Development and Validation of a Model to Predict Absolute Vascular Risk Reduction by Moderate-Intensity Statin Therapy in Individual Patients With Type 2 Diabetes Mellitus

The Anglo Scandinavian Cardiac Outcomes Trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and Collaborative Atorvastatin Diabetes Study

Lotte Kaasenbrood, MD; Neil R. Poulter, F Med Sci; Peter S. Sever, FRCP, PhD; Helen M. Colhoun, MD; Shona J. Livingstone, MS; S. Matthijs Boekholdt, MD, PhD; Sara L. Pressel, MS; Barry R. Davis, MD, PhD; Yolanda van der Graaf, MD, PhD; Frank L.J. Visseren, MD, PhD; on behalf of the CARDS, ALLHAT, and ASCOT Investigators

Background—In this study, we aimed to translate the average relative effect of statin therapy from trial data to the individual patient with type 2 diabetes mellitus by developing and validating a model to predict individualized absolute risk reductions (ARR) of cardiovascular events.

Methods and Results—Data of 2725 patients with type 2 diabetes mellitus from the Lipid Lowering Arm of the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT-LLA) study (atorvastatin 10 mg versus placebo) were used for model derivation. The model was based on 8 clinical predictors including treatment allocation (statin/placebo). Ten-year individualized ARR on major cardiovascular events by statin therapy were calculated for each patient by subtracting the estimated on-treatment risk from the estimated off-treatment risk. Predicted 10-year ARR by statin therapy was <2% for 13% of the patients. About 30% had an ARR of >4% (median ARR, 3.2%; interquartile range, 2.5%–4.3%; 95% confidence interval for 3.2% ARR, –1.4% to 6.8%). Addition of treatment interactions did not improve model performance. Therefore, the wide distribution in ARR was a consequence of the underlying distribution in cardiovascular risk enrolled in these trials. External validation of the model was performed in data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT; pravastatin 40 mg versus usual care) and Collaborative Atorvastatin Diabetes Study (CARDS; atorvastatin 10 mg versus placebo) of 3878 and 2838 patients with type 2 diabetes mellitus, respectively. Model calibration was adequate in both external data sets, discrimination was moderate (ALLHAT-LLT: c-statistics, 0.64 [95% confidence interval, 0.61–0.67] and CARDS: 0.68 [95% confidence interval, 0.64–0.72]).

Conclusions—ARRs of major cardiovascular events by statin therapy can be accurately estimated for individual patients with type 2 diabetes mellitus using a model based on routinely available patient characteristics. There is a wide distribution in ARR that may complement informed decision making.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00327418 (CARDS) and NCT00000542 (ALLHAT). (Circ Cardiovasc Qual Outcomes. 2016;9:213-221. DOI: 10.1161/CIRCOUTCOMES.115.001980.)

Key Words: cardiovascular diseases ■ decision making, shared ■ diabetes mellitus ■ precision medicine ■ statins, HMG-CoA ■ treatment outcome

Statin therapy is effective in preventing major cardiovascular events in patients with type 2 diabetes mellitus with an average relative risk reduction that is similar to the effect of statins in patients without type 2 diabetes mellitus. Based on this, guidelines recommend statin therapy for most patients with type 2 diabetes mellitus.2,3 In clinical practice, decision making is based on patient characteristics and preferences.2,3

Editorial, see p 191
WHAT IS KNOWN

• Moderate-intensity statin therapy shows a significant relative reduction in risk of cardiovascular events in patients with type 2 diabetes mellitus.

• Individualized absolute effects from statin therapy, instead of average relative effects, are more informative for patients and clinicians and may contribute to shared decision-making as part of personalized cardiovascular medicine.

WHAT THE STUDY ADDS

• There is a wide distribution in 10-year absolute treatment effects of moderate-intensity statin therapy in patients with type 2 diabetes mellitus, ranging from low to high absolute risk reductions.

• The net benefit of applying a prediction model for selective treatment of patients with type 2 diabetes mellitus with a statin is higher than a strategy in which all patients are treated, especially for 10-year numbers willing to treat of ≤50.

• Individualized predicted absolute risk reductions can therefore be used for informed clinical decision-making for statin therapy in patients with type 2 diabetes mellitus.

WHAT IS KNOWN

- Moderate-intensity statin therapy shows a significant relative reduction in risk of cardiovascular events in patients with type 2 diabetes mellitus.
- Individualized absolute effects from statin therapy, instead of average relative effects, are more informative for patients and clinicians and may contribute to shared decision-making as part of personalized cardiovascular medicine.

WHAT THE STUDY ADDS

- There is a wide distribution in 10-year absolute treatment effects of moderate-intensity statin therapy in patients with type 2 diabetes mellitus, ranging from low to high absolute risk reductions.
- The net benefit of applying a prediction model for selective treatment of patients with type 2 diabetes mellitus with a statin is higher than a strategy in which all patients are treated, especially for 10-year numbers willing to treat of ≤50.
- Individualized predicted absolute risk reductions can therefore be used for informed clinical decision-making for statin therapy in patients with type 2 diabetes mellitus.

WHAT IS KNOWN

- Moderate-intensity statin therapy shows a significant relative reduction in risk of cardiovascular events in patients with type 2 diabetes mellitus.
- Individualized absolute effects from statin therapy, instead of average relative effects, are more informative for patients and clinicians and may contribute to shared decision-making as part of personalized cardiovascular medicine.

WHAT THE STUDY ADDS

- There is a wide distribution in 10-year absolute treatment effects of moderate-intensity statin therapy in patients with type 2 diabetes mellitus, ranging from low to high absolute risk reductions.
- The net benefit of applying a prediction model for selective treatment of patients with type 2 diabetes mellitus with a statin is higher than a strategy in which all patients are treated, especially for 10-year numbers willing to treat of ≤50.
- Individualized predicted absolute risk reductions can therefore be used for informed clinical decision-making for statin therapy in patients with type 2 diabetes mellitus.

WHAT IS KNOWN

- Moderate-intensity statin therapy shows a significant relative reduction in risk of cardiovascular events in patients with type 2 diabetes mellitus.
- Individualized absolute effects from statin therapy, instead of average relative effects, are more informative for patients and clinicians and may contribute to shared decision-making as part of personalized cardiovascular medicine.

WHAT THE STUDY ADDS

- There is a wide distribution in 10-year absolute treatment effects of moderate-intensity statin therapy in patients with type 2 diabetes mellitus, ranging from low to high absolute risk reductions.
- The net benefit of applying a prediction model for selective treatment of patients with type 2 diabetes mellitus with a statin is higher than a strategy in which all patients are treated, especially for 10-year numbers willing to treat of ≤50.
- Individualized predicted absolute risk reductions can therefore be used for informed clinical decision-making for statin therapy in patients with type 2 diabetes mellitus.

WHAT IS KNOWN

- Moderate-intensity statin therapy shows a significant relative reduction in risk of cardiovascular events in patients with type 2 diabetes mellitus.
- Individualized absolute effects from statin therapy, instead of average relative effects, are more informative for patients and clinicians and may contribute to shared decision-making as part of personalized cardiovascular medicine.

WHAT THE STUDY ADDS

- There is a wide distribution in 10-year absolute treatment effects of moderate-intensity statin therapy in patients with type 2 diabetes mellitus, ranging from low to high absolute risk reductions.
- The net benefit of applying a prediction model for selective treatment of patients with type 2 diabetes mellitus with a statin is higher than a strategy in which all patients are treated, especially for 10-year numbers willing to treat of ≤50.
- Individualized predicted absolute risk reductions can therefore be used for informed clinical decision-making for statin therapy in patients with type 2 diabetes mellitus.
being easily calculated, having good predictive value for cardiovascular events, and being increasingly recommended in guidelines to be used in clinical practice.18–20 The other 3 predictors were history of cardiovascular events, fasting plasma glucose level, and treatment allocation (statin or placebo). History of cardiovascular events was a self-reported or physicians’ record of overt clinically manifest disease including peripheral artery disease, coronary heart disease, or cerebrovascular disease. In ASCOT, this variable consisted of a history of vascular disease other than coronary heart disease because this was an exclusion criterion. CARDS included a few patients with nonsevere peripheral artery disease. Fasting plasma glucose was chosen because hemoglobin A1c (HbA1c) or details on diabetes mellitus duration were not available in ASCOT and ALLHAT. No additional predictor selection was performed because the predefined predictors were known predictive for cardiovascular disease.21 The outcome of interest was a composite of nonfatal myocardial infarction, nonfatal ischemic or hemorrhagic stroke, and cardiovascular death, which was chosen because this is a clinically relevant outcome and is the most accepted outcome for prediction models in clinical guidelines. In all trials, a total of 1,645 cardiovascular events occurred during a median follow-up of 3.2 years, this was 454 in ALLHAT during 4.5 years, and 172 in CARDS during 4.0 years. To obtain reliable predictions, the baseline survival of the model was estimated at the median follow-up time in ASCOT and extrapolated to 10 years to result in predictions that are consistent with the 10-year time span that is generally applied in clinical guidelines. Linear extrapolation of the baseline hazard was performed, assuming a constant hazard and thus exponential survival over time, which is a reasonable assumption for cardiovascular disease.22 Multivariable effect modification was tested by comparing a model with all interactions between treatment allocation and single predictor to the model without interactions with a likelihood ratio test. No single interactions with treatment effect were tested because previous literature has not displayed any significant heterogeneity in the relative treatment effect between most subgroups examined, suggesting that an interaction between statin treatment and single patient characteristics is unlikely.1 Second, an interaction between baseline cardiovascular risk and treatment allocation was tested in all 3 data sets. Significance levels for likelihood ratio test and interaction terms were set at a P=0.05.

