Risk and Treatment Effect Heterogeneity: re-analysis of individual participant data from 32 large clinical trials

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Abstract

Background: Risk of the outcome is a mathematical determinant of the absolute treatment benefit of an intervention, yet this can vary substantially within a trial population, complicating interpretation of trial results.

Methods: We derived risk models using Cox or logistic regression on a set of large publically available RCTs. Risk heterogeneity was evaluated using the extreme quartile risk ratio (EQRR, the ratio of outcome rates in the lowest risk quartile to that in the highest). Skewness was evaluated with median to mean risk ratio (MMRR, the ratio of risk in the median risk patient to the average). Heterogeneity of treatment effect (HTE) across risk strata was also examined.

Results: We describe 39 analyses using data from 32 large trials, with event rates across studies ranging from 3%-63% (median=15%, interquartile range [IQR]=9%-29%). C-statistics of risk models ranged from 0.59-0.89 (median=0.70, IQR=0.65-0.71). The EQRR ranged from 1.9-35.2 (median=4.0, IQR=3.1-5.4). The MMRR ranged from 0.4-1.0 (median=0.86, IQR=0.80-0.92). EQRRs were predictably higher and MMRRs predictably lower as the C-statistic increased or the overall outcome incidence decreased. Among 18 comparisons with a significant overall treatment effect, there was a significant interaction between treatment and baseline risk on the proportional scale in only one. The difference in the absolute risk reduction between extreme risk quartiles ranged from -3.2-28.3% (median=5.1%; IQR=0.3-10.9).

Conclusions: There is typically substantial variation in outcome risk in clinical trials, commonly leading to clinically significant differences in absolute treatment effects**.** Most patients have outcome risks lower than the trial average reflected in the summary result. Risk stratified trial

analyses are feasible and may be clinically informative, particularly when the outcome is predictable and uncommon.

Key Messages:

- Outcome risk is a mathematical determinant of treatment effect yet can vary substantially across a trial population, making it unclear how treatment effects might vary in the trial population.
- Using simple risk models from available baseline patient characteristics, among a sample of trials from publically available sources, we found that outcome rates in the highest risk quartile were as high as 35-fold those in the lowest risk quartile; in fully a quarter of the trials, this ratio exceeded 5.
- Because outcome risk in the trials was generally skewed (log normal or logistic normal), with a small group of high risk patients accounting for a large number of outcomes, the outcome risk in most patients was almost always less than that reflected by the trial summary results.
- While we did not often detect treatment effect heterogeneity on the proportional scale across patients at different baseline risk in this set of trials, substantial differences in absolute treatment effects were common.
- Displaying subgroup results across subgroups defined by risk is feasible and can lead to clinically important findings.

A fundamental contradiction of evidence-based medicine (EBM) is that evidence is derived from groups of people yet medical decisions are made for individuals. Drawing direct inferences for individuals based on average effects measured in the heterogeneous groups to which those individuals belong relies on a fundamental flaw of logic, known as the fallacy of division. Popular approaches to EBM, which assume that patients meeting trial inclusion criteria are likely to benefit similarly, are based upon, and to some degree undermined by, this fallacy.[1]

The most commonly used method of examining whether treatment effects vary in a trial population is to serially divide patients into subgroups based on potentially relevant pre-treatment characteristics. The main problem with this conventional approach is that there are too many potentially influential characteristics. This leads to myriad “one-variable-at-a-time” subgroup analyses which are typically both underpowered and vulnerable to spurious false positive results due to multiple comparisons.[2,3] It can also be difficult to understand how to apply such analyses to individuals in clinical practice, since patients have multiple characteristics that vary from one another simultaneously.

In part for these reasons, subgroup analyses are usually "exploratory" and rarely actionable, leaving the clinician to assume that all patients meeting trial inclusion criteria should be similarly treated. EBM is thus methodologically canalized to “one-size-fits-all” recommendations, a problem increasingly recognized even as EBM has become the dominant paradigm.[4-6] This remains a central challenge to be addressed if EBM is to become more personalized and patient-centered.[4-6]

We recently proposed a framework for assessing heterogeneity of treatment effect (HTE) that seeks to address these issues.[7] The framework prioritizes the analysis and reporting

of multi-variable risk-based HTE and suggests that other subgroup analyses should be explicitly labeled either as primary subgroup analyses (well-motivated by prior evidence and intended to produce clinically actionable results) or secondary (exploratory) subgroup analyses (performed to inform future research). While other recommendations or guidance documents have (appropriately) emphasized the risks of over interpreting the results of subgroup analyses,[8,9] and the different goals of such analyses,[10] our framework is novel in that it also suggests that presenting summary results without examining and reporting how treatment effects change across subgroups with heterogeneous outcome risk is underutilizing trial data and tantamount to incompletely reporting trial results.

