Predicting the Effects of Blood Pressure–Lowering Treatment on Major Cardiovascular Events for Individual Patients With Type 2 Diabetes Mellitus

Results From Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation


Abstract—Blood pressure–lowering treatment reduces cardiovascular risk in patients with diabetes mellitus, but the effect varies between individuals. We sought to identify which patients benefit most from such treatment in a large clinical trial in type 2 diabetes mellitus. In Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) participants (n=11 140), we estimated the individual patient 5-year absolute risk of major adverse cardiovascular events with and without treatment by perindopril–indapamide (4/1.25 mg). The difference between treated and untreated risk is the estimated individual patient’s absolute risk reduction (ARR). Predictions were based on a Cox proportional hazards model inclusive of demographic and clinical characteristics together with the observed relative treatment effect. The group-level effect of selectively treating patients with an estimated ARR above a range of decision thresholds was compared with treating everyone or those with a blood pressure >140/90 mm Hg using net benefit analysis. In ADVANCE, there was wide variation in treatment effects across individual patients. According to the algorithm, 43% of patients had a large predicted 5-year ARR of ≥1% (number-needed-to-treat [NNT] ≤100) and 40% had an intermediate predicted ARR of 0.5% to 1% (NNT=100–200). The proportion of patients with a small ARR of ≤0.5% (NNT>200) was 17%. Provided that one is prepared to treat at most 200 patients for 5 years to prevent 1 adverse outcome, prediction-based treatment yielded the highest net benefit. In conclusion, a multivariable treatment algorithm can identify those individuals who benefit most from blood pressure–lowering therapy in terms of ARR of major adverse cardiovascular events and may be used to guide treatment decisions in individual patients with diabetes.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00145925. (Hypertension. 2015;65:115-121. DOI: 10.1161/HYPERTENSIONAHA.114.04421.) ● Online Data Supplement

Key Words: antihypertensive agents ■ diabetes mellitus ■ individualized medicine ■ medical decision making, computer-assisted

Type 2 diabetes mellitus (T2DM) is a growing worldwide health problem, with an estimated 439 million people living with diabetes mellitus in 2030. The lifelong incidence of vascular complications is extremely high, and >80% of patients with diabetes will die from a vascular cause. Blood pressure (BP) is strongly related to nonfatal vascular events, vascular, and all-cause mortality in patients with T2DM. The risk associated with BP already starts well below the BP level used to define hypertension, and BP-lowering agents have been shown to reduce vascular risk in patients with and without hypertension by an average of 15%. Yet, based on benefit and costs considerations, treatment with BP-lowering medication is only recommended according to guidelines if BP is >140/90 mm Hg. This BP threshold serves as a marker to identify patients who potentially benefit from treatment. However, even above this threshold, individual patients vary greatly in the combinations of decision-making, computer-assisted...
of characteristics that affect the amount of benefit they will receive from treatment.11–13 The absolute risk reduction (ARR) of BP-lowering treatment for individual patients depends not only on baseline BP but also on baseline risk, which is determined by the combined actions of multiple risk factors, such as age, cholesterol, and BP.14 Patients with high baseline risk tend to benefit more in terms of ARR.15,16 In addition, subgroup analyses have pointed out some characteristics that might influence the relative efficacy of treatment, such as age and pretreatment BP.17,18 Although some benefit from BP lowering may be seen across the entire range of background risk, it is to be expected that, in some cases, this benefit may be reduced by costs or adverse effects.19 Clinicians thus need to identify those individual patients where benefit from BP-lowering therapy outweighs potential treatment disadvantages, such as cough and hypotension, the inconvenience of daily taking a drug and the monetary costs of treatment. In the present study, we sought to predict the individual absolute effect of BP-lowering on the occurrence of major cardiovascular events in patients with T2DM using routine clinical data. For this purpose, we used data from the Action in Diabetes and Vascular Disease: Preterax and DiaMicon R Controlled Evaluation (ADVANCE) trial20 that randomly assigned patients with T2DM to receive a fixed combination of perindopril and indapamide. The effect of treatment for individual patients could then be estimated using a newly developed risk score and the relative treatment effect observed in the trial. These individualized estimates of treatment effect may help to guide treatment decisions in individual patients with T2DM in clinical practice.

