Estimated individual lifetime benefit from PCSK9-inhibition in statin-treated patients with coronary artery disease

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Abstract

Objective In statin-treated patients with stable coronary artery disease (CAD), residual risk of cardiovascular events is partly explained by plasma levels of low-density lipoprotein cholesterol (LDL-C). This study aimed to estimate individual benefit of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition in CAD patients already treated with high-dose statin.

Methods Individual lifetime benefit was estimated in months gain free of stroke or myocardial infarction (MI) until age 80. Predictions were based on two competing risk models developed in data from 4,853 patients with CAD originating from the atorvastatin 80 mg arm of the Treating to New Targets (TNT) trial. The relative effect of PCSK9-inhibition was added to the models and was assumed based on average estimates from large clinical trials. We accounted for individual LDL-C levels, assuming 50% LDL-C reduction by PCSK9-inhibition and 21% cardiovascular risk reduction per mmol/L (39 mg/dL) LDL-C lowering.

Results Estimated individual gain was <6 months in 61% of the patients, 6-12 months in 28% of the patients, and ≥12 months in 10% of the patients (median 5, quartiles 2-8 months). Highest estimated benefit was observed in younger patients (aged 40-60) with high risk factor burden, particularly if LDL-C levels were >1.8 mmol/L (>70 mg/dL). Estimated benefit was lowest (≤5 months) in older patients (≥70 years), in particular if LDL-C and other risk factors levels were low.

Conclusion The individual estimated lifetime benefit from PCSK9-inhibition in patients with stable CAD on high-dose statin varied from <6 to ≥12 months free of stroke or MI. Highest benefit is expected in younger patients (age 40-60) with high risk factor burden and relatively high LDL-C levels.

Keywords Individual benefit, lifetime, PCSK9-inhibition, lipid lowering, CAD

ClinicalTrials.gov identifier TNT trial: NCT00327691
KEY MESSAGES

What is already known about this subject?

In statin-treated patients with stable coronary artery disease, residual risk of cardiovascular events is partly explained by plasma levels of LDL-C. With the availability of highly effective but expensive PCSK9-inhibitors, there is a need to identify individual patients who will benefit most from this additional lipid-lowering treatment.

What does this study add?

The present study shows the great interpersonal variation in estimated benefit from PCSK9-inhibition in patients with stable coronary artery disease on high-dose statin, ranging from <6 months to ≥12 months free of stroke or myocardial infarction. Highest benefit is expected in younger patients (age 40-60) with a high risk factor burden and relatively high LDL-C levels.

How might this impact on clinical practice?

These findings may contribute to the discussion which patients with stable coronary artery disease should be eligible for treatment with PCSK9-inhibition. Also, individualized estimation of treatment benefit can be used to inform the patient and contribute to shared decision making on whether or not initiating PCSK9-inhibition on individual patient level.
Introduction

Patients with stable coronary artery disease (CAD) are at risk for developing new major adverse cardiovascular events (i.e. myocardial infarction (MI), stroke, or cardiovascular death), despite optimal secondary prevention according to guidelines.\textsuperscript{1-3} This residual risk is partly explained by low-density lipoprotein cholesterol (LDL-C) levels, even when on high-dose statin therapy.\textsuperscript{1} Recently, results from the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial have shown that Proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibitors attenuate residual risk by substantial additional LDL-C reductions.\textsuperscript{4} Currently, clinicians face the dilemma which patients should be treated with these effective but costly agents.\textsuperscript{5}

An estimation of the anticipated effectiveness derived by PCSK9-inhibition for individual patients can be extrapolated from the expected lipid lowering effect obtained through PCSK9-inhibition (50-60\%\textsuperscript{6}) and the robust relationship between LDL-C reduction and cardiovascular events (HR 0.79 per 1.0 mmol/L LDL-C (or per 39 mg/dL)), which was observed for both statins and ezetimibe, and more recently in the FOURIER study also for PCSK9-inhibition by evolocumab.\textsuperscript{4, 7, 8} This information can be incorporated in recently developed methods to estimate cardiovascular prognosis in individual patients with cardiovascular disease in order to estimate individualized benefit from PCSK9-inhibition.\textsuperscript{9-12}

