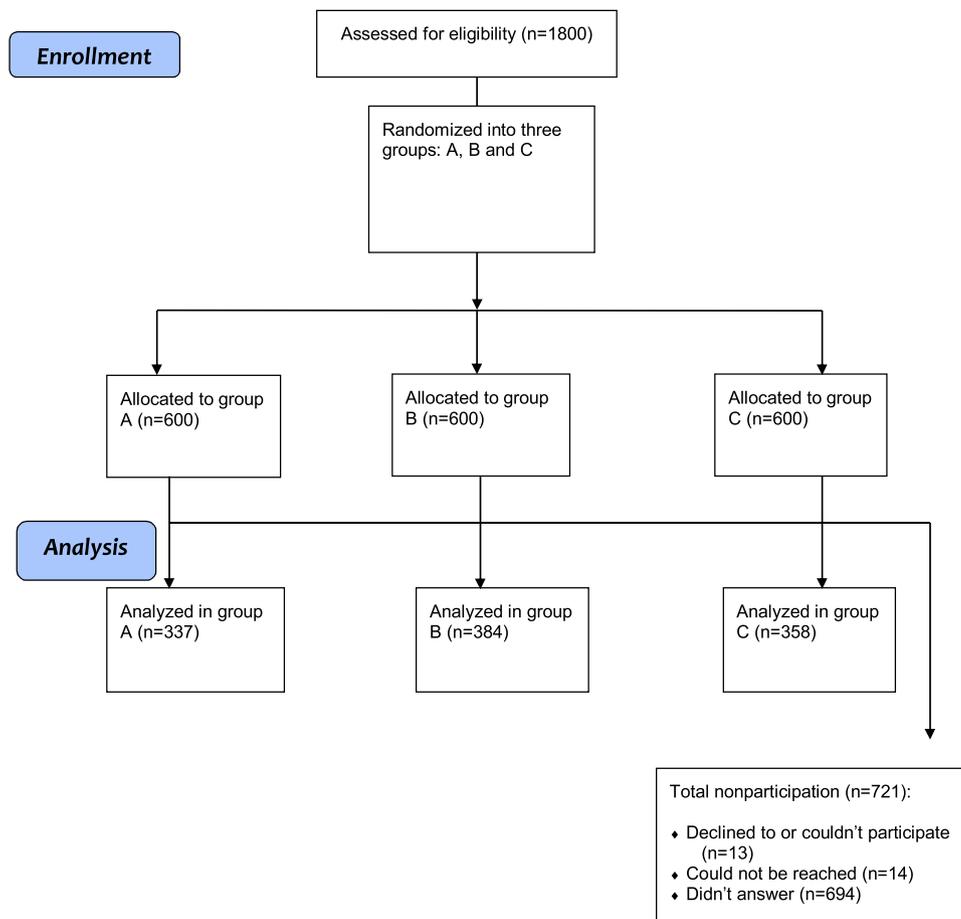


Fig. 1. The flow diagram shows group allocation and number of respondents in each group. Group A received treatment effect described as DoE, group B received information described as RRR and group C received information described as ARR.

2.2. Measures and survey experiment

The postal questionnaire contained a total of 55 questions. Demographic data were collected through questions that assessed the respondents' gender, age and educational level (categorized as compulsory school, secondary school or university). History of heart attack and/or angina was assessed with questions used in previous studies [26,27]. Data were also collected regarding whether the respondents were on current medical treatments, and if so, the number of prescription drugs. The written information about the effects and the outcome questions were tested in a pilot study and modified afterwards before they were included in this questionnaire.

2.2.1. Written information and survey experiment

This study was performed as a survey experiment [28,29]. All respondents were asked to imagine that they were at increased risk of cardiovascular disease, and that their physician had suggested a preventive cardiovascular drug treatment. The text was as follows: "Imagine that in the next five years you will have an increased risk of having a heart attack. Your physician offers you a drug, with infrequent and mild side effects, which is to be taken orally once daily. The usefulness of the drug has been evaluated in scientific studies, and the effect can be described as follows:" The following text described the effect differently based on group allocation, where the first group (A) received treatment effect described as Delay of Events, the second group (B) received information described as RRR and the third group (C) received information described as ARR (see Table 1). The different ways of displaying the same treatment benefit were all derived and calculated from the Scandinavian Simvastatin Survival Study (4S), a randomized controlled trial presenting the first evidence that statin treatment improves survival in patients with coronary heart disease [30]. In this survey the DoE figure was assessed at the end of the 4S study, at the same time as the point estimates for the other measures. The scenario and outcome questions was pre-tested in a primary care pilot survey (n=180) and then adjusted and finalized into its present form. The phrasings and methods are similar to other studies investing different ways of explaining medication benefit [31]. NNT was not included since previous research has found that the NNT measures are ineffective for communicating treatment benefits [14,15].

