Personalized Cardiovascular Disease Prevention by Applying Individualized Prediction of Treatment Effects

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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.

INTRODUCTION

- However, individual patients vary greatly in 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.
- 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.
- So far, there are no tools available that enable clinicians to estimate the absolute effect of treatment for individual patients.

INTRODUCTION

- In the prevention of cardiovascular diseases (CVD), even effective treatments require the treatment of many patients to prevent a single cardiovascular event, illustrated by substantial numbers needed-to-treat (NNT).
- 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.

INTRODUCTION

- Recognizing this limitation, some trial authors have begun to publish subgroup-specific NNT values which provide more granular data on absolute treatment effect.
- This approach remains limited in that clinical subgroups typically are defined only by a single clinical characteristic.

INTRODUCTION

- Existing trial data can be ‘re-used’ to develop multivariable prediction models that provide an estimate of absolute treatment effect for individual patients based on their specific characteristics.
- Based on individualized predictions of treatment effect, clinicians can decide together with a patient whether treatment is worthwhile for that particular individual before initiating therapy.
- The use of treatment effect prediction models to select the right patients for treatment has the potential to reduce the number of patients treated unnecessarily, to identify those patients benefitting the most, to reduce treatment-associated harm and to cut healthcare costs.

INTRODUCTION

- The aim of this paper was to illustrate how to translate group-level evidence from large cardiovascular risk management trials to the treatment of individual patients in everyday clinical practice by applying treatment effect prediction models.

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).
  - For patients with previous vascular disease or type 2 diabetes, risk scores are available (e.g. SMARTmrisk score, ADVANCE, or UKPDS algorithm35).

HOW CAN INDIVIDUAL TREATMENT EFFECT BE CALCULATED?

- 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
- 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 constant across various subgroups of patients (i.e. no treatment interactions).

HOW CAN INDIVIDUAL TREATMENT EFFECT BE CALCULATED?

- 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.

HOW CAN INDIVIDUAL TREATMENT EFFECT BE CALCULATED?

Box 3 Prediction of treatment effect for individual patients

Predicted treatment effect

= off-treatment risk minus on-treatment risk

Off-treatment risk

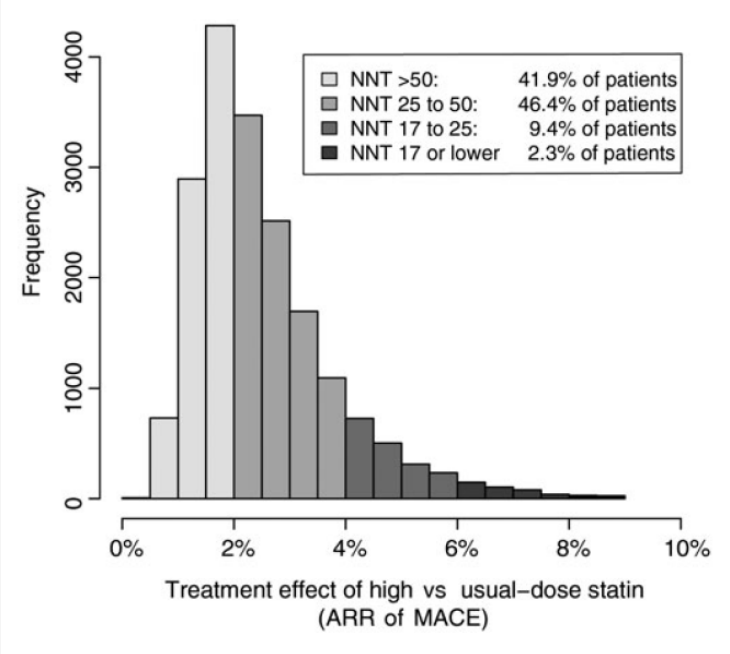
1) Absolute 10-year risk according to available risk score (e.g. Framingham Heart Study score or Reynolds Risk Score)
2) Newly develop risk score with treatment variable(s) set to NO (0) [e.g. model coefficients = 0.9 × age in years + 0.8 (if current smoker) + 3.1 × log(SBP) – 0.2 (if treated = 0) – 0.1 (if treated and smoker = 0)]

On-treatment risk

1) Absolute 10-year risk according to risk score multiplied by RR or HR (e.g. 0.80 × Framingham Heart Study Score or Reynolds Risk Score in the absence of treatment interactions)
2) Newly developed risk score with treatment variable(s) set to YES (1) [e.g. model coefficients = 0.9 × age in years + 0.8 (if current smoker) + 3.1 × log(SBP) – 0.2 (if treated = 1) – 0.1 (if treated and smoker = 0 or 1)]

EXAMPLES OF VARIATION IN INDIVIDUAL TREATMENT EFFECT

- Since no suitable model was available, the predictions of treatment effect were based on a newly developed prediction model which assumed constant relative risk reductions.



EXAMPLES OF VARIATION IN INDIVIDUAL TREATMENT EFFECT

- 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.