Methods

The design, rationale, and outcomes of the ADVANCE trial have been described elsewhere.20,21 Briefly, the ADVANCE study was a factorial randomized controlled trial evaluating the effect of intensive glucose control therapy and routine BP-lowering therapy with a fixed combination of perindopril and indapamide (4/1.25 mg) or placebo on vascular events and death. From 215 collaborating centers in 20 countries from Asia, Australasia, Europe, and North America, 11,410 participants diagnosed with T2DM and aged ≥55 years were included. Eligible patients also needed to have a history of macrovascular or microvascular disease or ≥1 risk factor. There were no BP criteria for inclusion. The end point of interest was major adverse cardiovascular events (MACE; ie, cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Approval for the trial was obtained from the institutional ethics committee of each center, and all participants provided written informed consent. Data were missing in 4.5% of participants for urinary albumin/creatinine ratio and in <1% for all other covariates. Missing data were reduced by single imputation methods using predictive mean matching.22,23

Model Derivation

We developed a new Cox proportional hazards model based on a set of clinical characteristics together with a treatment status covariate (placebo versus active treatment). The prespecified predictors were sex, age, diabetes mellitus duration, systolic BP, history of treated hypertension, current smoking, HbA1c, total cholesterol, high-density lipoprotein -cholesterol, waist circumference, urinary albumin/creatinine ratio, estimated glomerular filtration rate, history of major macrovascular disease, retinopathy, ethnicity, and treatment status. Ethnicity was classified into Asian and non-Asian because further subdivision would produce categories with too few participants. Diabetic retinopathy was defined as fundoscopic evidence of background or proliferative retinopathy, previous laser retinal therapy, macular edema, or blindness. Estimated glomerular filtration rate was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.24 Potential interactions between treatment and age, systolic BP, currently treated hypertension, estimated glomerular filtration rate, and baseline risk were considered.25 Continuous predictors were truncated at the 1st and 99th percentile to limit the effect of outliers.23 Restricted cubic splines were used to assess the linearity assumption for continuous predictors. As a result, estimated glomerular filtration rate was included both as a linear and as a squared term, and urinary albumin/creatinine ratio was natural log-transformed.

First, treatment interactions with a conditional likelihood ratio P value of ≥0.05 were removed from the starting model. Next, the model was further simplified by stepwise backward selection based on Akaike’s Information Criterion. To correct for overoptimism, 1000-fold bootstrap resampling was used and a factor of 0.967 was derived to shrink the model coefficients except for treatment uniformly.27 The proportional hazard assumption was verified by testing the correlation between scaled Schoenfeld’s residuals and time: no violations were observed. The final model was used to calculate the risk of MACE, with and without treatment, for every participant by fixing the treatment variable to placebo and active treatment, respectively. The difference is the individual patient’s ARR and can be translated to a patient-specific number-needed-to-treat (NNT=100/ARR). This individual NNT reflects the number of patients with exactly similar characteristics that need to be treated to prevent 1 event. The model was fitted for the prediction of 4.4-year (median follow-up) risk and extrapolated to yield 5-year estimates through exponentiation.

Sensitivity analyses encompassed the evaluation of individual treatment effect based on 2 existing risk algorithms (ADVANCE risk engine26 and recalibrated U.K. Prospective Diabetes Study [UKPDS] score) together with the observed overall relative risk reduction from ADVANCE. Because these algorithms were constructed for the use in patients without previous cardiovascular disease, these analyses were conducted in the subgroup of patients free from macrovascular disease at baseline.

Assessment of Model Performance

Calibration was assessed by plotting observed 5-year event-free survival against the average predicted 5-year event-free survival within groups defined by the deciles of predicted risk and by the Gronnesby and Borgan test.28 Discrimination was assessed by Harrell c-statistic and the optimism-corrected c-statistic was obtained by 1000-fold bootstrap resampling.29

Distribution of Individual Treatment Effect and Net Benefit

The distributions of estimated individual 5-year ARR of MACE are displayed in histograms. Next, we evaluated the group-level consequences of applying a prediction-based treatment strategy in clinical practice using the net benefit method.29 Net benefit is found from weighing the positive and negative effects of treatment and uses observed event rates and treatment rates in trial participants. The equipoise between benefit and disadvantages of treatment may be expressed by a threshold NNT. For example, a 5-year threshold NNT (NNT5) of 50 implies that the disadvantages of treating 50 patients for 5 years are considered to be well balanced by the benefit obtained by preventing one outcome. Net benefit is calculated as the observed ARR in patients for whom the treatment recommended by the decision strategy is congruent with randomized allocation minus the disadvantages of treatment. The disadvantages are expressed as the proportion of treated patients weighted by the inverse of the threshold NNT:

Net benefit = ARR−Pextra*(1/threshold NNT).

