**Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects**

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Large-scale randomized clinical trials have established the efficacy of cholesterol-lowering, blood pressure-lowering, and anti-platelet therapy to prevent cardiovascular diseases. A challenge for clinicians is to apply group-level evidence from these trials to individual patients. Trials typically report a single treatment effect estimate which is the average effect of all participants, comprising patients who respond poorly, intermediately, and well. Clinicians would preferably make patient-tailored treatment decisions. Therefore, one would require an estimate of an individual patient’s response to therapy. Although not yet widely recognized, trials contain this type of information. In this paper, we show how available information from landmark trials can be translated to an individual ‘treatment score’ through the use of multivariable therapeutic prediction models. These models provide an individual estimate of the absolute risk reduction in cardiovascular events given the specific combination of multiple clinical characteristics of a patient under care. Based on this individualized treatment estimate and metrics such as the individual number-needed-to-treat, clinicians together with their patients can decide whether drug treatment or what treatment intensity is worthwhile. Selective treatment of those who can anticipate the greatest benefit and the least harm on an individualized basis could reduce the number of unnecessary treatments and healthcare costs beyond that currently achievable by subgroup analyses based on single patient characteristics.

**Keywords** Individualized cardiovascular medicine • Prediction of treatment effect • Net benefit

**Introduction**

For optimal patient management, clinicians need to translate scientific evidence from large clinical intervention trials to the treatment of individual patients. Currently, trials typically report relative risks or hazard ratios, which are the averages of treating a heterogeneous group of participants. The single estimate of effect provided in trials is an average group-level estimate, implicitly considering that every participant has an average risk and the same average response to treatment.¹–⁴ However, individual patients vary greatly in (combinations of) characteristics that affect the absolute benefit they will receive from treatment. Some will benefit more than average, while others do not benefit or may even be harmed.⁵–⁷ Current practice is to administer the same treatment to a wide range of patients who are all presumed to resemble the ‘mean’ patient behind the single point estimate of treatment effect. However, there are no average patients and there is a wide range of treatment effects in individual patients. So far, there are no tools available that enable clinicians to estimate the absolute effect of treatment for individual patients.

In the prevention of cardiovascular diseases (CVD), even effective treatments such as cholesterol-lowering, blood pressure (BP)-lowering, or anti-platelet therapy require the treatment of many patients to prevent a single cardiovascular event, illustrated by substantial numbers needed-to-treat (NNT).⁸–¹⁰ Ideally, treatment is only given to those patients who can anticipate the greatest benefit and the least harm. Subgroup analyses take a step forward to consider some characteristics that could influence treatment effect, but this type of analyses returns relative effects and not absolute effect estimates.¹¹ Recognizing this limitation, some trial authors have begun to publish subgroup-specific NNT values which provide more granular data on absolute treatment effect.¹² Yet, this approach
Primary prevention of CVD is of utmost importance and is mainly based on BP and cholesterol thresholds. 

Consequently, in both primary and secondary prevention general risk stratification and dichotomous classification of ‘normal’ or ‘abnormal’ risk factor levels are insufficient to estimate the potential benefit an individual patient will derive from treatment. Rather, clinicians and patients would better be informed about the estimated treatment effect, in terms of ARR, given the specific combination of clinical characteristics of a patient under care.

How can individual treatment effect be calculated?

The effect of treatment for an individual patient can be calculated as the difference between the estimated risk of events without treatment and the estimated risk of events with treatment. The risk of CVD events without treatment in patients free of vascular disease can be estimated by existing risk prediction tools (such as Framingham Heart Study score, the Reynolds Risk Score, or the SCORE algorithm). Likewise, for patients with previous vascular disease or type 2 diabetes, risk scores are available (e.g., SMART risk score, ADVANCE, or UKPDS algorithm). Next, the risk for an individual patient with treatment can be obtained by multiplying pre-treatment risk by the average relative risk ratio observed in the trial (Box 2). The difference between these two is the estimated ARR for an individual patient. This straightforward approach only works if a risk prediction tool is available for a specific patient, for the outcome of interest and if the relative risk reduction as a result of treatment is known from landmark trials.
of treatment is constant across various subgroups of patients (i.e. no treatment interactions).

In the presence of treatment interactions, the relative risk reduction can be smaller or larger depending on specific patient characteristics. Treatment interactions are mostly related to differences in pathophysiology of a single clinical disease entity. For example, ACE-inhibitors could be more effective for the treatment of high plasma renin hypertension typically seen in young patients compared with low-renin hypertension seen in elderly patients. Further, the relative risk reduction of statin therapy could be greater in patients at low baseline CVD risk compared with patients at high-CVD risk. Given the pathophysiology of atherosclerosis, it is conceivable that statin treatment is more effective in the earlier stages of atherosclerotic disease marked by lower CVD risk.