In the present study we aimed to estimate individual benefit of PCSK9-inhibition in patients with stable CAD on high-dose statin therapy originating from the Treating to New Targets (TNT) trial.\textsuperscript{13} As preventive treatment is often continued lifelong, individual benefit was estimated from a lifetime perspective and expressed in terms of gain in life expectancy free of (recurrent) stroke or MI.
Methods

Study population

The design and results of the TNT trial have previously been published.\textsuperscript{13, 14} TNT was an international clinical trial that enrolled 10,001 men and women aged 35-75 with stable CAD (previous MI, angina with evidence of atherosclerotic coronary disease, or previous coronary revascularization) who had LDL-C levels <3.4 mmol/L (<130 mg/dL) after an open-label 8-week run-in period with atorvastatin 10 mg. Patients were randomized to either atorvastatin 80 or 10 mg daily. For the present analysis, we selected patients aged>40 years allocated to the atorvastatin 80 mg arm. We used the three-month on-treatment visit as starting point, when participants were in steady state on statin treatment. Covariate data were missing on 1% or less of participants and were reduced by single imputation using predictive mean matching (aregImpute-algorithm in R, Hmisc-package) based on other patient characteristics and outcomes.\textsuperscript{15} The TNT trial complied with the Declaration of Helsinki, approval was obtained from institutional review boards and all participants provided written informed consent.

Individual benefit

Individual benefit from PCSK9-inhibition in addition to high-dose statins was estimated based on: 1) Individual relative risk reduction, which estimate was derived from large clinical trial data and dependent on an individual’s LDL-c level; and 2) Individual cardiovascular disease prognosis, which was estimated based on two competing risk models that were derived from individual patient data from the TNT trial.

Individual relative risk reduction
An individual’s relative effect of PCSK9-inhibition was based on the expected LDL-C reduction, which is conditional to the baseline LDL-C level (i.e. on statin therapy). On average, PCSK9-inhibitors reduce LDL-C levels by 50-60%. To prevent overoptimistic estimates of treatment benefit, we assumed a 50% LDL-C reduction in the present study. Large meta-analyses have shown a hazard ratio of 0.79 for major cardiovascular events per mmol/L (39 mg/dL) LDL-C reduction and the results of the FOURIER trial confirm that the effect of PCSK9-inhibition is in line with this. Thus, an individualized relative effect of PCSK9-inhibition was defined as $0.79^{0.5\cdot \text{LDL-C}}$. Such individualized hazard ratios were calculated for each study participant. We assumed no effect of PCSK9-inhibitors on non-cardiovascular mortality (i.e. relative risk of 1).

**Individual cardiovascular disease prognosis**

Generally applied methods to estimate major cardiovascular events (e.g. Cox proportional hazard models) assume that when a patient is censored, the patient remains at risk of the event of interest, whilst in reality the patient may also have died from something else (i.e. non-cardiovascular mortality). Using such methods may result in overestimation of risk for the event of interest, in particular in the setting of lifetime predictions. Therefore, to allow lifetime prediction modeling, we used Fine and Gray competing risk models that account for competing events. These methods were described in detail previously. In short, we developed two competing risk models for cause-specific cumulative incidence, one for major cardiovascular events (stroke, MI or cardiovascular death) and one for non-cardiovascular mortality. We used age as the underlying time function, which allowed us to make lifetime predictions across the age range from the youngest age at study entry to the highest age at study exit. Risk factors in this model were pre-specified and based on a previous risk score in cardiovascular patients and the availability of predictors in TNT. As a result, both models contained the following nine predictors: sex, current
smoking, diabetes mellitus, systolic blood pressure (mmHg), total cholesterol (mmol/L), eGFR (MDRD) squared (umol/L), history of cerebrovascular disease, history of peripheral artery disease, history of abdominal aortic aneurysm. Pre-specified predictors (including the squared terms for eGFR) were chosen as this is likely to increase the external validity of the model compared to a newly developed best fit model. The calculation of lifetime estimates has been described in detail previously. Summarized, beginning at the starting age of each individual, the cumulative survival free of stroke or MI was estimated for each subsequent year. Therefore, the estimated survival free of stroke and MI at the beginning of each life-year was multiplied by the survival probability during that year. The survival probability was obtained by subtracting cardiovascular risk and non-cardiovascular mortality risk (estimated with the cardiovascular model and the non-cardiovascular mortality model respectively) from 1. This was repeated until the age of 80 as there were few observations beyond this age. Continuous predictors were truncated at the 1st and 99th percentile to limit the effect of outliers. The proportional hazards assumption of both models was assessed by testing the correlations between scaled Schoenfeld residuals for each predictor and age.