Net benefit can be interpreted as the excess number of events prevented per 100 patients on top of the minimally required number of events prevented to offset treatment disadvantages. We considered the following treatment decision strategies at a threshold NNT, between 25 and infinity: (1) treat everyone, (2) prediction-based treatment (ie, selective treatment of patients whose predicted individual treatment effect exceeds the specified threshold NNT), or (3) treat those with a BP>140/90 mm Hg. A detailed calculation example is provided in the online-only Data Supplement. Finally, we tabulated the clinical implications of prediction-based treatment on treatment rate and the
Results

Model Derivation and Performance

Baseline characteristics of the ADVANCE participants are shown in Table 1. During a median follow-up of 4.4 years, 1000 major cardiovascular events occurred. The final algorithm contained 14 variables (Table 2). None of the treatment interactions (including the risk-based interaction) were significant. The risk score showed good calibration ($P_{20:42};$ Figure 1). Discrimination was moderate with an apparent c-statistic of 0.70 (95% confidence interval, 0.68–0.72). The optimism-corrected c-statistic was 0.69 (95% confidence interval, 0.67–0.71).

Distribution of Baseline Risk and Treatment Effect

The median 5-year MACE risk on placebo was 8% (interquartile range, 6%–13%). Of the ADVANCE participants, 21% were at low-risk MACE (<5%), 40% at intermediate risk (5%–10%), 20% at high risk (10%–15%), and 20% at very high risk (>15%). According to the risk algorithm, 43% of patients had a large predicted 5-year ARR of ≥1% (NNT≤100) and 40% had an intermediate predicted ARR of 0.5% to 1% (NNT=100–200). The proportion of patients with a small ARR of ≤0.5% (NNT≥200) was 17% (Figure 2).

In patients free from major macrovascular disease, the median 5-year MACE risk was 7% (interquartile range, 5%–10%) and a proportion of 28% was identified to have a large ARR of ≥1%. By contrast, median risk was 13% (interquartile range, 9%–20%) in patients with previous major macrovascular disease, and 74% of patients had a large predicted ARR of ≥1% (Figure S1; Table S1 in the online-only Data Supplement). Sensitivity analyses in the patients free from major macrovascular disease using the previously published ADVANCE and UKPDS risk scores produced similar distributions of risk and treatment effect (Figure S2).

Net Benefit and Clinical Implications

For threshold NNT<200 (or 5-year ARR>0.5%), prediction-based treatment was associated with higher net benefit at a

<p>| Table 2. Details of Final Cox Proportional Hazards Model for the Prediction of MACE Risk |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (women vs men)</td>
<td>−0.4103</td>
<td>0.65</td>
<td>0.57–0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (per 1 y)</td>
<td>0.0437</td>
<td>1.05</td>
<td>1.04–1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of diabetes mellitus (per 1 y)</td>
<td>0.0164</td>
<td>1.02</td>
<td>1.01–1.03</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (per 1 mmHg)</td>
<td>0.0037</td>
<td>1.00</td>
<td>1.00–1.01</td>
<td>0.012</td>
</tr>
<tr>
<td>Treated hypertension (yes vs no)</td>
<td>0.1828</td>
<td>1.21</td>
<td>1.04–1.41</td>
<td>0.014</td>
</tr>
<tr>
<td>Total cholesterol (per 1 mmol/L)</td>
<td>0.1470</td>
<td>1.16</td>
<td>1.10–1.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-cholesterol (per 1 mmol/L)</td>
<td>−0.3799</td>
<td>0.68</td>
<td>0.55–0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (per 1%)</td>
<td>0.0830</td>
<td>1.09</td>
<td>1.05–1.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UACR (per 1 log µg/mg)</td>
<td>0.1693</td>
<td>1.37</td>
<td>1.27–1.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (per 1 mL/min)</td>
<td>−0.0258</td>
<td>0.84</td>
<td>0.75–0.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR squared (per 1 squared mL/min)</td>
<td>0.0001</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Retinopathy (yes vs no)</td>
<td>0.3293</td>
<td>1.41</td>
<td>1.23–1.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of macrovascular disease (yes vs no)</td>
<td>0.6288</td>
<td>1.92</td>
<td>1.69–2.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Randomized treatment (active vs placebo)</td>
<td>−0.1162</td>
<td>0.89</td>
<td>0.79–1.01</td>
<td>0.067</td>
</tr>
</tbody>
</table>