If there is evidence of such treatment interactions or if no suitable model is available, a new model to predict event risk can be developed on the data of the clinical trial. By including a treatment term and potential treatment interactions in the prediction model, event risk can be estimated for every patient as if they received active treatment or placebo (Box 3). Importantly, the random allocation of treatment ensures that the model estimate for treatment effect is unbiased.

**Examples of variation in individual treatment effect**

Figure 1 shows the distribution of predicted 5-year absolute treatment effect of high-dose vs. usual-dose statin Treating to New Targets (TNT) and Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trials. Since no suitable model was available, the predictions of treatment effect were based on a
A newly developed prediction model which assumed constant relative risk reductions. A wide range of absolute treatment effects was observed; 41.9% of patients had a predicted 5-year NNT > 50, whereas 11.7% of patients had an NNT5 < 25. While current guidelines recommend intensive lipid lowering for all patients with vascular disease and an LDL-c ≥ 1.8 mmol/L, the absolute benefit of intensive treatment varies widely. For a 55-year-old smoking female patient with a history of myocardial infarction, an SBP of 140 mmHg, an HDL-c of 1.3 mmol/L, an LDL-c of 3.3 mmol/L, and an eGFR of 70 mL/min the 5-year ARR is 1.3% corresponding to an NNT5 of 79 to prevent one CVD event. On the other hand, a patient with a similar LDL-c of 3.3 mmol/L who also has diabetes, a treated SBP of 160 mmHg and an HDL of 1.0 mmol/L, will have a 5-year predicted ARR of 3.4% requiring only 29 similar patients to be treated with intensive lipid-lowering therapy to prevent one CVD event.

In Figure 2, the treatment effect of aspirin in terms of ARR of major cardiovascular events for individual patients in the Women’s Health Study is shown. Development of a new prediction model showed treatment interactions with age, smoking, high-sensitive C-reactive protein, and body mass index so that similar pre-treatment risk resulted in different ARR. Using the last model, treatment with aspirin was shown to be marginally effective or even harmful for the majority of patients as 90% had a predicted 10-year NNT of > 100 and 4.4% had a predicted NNT10 < 50.

Interpretation of treatment effects with individual number-needed-to-treat

An average ARR is typically reported in clinical trials, but can be difficult to interpret and difficult to apply to single patients in clinical practice. For most clinicians, the NNT (1 divided by ARR) is a more intuitive method to express the benefit that can be expected from treatment. For proper interpretation, NNT data must incorporate information on treatment duration and specify the endpoint of interest. However, the NNT is a point estimate based on the average result of a clinical trial. For example, a traditional NNT5 of 50 refers to treatment of 50 ‘average’ individuals for 5 years. Differences between patients (in age, gender, BP levels, cholesterol values, parental histories etc.) have an impact on an individuals’ risk and the amount of treatment effect. Instead of using the average NNT from a trial or a simple subgroup NNT based on single clinical characteristics such as gender or smoking status, an individual number-needed-to-treat (iNNT) based on multiple patient characteristics could be calculated with multivariable prediction models using data available from trials. This iNNT represents the number of individuals with the same characteristics (same age, same gender, same BP, same medical history, etc.) that need to be treated to prevent one event. Although, still a group-level estimate, the iNNT conveys much more precise information.
information about a very specific set of clinical characteristics that reflect the individual patient. We previously developed a prediction model to estimate the iNNT for the high-dose statin therapy when compared with usual dose in the TNT and IDEAL trials.\textsuperscript{18} Based on multiple easily available clinical and laboratory predictors, an iNNT was calculated for every patient using a calculation sheet (Figure 3).

**Weighing treatment benefits and harms for individual patients**

Physicians and patients need to consider whether treatment of a CVD risk factor is worthwhile for a specific patient. Not in terms of expected BP-lowering or cholesterol-lowering, but in terms of reduction in the risk of vascular events. Expected beneficial effects need to be weighed against potential negative effects. All therapeutic interventions (medical, surgical, and lifestyle) are associated with some level of disutility such as the burden of daily taking a drug, costs of treatment and mild-to-severe adverse reactions. The (perceived) disadvantages of a specific treatment differ between patients, differ between countries, and may change over time on a patient or societal level. Whether a patient decides to undergo preventive treatment is determined by the relative weighing of positive and negative effects of treatment.