Continuous predictors were truncated at the 1st and 99th percentiles to limit the effect of outliers because outliers may be unrealistic values and may be of such influence to the effect estimates that this limits generalizability of the model to patients outside the derivation data set.21 Linearity of continuous predictors was assessed with restricted cubic splines and transformed if this improved model fit based on Akaïke’s Information Criterion.21 Proportional hazard assumptions were evaluated using scaled Schoenfeld residuals. Missing data were singly imputed using predictive mean matching (aregImpute-algorithm in R, Hmisc-package), assuming these values were missing at random because excluding patients with missing values may lead to bias and loss of statistical power and we did not consider a multiple imputation technique of additional value as we were interested in the predictor coefficients (rather than the uncertainty around the coefficients for which multiple imputation is recommended).21 Moreover, 3 external populations were available based on which we were able to judge the external validity of the developed model. Analyses were conducted with R statistical software V.3.1.0 and V.3.0.1 (www.R-project.org). This article was written in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guidelines (www.tripod-statement.org).21

ARR Calculation

Estimated 10-year risks with and without treatment were calculated for each patient. ARR by statin therapy was calculated by subtracting a patient’s predicted risk on treatment, from the predicted risk on placebo/usual care (ARR=risk off treatment–risk on treatment). Distributions of estimated risk and ARR were shown in histograms. Based on the estimated ARR, a 10-year individualized number needed to treat (tNNT) was calculated (tNNT=1/ARR×100), indicating how many patients with similar characteristics would have to be treated to prevent 1 cardiovascular event.24

External Validation and Net Benefit

The agreement between quintiles of predicted and observed event-free survival (calibration) was shown in calibration plots and formally tested with the Gronnesby and Borgan goodness-of-fit test.23 Discrimination was expressed by c-statistics. Because individualized treatment effects may support the process of shared decision making, we aimed to evaluate the net benefit of using such a prediction model for treatment decisions on a population level. A net benefit analysis, as suggested by Vickers et al.24 was performed for several levels of 10-year numbers willing to treat (NWT) in the pooled validation sets (ALLHAT and CARDS). A 10-year NWT is defined as the amount of patients with type 2 diabetes mellitus that one is willing to treat with a statin for 10 years to prevent 1 major cardiovascular event. The NWT thereby defines the threshold (1/NWT×100=threshold ARR) above which the expected benefit from treatment with a statin is considered to outweigh disadvantages of treatment, such as side effects and costs. The NWT is thus subjective and conditional on disadvantages of 10-year treatment. The prediction-guided treatment strategy was compared with treating no one and treating everyone (Methods in the Data Supplement)

Results

Baseline Characteristics

Baseline characteristics of the study populations are shown in Table 1. Baseline low-density lipoprotein-cholesterol varied with an average of 3.0 mmol/L in CARDS, 3.3 mmol/L in ASCOT, and 3.8 mmol/L in ALLHAT as defined by the inclusion criteria of the trials. The percentage of women was relatively low in ASCOT (23%) and CARDS (32%) compared with ALLHAT (52%), and the average blood pressure was higher in ASCOT than in ALLHAT and CARDS. In contrast to ASCOT and CARDS, the ALLHAT population was ethnically heterogeneous and included the highest proportion of patients with a history of cardiovascular events.

Prediction of ARR by Statin Therapy in Individual Patients

The fitted model and its coefficients and hazard ratios are presented in Figure 1 and Table III in the Data Supplement. The addition of treatment interactions with all predictors did not improve model fit (likelihood ratio test, P=0.76). The relative effect of statin therapy was independent of a patient’s baseline cardiovascular risk in all 3 data sets with P values for the interaction term of 0.89, 0.94, and 0.39 in ASCOT, ALLHAT, and CARDS respectively. The predicted and observed event-free survival showed adequate agreement, as presented in the calibration plots in Figure 2 and supported by nonsignificant Gronnesby and Borgan tests (P=0.33 and 0.42 in ALLHAT and CARDS, respectively). Discrimination was moderate with c-statistics of 0.64 (95% CI, 0.61–0.67) in ALLHAT and 0.68 (95% CI, 0.64–0.72) in CARDS. A sensitivity analysis of the validity of the prediction model in observational data from patients with type 2 diabetes mellitus showed similar performance, with a c-statistic of 0.65 (95% CI, 0.61–0.68), and reasonable calibration (Figure I in the Data Supplement and a Gronnesby and Borgan P=0.37), with a tendency toward overestimation of risk in the higher risk patients and underestimate in lower risk patients (expected/observed ratio 0.74;
Figure 1 in the Data Supplement). Some nonproportionality was observed for the coefficients of sex and fasting glucose ($P=0.03$ and $P=0.02$, respectively), although visual exploration of the residual plots showed reasonable proportionality for both predictors (Figure II in the Data Supplement). Nevertheless, the coefficients for these predictors should be interpreted as the weighted average effect over follow-up. For the other coefficients and the overall model, the proportionality assumption was met.

The median estimated 10-year risk of major cardiovascular events without a statin was 17% (IQR, 13%–23%) in ASCOT, 21% (IQR, 16%–30%) in ALLHAT, and 15% (IQR, 11%–19%) in CARDS (Figure 3). As a consequence of the distribution in cardiovascular risk, the predicted 10-year ARR also varied widely with a median of 3.2% (IQR, 2.5%–4.3%) or a median 10-year iNNT of 31 (IQR, 23%–41%). The 95% CI for an individualized ARR of 3.2% was −1.4% to 6.7% and estimations were most precise for low ARRs (eg, ARR of 1.0%; 95% CI, −0.5% to 2.1%) compared with high ARRs (ARR of 5.0%; 95% CI, −2.2% to 10.7%). ARR by statin therapy was <2% for 13% of the patients with type 2 diabetes mellitus (Figure 3), translating to a 10-year iNNT that

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ASCOT</th>
<th>ALLHAT</th>
<th>CARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=2725</td>
<td>Missing</td>
<td>n=3906</td>
<td>Missing</td>
</tr>
<tr>
<td>Age (y)</td>
<td>64 (8)</td>
<td>66 (7)</td>
<td>62 (8)</td>
</tr>
<tr>
<td>Female</td>
<td>621 (23)</td>
<td>2035 (52)</td>
<td>909 (32)</td>
</tr>
<tr>
<td>Non-white ethnicity</td>
<td>247 (9)</td>
<td>1824 (47)</td>
<td>162 (6)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>600 (22)</td>
<td>501 (13)</td>
<td>631 (22)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>165 (17)</td>
<td>147 (15)</td>
<td>144 (16)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>93 (10)</td>
<td>84 (10)</td>
<td>83 (8)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30 (5)</td>
<td>31 (6)</td>
<td>29 (4)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.4 (0.8)</td>
<td>5.8 (0.7)</td>
<td>5.4 (0.8)</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3.3 (0.7)</td>
<td>3.8 (0.6)</td>
<td>3.8 (1)</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.3)</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 (1.2–2.4)</td>
<td>1.7 (1.2–2.4)</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mmol/L)</td>
<td>4.1 (0.8)</td>
<td>4.6 (0.7)</td>
<td>4.6 (0.7)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>8.5 (2.7)</td>
<td>9.3 (3.7)</td>
<td>9.3 (3.7)</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>98 (17)</td>
<td>86 (25)</td>
<td>86 (25)</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>393 (14)</td>
<td>1171 (30)</td>
<td>97 (3)</td>
</tr>
<tr>
<td>Previous antihypertensive treatment</td>
<td>2290 (84)</td>
<td>3606 (92)</td>
<td>1896 (67)</td>
</tr>
</tbody>
</table>

All data are displayed as mean (SD), median (interquartile range) or n (%). Because of inclusion criteria, in ALLHAT, lipid levels are on average lower in patients with a history of CHD (mean LDL-cholesterol, 3.6 mmol/L or without CHD (mean LDL-cholesterol, 3.8 mmol/L). ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT, Anglo Scandinavian Cardiac Outcomes Trial; CARDS, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

---

### Predicted 10-year absolute risk reduction by statin therapy based on the prediction model

1. Off-treatment risk – on-treatment risk

#### Off-treatment predicted risk

**Prediction model**: $1-0.8423\exp(A)$, where

$A = 0.0395*\text{age in years} - 0.1902*\text{(if female)} + 0.2390*\text{(if currently smoking)} + 0.0017*\text{systolic blood pressure in mmHg} + 0.2539*\text{non-HDL cholesterol in mmol/L} + 0.7655*\text{(if history of cardiovascular disease)} + 0.0465*\text{glucose level in mmol/L} - 4.2627$

#### On-treatment predicted risk

$0.80*\text{predicted risk}$

---

**Figure 1.** Calculation of statin treatment effect on major cardiovascular events for the individual patient with type 2 diabetes mellitus. HDL indicates high-density lipoprotein.
exceeds 50 for 13% of the patients with type 2 diabetes mellitus. Approximately 30% of the patients had an ARR of >4%, which translates to a 10-year iNNT <25.

**Net Benefit**
A translation of the model to clinical practice is shown in Table 2 and the net benefit curve in Figure 4 for a range of 10-year NWT. The treat none line in Figure 4 represents the net benefit of treating no one which is zero for all NWT. For 10-year NWT of <100, the net benefit of using individual predictions for decision making is slightly higher compared with a strategy in which all patients are treated.

**Discussion**
In this analysis of the ASCOT, ALLHAT, and CARDS data, the ARRs of major cardiovascular events by moderate-intensity statin treatment were predicted in individual patients with type 2 diabetes mellitus. Among these trial participants there is a wide range (from 1% to 8%) in predicted treatment effect. Of all patients with type 2 diabetes mellitus, 13% had <2% 10-year ARR (individualized 10-year NNT >50) and about one third of the patients had a 10-year ARR of >4% (10-year iNNT <25). This distribution in individual ARR is a consequence of the distribution in their baseline absolute cardiovascular risk. Depending on the NWT, prediction-guided clinical decision-making results in slightly higher net benefit compared with treating all patients with type 2 diabetes mellitus.

The present findings are consistent with a similar analysis for statin therapy in the primary prevention in patients without diabetes mellitus, in which also a wide variation was found in predicted ARR from statin therapy and the prediction model was associated with a higher net benefit than treating all patients for 10-year NWTs of ≤50. This study shows that these conclusions are also applicable to patients with type 2 diabetes mellitus.

Our findings confirm standard expectations that the relative effect of statin therapy is not affected by a patient’s baseline risk in 3 separate type 2 diabetes mellitus populations despite different risk profiles. This finding of a constant relative effect of statin across risk groups is important because it supports a risk-based approach to select patients with type 2 diabetes mellitus for statin therapy, resulting in highest benefit by treating higher risk patients.