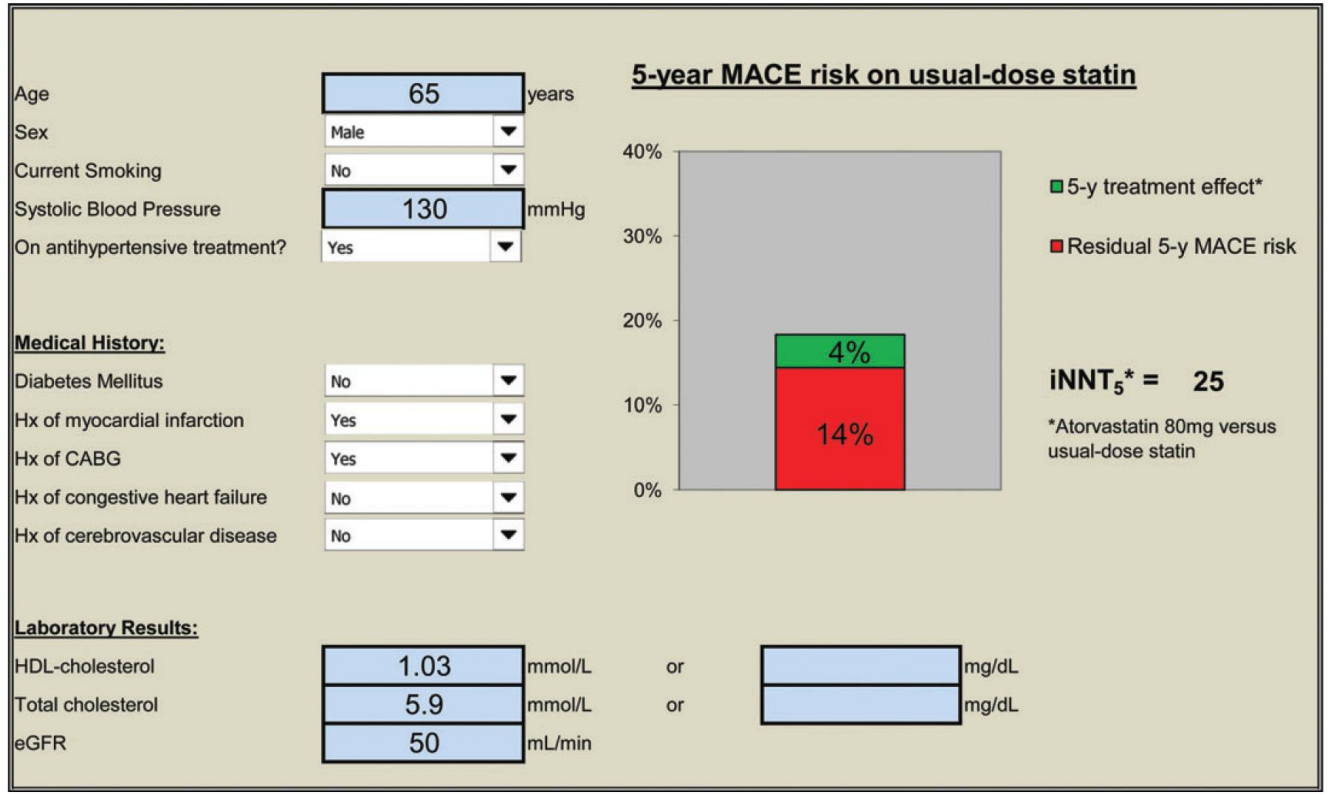
INTERPRETATION OF TREATMENT EFFECTS WITH INDIVIDUAL NUMBER-NEEDEDTO-TREAT

- 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 about a very specific set of clinical characteristics that reflect the individual patient.

INTERPRETATION OF TREATMENT EFFECTS WITH INDIVIDUAL NUMBER-NEEDEDTO-TREAT

- 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.
- Based on multiple easily available clinical and laboratory predictors, an iNNT was calculated for every patient using a calculation sheet.