Despite compelling theoretical arguments, a risk modeling approach is rarely applied. Empirical evidence for its importance remains anecdotal and there are concerns about the feasibility of routine and broad application of this analytic approach in datasets collected in typical randomized trials. To address these concerns, we examined the distribution of outcome risk across a broad range of trials and examine how the effects of therapy were related to this risk.

Methods

We searched for publically available individual participant datasets of randomized clinical trials from the National Heart, Lung, and Blood Institute (NHLBI, last search August 2013),[11] the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, last search July 2013),[12] the journal *Trials*, and GlaxoSmithKline.[13] We required that eligible studies had enrolled at least 1000 participants (some sub-cohorts entered in our analyses had fewer

than 1000 participants) randomized to at least two treatment groups, and had a binary (or time-to-event) clinical (i.e., not surrogate) outcome.

Predicting outcome risk using baseline covariates

Risk modeling for each trial was informed by examining previously developed published predictive models "matched" to each trial on the basis of the index condition of the population and the primary outcome.[14] We identified risk predictors that had been used in the published models and the corresponding variables in the trial datasets. Because trial datasets were often not fully compatible with externally developed predictive models, we developed "internal models" on the trial data using risk predictors that were as close as possible to those in published models. To verify that the use of internal models would not bias estimates of HTE across risk groups, we performed a series of simulations described in a separate publication [15]. Briefly, the simulations revealed that, across a range of scenarios, analyses based on internal models developed on trial participants yield results similar to analyses based on external models developed on non-trial participants sampled from the same super-population.

All available established risk predictors were entered into a regression model to predict the primary outcome for all patients in the trial. Both trial arms were used in model development, without using the treatment assignment indicator, to avoid differential model fit across the trial arms, potentially inducing a spurious risk-by-treatment interaction.[15] To minimize model complexity for trials for which there were many established predictors, non-significant risk predictors were ranked in order of significance and removed until no more than

20 variables were entered into the model. (This was needed in only 3 of the 32 trials.) No other formal variable selection process or attempt at model respecification was performed.

In trials with non-statistically significant overall treatment effects for the primary outcome and a statistically significantly treatment effect for a binary (or time-to-event) clinical secondary outcome, an additional regression model was fit to predict the secondary outcome. When the treatment effect was statistically significant for more than one secondary outcome, we selected the outcome identified as most clinically relevant in the published trial report. To minimize bias due to missing data, multivariate normal multiple imputation was used when a complete case analysis would exclude more than five percent of trial participants. Risk factors with missing information from more than 20 percent of trial participants were not used in analyses. The statistical analysis model (Cox proportional hazards regression for time-to-event outcomes or logistic regression for binary outcomes) was selected on the basis of the primary analysis of the clinical trial and determined by the nature of the trial data. In general, we included variables as main effects in their original scale, unless published predictive models specified the use of interactions or variable transformations.

Model performance was assessed with respect to discrimination, calibration, and over-fitting. Discriminatory ability was quantified using the c-statistic.[16] Calibration was assessed visually using calibration plots. Over-fitting was assessed with bootstrap validation.[17] We report the number of events per variable in each trial as an indicator for the risk of over-fitting.

We evaluated the distribution of baseline predicted risk in the overall study population and separately in each treatment arm. Visual examination of the risk distribution was facilitated by the use of box plots which indicate the mean, median, range, and interquartile values of the

predicted baseline risk of the outcome. In addition, we plotted histograms of the empirical distribution of predicted risk in each study to assess how closely the distribution conformed to the truncated log-normal (for risk predicted by proportional hazard models) or the logistic-normal distribution (for risk predicted by logistic regression models).