Current clinical guidelines recommend statin therapy for the majority of the patients with type 2 diabetes mellitus. The American Diabetes Association and the American College of Cardiology/American Heart Association guidelines, for example, recommend statin therapy for all patients with type 2 diabetes mellitus aged >40 years. The recent National Institute for Health and Care Excellence guidelines introduce risk estimation in patients with type 2 diabetes mellitus and recommend treatment above a 10-year risk threshold of 10%. The appropriate selection strategy for statin use is currently controversial following the publication of the 2013 American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol. Clearly, clinicians are reluctant to treat all patients regardless of individual characteristics or risk profiles. Individualized estimates of statin treatment effect may be complementary to current guidelines in several ways. First, because adherence to statin therapy is known to be poor, a targeted approach with appropriate informing of the individual patient may improve adherence. Previous studies have shown that communicating individual risk to the patient resulted in marginally better...
control of modifiable risk factors.\textsuperscript{4,35,36} The potential additional value of communicating predicted treatment effects is just an hypothesis which could be evaluated in a future study. Additionally, because recommendations in guidelines are changing toward a more aggressive lipid-lowering treatment strategy for patients with diabetes mellitus,\textsuperscript{3,28} information about the remaining 10-year risk of cardiovascular events if a patient is treated with a moderate-intensity statin (Figure III in the Data Supplement) can be used to discuss the need for further low-density lipoprotein lowering. Based on the presented model incorporated in electronic patient records or by the use of an online calculator, the estimated effect of statin therapy, as well as the on-treatment remaining risk of the individual patient, can easily be calculated and presented to the patient.

If patient selection for statin therapy would be based on the presented prediction model, this is likely to result in higher net benefit than a strategy in which all patients are treated

---

**Figure 3.** Distribution of estimated absolute 10-y risk of major cardiovascular events and treatment effects of statin therapy. **A**, Distribution of estimated absolute risks and individualized treatment effects of statin therapy in Anglo Scandinavian Cardiac Outcomes Trial (ASCOT), Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), and Collaborative Atorvastatin Diabetes Study (CARDS). **B**, Individualized treatment effects in all 9441 patients with type 2 diabetes mellitus.
with type 2 diabetes mellitus. The treatment threshold indicates the percent of absolute risk reduction.

Net benefit decision curve for statin therapy in patients with type 2 diabetes mellitus (Figure 4), especially for 10-year NWTs of ≤50. This gain in net benefit is a result of not treating those patients for whom burdens of taking medicine exceed the potential individual benefit, that is, whose predicted individual benefit of treatment does not exceed the predefined decision threshold. A 10-year NWT of 50 corresponds with initiation of statins in patients whose predicted 10-year risk exceeds 10%. This seems a reasonable threshold when compared with the thresholds of 7.5% to 10% that are applied in current clinical guidelines for primary prevention and even more when compared with the secondary prevention setting, in which NNTs are clearly lower with average 5-year NNTs ranging from 15 to 33, corresponding with 10-year NNTs of 8 to 17. For preventive therapies that are associated with considerably higher NNTs, such as blood-pressure–lowering therapy (5-year NNTs between 80 and 160, corresponding with 10-year NNTs between 40 and 80), previous studies have shown that applying a prediction model may similarly result in higher net benefit compared with a strategy in which all patients are treated.

Importantly, in patients at relatively high risk of cardiovascular events, the net benefit of a prediction-based treatment strategy will be comparable to a strategy in which all patients are treated because high-risk patients are likely to exceed the treatment threshold and therefore all will be treated in both scenarios. Therefore, the additional value of a prediction-based strategy lies in selective treatment of patients in the lower risk groups (not exceeding the treatment threshold). Because of inclusion criteria, all patients in this study populations had at least 1 additional risk factor. In daily clinical practice, however, the risk factor distribution is known to be more favorable (eg, lower levels for blood pressure and lipids and less patients with a history of cardiovascular disease compared with the present study populations). Therefore, the net benefit of the prediction model is likely to be even higher in daily clinical practice in which the prevalence of lower risk patients is higher than in the present study populations.

Some limitations of randomized trials are not overcome with the method presented in this study. First, the choice of predictors was limited by the variables available in the 3 trials. For example, we aimed to include a diabetes mellitus specific predictor. Although other measures of diabetes mellitus regulation, such as HbA1c or diabetes mellitus duration, would have been preferred, fasting glucose is known to be strongly correlated to HbA1c and is predictive for cardiovascular disease. Second, we did not make a comparison with currently existing risk scores. Reasons for this included the fact that risk scores for patients with diabetes mellitus that are currently adopted in clinical guidelines, such as the North American AtheroSclerotic CardioVascular Disease (ASCVD) model, the Joint British Societies 3 (JBS3) calculator, or the British cardiovascular disease risk score (Qrisk) models are not applicable to patients with a history of cardiovascular events, whereas our study aimed to cover a broad population including patients with a history of cardiovascular disease. Also it should be noted that existing prediction models for patients with type 2 diabetes mellitus are known to perform generally moderate, even after recalibration. Moreover, it was recently shown that ARRs estimated with models that are internally developed in trial data result in limited bias compared with predictions based on existing external risk scores, given that the number of events per predictor does not exceed 10. Also the fact that the newly developed model performs well in 2 external validation sets in which the patients differ considerably in baseline characteristics (Table 1) as well as in an observational cohort of patients with type 2 diabetes mellitus (Figure I in the Data Supplement) is reassuring for the generalizability of this model to a broad range of patients with type 2 diabetes mellitus.

Finally, as with all risk models, risk predictions include a variable degree of uncertainty. Highest accuracy was seen for the lower ARRs, for which individualized weighing of benefit and disadvantages of treatment is most relevant. The single imputation methods used in this study might have resulted in some overstatement of this precision. Nevertheless, the estimates made are the best available for each individual and the

<table>
<thead>
<tr>
<th>10-y NWT</th>
<th>Treatment Threshold (in % ARR)</th>
<th>% of Patients Withheld From Treatment*</th>
<th>Mean Tx-Effect (ARR)†, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100</td>
<td>&lt;1</td>
<td>0</td>
<td>3.5</td>
</tr>
<tr>
<td>75</td>
<td>1.3</td>
<td>2</td>
<td>3.6</td>
</tr>
<tr>
<td>50</td>
<td>2</td>
<td>13</td>
<td>3.8</td>
</tr>
<tr>
<td>33</td>
<td>3</td>
<td>53</td>
<td>4.8</td>
</tr>
<tr>
<td>&lt;25</td>
<td>&gt;4</td>
<td>69</td>
<td>5.4</td>
</tr>
</tbody>
</table>

ARR indicates estimated individualized absolute risk reduction; NWT, number willing to treat; and Tx, treatment.

*Percentage of patients that would not be treated with a statin given the 10-year NWT.
†Predicted mean reduction in absolute risk of major cardiovascular events in those patients treated with statin.
uncertainty around that prediction therefore is of less clinical relevance because the point estimate is the most reliable prediction for clinical decision making.

In conclusion, the absolute reduction of cardiovascular risk by moderate-intensity statin therapy and the remaining risk when on statin therapy can be predicted for individual patients with type 2 diabetes mellitus using a prediction model based on trial data. There is a wide range in ARR which is a consequence of the distribution in baseline cardiovascular risk. The approach presented in this article may be of additional value in personalizing cardiovascular medicine in patients with type 2 diabetes mellitus.

Sources of Funding
This work was financially supported by the Stichting Wellendorp-de Goede Fonds, the Netherlands (project 12.095) and by ZonMw, the Netherlands Organization for Health Research and Development (grant No 836011027). The original Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) study was supported by Pfizer, Servier Research Group (Paris, France), Leo Laboratories (Copenhagen, Denmark), and Solvay Pharmaceuticals (Brussels, Belgium). The original Collaborative Atorvastatin Diabetes Study (CARDS) was funded by Diabetes UK, the UK Department of Health, Pfizer UK, and Pfizer Inc (manufacturers of atorvastatin). The original Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study was supported by contract NO1-HC-35130 with the National Heart, Lung, and Blood Institute and study medications were supplied by Bristol-Meyers Squibb (pravastatin), and financial support was provided by Pfizer. For the present study, the above supporting sources had no involvement in study design, analysis, interpretation and writing of the results and decision to submit the report for publication.

Disclosures
N.R. Poulter reports grants and personal fees from Pfizer, personal fees from Roche, personal fees from Agen, personal fees from Menorini, during the conduct of the study; personal fees from Gilead, personal fees from Takeda, personal fees from Novo Nordisk, personal fees from Menorini, personal fees from Pfizer, grants from Agen, personal fees from Takeda, personal fees from Servier, grants from Pfizer, outside the submitted work; and Chairman of the BHS Guidelines and Information Service Working Party Member of Council of ISH. Dr Sever reports receipt of grant for Pfizer for the conduct of ASCOT. Dr Colhoun reports grants, personal fees and other from Pfizer Inc., other from Sanofi Aventis, other from Novartis Pharmaceuticals, other from Eli Lilly & Company, grants and other from Roche Pharmaceuticals, grants from Boehringer Ingelheim, grants from AstraZeneca LP, outside the submitted work. S.L. Pressel reports grants from National Heart, Lung, and Blood Institute, during the conduct of the study. Dr Boekholdt reports having received consultancy fees from Pfizer. The other authors report no conflicts.

References


Development and Validation of a Model to Predict Absolute Vascular Risk Reduction by Moderate-Intensity Statin Therapy in Individual Patients With Type 2 Diabetes Mellitus: The Anglo Scandinavian Cardiac Outcomes Trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and Collaborative Atorvastatin Diabetes Study
on behalf of the CARDS, ALLHAT, and ASCOT Investigators

_Circ Cardiovasc Qual Outcomes_. 2016;9:213-221; originally published online May 11, 2016; doi: 10.1161/CIRCOUTCOMES.115.001980
_Circulation: Cardiovascular Quality and Outcomes_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/9/3/213

Data Supplement (unedited) at:
http://circoutcomes.ahajournals.org/content/suppl/2016/05/10/CIRCOUTCOMES.115.001980.DC1

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Quality and Outcomes_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to _Circulation: Cardiovascular Quality and Outcomes_ is online at:
http://circoutcomes.ahajournals.org//subscriptions/
**Supplemental Methods Net benefit decision curve**

The net benefit decision curve, suggested by Vickers et al., provides the net benefit on group level for several decision-making strategies and for a range of 10-year treatment thresholds. The treatment threshold is the ARR above which the effect of treatment is considered to outweigh disadvantages of treatment, such as side effects and medicalization. For this consideration, a 10-year number willing to treat (NWT) can be defined, expressing the amount of patients that one is willing to treat for 10 years, to prevent one major cardiovascular event. The net benefit on a group level can be increased compared to a strategy in which all patients are treated, by selecting patients that exceed this threshold and not treating those patients for whom burdens of taking medicine exceed the potential individual benefit. Although for statin therapy in patients with type 2 diabetes the 10-year NWT is likely to be high, the NWT may change between guideline makers, health care providers and patients. Therefore the net benefit of ARR-guided treatment decisions was evaluated for several ARR thresholds (thus for several NWTs).