INTERPRETATION OF TREATMENT EFFECTS WITH INDIVIDUAL NUMBER-NEEDEDTO-TREAT



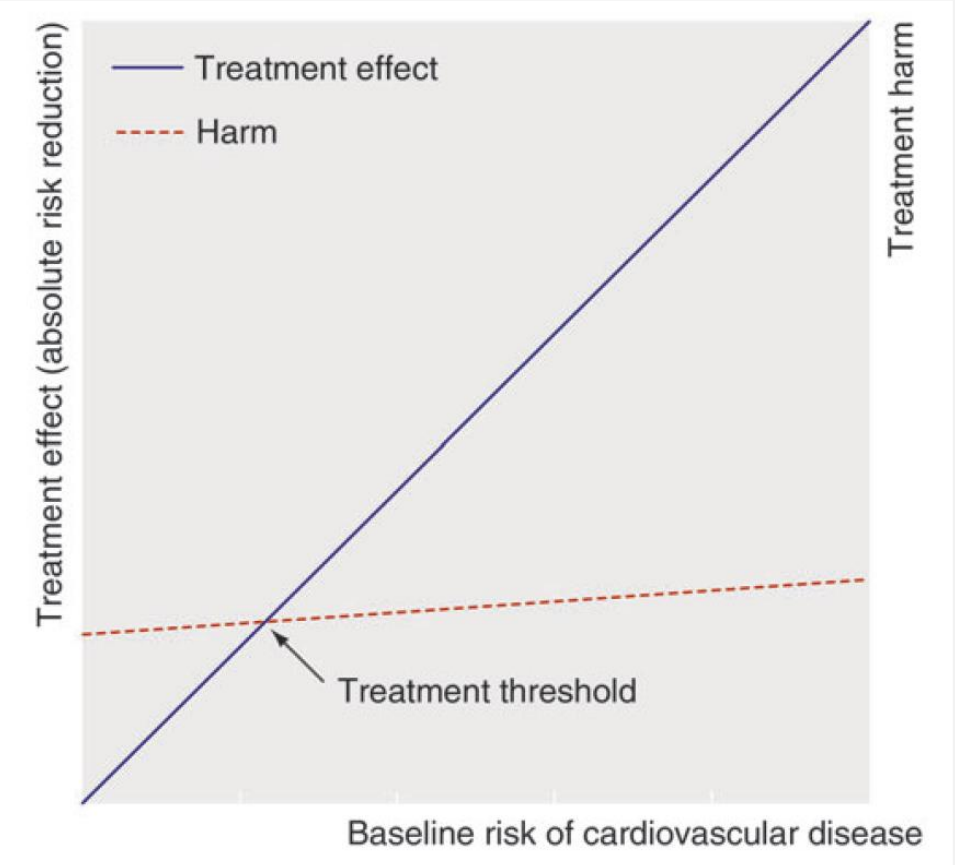
WEIGHING TREATMENT BENEFITS AND HARMS FOR INDIVIDUAL PATIENTS

- 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.

WEIGHING TREATMENT BENEFITS AND HARMS FOR INDIVIDUAL PATIENTS

- 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.
- 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.

WEIGHING TREATMENT BENEFITS AND HARMS FOR INDIVIDUAL PATIENTS



WEIGHING TREATMENT BENEFITS AND HARMS FOR INDIVIDUAL PATIENTS

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

NNT = 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

iNNT = 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.

NWT = 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

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 practise is a better approach than the strategies currently advocated in guidelines.

EFFECTS OF INDIVIDUALIZED TREATMENT PREDICTION ON POPULATION LEVEL

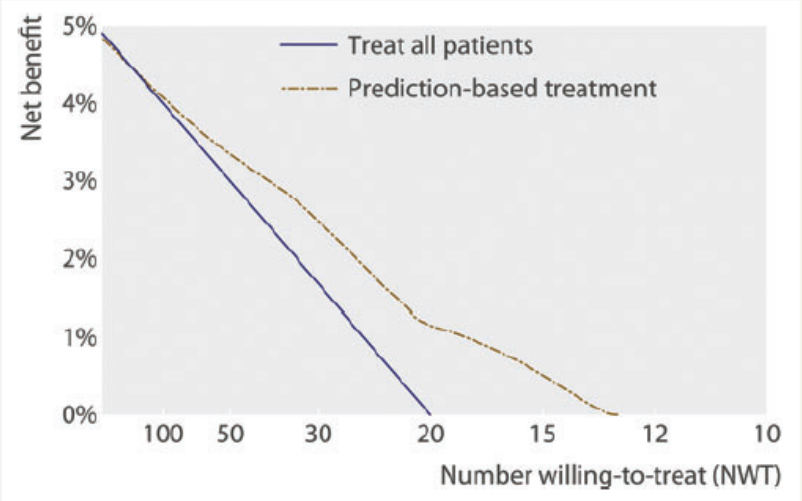
- Prediction-based treatment of patients with the highest estimated effect can result in treating fewer patients while still preventing the majority of events.
- The trade-off between preventing as many events as possible and minimizing the number of treatments need to be considered.
- The net clinical benefit of prediction-based treatment can be compared with current guideline strategies of treating all patients or treating no one.

EFFECTS OF INDIVIDUALIZED TREATMENT PREDICTION ON POPULATION LEVEL

- 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.

EFFECTS OF INDIVIDUALIZED TREATMENT PREDICTION ON POPULATION LEVEL

- 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 shows that prediction-based treatment is associated with highest net benefit if the 10-year treatment threshold is an NWT between 15 and 50.



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.

LIMITATIONS

- 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.

LIMITATIONS

- 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.

LIMITATIONS

- 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.59

LIMITATIONS

- Another concern that applies to clinical trials is the generalizability of findings.
- Trial participants are often selected based on strict eligibility criteria and are usually healthier and more compliant than patients in daily clinical practice.60

LIMITATIONS

- Lastly, 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

- 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.

THANK YOU