To describe and quantify risk heterogeneity using clinically interpretable metrics, we used two indexes, the extreme quartile risk ratio (EQRR) and the median-to-mean risk ratio (MMRR). To calculate the EQRR we stratified the trial population into equal-sized quartiles according to the baseline predicted risk from the model [18]. We then calculated the ratio of the predicted outcome risk in the extreme quartiles (high-risk quartile outcome probability divided by the low-risk quartile outcome probability, $EQRR_{predicted}$). We calculated the same index based on the observed outcome rate ($EQRR_{observed}$). Greater EQRR values indicate greater risk heterogeneity in the risk stratified patient population. The MMRR is a clinically interpretable measure of skewness calculated as the ratio of the median predicted outcome probability to the mean predicted outcome probability. As the MMRR deviates from one, it reflects the degree to which the summary (average) result may not reflect the effects in the "typical" patient in the trial. We also calculated Pearson's median skewness coefficient [3*(mean-median)/standard deviation], a more common measure of skeweness.

We also examined the relationship between the outcome prevalence and the c-statistic, and the EQRR and MMRR, visually and using a linear regression approach.

Evaluating HTE over predicted outcome risk

Additionally, we analyzed the relationship between treatment effect and predicted outcome risk. Treatment effects within each risk quartile were estimated on relative and absolute scales. Relative treatment effects were estimated using logistic regression (using odds ratios as the measure of effect) or Cox regression (using hazard ratios as the measure of effect). Absolute treatment effects were estimated using linear probability models for binary outcomes (using absolute risk reduction as the measure of effect). For time-to-event analyses, absolute risk reduction was calculated as the difference in Kaplan-Meier survival probabilities between the intervention and comparator treatment arms.[19] We tested the null hypothesis of no HTE over predicted outcome risk using a product term ("interaction") between the fitted value of the linear predictor (from the risk model) and the treatment assignment indicator. We also compared relative and absolute risk reduction between the extreme risk quartiles in each trial. We summarized these metrics for the subset of trials with statistically significant overall treatment effects, i.e. those trials showing statistically significant benefit or harm on either a primary or a secondary outcome.

Statistical analyses was performed using SAS version 9.3[20], R open-source software version 3.1.2 (The R Foundation for Statistical Computing), and Stata version 13.1 (Stata Corp., College Station, TX).

Results

We identified 32 trials meeting our inclusion criteria (Table 1). Most trials were in the field of cardiovascular disease, including trials testing interventions in atrial fibrillation,

coronary heart disease, acute myocardial infarction, heart failure, hypertension, and acute stroke. We also included trials of other conditions, such as prediabetes, acute kidney failure, chronic hepatitis C, and prostatic hyperplasia. The number of patients in the analyzed trial cohorts range from 715 to 33,357, and totaled 180,291. Trials had been conducted over a span of several decades; the earliest trial had been published in 1979 and the latest in 2008. Of note, our trials generally did not include interventions with harms anticipated to affect the primary outcome (e.g. as in carotid endarterectomy, which both prevents and causes stroke).

One trial had more than one patient cohort (DCCT,[21]), one trial had more than one primary outcome (IST[22]), and five trials had non-statistically significant results for their primary outcome but significant results for a secondary outcome (ACCORD,[23] ALLHAT HTN,[24] BEST,[25] DIG,[26] SOLVD[27,28]). Thus, we performed a total of 39 unique analyses. The median number of risk factors used in these 39 risk models was 10 (average=10.9; range=4-20) (Table 2). The median number of events per variable was 51.3 (average=107.0; range=12.5-907.1), suggesting that models were unlikely to overfit the data. The median c-statistic was 0.69 (average=0.70; range=0.59-0.89). Bootstrap validation produced optimism-corrected c-statistics in the range of 0.58 to 0.88 (median = 0.68, IQR=0.64-0.70). The difference between original and optimism-corrected c-statistics ranged from 0.001 to 0.02 (median = 0.007, IQR = 0.004-0.009), again suggesting the absence of substantial overfitting.

Distribution of predicted outcome risk in large randomized trials

The median overall event rate in the trials was 15% (average=20%; range =3%-63%). Summary statistics describing the risk heterogeneity of the population are shown in Table 2.

The median predicted EQRR was approximately 4, but more than a quarter of all analyses had an EQRR over 5 and the range exceeded 30. Similarly, while the median MMRR was 0.86 (indicating that the typical patient was at 86% the outcome risk compared to the average), this index ranged as low as 0.4—and only twice exceeded 1 (ATN,[29] IST[22] 6 month outcome), both times for trials with high outcome rates (52.6% in ATN and 62.6% in IST).