The treatment threshold at which a patient and doctor will opt for treatment, is the point where the positive and negative effects of treatment are considered to be equal.\textsuperscript{15} A treatment threshold of 2% ARR implies that the negative effects of treatment are thought to be 2% thereby cancelling out the expected reduction in event risk. Unfortunately, it can be difficult to accurately model the excess risk of adverse events on an individualized basis as even in extremely large trials the prevalence of side-effects is low and patients at an increased risk of side-effects are excluded during run-in periods. Alternatively, risk scores developed in large cohort studies can be used, but they do not estimate excess risk of treatment and partly reflect the inherent risk of patients who require the drug.\textsuperscript{46} In some cases it might be inevitable to define a treatment threshold based on an average estimate of harm, for example, the yearly average excess bleeding risk of 0.2% associated with aspirin treatment.\textsuperscript{47} Further, aside from explicit harms, the implicit harms of daily taking a drug, minor inconveniences, and costs need to be considered as well and can be incorporated by increasing the treatment threshold. A graphical representation of this treatment threshold is given in Figure 4. The threshold ARR can also be expressed as a number willing to treat (NWT) which represents the number of patients one is prepared to treat to prevent 1 event (Box 4).

**Effects of individualized treatment prediction on population level**

As described above, the effect of treatment of CVD risk factors can be predicted for individual patients and weighted against a treatment threshold. The next question is whether the standard use of treatment effect prediction models in clinical practice is a better approach than the strategies currently advocated in guidelines.\textsuperscript{45,46} Vickers et al.\textsuperscript{45,46} proposed a decision analytic approach to evaluate the net clinical benefit of different treatment strategies.\textsuperscript{49}

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**Box 4. Definitions of number needed-to-treat, individual number needed-to-treat and number willing-to-treat**

\[
\text{NNT} = \text{number needed-to-treat (i.e. 100 divided by ARR)}
\]

Number of patients that need to be treated during a certain time period (e.g. 10 years) to prevent one event based on the average treatment effect observed in a trial

\[
\text{iNNT} = \text{individual number-needed-to-treat (i.e. 100 divided by individual ARR)}
\]

Number of patients that need to be treated during a certain time period (e.g. 10 years) to prevent one event based on a predictive model of treatment effect for an individual with specific clinical characteristics.

\[
\text{NWT} = \text{Number Willing-to-Treat}
\]

Treatment threshold; the maximum number of patients one is prepared to treat during a certain time period (e.g. 10 years) in order to prevent one event

Prediction-based treatment of patients with the highest estimated effect can result in treating fewer patients while still preventing the majority of events. The trade-off between preventing as many events as possible and minimizing the number of treatments need to be considered. The net clinical benefit of prediction-based
treatment can be compared with current guideline strategies of treating all patients or treating no one. Treating all patients will generally result in the greatest reduction in event rate but comes at the expense of many unnecessary treatments and greater economic cost. Treating no one is the reference category resulting in zero net benefit, but also in no adverse reactions and no treatment costs (except those associated with events that could have been avoided had treatment been given). The net benefit of various strategies plotted at different treatment thresholds results in a decision curve. For example, in the JUPITER trial we compared the net clinical benefit of selectively treating patients with a statin based on their predicted treatment effect vs. treating all patients with statins regardless of predicted effect. The decision curve (Figure 5) shows that prediction-based treatment is associated with highest net benefit if the 10-year treatment threshold is an NWT between 15 and 50. For drug treatment in clinical practice, an NNT10 between 15 and 50 is generally considered acceptable. Therefore, prediction-based treatment would be the preferable strategy on a population level for the use of statins in patients at moderately elevated risk. If one is of the opinion that treatment is nearly without disadvantages (e.g. NWT10 > 100), the strategy of choice would be to treat everyone. Hence, the optimal strategy on a population level depends on the relative weighing of positive and negative effects of treatment.

**Current and future perspective of individualized treatment prediction for clinical practice**

Currently, practice guidelines tend to describe how to treat ‘average’ patients, not specific individuals. The approach we described in this paper results in calculated treatment effects for individual patients given their specific characteristics. Treatment effect calculators to estimate the individual effect of statins and aspirin in primary prevention of CVD derived from the JUPITER and WHS trials as well as for calculation of the individual incremental benefit of high vs. usual-dose statin therapy in secondary prevention based on the TNT and IDEAL trials are already published and made available (www.vasculargeneeskundundeutrecht.nl/calculators). Individualized treatment effect predictions are now developed for BP-lowering, lipid-lowering, and anti-platelet treatment for patients at increased vascular risk, patients with clinical manifest vascular disease, and patients with type 2 diabetes. An integrated calculator estimating individualized treatment effects for all these treatments could be linked to electronic patient records and automatically present up-to-date individual effect estimates. Physician and patient could then use this information to decide whether or not to start a specific treatment. This could be a step towards personalized medicine by better using available clinical trial data.