The net benefit represents the balance between benefit and disadvantages of treatment for a specific treatment threshold. The net benefit is calculated as the benefit of treating the subgroup of patients that exceed a predicted ARR treatment threshold, expressed as the decrease in event rate, minus the disadvantages of treatment, expressed as the treatment rate multiplied by the treatment threshold (net benefit = decrease in event rate – treatment rate × treatment threshold, table 2). Since the appropriate threshold may vary between different patients and clinicians, the net benefit was calculated for several treatment thresholds ranging from a 10-year ARR treatment threshold of 0% to 5% (10-year NWT between infinite and 20).

For example, say the 10-year NWT is 50. This means that one is willing to treat 50 patients for 10 years to prevent one major cardiovascular event. The treatment threshold of a 10-year NWT of 50 is 2% (1/50). If this treatment threshold would be applied to all 9,441 study participants, this would result in 87% of the patients being treated with an average ARR on group level of 3.8% (Supplemental table 3). As can be seen from the net benefit curve (figure 3), if a treatment threshold of 2% would be applied on a group level, this would result in similar to slightly higher net benefit than treating all patients.
**Supplemental Table 1. Baseline characteristics of the observational SMART population**

<table>
<thead>
<tr>
<th></th>
<th>SMART (n = 1,758)</th>
<th>missings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>60 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Female (%)</td>
<td>537 (31)</td>
<td>0</td>
</tr>
<tr>
<td>Non-white ethnicity (%)</td>
<td>0 (0)</td>
<td>NA&lt;sup&gt;y&lt;/sup&gt;</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>436 (25)</td>
<td>15 (1)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>146 (21)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>83 (12)</td>
<td>17 (1)</td>
</tr>
<tr>
<td>Body mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>29 (5)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.9 (1.4)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>2.8 (1.1)</td>
<td>164 (9)</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.1 (0.3)</td>
<td>14 (1)</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/l)</td>
<td>1.7 (1.2-2.5)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mmol/l)</td>
<td>3.7 (1.4)</td>
<td>15 (1)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>8.8 (3.0)</td>
<td>13 (1)</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>93 (43)</td>
<td>8 (&lt;1)</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>1207 (69)</td>
<td>72 (4)</td>
</tr>
<tr>
<td>Previous antihypertensive treatment</td>
<td>1344 (76)</td>
<td>0</td>
</tr>
</tbody>
</table>

*All data are displayed as mean (SD), median (interquartile range) or n (%)*

<sup>y</sup> In SMART, no details on ethnicity were available, however most participants are of Caucasian ethnicity
### Supplemental Table 2. Diabetes diagnoses in ASCOT, ALLHAT and CARDS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Applied definition of diabetes mellitus type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASCOT</strong></td>
<td>Self-reported history <em>and</em> receiving any treatment including dietary advice, oral hypoglycemic agents, or insulin. Participants were also considered to have type 2 diabetes if they had a fasting glucose &gt;6.0 mmol/L and a 2 hour value of ≥11.1 mmol/L after a 75 g oral glucose load at baseline.³</td>
</tr>
<tr>
<td><strong>ALLHAT</strong></td>
<td>Plasma glucose &gt;7.8 mmol/L (fasting) or &gt;11.1 mmol/L (nonfasting) or on oral hypoglycemic agents.⁴</td>
</tr>
<tr>
<td><strong>CARDS</strong></td>
<td>WHO criteria 1985: fasting glucose ≥7.8 mmol/L or ≥11.1 mmol/L 2 hours after a 75 g oral glucose load.⁵</td>
</tr>
<tr>
<td><strong>SMART cohort</strong></td>
<td>Self-reported history of type 2 diabetes, use of oral glucose-lowering therapy or insulin, or a fasting plasma glucose ≥7.0 mmol/L with the start of diabetes treatment (dietary advice, weight reduction, or medication) within 1 year from inclusion.</td>
</tr>
</tbody>
</table>
Supplemental Table 3. Model coefficients and HRs

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>LRT</th>
<th>p-value</th>
<th>HR</th>
<th>lower.95</th>
<th>upper.95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>0.0395</td>
<td>14.0</td>
<td>&lt;0.01</td>
<td>1.04</td>
<td>1.02</td>
<td>1.06</td>
</tr>
<tr>
<td>Female sex</td>
<td>-0.1902</td>
<td>1.1</td>
<td>0.30</td>
<td>0.83</td>
<td>0.57</td>
<td>1.19</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.2930</td>
<td>2.4</td>
<td>0.12</td>
<td>1.34</td>
<td>0.93</td>
<td>1.92</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>0.0017</td>
<td>0.1</td>
<td>0.71</td>
<td>1.002</td>
<td>0.993</td>
<td>1.011</td>
</tr>
<tr>
<td>Non-HDL cholesterol in mmol/l</td>
<td>0.2539</td>
<td>6.8</td>
<td>&lt;0.01</td>
<td>1.29</td>
<td>1.07</td>
<td>1.56</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>0.7655</td>
<td>16.8</td>
<td>&lt;0.01</td>
<td>2.15</td>
<td>1.52</td>
<td>3.04</td>
</tr>
<tr>
<td>Fasting glucose in mmol/l</td>
<td>0.0465</td>
<td>2.4</td>
<td>0.12</td>
<td>1.05</td>
<td>0.99</td>
<td>1.11</td>
</tr>
<tr>
<td>Treatment with statin (versus placebo)</td>
<td>-0.2216</td>
<td>2.0</td>
<td>0.16</td>
<td>0.80</td>
<td>0.59</td>
<td>1.09</td>
</tr>
</tbody>
</table>

*LRT: likelihood ratio test; HR: hazard ratio*
Supplemental Figure 1  External calibration in the observational SMART population of 1,758 patients with type 2 diabetes

Predicted and observed event-free survival for major cardiovascular events within quintiles of predicted risk and plotted at the median follow-up time in SMART, Gronnesby and Borgan p-value 0.37, c-statistic 0.65 (95% CI 0.61-0.68).
Supplemental Figure 2 Plotted Schoenfeld Residuals for the predictors sex and fasting glucose
Absolute treatment effect of moderate-intensity statin therapy - Calculation Sheet

*Estimating absolute treatment effects for individual patients with type 2 diabetes mellitus based on the results of randomized clinical trials - results from ASCOT-LLA, ALLHAT-LLT and CARDS*

<table>
<thead>
<tr>
<th>Sex</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>Yes</td>
</tr>
<tr>
<td>History of CVD</td>
<td>No</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>140 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>7.8 mmol/l</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>4.9 mmol/l</td>
</tr>
</tbody>
</table>

**Note:** only apply to patients that are similar to the type 2 diabetes mellitus patients in ASCOT-LLA, ALLHAT-LLT and CARDS.

**10-y risk of major cardiovascular events without treatment**

(3%)

iNNT$_{10}^*$ = 33

*Moderate-intensity statin versus placebo/usual care*

*10-year treatment effect*

**10-year treatment effect**

<table>
<thead>
<tr>
<th>10-year treatment effect*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3%</td>
</tr>
<tr>
<td>15%</td>
</tr>
</tbody>
</table>

**Note:** only apply to patients that are similar to the type 2 diabetes mellitus patients in ASCOT-LLA, ALLHAT-LLT and CARDS.
References


ASCOT Investigators (as published in Lancet 2005; 366: 895–906)


ALLHAT investigators (as published in the ALLHAT rationale: Am J Hypertens 1996;9:342-360)

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000542 (ALLHAT).