2.2.2. Outcome variables

Information about willingness to initiate treatment was assessed using the question: "If you were in the same situation as the person in this case would you initiate treatment?" Answers were dichotomous: "yes" or "no." Other questions that were used to evaluate the views on the treatment were: "To what extent does the description help you make a medical decision?"; "How much benefit do you think that the drug would have?"; "Would you feel safe to take the drug?"; "Would you, based on the description, be

motivated to take the medication on a daily basis?"; and "How important do you consider it to adhere to the treatment?" The answers to these questions were assessed on seven-point Likert scales ranging from 1 (not at all) to 7 (very much). Willingness to pay is an assessment of the (maximum) amount of money that must be paid by an individual to equalize a utility change [25]. To evaluate willingness to pay (WTP), the contingent valuation method (CVM) was used. The CVM is a questionnaire-based method first proposed as a method for eliciting market valuation of nonmarket goods and public goods [24,25]. The method is widely used to elicit the monetary value a person is willing to pay for health-care services [32], and likewise as a complementary measure of the expected utility. In this study WTP was assessed by one open-ended question: "What is the maximum amount you would pay per month over a five-year period to receive the treatment?" WTP was assessed in Swedish currency (SEK), and was converted in this study to euros (€) at an exchange rate of 0.10.

2.3. Statistical analysis

Differences in proportions between groups were tested using Chi-square analyses, and differences in ordinal data were assessed using the Kruskal-Wallis H test. Pairwise comparisons were performed with the Mann-Whitney U test using Bonferroni correction to maintain the risk of type 1 error at 0.05 [33]. In Bonferroni correction for pairwise comparisons among three groups, the significance level is set to a p-value ≤ 0.017 ($0.05/3 \approx 0.017$). Binary logistic regression models were used to analyze associations between different effect prescriptions, gender, age, education level, history of heart disease, number of prescribed medications and willingness to initiate treatment. Sample size was determined prior to the study to have an 80% power to determine a 10% difference in proportion to the main outcome with a significance level of 0.05%. The Statistical Package for the Social Sciences (SPSS) version 20 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp Chicago, IL, USA) was used for descriptive statistics and statistical tests.

2.4. Ethical consideration

The study was approved by the regional Ethical Committee of Clinical Investigation in Uppsala. Participation was voluntary and performed under informed consent.

3. Results

The study population was on average 61.9 years old and consisted of slightly more women than men. Secondary school was the most common completed education level. The distribution of demographic variables, overall and according to group allocation, is shown in Table 2.

Table 1
Three different ways of communicating treatment information.

Shared setting		Imagine that in the next five years you will have an increased risk of having a heart attack. Your physician offers you a drug with rare and mild side effects, to be taken in pill form once daily. The usefulness of the drug has been evaluated in scientific studies, and the effect can be described as follows:	
Group	Effect measure	Magnitude	Text in survey
A.	Delay of events (DoE)	18 months	If you have a heart attack in the next five years it will be delayed by up to 1.5 years if you take the treatment.
B.	Relative risk reduction (RRR)	27%	If you take the treatment for five years, you will reduce the risk of a heart attack by 27%.
C.	Absolute risk reduction (ARR)	2%	Without treatment, your risk of a heart attack in the next five years is 8%, and if you take the treatment, the risk of a heart attack in the next five years will be 6%.

Table 2
Distribution of characteristics among participants.