**Estimation of individual absolute treatment benefit**

Subsequently, the prediction model was used to estimate for each study patient 10-year risk of stroke, MI or cardiovascular death, and survival free of (recurrent) stroke or MI until age 80 (later referred to as lifetime prediction). The added effect of PCSK9-inhibition on survival was estimated by adding the estimated individual relative risk reductions as a coefficient in the competing-risk adjusted model. Individual’s treatment benefit was defined as the estimated improvement of each survival parameter and expressed in months gain in life expectancy free of (recurrent) stroke or MI. In order to draw 95% prediction intervals around individual treatment benefit estimations,
these analyses were repeated in 1000 bootstrap samples from which 95% prediction intervals were derived.

Sensitivity analyses

In TNT, patients were not treated with ezetimibe. It is however common practice to first add ezetimibe before considering PCSK9-inhibition. Therefore, we performed a sensitivity analysis assuming patients were on both high-dose statin and ezetimibe before the initiation of PCSK9-inhibition. We assumed 24% LDL-C reduction by ezetimibe\textsuperscript{21} and an HR of 0.79 cardiovascular risk reduction per 1.0 mmol/L (39 mg/dL) LDL-C lowering.

In a second sensitivity analysis we assumed a lower adherence rate to PCSK9-inhibition. Instead of an adherence rate of 87.5\% as observed in the FOURIER trial,\textsuperscript{4} an adherence of 50\% was assumed which is generally reported for preventive cardiovascular medication.\textsuperscript{22} This resulted in 29\% (compared to 50\%) LDL-C reduction (50\%/87.5\%*50\% LDL-C reduction).

Results

Table 1 shows the characteristics of the study population (n=4,853). On average, patients were 61 (±SD 9) years old and 81\% were male. More than half of the patients (59\%) had a history of MI. In addition to CAD, 5\% of the patients had a history of cerebrovascular disease (transient ischemic attack or stroke) and 12\% had a history of peripheral artery disease. LDL-C levels on atorvastatin 80 mg were on average 1.9 (±SD 0.6) (73 mg/dL ±SD 23) mmol/L and residual 10-year estimated risk ranged from <10\% in 30\% to >30\% in 3\% of the patients (Supplemental Figure 1).

Table 1. Patient characteristics
### TNT participants on atorvastatin 80 mg

(n = 4,853)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>61 (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;50 years</td>
<td>551 (11%)</td>
</tr>
<tr>
<td>Age 50-60 years</td>
<td>1,486 (31%)</td>
</tr>
<tr>
<td>Age 60-70 years</td>
<td>1,928 (40%)</td>
</tr>
<tr>
<td>Age ≥70 years</td>
<td>888 (18%)</td>
</tr>
<tr>
<td>Male sex</td>
<td>3,929 (81%)</td>
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<tr>
<td>Smoking status</td>
<td>635 (13%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>740 (15%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28 (4)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>131 (17)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78 (9)</td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>3,872 (80%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>4,212 (87%)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>3.8 (0.7)</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>1.9 (0.6)</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.2 (0.3)</td>
</tr>
<tr>
<td>eGFR (MDRD) (mL/min/1.73m²)</td>
<td>65 (11)</td>
</tr>
</tbody>
</table>