Five-year MACE risk (%)=(1−S0(5)exp(A−3.9694))×100%, where A is the sum, over all variables in the model, of the patient’s specific value times the corresponding coefficient. CI indicates confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HDL, high-density lipoprotein; MACE, major adverse cardiovascular events; S0(5)=5-year baseline survival; and UACR, urinary albumin/creatinine ratio.

*Coefficients were penalized to increase external validity, whereas unbiased HRs and statistics were derived from an unpenalized Cox model.

†Risk model contains linear and squared terms for eGFR and a natural log-transformed term for ACR. HRs were computed for the difference between the 75th and 25th percentile of eGFR and UACR (88 vs 62) and UACR (40 vs 7).
Discussion

The present analysis from the ADVANCE trial demonstrates that a treatment algorithm based on routine clinical data can identify individual patients with T2DM who benefit most from BP-lowering treatment with perindopril–indapamide in terms of ARR of MACE. At a group level, prediction-based treatment can result in a more optimal trade-off between number of patients treated and number of events prevented depending on the relative weighing of treatment benefits and disadvantages.

The ADVANCE trial was designed to evaluate the efficacy of a fixed-dose combination of BP-lowering drugs in patients with diabetes mellitus irrespective of initial BP or other antihypertensive drugs. Not selecting patients based on BP is less resource intensive and more inclusive than treatment based on BP thresholds, and this policy did lower the risk of MACE and mortality at a group level.20 The present post hoc analysis showed that individual treatment effect varied widely across individual patients with T2DM. We found no evidence for heterogeneity of the relative treatment effect by patient characteristics or baseline risk, in concurrence with results from previous meta-analyses.4,18 Hence, the most important determinant of the absolute individual treatment effect of BP lowering was pretreatment cardiovascular risk. Formerly diabetes mellitus was regarded as a coronary heart disease equivalent, suggesting a 10-year cardiovascular risk of >20%.31 However, this concept is debated and heterogeneity in risk is illustrated in ADVANCE by the identification of 29% of patients without previous macrovascular disease with a 5-year cardiovascular risk of ≤5%. Hence, the designation of diabetes mellitus per se as a high-risk equivalent is inaccurate. In the present analysis, we also included patients with a history of macrovascular disease and covered the broad range of patients with diabetes mellitus encountered in clinical practice. The use of prediction models that consider a combination of multiple risk factors can individualize the estimate of treatment effect and provides a tool to direct treatment to patients who might expect

Figure 1. Calibration plot. Predicted vs observed 5-year major adverse cardiovascular events risk in Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) participants (n=11140).

Figure 2. Distribution of baseline risk and individual treatment effect. Predicted 5-year major adverse cardiovascular event (MACE) risk and absolute risk reduction (ARR) with perindopril–indapamide for all Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) participants (n=11140). NNT indicates number-needed-to-treat.
the most benefit from treatment. Furthermore, providing patients with individualized estimates of treatment effect can enhance knowledge translation and engage patients in shared decision making by raising awareness of their individualized risks and benefits of treatment.32

Furthermore, this individualized approach could replace the sole reliance on BP levels to decide on treatment initiation or intensification. Current guidelines recommend medical treatment of BP values $>140/90$ mm Hg in patients with diabetes mellitus, falsely suggesting that risk suddenly increases when BP reaches this specific cutoff.13,14 Given that the ultimate goal of BP-lowering treatment is to reduce cardiovascular risk, BP levels are best viewed in the broader context of the individual patient’s cardiovascular risk. For example, BP-lowering treatment of a high-risk patient with an systolic BP of 135 mm Hg can produce a large ARR of 1.8%, whereas treatment of a low-risk patient with an systolic BP of 155 mm Hg would result in a small ARR of 0.4% (Table 4). Ideally, this individualized assessment of BP-lowering medication on cardiovascular outcomes would be part of a personalized strategy to manage all major cardiovascular risk factors.