Category	Subcategory	DoE	RRR	ARR	Overall
Gender	Women, % (n)	55.7 (186)	49.2 (174)	55.1 (211)	53.3 (571)
	Men, % (n)	44.3 (148)	50.8 (180)	44.9 (172)	46.7 (500)
Age	Mean (s.d.)	61.8 (8.6)	62.2 (8.7)	61.6 (8.7)	61.9 (8.5)
Education level	Compulsory school, % (n)	27.5 (92)	28.7 (100)	27.1 (103)	27.8 (295)
	Secondary school, % (n)	35.8 (120)	38.8 (135)	37.6 (143)	37.4 (398)
	University, % (n)	36.7 (123)	32.5 (113)	35.3 (134)	34.8 (370)
History of cardiovascular diseases	No heart attack, % (n)	97.3 (321)	95.4 (330)	95.8 (363)	96.1 (1014)
	Heart attack, % (n)	2.7 (9)	4.6 (16)	4.3 (16)	3.9 (41)
	No angina, % (n)	96.4 (318)	94.3 (328)	97.4 (369)	96.0 (1015)
	Angina, % (n)	3.6 (12)	5.8 (20)	2.6 (10)	4.0 (42)
Quantity of prescription medications	No use, % (n)	39.0 (124)	38.0 (125)	42.8 (154)	40.0 (403)
	1, % (n)	20.4 (65)	16.7 (55)	16.1 (58)	17.7 (178)
	4–2, % (n)	30.2 (96)	31.0 (102)	31.9 (115)	31.1 (313)
	>5, % (n)	10.4 (33)	14.3 (47)	9.2 (33)	11.2 (113)

3.1. Cardiovascular diseases and medical treatments

In the study population, 6.5% reported a history of established cardiovascular disease. The reported medical history of heart attack was 3.9% and for angina 4.0% (see Table 2). Significantly more men (10.0%) than women (3.4%) reported a history of cardiovascular disease ($p < 0.001$).

About 60% of the group used one or more prescribed medications. There were no significant sex differences regarding use of prescription medication.

3.2. Willingness to initiate treatment

A total of 80.5% were willing to take the medication when the effect was described as DoE, 83.0% when it was described as RRR and 62.8% when it was described as ARR. Pairwise comparisons revealed that there were significant differences between DoE and ARR ($p < 0.001$), and between RRR and ARR ($p < 0.001$), but not between DoE and RRR ($P = 0.396$) (see Table 3). The willingness to initiate treatment was further investigated in multiple logistic regressions using the different effect descriptions as independent variables (see Table 4). There was a significantly higher willingness to initiate treatment in the fully adjusted models when the effect was described as DoE (OR 2.64, 95% CI 1.81–3.85) and RRR (OR 3.12, 95% CI 2.11–4.61) as compared to ARR.

3.3. Views on treatment and WTP

There were significant differences regarding respondents' views on the benefit from treatment, motivation to take treatment, the importance of adhering to treatment and WTP.

Table 3
Treatment decision and views of treatment according to different treatment descriptions.

Outcome	DoE	RRR	ARR	Overall	Test statistics	p-value
Willingness to initiate treatment, % (n)	80.5 (268)	83.0 (288)	62.8 (238)	75.0 (794)	47.24 ^a	<0.001
Use of information, md (q1, q3)	5 (4,6)	5 (4,6)	5 (4,6)	5 (4,6)	0.61 ^b	0.736
Benefit from medication, md (q1, q3)	5 (4,6)	5 (3,6)	4 (2,5)	4 (3,6)	34.57 ^b	<0.001
Feel safe with medication, md (q1, q3)	4 (3,6)	4 (3,5)	4 (2,6)	4 (3,6)	2.29 ^b	0.318
Be motivated to take medication, md (q1, q3)	5 (3,6)	5 (4,6)	4 (2,6)	5 (3,6)	27.56 ^b	<0.001
Importance to adhere, md, (q1, q3)	6 (5,7)	6 (5,7)	6 (4,7)	6 (5,7)	8.53 ^b	0.014
Willingness to pay ^c (Euro), md (q1, q3), mean	20 (10,30), 25.7	15 (10,30), 22.9	10 (5,25), 18.9	10 (8.3,30), 22.5	13.17 ^b	0.001

^a Pearson Chi-Square.

^b Kruskal-Wallis H test.

^c Willingness to pay was measured in Swedish krona (SEK) 1 SEK/0.10 Euro (€).