Clinical Centers: VAMC Allen Park, Allen Park, MI: James R. Sowers, MD (PI); Martin Berman, DO; Carol E. Bodrie, RN; Elizabeth Jones; Kathy M. Rice. Wade Park VAMC, Cleveland, OH: Eleni I. Pelecanos, MD, MPH (PI); Dorothy Herd, CNP. Memphis VAMC, Memphis, TN: Gale H. Rutan, MD, MPH (PI); Roger G. Smith, MD; Anita W. McKnight, BSN, RN. Miami VAMC, Miami, FL: Barry J. Materson, MD, MBA (PI); Gustavo Godoy, MD; Richard Preston, MD; Mary Healy Smith, ARNP-CS, BSN, MS. Manhattan VAMC, New York, NY: Lois Anne Katz, MD (PI); Mary Keary, RN. Dallas County Health department, Selma, AL: Sherri Nichols, RN (PI); Joan Stewart, RN. The Wellness Plan, Detroit, MI: Marc Keshishian, MD (PI); Richard Miller, MD; Marlene Vaughn, RN. RUSH Prudential HMO, Van Buren Office, Chicago, IL: Vance Lauderdale, MD (PI); Terese Bertucci, RN, MS. RUSH Prudential HMO, Coleman Office, Chicago, IL: Howard Martin, MD (PI); Sandy Gibson, MD; Marie Bosley, RN; Donna Lee Patterson, RN. University of South Carolina, Columbia, SC: G. Paul Eleazer, MD (PI); Carlton A. Hornung, PhD (PI); Davinder Lally, MD (PI); Mya D. Kline. University of South Carolina Medical School, Columbia, SC: Lisa Bethea, MD; Sharm Steadman, PharmD; Mya D. Kline. People's Health Centers, St. Louis, MO: Kelly D. Gage, MD (PI); Betty Kerr, MA, PNP; Elaine Feehan, RN; Clara Scott. UT-HHSC / MS, Houston, TX: Carlos Herrera, MD (PI); Tina Cormier, Research Assistant. West Alabama Health Services, Inc., Eutaw, AL: Sandral Hullett, MD (PI); Glenn Hughes, PhD; Voncelia Hall, LPN. West Alabama Health Services-Greensboro Center #2, Greensboro, AL: Sandral Hullett, MD (PI); Glenn Hughes, PhD; Voncelia Hall, LPN. WAHS-Livingston Health Center, Livingston, AL: Sandral Hullett, MD (PI); Glenn Hughes, PhD; Voncelia Hall, LPN. WorkSite Treatment, New York, NY: Karen M. Johnston, MD (PI); Karen Fuller, BSN. Stoweworkers' Local #3, New York, NY: Karen M. Johnston, MD (PI); Karen Fuller, BSN. University of NV School of Medicine, Las Vegas, NV: Stephen Newmark, MD (PI); Gail Vranesh, RN. West Gastroenterology Group, Inglewood, CA: Timothy e. Simmons, MD (PI); Fred Gletten, MD; Donald Henderson, MD; Adebambo Ojuri, MD; Bisrat Yirgou. Newark Community Health Center, Newark, NJ: Jonathan N. Tobin, PhD (PI); Anita Vaughn, MD (PI); Prabal Ray, MD; Judith Quiles, RN. Bedford-Stuyvesant Family Health Center, Brooklyn, NY: M. Monica Sweeney, MD (PI); Jonathan N. Tobin, PhD (PI); Maria Jaime, RPA. Lyndon B. Johnson Health Complex, Inc., Brooklyn, NY: Jonathan N. Tobin, PhD (PI); Marie Therese DeCastro, MD; Sheila Hood, RN. Osteopathic Health Care Center, Philadelphia, PA: George D. Vermeire, DO (PI); Shirley Combs. PCOM Cambria Street Healthcare Center, Philadelphia, PA: Patrice Taylor, DO (PI). Jackson-Hinds Comp Hlth Care Center, Jackson, MS: Evelyn R. Walker, MD (PI); Adonna James, RN. UCL-King/Drew Medical Center, Los Angeles, CA: Harry J. Ward, MD (PI); Benjamin Scott; Sedonia V. Prets. Mobile Medical and Diagnostic Center, Mobile, AL: Raymond L. Bell, MD (PI); Beverly K. Johnson, RN. Oakhurst Community Health Center, Decatur, GA: Robert Kimbrough, MD (PI); Robert J. Anderson, PharmD; Betsy Redmond, RD. Kaiser Permanente of Georgia, Tucker, GA: Joshua Barzilay, MD (PI); Jeanne Jordan, RN, BSN. Candler Medical Group, Savannah, GA: Joshua C. Bradley, MD (PI); Ray R. Maddox, PharmD. Forest Hill Family Practice, Richmond, VA: Benjamin F. Zambrana, PhD, MD (PI); Kay Zambrana. AHEC Family Practice Center, Pine Bluff, AR: Herbert F. Fendley, MD (PI); Julian Eddie Maples, Jr., RN, RRT. Cardiovascular Physicians, Ltd., Milwaukee, WI: Burton J. Friedman, MD (PI); Barbara Ullsperger. Albert Einstein Hospital, Bronx, NY: William H. Frishman, MD (PI); Suzanne E. Furia, RN, BSN. The Medical Research Center, Inc., Washington, DC: Bruce N. Garrett, MD (PI); Patricia Sullivan, RN, BS. Outreach Health Services, Shubuta, MS: James e. Graham, MD (PI); Cathy Duvall, LPN. University Health
Brooklyn, NY: Samuel Spitalewitz, MD (PI); Alba Correa, RN. Clearwater Cardiovascular Consultants, Largo, FL: Jorge P. Navas, MD (PI); Kay Livingston, RN. Baylor College of Medicine, Houston, TX: Carlos Vallbona, MD (PI); Glori Chauca, MD; Valory Pavlik, PhD. Loma Linda Faculty Medical Offices, Loma Linda, CA: Gregory Wise, MD (PI); Denise Jackson, MD; Leslie Albert, RN. United Hospital, Grand Forks, ND: Richard J. Gray, MD (PI); Kelly Hagen, RN. ALLHAT Clinical Center 084A, Pine Bluff, AR: Martha Ann Flowers, MD (PI); Stacey D. McLemore. UT Southwestern Medical Center, Hypertension Division, Dallas, TX: Norman Kaplan, MD (PI); Patsy Hargrave. ALLHAT Clinical Center 086A, Gahanna, OH: Albert M. Salomon, DO (PI); Marjorie A. Considine. Pulsifer Medical Associates PC, Rochester, NY: David Dobrzynski, MD (PI); Joyce Hackemer, RPA-C The Med / Peds Managed Care Clinic, WBAMC, El Paso, TX.: Andrew C. Quint, MD (PI); Elisabeth Marcus. Valley Medical Group, Bakersfield, CA: Carlos A. Alvarez, MD (PI); Laurie Mitchell, RN. South Carolina Heart Center, Columbia, SC: William Lawrence Schoolmeester, MD (PI); Jacqueline Sheriod, BSN. The Mt. Sinai Medical Center, Cleveland, OH: Joseph P. Frolkis, MD, PhD(PI); Robert L. Haynie, MD, PhD; Pamela Suhun, RN. Beaverton Medical Clinic, Beaverton, OR: Scott W. Falley, MD (PI). Mayo Clinic, Division of Hypertension, Rochester, MN: Daniel J. Wilson, MD (PI); Vincent J. Czanzel, MD; Lois Klein. Cardiology Foundation of Lankenau, Wynnewood, PA: James F. Burke, MD (PI); Heather L. Horton, MD; Bettye Briggs, BSN. Dekalb Medical Specialty Center, Decatur, GA: Charles A. Gilbert, MD (PI); Elaine Furka, RN, CCRN. VAMC Augusta, Augusta, GA: Thomas J. Hartney, MD (PI); Nand McPhail, MD; Thomas J. Hartney, MD. VAMC Baltimore, Baltimore, MD: Bruce P. Hamilton, MD (PI); Mary Dangleis, RN, CRNP. VAMC Kansas City, Kansas City, MO: Thomas B. Wiegemann, MD (PI). VAMC Bronx, Bronx, NY: Clive Rosendorff, MD, PhD (PI); Steven A. Atlas, MD, PhD; Clive Rosendorff, MD, PhD. VAMC Brooklyn #1, Brooklyn, NY: Donald F. Kreuz, MD (PI); Stacy Robinson, RN. VAMC Buffalo, Buffalo, NY: James Lohr, MD (PI); Peggy Gugliuzza, RN. VAMC East Orange, East Orange, NJ: Sithiorn Sastrasinh, MD (PI); Vicky Johnson. VAMC Houston, Houston, TX: Gabriel B. Habib, MD (PI); Florence Chodkiewicz. VAMC Indianapolis, Indianapolis, IN: J. Howard Pratt, MD (PI); Jerrilyn Jones, MSN. VAMC Louisville, Louisville, KY: Vasti L. Broadstone, MD (PI); Eloise Campbell, RN. VAMC Milwaukee, Milwaukee, WI: Mahendr S. Kochar, MD (PI); Gloria Kotecki, LPN. VAMC New Orleans, New Orleans, LA: Vecihi Batuman, MD (PI); Patricia Willhoit, RN, NP. VAMC Kansas City, MO, Kansas City, MO: Santosh Sharma, MD (PI); Cheryl Holt, RN. VAMC St. Louis, St. Louis, MO: David W. Moskowitz, MD (PI); Sharon Carmody. VAMC Washington, DC, Washington, DC: Vasilios Papademetriou, MD (PI); Barbara Gregory, RN. VAMC Alexandria, Alexandria, LA: Jerome M. Sampson, MD (PI); Everett W. Witzel, MD; Janet Schmitt, PharmD. VAMC Battle Creek, Battle Creek, MI: David Hallegau, MD (PI); Michael J. Underwood, MA. VAMC Bay Pines, Bay Pines, FL: Ramon Lopez, MD (PI); Debbie Williams, RN. VAMC Brooklyn #2, Brooklyn, NY: William L. Green, MD (PI); Amal Farag, MD; Estelita Anteola, RN. VAMC Charleston, Charleston, SC: Jan N. Basile, MD (PI). VAMC Dayton, Dayton, OH: Mohammed Saklayen, MD (PI); Anil Kumar MandaI, MD; Helen J. Neff, RN. VAMC Dublin, Dublin, GA: Avinash C. Pradhan, MD (PI); Dianne K. Harrison, RN. VAMC Lake City, Lake City, FL: Girish Bhaskar, MD (PI); Ut Van Tran, MD; Gloria Duren. VAMC Jackson, Jackson, MS: C Andrew Brown, MD (PI); Ardell Hinton, MS. VAMC North Little Rock, North Little Rock, AR: William J. Carter, MD (PI); Miriam Rose Oakum, MD; Kathrine Holland, RNP. VAMC Loma Linda, Loma Linda, CA: Paul G. St. John Hammond, MD (PI); Jan Scott, RN. VAMC Long Beach, Long Beach, CA: Michael A. Weber, MD (PI); Deanna G. Cheung, MD; Gaurang Shah, MD; Eric Bowes. VAMC Minneapolis, Minneapolis, MN: Jordan Holtzman, MD (PI); Denise Finley, RN. VAMC Murfreesboro, Murfreesboro, TN: Rimda Gupta, MD (PI); Regina Cassidy, PharmD. VAMC Nashville, Nashville, TN: Ghodrat A. Siami, MD, PhD (PI); Walter Wilkins, RN. VAMC Northport Medical Services, Northport, NY; Joanne Holland, MD (PI); Christine
Spiller, RN. VAMC Phoenix, Phoenix, AZ: James V. Felicetta, MD (PI); Karen Bowen, RN.
VAMC Richmond, Richmond, VA: Pramod Mohanty, MD (PI); Edie Earley, RN. VAMC
Salisbury, Salisbury, NC: Ronald D. Smith, MD (PI); Valeria Shipp, RN. VAMC-1 San
Francisco, San Francisco, CA: Barry Massie, MD (PI); Elaine Der, RNP. VAMC-2 San
Francisco, San Francisco, CA: Marvin Siperstein, MD (PI); Edward Jai, PharmD. VAMC San
Juan, San Juan, PR: Jose Luis Cianchini, MD (PI); Jean DaMore, RN. VAMC Columbia, SC,
Columbia, SC: Alberto Saenz, MD (PI); Della C. Hart, RN, BSN; Wendy Nicholson, RN,
BSN. VAMC North Chicago, North Chicago, IL: Sant P. Singh, MD (PI); Jen-Chieh Cheng,
MD; Laura Kirkham, RN. VAMC Leavenworth, Leavenworth, KS: Donald L. Courtney, MD
(PI); Marie Cook. VAMC Shreveport, Shreveport, LA: Arthur Chausmer, MD, PhD (PI); Ann
Leitz, RN, MSN. VAMC Pittsburgh, Pittsburgh, PA: Melissa McNeil, MD (PI); Catherine
Kelley, PharmD. VAMC Tampa, Tampa, FL: Raquel Rosen, MD (PI); Nancy Rolbiecki, LPN.
Camden Internal Medicine Associates, PA, Camden, SC: John B. DuBose, III, MD (PI); Dale
S. Barwick, MSN, RN, CS. Raleigh Internal Medicine Associates, PA, Raleigh, NC:
Christopher M. Perkins, MD (PI); James O’Rourke, MD; Lynda E. Seal, RN. Morehouse
School of Medicine, Atlanta, GA: Edward F. Parrish, III, MD (PI); Tim Briscoe, PharmD.
Morehouse Medical Associates, Atlanta, GA: Elizabeth Ofishi, MD (PI); Victoria M. Calhoun,
BSN; Marion Chancellor, RN. E.O. Family Health Center, Inc., Miami, FL: Fatima A. Zafar,
MD (PI); Patricia A. Seabrooks, ARNP, DNSc. Family Practice Group, Pocatello, ID:
Michael S. Baker, MD (PI); Trish Berglund, PA-C New Britain General Hospital, New
Britain, CT: Sandra Raff, MD (PI); James Bernene, MD; Lawrence Koch, MD; Anthony
Lachman, MD; Elizabeth Solano, MD; Diane Bernene, RN; Linda Ciarcia, RN. ALLHAT
Clinical Center 147B, Unionville, CT: Sandra Raff, MD (PI); James Bernene, MD; John
Lawson, MD; Diane Bernene, RN; Linda Ciarcia, RN. ALLHAT Clinical Center 148A,
Shreveport, LA: Byron Andra M. Jackson, MD (PI); Van Cleary, MD; Byron Andra M.
Jackson, MD. Marshfield Clinic, Marshfield, WI: Richard Dart, MD (PI); Dawn David.
Lakeland Center-Marshall Clinic, Minocqua, WI: Richard Dart, MD (PI); Linda Powers,
MD; Jane Carl. MedQuest Research Group, Ocala, FL: Robert L. Feldman, MD (PI); Lynn
Craggs, BS; Veta Page, RN; Mary Standley, RN, BS; Shari Strickland, LPN. Blackstone
Cardiology Associates, Pawtucket, RI; Kenneth A. LaBresh, MD (PI); Elizabeth Burns.
Chinatown Service Center, Los Angeles, CA: Diana J. Lee, MD (PI); Jin Sin Khoo, MD;
Phraphone Insixiengmay, MPH. Koryo Health Foundation, Los Angeles, CA: Diana J. Lee,
MD (PI); Sang Lee, MD; Phraphone Insixiengmay, MPH. T.H.E. Clinic, Inc., Los Angeles,
CA: Diana J. Lee, MD (PI); Marilyn Z. Norwood, RNP; Phraphone Insixiengmay, MPH.
Asian Pacific Health Care Venture, Inc., Los Angeles, CA: Diana J. Lee, MD (PI);
Phraphone Insixiengmay, MPH. The Mary Imogene Bassett Hospital, Cooperstown, NY:
Anne N. Nafziger, MD, MHS (PI); Roberta L. Steere, RN. 1199 Worksite Hypertension
Program, New York, NY: Geoffrey Gibson, PhD (PI); Celia Shmukler, MD; Norma Martinez,
RN. University of South Dakota, Sioux Falls, SD: Angelina Trujillo, MD (PI); Linda
Williams, RN. University Physicians-Rapid City, Rapid City, SD: Angelina Trujillo, MD (PI);
Cindy Needham. Ogden Research Foundation, Ogden, UT: e. Basil Williams, MD (PI);
Cynthia L. Slot, CRe. Southern Drug Research, Inc., Birmingham, AL: Barry K. McLean,
MD (PI); Melinda L. Wainwright; Gail Wingo. Northwestern Medical Faculty Foundation,
Chicago, IL: Martin J. Arron, MD (PI). Erickson Medical Clinic, Park Rapids, MN: Vern E.
Erickson, MD (PI); Karen Benson. Centro Cardiovascular de Caguas, Caguas, PR: Pedro J.
Colon, MD, FACC (PI); Nivea I. Vazquez, BBA. Woodland Avenue Health Center,
Philadelphia, PA: Paul D. Donnan, MD (PI); Michelle Fialkowski, PAe. Columbia Medical
Plan, Columbia, MD: George Gromon, MD (PI); Michael Kelemen, MD; Eileen Brightwell,
BS. University of Arkansas Medical Center, Little Rock, AR: Stephanie L. Lawhorn, MD (PI);
Carol Davison, RN. Southwest Medical Associates, Las Vegas, NV: James W. Snyder, MD
(PI); Barbara Adelman, RN; Janice Christopher, LPN II, CCRe. Cardiovascular Institute of
the South, Lake Charles, LA: Jose A. Silva, MD (PI); Nairn Mahmoud Adli, MD; Luis Felipe
Tami, MD, FACC, FCCP, FACA; Catherine Mary Tami, RN, BSN. Cardiology Clinic of Muskogee, Inc., Muskogee, OK: Yee See E. Onh, MD (PI); Viola Christy, RN. East Side Internists, Inc., Providence, RI: Richard J. Ruggieri, MD (PI); Susan Ruggieri. Sigurds fanners, MD, PC, Hancock, MI: Sigurds fanners, MD (PI); Candace E. Koski Janners, RN, BSN. University of Kansas Medical Center, Kansas City, KS: Brian Friedman, MD (PI); Linda Gerrond, MD; David B. Wilson, MD; Leigh Ann Price, BS. Cardiology Associates, Port Charlotte, FL: Louis D. Rosenfield, MD (PI); Terra McDonald. Christ Hospital Cardiovascular Research Center, Cincinnati, OH: Robert Toltzis, MD (PI); Linda Martin, RN, BSN, MBA. Truman Medical Center UMKC School of Medicine, Kansas City, MO: Nathaniel Winer, MD (PI); Carol Tudor. Atlantic Cardiology Associates, Exeter, NH: Mark 1. Jacobs, MD (PI); Jennifer M. Doane, RN.