We used net benefit analyses to evaluate the application of treatment effect prediction models in clinical practice. Notably, net benefit does not refer to treatment decisions for specific patients but evaluates the consequences of applying a treatment strategy to a whole population. Selective treatment of patients will inevitably result in a small increase in event rate that is balanced by a reduction in treatment rate. The choice of an appropriate treatment threshold can be difficult. The ADVANCE trial evaluated a combination of 2 drugs at lower dose that was suggested to cause fewer side effects.33 Indeed, active treatment was well tolerated, and the most frequent reasons for study discontinuation were cough (excess risk, 2.0%; 95% confidence interval, 1.4–2.6) and hypotension or dizziness (excess risk, 0.8%; 95% confidence interval, 0.5–1.2).20 Nevertheless, other negative effects of treatment, such as the inconvenience of daily taking a drug and monetary costs, merit consideration. We displayed net benefit across a range of treatment thresholds to allow for a different appraisal of positive and negative effects of treatment. We did not provide confidence limits for the net benefit curves because for medical decision making the point estimates is guiding. That is, even if a certain strategy were better in only 51% of times, this strategy would still be preferable over the

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### Table 3. Group-Level Effect of Selectively Treating ADVANCE Participants Based on a Prediction Score Using Different Treatment Thresholds

<table>
<thead>
<tr>
<th>5-year Threshold NNT</th>
<th>Treatment Strategy</th>
<th>Average 5-y ARR†, %</th>
<th>Average 5-y NNT†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infinite</td>
<td>Treat all</td>
<td>1.1</td>
<td>92</td>
</tr>
<tr>
<td>200</td>
<td>Prediction based</td>
<td>1.2</td>
<td>81</td>
</tr>
<tr>
<td>100</td>
<td>Prediction based</td>
<td>1.7</td>
<td>59</td>
</tr>
<tr>
<td>50</td>
<td>Prediction based</td>
<td>2.7</td>
<td>37</td>
</tr>
</tbody>
</table>

*Percentage of population treated with perindopril–indapamide.
†Predicted average absolute risk reduction (ARR) or number-needed-to-treat (NNT) with treatment in the selected group of patients with a predicted ARR exceeding the decision threshold. ADVANCE indicates Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation.
alternative. For a range of treatment thresholds that might be considered acceptable in clinical practice (ie, threshold NNT, <200), prediction-based treatment was associated with the highest net benefit. If resources would be unrestricted and one is inclined to maximize the number of events prevented regardless of the number of patients that must be treated (ie, threshold NNT, >200), the appropriate strategy would be to treat every patient with T2DM. After stratification by history of macrovascular disease, we observed the largest benefit of prediction-based treatment in patients free from macrovascular disease. This was expected, as a treat-all strategy in this population results in treating many lower risk patients with a small individual treatment effect while being exposed to the disadvantages of treatment. Overall, the net benefit analysis indicates that application of a treatment algorithm in clinical practice can improve the balance between number of events prevented and the number of patients treated if guideline committees agree that an acceptable threshold NNT is <200.

Some limitations need to be considered. First, the analyses and predictions apply to a specific drug regimen of perindopril–indapamide in patients who would be eligible for inclusion. Although the ADVANCE study included a broad range of patients, the presence of ≥1 additional cardiovascular risk factor in addition to T2DM was required, and patients with a definite indication for insulin therapy were excluded. Second, the overall treatment effect on macrovascular events was not significant although the effects on major vascular events, cardiovascular death, and all-cause mortality were. Because the observed macrovascular event rate was lower than expected, this could be because of a lack of power. Also, meta-analyses of angiotensin-converting enzyme inhibitors in patients with diabetes mellitus provide considerable reassurance of a real effect. Third, prediction models are likely to perform optimistically in the sample from which they were derived. Hence, we adjusted estimates of calibration and discrimination for overoptimism by bootstrap resampling. Furthermore, in patients free from macrovascular disease, similar estimates of individual treatment effect were obtained using the UKPDS risk score. Fourth, the net benefit method is not a cost effectiveness analysis because monetary values are not explicitly assigned to positive or negative outcomes. Rather, it provides a framework for comparing treatment strategies that allows both positive and negative consequences to be considered in general terms. Finally, prediction-based treatment might be more burdensome than prescribing treatment to every patient with diabetes mellitus. However, the use of prediction-based treatment in clinical practice can be facilitated by electronic calculators (online-only Data Supplement and accessible through www.vascularegenesiskundeunrheten.nl/calculators). The individual estimates of treatment effect can be displayed graphically and can be used to engage patients in shared decision making at an individual patient level.