In pairwise comparisons, DoE scored higher than ARR in assessments of benefit from treatment ($p < 0.001$), motivation to take treatment ($p < 0.001$) and importance to adhere ($p = 0.005$) (see Table 3). RRR scored higher than ARR in assessments of benefit from treatment ($p < 0.001$) and motivation to take treatment ($p < 0.001$). There were no significant differences between DoE and RRR in pairwise comparisons.

The median WTP for the three different treatment descriptions was €20 for DoE, €15 for RRR and €10 for ARR. In pairwise comparisons, WTP for DoE was significantly higher than that of ARR ($p = 0.001$), WTP for RRR was also significantly higher than that of ARR ($p = 0.008$). There were no significant differences between DoE and RRR in terms of WTP ($p = 0.353$).

4. Discussion

The objective of this study was to compare the proportional effect measures, RRR and ARR, with the time-based measure, DoE, to assess their association with people's willingness to initiate a preventive medication treatment. A further aim was to assess whether the different treatment effect descriptions affected favorable views and WTP in relation to the proposed medication.

A higher proportion of individuals were willing to initiate the treatment when the effect was presented as DoE or RRR than as ARR. Previous studies have shown that patients prefer medication when the benefit is presented in relative rather than in absolute terms [34]. The results in this study imply that DoE might serve as an adequate alternative or complement to other established measures. The results also imply that DoE and RRR are superior to ARR when it comes to giving patients positive views of the treatment effects as well as motivating them to take it.

Table 4
Results of logistic regression models of factors predicting patients' willingness to initiate treatment.

		Crude OR 95% CI	Model 1 OR 95% CI	Model 2 OR 95% CI
Treatment information	Effect description:			
	ARR	1	1	1
	DoE	2.44** (1.74–3.44)	2.67** (1.86–3.83)	2.64** (1.81–3.85)
	RRR	2.89** (2.04–4.10)	3.18** (2.20–4.60)	3.12** (2.11–4.61)
Demographic	Gender:			
	Female	1	1	1
	Male	0.95 (0.72–1.25)	0.88 (0.65–1.19)	0.95 (0.69–1.31)
	Age	1.07** (1.05–1.09)	1.07** (1.05–1.09)	1.05** (1.03–1.07)
	Education level:			
	University	1	1	1
Secondary school or equal	3.27** (2.17–4.91)	2.54** (1.65–3.92)	2.25** (1.44–3.52)	
Compulsory school	1.26 (0.92–1.72)	1.40 (0.99–1.95)	1.21 (0.85–1.72)	
Health-related factors	History of heart attack:			
	No heart attack	1		1
	One or more heart attack	3.13* (1.10–8.86)		1.11 (0.35–3.54)
	History of angina:			
	No angina	1		1
	One or more angina attack	7.03** (1.69–29.27)		5.53 (0.71–43.33)
	Prescribed medications:			
	No use	1		1
	One	15* (1.4–2.26)		1.44 (0.94–2.21)
	Two to four	3.02** (2.09–4.37)		2.32** (1.56–3.44)
Five or more	5.71** (2.89–11.28)		3.12** (1.49–6.54)	
Nagelkerke r^2	–	0.18	0.21	

Odds ratio (OR), significance level and confidence interval (CI) for the binary logistic regressions.

Model 1 = Treatment information + gender + age + education level + occupation.

Model 2 = Model 1 + history of heart attack + history of angina + prescribed medications.

* $p \leq 0.05$.

** $p \leq 0.01$.

Respondents' willingness to pay for the treatment was also higher for DoE and RRR than for ARR, implying that a gain in disease-free time is valuable to individuals.

There is a critical difference between the compared measures. Proportional measures, such as RRR and ARR depict treatment benefits as increased chances of avoiding disease events. While this is true within a limited study time period, it is less likely to be true from an individual's lifetime perspective. Chronic diseases, such as cardiovascular disease, develop over the life course and preventive interventions are from that perspective more likely to delay disease events rather than fully avoid them. RRR is a well-established effect measure. It is suitable since it gives an estimate of the risk reduction from the individual point of view. RRR may, however, be problematic in shared decision-making as, if rightfully used, it pre-assumes that the decision-maker has a sound understanding of the baseline risk, which is rarely likely to be the case. Furthermore, it is difficult to intuitively say when an RRR is low or high, and lay people seem to have difficulties in discriminating between levels of effectiveness in RRR [12]. For these reasons, health professionals may choose to use absolute measures or its mathematical reciprocal, NNT, when describing a treatment's effect. These measures are, however, also problematic as they are time- and population-specific and display the group perspective, which is not optimal in individual shared decision-making.