**Potential effects on adherence**

The individualized estimate of absolute treatment effect (iNNT) can enhance knowledge translation to patients as well as engage patients in treatment decisions by raising awareness of their individualized risks and benefits of treatment. This could also have a positive influence on treatment adherence. For preventive therapies, compliance is generally poor. Important determinants of treatment adherence are patient education and engagement of patients in shared decision-making. A randomized trial evaluating a decision aid for statin therapy in patients with diabetes, showing patients their pre-treatment CVD risk, estimated ARR, and potential disadvantages of statin therapy, demonstrated favourable effects on their CVD risk profile and treatment adherence.

**Limitations**

The benefits of treating patients according to their risk level instead of treatment based on single risk factor thresholds has been demonstrated in various modelling studies for BP-lowering, lipid-lowering, and anti-platelet treatment. In the present paper, we take a

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**Figure 5** Decision curve: graphical representation of net clinical benefit for statin treatment in primary prevention (JUPITER). Net benefit analysis is used to evaluate whether the standard use of therapeutic prediction models in clinical practice is a better approach than the strategies advocated in current guidelines. Net clinical benefit of various treatment strategies is displayed at different treatment thresholds to allow for a different weighing of positive and negative effects of treatment among physicians and patients. Reading a decision curve starts with choosing a treatment threshold on the x-axis. An NWT of 50 implies that for every 50 treated patients at least 1 event needs to be prevented (or 1/50 event for every treated patient) before net clinical benefit accrues. A low NWT implies that treatment is associated with considerable disadvantages (side-effects, inconveniences, costs, etc.), whereas a high NWT implies almost no treatment disadvantages (infinite NWT). For example, at a threshold NWT of 20, the net benefit of prediction-based treatment can be extracted from the graph and is 1.1%. Net benefit is calculated as the benefit of selective treatment of patients whose predicted effects exceed the treatment threshold (ARR of 2.8%) minus harms of treatment expressed as the proportion of patients receiving treatment (34%) weighted by the inverse of the treatment threshold [net benefit = 0.028 – (0.34 x 0.05) = 1.1%]. For statin therapy in JUPITER, prediction-based treatment was associated with greater net benefit than treating everyone or no one, at a 10-year NWT between 15 and 50. In this range of treatment thresholds, the standard use of therapeutic prediction models in clinical practice is the preferable treatment strategy.
step further and show that therapeutic prediction models can provide a predicted individual absolute treatment effect of lipid-lowering, BP-lowering, and anti-platelet therapy to enable patient-tailored treatment.

The most important criticism of prediction-based treatment is probably that prediction models are of limited use in clinical practice because doctors do not use them, as they are complicated and time consuming. However, widespread use of electronic patient records have made implementation of prediction models in clinical practice easier and required information for treatment effect calculators can be automatically supplied (Figure 3). Further, patients can use prediction rules themselves on websites, and this would help empower them.

Some limitations should be considered in the development of individual treatment prediction models. They are based on available clinical trials and thus on general relatively short follow-up time. As meaningful CVD predictions usually cover a 10-year period, model predictions often need to be extrapolated to cover broader time-horizons than trials provide. This limitation is, however, not unique to individual treatment effect prediction. It also applies to the interpretation and use of the 'average' treatment effect provided by most trials. Furthermore, the estimates of ARR for individual patients depend on the multivariable prediction model that is used. Therefore, it is important that the predictive risks with and without treatment are in agreement with observed risks (i.e. calibration). Internal validation of a newly derived model can help to verify the predictive performance and external validation of the therapeutic prediction model should be aimed for. Further, patients can use prediction rules themselves on websites, and this would help empower them. Nevertheless, current guidelines are also based on the findings from the same clinical trials, however, basing the recommendations on the 'average' treatment effects of trials. Last, prediction models assessing the effect of a single treatment only partly reflect clinical practice where patients are treated with a combination of drugs. However, when managing various CVD risk factors, the estimated ARR of each treatment separately may be helpful to prioritize risk factor treatment.

Conclusions

Clinical trials contain a wealth of information that is underused by only presenting an average effect of treatment that cannot be applied to the wide variety in patients seen in clinical practice. By incorporating multiple patient characteristics into a therapeutic prediction model, individual estimates of treatment effect can be provided in terms of ARR of cardiovascular events and can be expressed by an iNNT. This will help to improve individual patient management and has the potential to identify those individual patients that benefit the most from treatment, to reduce the number of unnecessary treatments and to cut healthcare costs.

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