UAB / Montgomery Internal Medicine Residency Program, Montgomery, AL: Stephen S. Brady, DO (PI); Theresa L. Dorminey. Howard S. Ellison, MD, PC, Conyers, GA: Howard S. Ellison, MD (PI); Jamie D. Ellison. Maimonides Primary Care, Brooklyn, NY: Andrew Conti, MD (PI). Tatum Family Health Clinic, Gary, IN: David E. Ross, MD (PI); Henedina W. Macababatid, MD; Barbara Johnson, RN, NNP. Medical Diagnostics Center, Indianapolis, IN: John Howard Pratt, MD (PI); Jerrilyn Jones, MSN. The Health Associates, Baltimore, MD: Boris Kerzner, MD (PI); Susan E. Childs, BS, BSN, MS. Winona Memorial Hospital, Indianapolis, IN: Jack H. Hall, MD (PI); Dottie Fausset, MBA, RN; Pam Linden, RN. Faculty-Resident Group Practice, Michael Reese Hospital, Chicago, IL: Kevin E. Hunt, MD (PI); Rosemary Dawkins, RN. Maricopa Medical Center, Phoenix, AZ: William Dachman, MD (PI); Marla Dachman, RN. University of California Davis Medical Center, Sacramento, CA: Charles Whitcomb, MD, FACC (PI); Jennie Robertson.