Perspectives

Individual patients with T2DM have multiple characteristics that influence the effect of BP-lowering treatment with perindopril–indapamide. A multivariable treatment algorithm can be used to quantify the anticipated patient-specific effect of BP-lowering treatment in terms of absolute risk reduction of major cardiovascular events. Individualized estimates of treatment effect may be used to guide treatment decisions by prescribing treatment to patients who can expect the greatest benefits and withholding treatment for patients with little chance of benefit while being susceptible to the negative effects of treatment.

Sources of Funding

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Disclosures

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References

Individual Effects of BP-Lowering Treatment

van der Leeuw et al


**Novelty and Significance**

**What Is New?**

- This is the first study to quantify the anticipated treatment effect of blood pressure-lowering treatment with perindopril–indapamide for individual patients with type 2 diabetes mellitus in terms of absolute risk reduction of major cardiovascular events and to weigh beneficial effects against potential disadvantages of treatment.

**What Is Relevant?**

- Our findings showed that there is a wide variation in treatment effects across individual patients, ranging from a large 5-year absolute risk reduction of ≥1% (NNT≤100) in 43% of patients to a small 5-year absolute risk reduction of ≤0.5% (NNT≥200) in 17% of patients. These individualized predictions can be used to identify patients who are most likely to benefit from blood pressure-lowering and to spare treatment for patients with little benefit, while being susceptible to the disadvantages of treatment.

**Summary**

A multivariable prediction algorithm derived from randomized trial data can be used to quantify the estimated individual patient’s absolute effect of blood pressure-lowering treatment. These patient-specific effect estimates can be used to guide treatment decisions for individual patients with type 2 diabetes mellitus in clinical practice.
Predicting the Effects of Blood Pressure–Lowering Treatment on Major Cardiovascular Events for Individual Patients With Type 2 Diabetes Mellitus: Results From Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation

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Data Supplement (unedited) at:
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http://hyper.ahajournals.org/content/suppl/2016/04/11/HYPERTENSIONAHA.114.04421.DC2

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Predicting the effects of blood pressure-lowering treatment on major cardiovascular events for individual patients with type 2 diabetes – results from ADVANCE

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\textsuperscript{h} Imperial College London, London, United Kingdom
Data supplement S1. Calculation example of Net Benefit

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Treat no one</th>
<th>Treat everyone</th>
<th>Prediction-based treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year event rate</td>
<td>10.74%</td>
<td>9.75%</td>
<td>9.66%</td>
</tr>
<tr>
<td>Decrease in 5-year event rate</td>
<td>0%</td>
<td>0.98%</td>
<td>1.07%</td>
</tr>
<tr>
<td>Numer of patients treated (%)</td>
<td>0 (0%)</td>
<td>5,569 (100%)</td>
<td>2,407 (43%)</td>
</tr>
<tr>
<td>Net benefit</td>
<td>0%</td>
<td>-0.02%</td>
<td>0.64%</td>
</tr>
</tbody>
</table>

The net benefit method is described in detail by Vickers et al. and is found from weighing the positive and negative effects of treatment and uses observed event rates and treatment rates in trial participants. Here we provide an example of how net benefit is calculated at a specific decision threshold of 1% ARR (NNT$_5$=100) for three different treatment strategies. Similar calculations were repeated at each threshold and for every treatment strategy discussed.

1. The net benefit of treating no one serves as the reference category. The observed 5-year event rate was found from extrapolating the median Kaplan-Meier survival estimator in the placebo arm of the trial. The 5-year event rate was 10.74% at the cost of zero treatment.