**Cardiovascular history**
- Myocardial infarction: 2,855 (59%)
- Coronary artery bypass grafting: 2,261 (47%)
- Cerebrovascular disease: 247 (5%)
- Peripheral artery disease: 590 (12%)
- Abdominal aortic aneurysm: 86 (2%)
- Congestive heart failure: 360 (7%)

*All data are displayed as mean (standard deviation) or number (percentage)*

*Individual benefit of PCSK9-inhibition*
The median estimated lifetime benefit from initiating PCSK9-inhibition was 5 months (IQR 2-8) and varied substantially (Figure 1), ranging from <6 months in 61% of the patients to >12 months in 10% of the patients. Table 2 shows patient characteristics stratified for estimated benefit. Patients with highest estimated benefit (≥12 months) were younger (mean age 50 years ±SD 6), had higher LDL-C levels (mean 2.4 mmol/L ±SD 0.7 (93 mg/dL ±SD 27)) and risk factors were more prevalent, i.e. more smokers, diabetes compared to patients with lowest estimated benefit (<6 months) with a mean age of 66 years (±SD 6 years) and an average LDL-C level of 1.8 mmol/L (±SD 0.5 mmol/L) (70 mg/dL ±SD 19). Table 3 shows median expected benefit for subgroups of several combinations of age, LDL-C level and estimated 10-year cardiovascular risk. Highest benefit was seen in middle-aged patients (age 40-60 years), in particular if LDL-C levels were >1.8 mmol/L (>70 mg/dL). Treatment benefits truncated after the first 10 years of treatment turned out to be similar across different age groups (≤8 months). However, the model estimated more benefit in younger patients and those with higher risk and higher LDL-C levels based on 20-year or lifelong predictions.

Supplemental Tables 1 and 2 show the coefficients and age-specific baseline survivals of both the cardiovascular and non-cardiovascular death competing risk models. The proportional hazard assumption was met for the cardiovascular event model. In the non-cardiovascular death model, non-proportionality was observed for current smoking. Therefore, an interaction between age and smoking status was included in this model. Supplemental Figure 2 shows the agreement between the predicted and observed survivals free of stroke or MI in the study population.

Table 2. Baseline characteristics stratified for benefit from lifelong PCSK9-inhibition in terms of months gain free of stroke or MI
<table>
<thead>
<tr>
<th></th>
<th>&lt;6 months gain (n = 2,957)</th>
<th>6-12 months gain (n = 1,323)</th>
<th>≥12 months gain (n = 461)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 (6)</td>
<td>55 (6)</td>
<td>50 (6)</td>
</tr>
<tr>
<td>Male sex</td>
<td>2,274 (77%)</td>
<td>1,150 (87%)</td>
<td>425 (92%)</td>
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<tr>
<td>Smoking status</td>
<td>204 (7%)</td>
<td>259 (20%)</td>
<td>170 (37%)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>385 (13%)</td>
<td>222 (17%)</td>
<td>108 (23%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28 (4)</td>
<td>29 (5)</td>
<td>30 (5)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>131 (17)</td>
<td>129 (16)</td>
<td>129 (16)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77 (9)</td>
<td>79 (9)</td>
<td>80 (10)</td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>2,366 (80%)</td>
<td>1,048 (79%)</td>
<td>363 (79%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>2,568 (87%)</td>
<td>1,167 (88%)</td>
<td>388 (84%)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>3.6 (0.6)</td>
<td>3.9 (0.7)</td>
<td>4.3 (0.8)</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>1.8 (0.5)</td>
<td>2.0 (0.5)</td>
<td>2.4 (0.7)</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.3 (0.3)</td>
<td>1.2 (0.3)</td>
<td>1.1 (0.2)</td>
</tr>
<tr>
<td>eGFR (MDRD) (mL/min/1.73m²)</td>
<td>63 (10)</td>
<td>67 (11)</td>
<td>71 (12)</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1,673 (57%)</td>
<td>808 (61%)</td>
<td>308 (67%)</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>1,435 (49%)</td>
<td>583 (44%)</td>
<td>176 (38%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>116 (4%)</td>
<td>74 (6%)</td>
<td>49 (11%)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>306 (10%)</td>
<td>181 (14%)</td>
<td>73 (16%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>203 (7%)</td>
<td>104 (8%)</td>
<td>36 (8%)</td>
</tr>
<tr>
<td>Estimated 10-year risk of stroke, MI or vascular death (%)</td>
<td>11 (9-15)</td>
<td>12 (10-16)</td>
<td>16 (13-20)</td>
</tr>
</tbody>
</table>