Colorado Family Medicine, PC, Denver, CO: Constantine J. Tsamasfyros, MD (PI); Laura Clayton. Montefiore Medical Center, Bronx, NY: Janet U. Gorkin, MD (PI); Mark Menegus, MD; Laurie Posner, MD; Linda Solomon. Cardiovascular Medical Specialists, PA, Hollywood, FL: Jonathan R. Jaffe, MD (PI); Lisa Nitzberg, MD. Intermedic Health Center, Port Charlotte, FL: Terence P. Connelly, MD (PI); Denise Eckstein, BSN. DomiMed, Inc., Chamblee, GA: Donald J. Weidler, MD, PhD (PI); Mayra Baez. Morehouse Family Practice Center, Atlanta, GA: Donald J. Weidler, MD, PhD (PI). Lutheran Geriatric Care Services, Fort Wayne, IN: Jerald L. Andrew, MD (PI); Christy Cobbum, MA; Beth Molnar, RN, NP. University of Louisville Hypertension Section, Louisville, KY: Gurdarshan S. Thind, MD, MS, FACP, FACC; Cathy Faughn, CMA. Trover Clinic-Madisonville, Madisonville, KY: Abi V. Rayner, MD (PI); Connie R. Tyler, RN. Trover Clinic-Earlington, Earlington, KY: Abi V. Rayner, MD (PI); Connie R. Tyler, RN. Wyman Park Medical Associates, Baltimore, MD: Naomi R. Feldman, MD (PI); Loretta Vogtman, LPN. Good Samaritan Hospital, Inc., Baltimore, MD: Duncan Salmon, MD, FACC (PI). HealthSpan Health Systems Corporation-United Family Health Center, Minneapolis, MN: Katherine F. Guthrie, MD (PI). ALLHAT Clinical Center 203A, Silver Spring, MD: Ravi Passi, MD (PI); Anita Passi. Kenneth H. Williams and Associates, Baltimore, MD: Kenneth H. Williams, MD (PI); Barbara Socha, MD; Kenneth H. Williams, MD. Deaconess Central Hospital, St. Louis, MO: Madan Chilappa, MD (PI); Dannielle Corboy, PharmD: Cheryl Miller, PharmD. Bellevue Hospital Center-Ambulatory Care Practice, New York, NY: Richard I. Levin, MD, FACP, FACC (PI). New York Downtown Hospital, New York, NY: Ira C. Schulman, MD (PI); William J. Cole, MD; KellyAnn Mele, RN. Bellevue Hospital Center-Met Plan, New York, NY: Stuart A. Dickerman, MD (PI); Andre Neusy, MD; KellyAnn Mele, RN. Valley Medical Center, Ketterillg, OH: Meenakshi Patel, MD (PI); Jill Blum, RN. Ringrose Clinic, Inc., Guthrie, OK: Robert E. Ringrose, MD (PI); Laura Parham. Altus Medical and Surgical Clinic, Altus, OK: Joe Leverett, MD (PI); Sharon Van Pelt, LPN. Cardiology Associates of Johnstown, Johnstown, PA: Charles J. Oeschwald, MD, FACC (PO); Amanda Boring, EMT. Lancaster Heart Foundation, Lancaster, PA: Seth J. Worley, MD, FACC (PI);
Linda Burkhardt, RN. *Family Medicine, Brent Clark, MD, Pittsburgh, PA: Brent Clark, MD (PI), Sant Ram Medical Associates, West Grove, PA: Deepak Sant Ram, MD (PI), Family Medical Center, Johnstown, PA: Michael Tatarko, Sr., MD (PO; Jeanne Spencer, MD; Loretta Nagy, LPN, Vinco Medical Center, Conemaugh, PA: Michael Tatarko, Sr., MD (PI); Patty Allbaugh, RN. Ebandjief Medical Center, Nanty Glo, PA: Michael Tatarko, Sr., MD (PI); Jean Marie Koh, MD. Associates in Diagnostic Internal Medicine, Pittsburgh, PA: Peter P. Tanzer, MD (PI); Roberta A. Mueller, RN. Cardiology Outpatient Clinic-University of Pittsburgh, Pittsburgh, PA: Galal M. Ziady, MD (PI); Deborah Dongilli, BSN. Excelsior Medical Clinic, Sumter, SC: Joseph C. Williams, MD (PI); Beverly Hill, Medical Assistant. Memphis Medical Specialists, Inc., Memphis, TN: Howard W. Marker, MD (PI). University of Texas Health Center at Tyler, Tyler, TX: David R. Shafer, MD (PI); Barbara Hiltischer, RN. Consultants in Medicine, Inc., PS, Bellingham, WA: Grant E. Deger, MD (PI). University of Arkansas for Medical Sciences Diabetes Clinic, Little Rock, AR: Vivian A. Fonseca, MD, MRCP (PI); Janet Hinson, RN. Howard University Hypertension and Lipid Clinic, Washington, DC: Tamrat M. Retta, MD, PhD (PI); Otello S. Randall, MD; Shichen Xu, MD; Tamrat M. Retta, MD, PhD. Internal Medicine Associates, Washington, DC: Jerry M. Earll, MD (PI), Hypertension Center, Medical Center of Delaware, Wilmington, DE: William E. Miller, MD (PI); Matthew Burday, DO. Palm Beach Center for Clinical Investigation, West Palm Beach, FL: Lee A. Fischer, MD (PI); Holly Hadley, MD; Pearlie Singleton. Uchenna A. Okoronkwo, II, MD, PC, Oakland, CA: Uchenna A. Okoronkwo, II, MD (PI); Jerryn Dunmore. LSU Clinics, New Orleans, LA: Henry Rothschild, MD, PhD (PI). LSU Hypertension Research Clinic, New Orleans, LA: M. Eileen Cook, MD (PI); Nancy Bark, BS. Acadian Cardiology, Lafayette, LA: Vernon A. Valentino, MD (PI); Traci Qualls, RN, BSN. Androscoggin Cardiology Associates, Auburn, ME: Robert J. Weiss, MD, FACC, FACP (PI); Carol Ridley, RN. Hahnemann University Hospital, Philadelphia, PA: Steven P. Kutalek, MD, FACC (PI); Christina Ann Baessler, RN. Chapel Hill Internal Medicine, Chapel Hill, NC: Paula F. Miller, MD (PI). United Hospitals Medical Center, Newark, NJ: Aloysius B. Cuyjet, MD, FACC (PI); Thelma Allen Stich, MS, RNC, CS, CDE. Family Practice Center, Columbus, GA: Michael F. Walsh, MD (PI); S. Troy Smith, PharmD. MSU-KCMS Internal Medicine, Kalamazoo, MI: Anne Cavanagh, MD (PI); Kathy S. Church, BSN, CEN. ; Danny M. Anderson, MD, Inc., Sonora, CA: Danny M. Anderson, MD (PI); Judith Joy Bogness, MD; Linda B. Johnson, LVN. St. Thomas Medical Group, Nashville, TN: Mark C. Houston, MD (PI); Laurie Hays, RN. Heart Center of Salt Lake, Salt Lake City, UT: J. Joseph Perry, MD (PI); Wendy Schvaneveldt, RN. Central North Alabama Health Services, Inc., Huntsville, AL: Ronald M. Wyatt, MD (PI); Deborah Degree, RN, BS. Bernard M. Sklar, MD, Inc., Alameda, CA: Bernard M. Sklar, MD (PI); Maile C. Matier, MS, FNP. Knoxville Cardiology Associates, Alcoa, TN: Alan Lee Smuckler, MD (PI); Jamie E. Etherton, RN. Knoxville Medical Group-Knoxville, Knoxville, TN: Lee R. Dilworth, MD (PI); Jamie E. Etherton, RN. Talladega Internal Medicine, Pch, Talladega, AL: Simon Gebara, MD (PI); Gina Bliss, RN. Clinical Hypertension Center, Los Angeles, CA: Vincent DeQuattro, MD (PI); L. Julian Hayward, MD; DePing Lee, MD. Brevard Cardiology Group, Merritt Island, FL: Khalid H. Sheik, MD, FACC (PI); Eugene Kileleavy, MD, FACC, Terri Henegen, RN. Washington County Internal Medicine, Pch, Sandersville, GA: William Rawlings, MD (PI); Wentzelle Kim Kitchens, MD; Jean Rawlings Sumner, MD; Jessica Heldreth, LPN. Family Practice Center Comprehensive Medical Corporation, Indianapolis, IN: David L. Fryman, MD (PI); Neeta O’Mara, PharmD. Goel Medical Corporation, Merrillville, IN: Harish A. Shah, MD (PI); Arun Goel, MD; T. Nguyen, MD; Kari Smith, RMA. The Heart Clinic PA, Kansas City, KS: Nalini G. Premisring, MD (PI); Kirit Masrani, MD; Rita Brown, PA. Kaiser Landover Center, Landover, MD: John S. Golden, MD (PI); Valerie Walls. ALLHAT Clinical Center 256A, Bridgewater, NJ: Alexander B. Kudryk, MD (PI); Fred M. Tepper, MD. ALLHAT Clinical Center 257A, Mount Holly, NJ: R. Bruce Denniston, MD, FACP(PI); Annette Pagano, RN. University of Washington, Seattle, WA: Allan J. Ellsworth.
PharmD (PI). Denmark Medical Center, Denmark, SC: Monnieque Singleton, MD (PI); Barbara Boineau, MOT. Family Medical Center, Charleston, SC: C. Wayne Weart, PharmD, FASP, BCPS (PI); Teresa Price. The Frist Clinic, Nashville, TN: Byron Haitas, MD (PI); Cynthia A. Borum, BSN. Illinois Center for Clinical Trials, Chicago, IL: Glen A. Sussman, PhD (PI); Seth Tannenbaum, MD; Leslie Zun, MD, MBA, FACEP; Kathleen Colombo, BSN. North General Hospital, New York, NY: Myo Maw, MD (PI); Karen Adamson, MD. Charles F. Scott, MDPC, East Point, GA: Charles F. Scott, MD (PI); Cynanthia Crowley, MA. Memorial Medical Center, Savannah, GA: Lloyd S. Goodman, MD (PI); Theodora L. Gongaware, MD; Nasser Mikhail, MD; Donna Tuten, RN. Simon-Williamson Clinic, Pts, Birmingham, AL: Richard Fuller, MD (PI); Marla Harper, RN; James Richard Kilgore, PA. Indianapolis Cardiovascular Research Office, Indianapolis, IN: Bradley A. Weinberg, MD (PI); David Quinn, CCRN. East Carolina University School of Medicine, Greenville, NC: Mark D. Darrow, MD (PI); Elizabeth A. Mahoney, PA. Selma Medical Associates, Winchester, VA: Randolph H. Renzi, MD (PI); Linda Stollings, RN. Naval Medical Center San Diego, San Diego, CA: Hollace D. Chastain, II, MD (PI); Ker Boyce, MD. Thomas A. McKnight, MD, PC, Fremont, NE: Thomas A. McKnight, MD (PI); Jean K. Schaefersman, CMA. ALLHAT Clinical Center 27SA, Philadelphia, PA: Pasquale F. Nestico, MD (PI); Amy Signell. Mobile Diagnostic Center, Mobile, AL: Thomas A. Kessler, MD (PI); Nancy P. Wettermark. Truman Medical Center-East, Kansas City, MO: Diane M. Harper, MD (PI); Roberta L. o'Kelly, BA. Ong Medical Center, Oxon Hill, MD: Stephen T. Ong, MD, MPH (PI); Debbie Clements, Clinical Supervisor. St. John Family Practice, St. Petersburg, FL: Hugo A. St. John, MD (PI); Teresa St. John, BSN. Internal Medicine Center of Akron, Akron, OH: Joseph A. Finocchio, MD (PI); Irene Chenowith, MD; Norma Durbin, RN, BSN. UMDNJ-New Jersey Medical School, Newark, NJ: Maya P. Raghuwanshi, MD (PI); Lester Muhammad. Beaumont Internal Medicine Associates PA, Beaumont, TX: Carlos Arroyo, MD (PI) Judy Freeman. VAMC East Orange, East Orange, NJ: Suat Akgun, MD (PI); Eileen Moser, MD; Linda Condit, RN. VAMC Danville, Danville, IL: William Marshall, MD (PI); Richard Jones, PA. VAMC Las Vegas, Las Vegas, NV: Gopal Das, MD (PI); Carol A. King, DrPH. VAMC Albany, NY, Albany, NY: James T. Higgins, MD (PI); Robert Garris, PharmD; J.B. Goss, RPh; Kerry Johnston, RPh; Michael Levin, MD; Marc Stern, MD; Julie Hassenfeld, BA. VAMC Providence, Providence, RI: Satish Sharma, MD (PI); Elizabeth Coccio, RN. VAMC Batavia, Rochester, NY: Thomas Pingree, MD (PI); Rebekah Loy, PhD. VAMC Marion, Marion, IL: Mohammed Mansuri, MD (PI); Shaheda Mansuri, MD; Melissa Guess, RN. VAMC Des Moines, Des Moines,
IA: Russell Glynn, MD (PI); Beth Hargens, RN. VAMC Salt Lake City, Salt Lake City, UT: Rajat Kaul, MD (PI); Jeanie O'Donnell, MSN. VAMC Fargo, Fargo, ND; Kushal Handa, MD, BSc (PI); Twila Keim, BS. VAMC Decatur, Decatur, GA: W. Virgil Brown, MD (PI); Anh Le, MD; M. Martinez-Maldonado, MD; Luis Pimentel, MD; Mary Ellen Sweeney, MD. Cleveland Clinic Florida, Ft. Lauderdale, FL: Jerry O. Ciocon, MD, FACP, FAC, AGSF (PI); Gregory Cohn, MD; Lori Blanco, RN. Sinai Hospital, Center for Cardiovascular Research, Detroit, MI: Nicholas Z. Kerin, MD (PI); Kathy Faitel, RN, BSN. Diabetes and Metabolism Associates, APMC, New Orleans, LA: Jonathan K. Wise, MD, FACP (PI); Skye N. Noble, LPN. I.B. Price, MD, PA, Quincy, FL: Ira B. Price, MD (PI); Patricia Walden. Family Practice Center, Ottumwa, IA: Robert H. Schneider, MD (PI); Veronica Butler, MD; Linda Hoffman; Joyce Horan, LPN. Family Practice Residency Florida Hospital, Orlando, FL: David G. Pocock, MD (PI); Karen L. Kunding, RN, BSN. Marc S. Posner, MD, PA, Baltimore, MD: Marc S. Posner, MD (PI); Cyndy Compton. ALLHAT Clinical Center 302A, Portsmouth, VA: Doris M. Rice, MD (PI); Bonnie Stadtler. Deaconess Research Institute, Billings, MT: Stuart J. Ruben, MD (PI); Connie D. Hamilton, RN. Medicine 11 Clinic E.A. Conway Hospital, Monroe, LA: Barbara Beard, DO (PI); Tammy V. Jones, DO; Regena Trichell. Springfield Medical Center, Panama City, FL: Misal Khan, MD (PI); Sandra Fernandez. Cardiology Consultants, Pensacola, FL: Brent D. Videau, MD (PI); Elizabeth Stock; Terri Wilcox, RN. The Bowling Green Study Center, Bowling Green, OH: William E. Feeman, Jr., MD (PI); Gwenda Sue Schroeder. Comprehensive Adult Risk Evaluation (CARE), Oakland, CA: General K. Hilliard, MD (PI); Barbara Holmes, MA. David A. Jolivet, MD, PA, Houston, TX: David A. Jolivet, MD (PI); Monica Brizuela. Temple University School of Medicine, Philadelphia, PA: David S. Kountz, MD, FACP (PI); Margot Boigon, MD; Michael Jacobs, PharmD; Nancy Moffatt, MSN, CRNP. Health Care Plan Inc., West Seneca, NY: Brian D. Snyder, MD (PI); Kelly Thomas, RN. Eastwick Medical Associates, Philadelphia, PA: Donald Fox, MD (PI); Robert A. Centrone, DO; Steven A. Feinsteinst, MD; Harvey A. Soifer, DO; Marie T. Cipollone, MT. Andre K. Artis, P.C, Gary, IN: James E. Carter, Jr., MD (PI); Mary Hutchinson. Warrior Family Practice, Tuscaloosa, AL: H. Joseph Fritz, MD (PI); Carolyn S. Buford, LPN.