2. The net benefit of treating everyone was calculated based on the observed event rate in the intervention arm of the trial. The 5-year event rate was 9.75%. The decrease in of 0.98% compared to the placebo arm was achieved at the cost of treating 5,569 (100%) of patients. At a decision threshold of NNT$_5$=100 we consider that treating 100 patients during 5 years is balanced by the prevention of one outcome. Therefore, net benefit only accrues if at least one event is prevented per 100 treated patients. Net benefit can now be calculated as follows: 0.98% – 100% * (1/100) = −0.02%. The negative sign means that the observed ARR was not sufficient to overcome treatment disadvantages.

3. The net benefit of the prediction-based treatment was based on the observed event rate in patients whose randomized allocation was congruent to the treatment recommended by the model. Patients with a predicted treatment effect of ≥1% ARR were selected from the intervention arm (n=2,407 & 5y risk 15.47%) and patients with a predicted effect of <1% ARR were selected from the placebo arm (n=3,241 & 5y risk 5.35%). The combined observed event rate in this newly assembled group was 9.66% resulting in a decrease in event rate of 1.07% compared to the placebo arm. To achieve this reduction in event rate 43% of patients were treated. Consequently, net benefit was calculated as 1.07% – 43% * (1/100) = 0.64%. Hence, at this specific decision threshold, a prediction-based strategy resulted in a more favourable trade-off between events prevented and number of patients treated.
References

Table S1. Baseline characteristics of ADVANCE participants stratified according to history of major macrovascular disease at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants free from major macrovascular disease (n=7,550)</th>
<th>Participants with previous major macrovascular disease (n=3,590)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n(%)</td>
<td>3521 (47)</td>
<td>1214 (34)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66 (6)</td>
<td>66 (7)</td>
</tr>
<tr>
<td>Asian ethnicity, n(%)</td>
<td>2939 (39)</td>
<td>1303 (36)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>8 (6)</td>
<td>8 (7)</td>
</tr>
<tr>
<td><strong>Blood pressure control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>145 (21)</td>
<td>144 (22)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81 (11)</td>
<td>80 (11)</td>
</tr>
<tr>
<td>History of treated hypertension, n(%)</td>
<td>4878 (65)</td>
<td>2777 (77)</td>
</tr>
<tr>
<td><strong>Other risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking, n(%)</td>
<td>1222 (16)</td>
<td>460 (13)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.3 (1.2)</td>
<td>5.0 (1.2)</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3.1 (1.0)</td>
<td>3.0 (1.1)</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.3 (0.4)</td>
<td>1.2 (0.3)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.6 (1.2 - 2.3)</td>
<td>1.7 (1.2 - 2.3)</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>8.6 (2.8)</td>
<td>8.3 (2.7)</td>
</tr>
<tr>
<td>Serum hemoglobin A1c concentration (%)</td>
<td>7.5 (1.6)</td>
<td>7.5 (1.5)</td>
</tr>
<tr>
<td>Serum hemoglobin A1c concentration (mmol/mol)</td>
<td>58 (18)</td>
<td>58 (16)</td>
</tr>
<tr>
<td>Urinary albumin:creatinine ratio (μg/mg)</td>
<td>15 (7 - 37)</td>
<td>16 (7 - 47)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>75 (63 - 89)</td>
<td>73 (60 - 87)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>98 (13)</td>
<td>100 (13)</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins, n(%)</td>
<td>1627 (22)</td>
<td>1519 (42)</td>
</tr>
<tr>
<td>Aspirin, n(%)</td>
<td>2417 (32)</td>
<td>2477 (69)</td>
</tr>
<tr>
<td>Any oral hypoglycemic drug, n(%)</td>
<td>6848 (91)</td>
<td>3281 (91)</td>
</tr>
<tr>
<td>Insulin, n(%)</td>
<td>118 (2)</td>
<td>41 (1)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (standard deviation), median (interquartile range) or count (percentage); LDL: low density lipoprotein, HDL: high density lipoprotein; eGFR: estimated glomerular filtration rate.
Figure S1. Distribution of 5-year baseline major adverse cardiovascular event (MACE) risk and individual effect of perindopril-indapamide treatment according to history of major macrovascular disease. A. Participants free from major macrovascular disease at baseline (n=7,550) and B. Participants with major macrovascular disease at baseline (n=3,590).
Figure S2. Distribution of 5-year individual effect of perindopril-indapamide treatment using previously developed scores. Absolute risk reductions with treatment in ADVANCE participants free from major macrovascular disease based on the ADVANCE risk engine and UKPDS risk score together with the overall relative risk reduction observed in the trial.
Figure S3. Net benefit of different strategies stratified according to history of major macrovascular disease. Net benefit in ADVANCE participants free from major macrovascular disease at baseline (n=7,550) (left) and in participants with a history of major macrovascular disease at baseline (n=3,590) (right).
Figure S4. Net benefit of prediction-based treatment strategies using previously developed scores. Net benefit based on estimated treatment effect using the ADVANCE risk engine and the UKPDS risk score combined with the overall relative risk reduction of trial in ADVANCE participants free from major macrovascular disease at baseline (n=7,550).
临床试验（摘要）