All data are displayed as mean (standard deviation), median (interquartile range) or number (percentage).
Table 3. Estimated individual gain of PCSK9-inhibition in months free of (recurrent) stroke or MI during lifelong, 20-year or 10-year treatment

<table>
<thead>
<tr>
<th>Risk</th>
<th>Initiation age ≥40-&lt;50</th>
<th>Initiation age ≥50-&lt;60</th>
<th>Initiation age ≥60-&lt;70</th>
<th>Initiation age ≥70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lifetime</td>
<td>20 years</td>
<td>10 years</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Risk &lt;10%</td>
<td>LDL&lt;1.8</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>LDL 1.8-2.6</td>
<td>10</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>LDL ≥2.6</td>
<td>14</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Risk 10-20%</td>
<td>LDL&lt;1.8</td>
<td>10</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>LDL 1.8-2.6</td>
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<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>LDL ≥2.6</td>
<td>22</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Risk 20-30%</td>
<td>LDL&lt;1.8</td>
<td>15</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>LDL 1.8-2.6</td>
<td>22</td>
<td>10</td>
<td>3</td>
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<tr>
<td></td>
<td>LDL ≥2.6</td>
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<td>13</td>
<td>4</td>
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<tr>
<td>Risk &gt;30%</td>
<td>LDL&lt;1.8</td>
<td>21</td>
<td>11</td>
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<td>23</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>LDL ≥2.6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Median values were shown based on the estimates in the study population. NA means there were no or only one patients in the study population with this combination of characteristics to derive a reliable median. Importantly, expected benefit is also determined by a patient’s risk of other causes of mortality. For the individual patient, expected benefit should thus be estimated using a calculator and should not be derived from this table. NOTE: as treatment effects were truncated at age 80, in patients aged ≥ 70, the lifetime, 20-year and 10-year predictions are similar. Therefore, only 10-year predictions were shown. For patients aged 60-70, the lifetime and 20-year predictions are similar. Therefore, only 20-year and 10-year predictions were shown. The subgroup of patients aged ≥ 70 consists of patients aged 70-75 due to inclusion inclusion criteria.
**Individual benefit of PCSK9-inhibition: case illustrations**

Patient A is 40 years old and has an estimated 10-year cardiovascular risk of 10% and an LDL-C of 1.8 mmol/L (70 mg/dL) (Figure 2). His estimated gain from lifelong PSCK9-inhibition is 14 months free of (recurrent) stroke or MI (95% prediction interval (PI) 10-20 months), counting only a first recurrent event. For patient E with similar estimated risk and residual LDL-C level but aged 70, this gain would be only 1 month (95%-PI 1-2). Due to her higher age, patient E has shorter remaining life expectancy in which she can benefit from treatment and reduction of cardiovascular event risk will be counterbalanced by competing risks due to non-cardiovascular mortality. If these patients had higher LDL-C levels, i.e. 3.0 mmol/L (116 mg/dL), this would result in higher lifetime benefits of 22 (95%-PI 16-32) months (patient B) and 2 (95%-PI 1-3) months (patient F). The right part of Figure 2 shows examples of high-risk patients, i.e. 25% 10-year risk. Compared to low-risk patients, i.e. 10% 10-year cardiovascular risk, high-risk patients have higher estimated treatment benefit.