Relative and absolute risk reductions are point estimates, which means that they are summary statistics of group differences at a specific point in time: usually at the end of the follow-up. DoE is not a point estimate, but a curve of how the effect is delayed (or hastened) during the follow-up period [22]. The Delay of Event measure demonstrates treatment effect as a gain in disease-free time, which captures the magnitude of treatment effect from the individual perspective. Since the DoE

is conditional having an event, if untreated, a patient has to assume to have the event in the time period corresponding to the clinical study follow-up to understand the benefit as DoE. This means that patients, in contrast to the RRR, intrinsically face the question about their own absolute base line risk. Time-based effects have been shown to be more easily understood than other figures [15]. Statements about time periods can be understood differently by people and patients in treatment situations. Time can be seen as a scarce resource [35], and when time is related to health it may be an even more scarce resource. When time is a part of consumer models it is often viewed as less transferable than other "types" of wealth [35]; uncertainty in relation to time may also be more aversive [35]. This makes planning in terms of time especially important for individuals; conversely uncertainty can disrupt planning, and makes planning more difficult. The DoE curve may also apply to the patient lifetime perspective as it likely increases with treatment time, in contrast to the RRR. If the curve shows an increased effect throughout the treatment period, this may encourage persons to continue treatment beyond the time frames from controlled clinical trials. Consequently, an effect measure that describes a time period, such as DoE, may be of great importance in helping people with their planning, and medical decision-making. DoE as a communication strategy may be of certain value in increasing treatment uptake in patients with poor health literacy when simple and direct diction is desirable [36].

The Delay of Event measure calls for a shift in thinking of events of chronic disease as delayable rather than fully avoidable. This is arguably a justified view given the underlying pathology and that the risk of events increases with age for most chronic disease. This shift in thinking may affect patient's views on preventive treatments' ability as well as their view of the disease itself. It is possible

that a view of disease as merely delayable with treatment affects patient's health beliefs, health behaviors and subjective health in both positive and negative ways. It is suggested that the effects of viewing disease as delayable rather than avoidable is a topic for future research.

One finding in this study was that having a history of heart attack or angina was associated with higher patient willingness to initiate treatment in crude analyses but not in the adjusted models. These results may have occurred due to a small number of respondents with a history of heart attack or angina.

4.1. Strengths and limitations

The strengths of this study include the community setting, the randomized survey experimental approach and the manner in which the treatment effects were presented to the respondents. This study also has some limitations worth noting. The response rate is reasonable in relation to what is anticipated from questionnaire-based studies, but there was no information about nonresponders. The hypothetical setting used in the questionnaires is, further, different from clinical situations where information may be individualized and clarified. Although many respondents reported using medication, the study population was a sample from the general population, which is not the same as a targeted patient population. The data used to calculate the effect came from a study of secondary preventive treatment, and therefore a study population at higher risk of CVD than the majority of the respondents in this study. Preventive treatment effects expressed as the novel approach Delay of Events or relative risk reduction were separately associated with a high willingness to initiate treatment.

4.2. Conclusion

The results in this study imply that DoE and RRR are comparable in a population setting, and that they are preferable to ARR, in motivating individuals to initiate a treatment. Preventive treatment effects expressed as the novel approach Delay of Events or relative risk reduction were separately associated with a high willingness to initiate treatment. Presenting preventive treatment effect as Delay of Events or relative risk reduction was further associated with positive views on treatment benefit, motivation, importance to adhere and willingness to pay for treatment. There is a need to further investigate if the novel DoE may have a role in clinical decision-making for specific patient groups and treatments, especially if it may improve long-term adherence.

4.3. Practice implications

Expressing treatment effect using the novel Delay of Events measure holds value for clinical communication and medical decision making, and this study implies that presenting treatment effect as Delay of Events might increase the likelihood that a patient will accept and adhere to a proposed preventive treatment.

Conflict of interest

All the authors declare that there is no potential conflict of interest.

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