降压治疗对2型糖尿病患者主要心血管事件的预测作用

来自糖尿病和血管疾病研究的结果: Preterax和达美康缓释片对照评价（ADVANCE）试验

Predicting the Effects of Blood Pressure-Lowering Treatment on Major Cardiovascular Events for Individual Patients With Type 2 Diabetes Mellitus

Results From Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation


赵琳蔚 译 高传玉 审校

降压治疗可降低糖尿病患者的心血管风险，但是效果因人而异。我们试图通过一项大型临床试验确定2型糖尿病患者中哪些患者进行降压治疗的获益最大。在ADVANCE（In Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation，ADVANCE）研究（n=11,140）中，评估个体是否使用培哚普利-吲达帕胺（4/1.25 mg）固定复方制剂治疗的5年不良心血管事件的绝对风险。治疗组和对照组发生不良心血管事件风险的差值即绝对危险度降低率（absolute risk reduction，ARR）。该预测研究基于一个包含人口统计学和临床特征的Cox比例风险模型以及观察到的治疗效果。通过净获益分析比较预测ARR高的选择性治疗患者组的效果和所有患者或血压＞140/90 mm Hg的患者的治疗效果的差异。ADVANCE研究发现，患者的治疗效果存在较大差异。通过计算，43%的患者5年预测ARR＞1%，即5年需要治疗的病例数（5-year threshold number-needed-to-treat，NNT5）＜100，40%的患者5年预测ARR在0.5%–1%（NNT5=100–200），17%的患者预测ARR＜0.5%（NNT5≥200）。以ARR风险预测为基础的治疗可以带来最高的获益，假设5年治疗至多200例患者以防止出现1例不良预后的发生。总之，这个多变量的处理算法可以通过主要不良心血管事件ARR来确定患者个体从降压治疗中获益情况，并可以指导糖尿病合并血压升高患者制订治疗方案。

（Hypertension. 2015;65:115-121.）

心（摘要）

伊伐布雷定可以改善慢性高血压猪模型的左室功能

Ivabradine Improves Left Ventricular Function During Chronic Hypertension in Conscious Pigs

Mario Rienzo, Jonathan Melka, Alain Bizé, Lucien Sambin, Mathieu Jomilat, Jin Bo Su, luc Hittinger, Alain Berdeaux, Bijan Ghaleh

赵琳蔚 译 高传玉 审校

在慢性高血压群体中，增加心率或者肾上腺素能刺激不能引起心脏等容收缩和舒张周期的缩短，进而影响心室的充盈。本实验旨在探究慢性高血压合并左室功能障碍时，伊伐布雷定对急性选择性心率减慢的作用。实验猪进行为期4周的血管紧张素Ⅱ抑制诱导形成慢性高血压模型，并对血管紧张素Ⅱ注射结束后模型的左室功能进行研究。在第0天和第28天分别单剂静脉使用伊伐布雷定，同时注射多巴酚丁胺。我们发现，与猪第0天的基础心率相比，第28天的心率有所升高，但是等容收缩期和舒张期时间并未发生明显变化（分别为57±3 ms，58±3 ms和74±3，70±3），第28天使用伊伐布雷定可使研究对象的心率降低27%，并明显缩短等容收缩和舒张时间，改善心室充盈，同时也可避免因多巴酚丁胺注射引起的心室等容收缩和舒张功能障碍。用起搏器校正心率后，我们发现非心率相关性的机制参与了这个过程。在这个慢性高血压和左室肥厚模型中，我们发现在安静状态或接受肾上腺素能刺激时，使用伊伐布雷定降低心率可纠正急性心率降低带来的心动周期期相上的不良改变，有助于心室充盈。

（Hypertension. 2015;65:122-129.）