**Sensitivity analyses**

The estimated benefit from PCSK9-inhibition when added to statin/ezetimibe combination therapy is less compared to the benefit when added to statin monotherapy (Supplemental Table 3) with a median estimated lifetime benefit of 3 months (IQR 2-6), ranging from < 6 months in 76% to >12 months in 4% of the patients. The sensitivity analysis assuming 50% (instead of 87.5%) adherence rate showed a median estimated benefit of 3 months (IQR 1-5 months), ranging from <6 months in 83% to >12 months in 2% of the patients (Supplemental Table 4).
**Discussion**

In the present study we estimated individual benefit from PCSK9-inhibition in terms of months gained free of (recurring) stroke or MI in statin-treated patients with stable CAD. There was substantial variation in individual estimated benefit ranging from less than 6 months in 61% of the patients to more than 12 months in 10% of patients. On average, estimated lifetime benefit was highest if treatment is initiated in younger patients (aged 40-60) with relatively high risk factor levels and particularly if LDL-C levels were >1.8 mmol/L (>70 mg/dL).

Which patients should be eligible for costly lipid lowering therapy with PCSK9-inhibitors is much debated. Intuitively, clinicians may tend to select patients for PCSK9-inhibition based on level of cardiovascular risk, e.g. patients with cardiovascular disease at multiple locations, or high estimated 10-year risk based on a risk algorithm. Indeed, in the first years after starting treatment this may result in slightly higher treatment benefit than selecting lower risk patients (Table 3). However, as preventive treatment is often continued lifelong, it is more relevant to estimate benefit from a lifetime perspective. Moreover, age itself is an important cardiovascular risk factor as it represents exposure time. Therefore, a short-term high-risk-based approach generally leads to selecting older patients for treatment (generally >60 years of age).\(^\text{19}\) This approach has been questioned, as many patients develop clinically manifest cardiovascular disease before the age of 60.\(^\text{23}\) The present study shows that indeed a risk-based approach may result in suboptimal treatment decisions, as greatest benefit can be achieved by starting treatment in middle-aged patients (aged 40-60) in particular if LDL-C levels are >1.8 mmol/L (>70 mg/dL) (Table 2 and 3). This is explained by the longer life expectancy in which these patients can benefit from therapy. In older patients (>70 years), the estimated benefit was limited, in particular if levels of LDL-C and other cardiovascular risk factor were low. Importantly, if ezetimibe is added before initiation of PCSK9-
inhibition, anticipated treatment benefits are somewhat lower for all subgroups (Supplemental Table 3). Also, lower adherence rates will result in lower treatment benefits (Supplemental Table 4).

What amount of benefit can be considered meaningful is subjective and conditional on several factors including costs, potential side effects and patient preferences. A comparison with benefit from other preventive treatments may contribute to the interpretation of treatment benefit from PCSK9-inhibition. For example, a microsimulation study on statin therapy in individuals without cardiovascular disease showed individualized benefits ranging from 4 to 18 months gain in cardiovascular event-free life expectancy. The patients in this microsimulation study were at relatively low cardiovascular risk (the majority had 10-year risk <20%). Compared with the subgroups at <20% 10-year risk in the present study, our findings are quite similar. Two recent studies evaluated the event-free months gained by aspirin treatment in the primary prevention setting and found small effects ranging from no gain to about 2 months estimated gain for an individual patient. The small effect size is explained by the much lower relative risk reduction of aspirin therapy compared to lipid lowering therapy and the relatively low risk population that was studied. Similar to the present study, all these studies show that expected treatment benefits were highest in younger patients, in particular in the presence of cardiovascular risk factors.