ALLHAT Clinical Center 318A, New York, NY: Mahshid Arfania Assadi, MD, FACP (PI); Cyrus Assadi, MD. Union Diagnostic Clinic, St. Louis, MO: Francois R. Charles, MD (PI); Mary L. Gregory, DA. University of Arizona, Tucson, AZ: Charles Y. Lui, MSc, MD, FACC, FACA (PI); Sharon Snyder, RN, MS. Family Medicine Clinic, PC, Onawa, IA: Curtis A. Mock, MD (PI); Rhonda R. Gibson, RN, BS. MacNeal Center for Clinical Research, Berwyn, IL: Charles J. Bareis,
MD (PI); Robert J. McNally, Jr., RN, BSN; Teresa Flegel, RN, BSN. *Gunnar Medical Group, Chicago, IL:*
Charles J. Bareis, MD (PI); Peter P. Mayock, MD; Robert J. McNally, Jr., RN, BSN. *Tri-County Emergency Medical Services Inc, Hartville, OH:*
Jean A. Lang, DO(PI); Thomas A. Gibbs, DO; Pamela Blankenship, MA, CPT. *Herman Rose, MD, PA, Fort Worth, TX:*
Herman Rose, MD, FACP (PI); Maxine Pickard. *Drs. Samuels and Huddleston APMC, Chalmette, LA:*
Bruce S. Samuels, MD (PI); Andre G. Smith, LPN. *Athens Internal Medicine, Athens, AL:*
Nauman Qureshi, MD (PI); Theresa Tucker, RN. *Doctors Diagnostic Center, Minneapolis, MN:*
David A. Berman, MD (PI); Diane Crimmins, RN, CCRN. *ALLHAT Clinical Center 328A, Buffalo, NY:*
Joseph L. Maddi, MD (PI); Johanna Canney, RN. *Summit Cardiology Associates, Inc., Cuyahoga Falls, OH:*
Alfred L. Narraway, DO, FACC (PI); Stephen L. DiBlasi, DO; Karen S. Kutomoski, DO; Mary L. Hughes, RN, PA-C. *Bethesda Family Practice, Cincinnati, OH:*
John G. O’Handley, MD (PI); Beth Akridge, RT. *Lawrence J. Misko, MD, Inc., Glendora, CA:*
Neil E. Doherty, III, MD (PI); Vivian Doherty, RN, MSN. *East Bay Cardiology Medical Group, San Pablo, CA:*
Gary B. Marcus, MD, FACC, FACP (PI); Brenda Perry, RN, MS, NP. *Falmouth Cardiology Associates, PC, Falmouth, MA:*
Thomas Sbarra, MD (PI); Catherine M. Geary, MSN, RN, CS. *UCI Heart Disease Prevention Program, Irvine, CA:*
Nathan D. Wong, PhD (PI); David Abrahamson, MB, BCh, FACC; Julius M. Gardin, MD, FACC; Jonathan M. Tobis, MD; Richard Willner, MD; Sheila Deakin, RN. *Napa Valley Cardiology, Napa, CA:*
Dale R. Stemple, MD, FACC (PI); Dan Lyle, RN. *Eastland Medical Primary Care, Bloomington, IL:*
Galen F. Weaver, MD, FACP (PI); Karen Nenne, RN. *Ben Taub General Hospital, Houston, TX:*
Horacio J. Adrogue, MD (PI); Debby S. Verrett. *Cardiovascular Laboratory, Ryder Memorial Hospital, Humacao, PR:*
Maria L. Rios, MD (PI); Marisol Rios. *Primary Health Care Practices PC, Macon, GA:*
William E. May, MD, FACP (PI); Caroline D. Martin, BA, MBA. *Michigan Medical Specialists PC, Grand Rapids, MI:*
Marian E. Oleszkowicz, MD (PI); Kyle A. Rasikas, MD; Barb Fritsma, LPN. *Lionel B. Katchem, DO, PC, Ontario, CA:*
Lionel B. Katchem, DO (PI); Arlene J. (Penny) Katchem. *ALLHAT Clinical Center 346A, New York, NY:*
Eduardo L. Pignanelli, MD (PI); Minucha Ferreira-Montesino. *Center for Family Medicine, Greenville, SC:*
Palmira S. Snape, MD (PI); Eva G. Darr, PharmD, BCPS. *Richmond Area High Blood Pressure Center, Richmond, VA:*
Dean e. Williams, MD (PI); Brian Rojas, NREMT-P; Linda Camplong, BA, MPH. *Howard S. Yager, MDPC, Atlanta, GA:*
Howard S. Yager, MD (PI); Faye Yager. *Stevens Cardiology Group, Edmonds, WA:*
Stephen R. Yarnall, MD, FACC (PI); Angelika Micketti, CMA. *Goshen Medical Center-Plainview Site, Rose Hill, NC:*
Francisco Becerra, MD (PI). *SUNY-HSC at Syracuse, Syracuse, NY:*
Gunnar H. Anderson, Jr., MD (PI); Nancy D. Blakeman, BSN. *New York Methodist Hospital, Brooklyn, NY:*
C.V. Ramana
Reddy, MB, BS (PI); Thayyullathil Bharathan, MD; Muthuswamy Krishnamurthy, MD, FACP; Manohar R. Angirekula, MD, UHSCOM, Kansas City, MO: Anthony Dekker, DO (PI); J. Lewis Alderman, PhD; Matt Furman, BA. UHSCOM-Excelsior Springs, MO, Excelsior Springs, MO: Anthony Dekker, DO (PI); James LaSalle, DO. Pitman Internal Medicine Associates, Pitman, NJ: Michael A. Farber, MD (PI); Lewis John DeEugenio, MD;

CARDS investigators (as published in the original CARDS paper: Lancet 2004; 364: 685–96)

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00327418 (CARDS).

Aberdeen Royal: J Broom; Studholme Medical Centre, Ashford: S Butt, K Tang; The Surgery, Ayr: B Lennox; Ayr Hospital: A Collier; Beehive Surgery, Bath: J Hampton; Oldfield Surgery, Bath: T J Harris, GD Walker; Pulteney Street Surgery, Bath: P J Tilley; Royal United, Bath: J Reckless; St Chad’s Surgery, Bath: E J Widdowson; St James’ Surgery, Bath: I M Orpen; Belfast City: M S Fetherston, J R Hayes; Royal Victoria, Belfast: D R McCance; Medical Centre, Chelmsley Wood, Birmingham: D M Allin; Birmingham Heartlands: P Dodson; Queen Elizabeth, Birmingham: U Martin; Synexus Limited, Birmingham: G S Jassal, M Salman; Bolton Diabetes Centre: J Dean; Bottreaux Practice, Boscastle: G D Garrod, C Jarvis; Royal Bournemouth: S Egan, D Kerr; St Alban’s Medical Centre, Bournemouth: I Nelemans; Health Centre, Bradford on Avon: J S Heffer; Frenchay, Bristol: C J Burns-Cox, V J Parfitt; Addenbrookes, Cambridge: M J Brown; Synexus Limited, Cardiff: C Godfrey, G L Newcombe; St Helier, Carshalton: J Barron; Aspire Research Limited, Chesterfield: M Blagden; Rowden Surgery, Chippenham: R M C Gaunt; Porch Surgery, Corsham: A Cowie; Coventry & Warwickshire: E Hillhouse; Bridge Medical Centre, Crawley: A L Cooper; Pound Hill Surgery, Crawley: N W Jackson; Derby City: R. Donnelly, A R Scott; Dewsbury District: T Kemp, C Rajeswaren; St James’, Dublin: J Nolan; Dumfries & Galloway Royal: J R Lawrence; St Michael’s, Dun Laoghaire: M J McKenna; Muirhead Medical Centre, Dundee: B Kilgallon; Ninewells, Dundee: G P Leese, A D Morris; Hairmyres, East Kilbride: S J Benbow, H Cohen, D Mathews; Edinburgh Royal: V McAuley, J D Walker; Western General, Edinburgh: J A McKnight; St Margaret’s, Epping: G B Ambeptiya; Epsom District: C Speirs; Health Centre, Falmouth: A Rotheray, A Seaman, V L Wight; River Practice, Fowey: A Middleton; Frome Medical Practice: T E Cahill; Queen Elizabeth, Gateshead: A Syed, J Weaver; Medway Maritime, Gillingham: I Scobie; Gartnaval General, Glasgow: M Small; Glasgow Royal: J Gray, K R Paterson; Southern General, Glasgow: L Fraser, S J Gallacher; Victoria Infirmary, Glasgow: C M Kesson; Harrogate District: P Hammond; Hartlepool General: G Hawthorne, J MacLeod; St Thomas Surgery, Haverfordwest: R W G Thompson; Withybush General, Haverfordwest: N Jowett; Princess Royal, Haywards Heath: T Wheatley;