As with all interventions which reduce cardiovascular risk, the individual treatment effect of PCSK9-inhibition needs to be interpreted in the light of other (less costly) interventions for risk reduction, such as life style improvements. For example, smoking cessation may yield more individual lifetime benefit than lipid lowering, as this reduces both cardiovascular and non-cardiovascular mortality. It is evident that such potential life style enhancements need to be taken into account on when considering to prescribe PCSK9-inhibition.
Initiating PCSK9-inhibition in relatively young patients is at the cost of longer treatment. The cost-effectiveness of PCSK9-inhibition in patients with cardiovascular disease has been evaluated.\textsuperscript{26-28} Although PCSK9-inhibition may on average be cost-effective, two studies concluded that to reach cost-effectiveness, the price of PCSK9-inhibitors would need to be reduced substantially. As there is great variation in LDL-C levels and cardiovascular risk among patients with cardiovascular disease (Supplemental Figure 1),\textsuperscript{29} a stratified cost-effectiveness analysis, for example for estimated 10-year risk, may help clarify in which patients the expected benefit of PCSK9-inhibition outweighs costs.

Individualized estimation of treatment benefit can be used to inform the patient and contribute to shared decision making on whether or not initiating PCSK9-inhibition. A benefit-based approach may be adopted in future clinical guidelines for treating the right patient and not prescribing costly treatment to patients with no or limited expected benefit in terms of survival free of stroke or MI.\textsuperscript{11, 12, 25, 30}

Our findings are generalizable to patients with stable CAD similar to the TNT trial population (Table 1). Importantly, as patients with severe comorbidity such as malignancy were excluded, our results apply to relatively healthy statin-treated patients with CAD, with low risk of non-cardiovascular mortality. For patients with CAD with higher expected non-cardiovascular mortality risk, the expected benefit is likely to be somewhat lower as a competing event may prevent long-term benefit of PCSK9-inhibition. Also, patients with familial hypercholesterolemia or with statin intolerance were excluded. As LDL-C levels are likely to be higher in these populations, lifetime benefit may also be larger particularly in those at younger age and if several other risk factors are present.
Strengths of this study are the relevant study population, as well as the individualized benefit approach from a lifetime perspective with adjustments for competing non-cardiovascular mortality. We acknowledge study limitations. Firstly, PCSK9-inhibition is likely to reduce the risk of both the recurrent event and subsequent events. As a result, disregarding subsequent events may result in an underestimation of the effect of this preventive treatment. A second limitation is that the effect of LDL-C reduction on cardiovascular events was extrapolated from meta-analyses (HR 0.79 per mmol/L (39 mg/dL) LDL-C reduction) to patients that already had relatively low LDL-C levels (<1.8 mmol/L (<70 mg/dL)). Since the effect of LDL-C lowering has been shown to be very robust across several subgroups, including lipid subgroups, we think it is unlikely that the effect in lower LDL-C ranges will differ greatly from this estimate.8,31 Nevertheless, future research in patients within lower LDL-C ranges is necessary as we show that in some patients LDL-C lowering may result in substantial benefit even if LDL-C levels are below 1.8 mmol/L (70 mg/dL) (Table 3). Finally, the lifetime estimates go beyond the 4 years of follow-up as observed in the study population. In a previous study it was shown that lifetime predictions based on the applied methods are valid for survival up to 17 years.18 Nevertheless, it could be argued that longer term validation is desirable.

In conclusion, the potential incremental benefit of PCSK9-inhibition varies greatly amongst patients with stable CAD on high-dose statin treatment, ranging from a few months to more than a year gain in life expectancy free of (recurrent) stroke or MI. In general, most benefit can be achieved in middle aged patients (aged 40-60) with relatively high levels of LDL-C and other risk factors. Treatment benefit is expected to be limited in patients ≥70 years, in particular if LDL-C
levels are low. Individualized estimations of treatment benefit may contribute to targeted treatment and shared-decision making on whether or not initiating PCSK9-inhibition in statin-treated patients with stable CAD.
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References


Figure legends

Figure 1. Distribution of estimated individual lifetime benefit from PCSK9-inhibition (in months free of stroke or MI) in stable CAD patients treated with high-dose statin

Figure 2. Individual patient illustrations of estimated benefit from PCSK9-inhibition (months gain free of stroke or MI)