We found the overall outcome rate in the trial and the c-statistic were strong determinants of the risk distribution. In linear regression, the outcome rate and c-statistic were shown to strongly predict the EQRR (R^2 = 0.86) and the MMRR (R^2 = 0.78) (Table 3). As discrimination improved, and as the overall outcome rate was lower, EQRR increased and MMRR decreased in a predictable fashion. Indeed, we found that knowing these two parameters (overall outcome incidence and c-statistic) essentially determine the full distribution of predicted risk, because the risk distributions were close to the log-normal (for risk predicted using Cox models) or logistic-normal shape (for risk predicted using logistic regression models) (Figure 2). This can be seen by comparing the fitted curves of the histograms (in black) to the fitted log normal curves (red) and logistic normal curves (blue)—largely overlapping in most studies.

HTE over predicted outcome risk

Among the 18 trials with statistically non-significant results, two trials showed statistically significant HTE across the estimated linear predictor from the risk model. In the AMIS trial,[30] high risk patients with acute myocardial infarction appeared to get more benefit from aspirin than low risk patients(p=0.02) on the relative risk scale; in IST,[22] for the combined

outcome of death or dependency at 6 months, low risk patients appeared to obtain more relative benefit than high risk patients (p=0.04).

In the 14 trials with statistically significant results, 18 unique treatment comparisons were analyzed. While the relative treatment effects appeared to decrease over risk quantiles in some trials (e.g. BEST, CPPT and MTOPS [Figure 2a]) and increase over risk quantiles in others (ACCORD, CAST and DPP [Figure 2b]), overall there was no apparent relationship between baseline risk and the hazard (or odds) ratios of treatment across trials. The median ratio of the hazard or odds ratio in the fourth quartile 4 over that in the first quartile was 1.02 (IQR 0.70 to 1.21) (Table 4). We found a statistically significant interaction between treatment and the estimated linear predictor on the proportional scale only in one of 18 analyses (DPP, metformin vs. placebo; high risk patients experienced greater benefit than low risk patients (p=0.0008)). Despite the absence of "statistically significant" HTE on the proportional scales, absolute risk reduction varied substantially over predicted outcome risk and was generally higher in high risk strata, ranging from -1.4 to 18.3% (median=4.7%; IQR=0.8-6.1%) in the first quartile of predicted risk and from 0.8 to 35.0% (median=9.0%; IQR=3.3-19.8%) in the fourth quartile. The difference in the absolute risk reduction between the extreme risk quartiles ranged from -3.2 to 28.3% (median=5.1%; IQR=0.3-10.9).

Discussion

Our results show that clinically significant risk heterogeneity is common even in phase III "efficacy" trials, which are often characterized as enrolling relatively homogeneous populations. While statistically significant HTE on the proportional scale was unusual in this set

of trials in which interventions generally did not have anticipated harms on the primary outcome, variability in predicted risk often gave rise to substantial HTE on the absolute risk scale. Though it is most common to test for heterogeneity on the proportional scale, absolute risk reduction (and its inverse, the number needed to treat) are generally considered the most relevant scales for clinical decision-making.[31] While we did not use formal criteria to assess clinically important HTE, it is noteworthy that, among treatment comparisons with statistically significant overall results, 25% showed differences in absolute risk differences greater than 10% between the extreme quartiles of predicted risk. We considered our analysis of two trials (MTOPS[32] and DPP[33]), encompassing 5 of our 18 treatment comparisons, to be of sufficient clinical interest to report in separate clinical manuscripts.[34,35] These papers join a growing list of papers showing clinically important variation in benefits when trial results are risk stratified, typically showing that an identifiable subgroup of higher risk patients often account for most of the treatment benefit.[36-46]

Another consistent finding was that the median predicted outcome risk in these trials was lower than the mean predicted risk (i.e. MMRR < 1). Since the summary results of trials reflect the arithmetic mean risk, rather than the median, this implies that the typical patient is often at somewhat lower risk—and sometimes at much lower risk--than one might infer from the overall result. When proportional effects are similar across risk groups, summary results may have a tendency to overestimate the degree of benefit on the absolute scale.[5,47] These concerns are especially germane when outcomes rates are predictable and outcome rates relatively low.

While several trials exhibited large heterogeneity in predicted outcome risk, the examples in our database of trials were somewhat less extreme than previous published examples might have suggested.[36-45] There are several explanations for this observation. First, risk heterogeneity may be somewhat restricted in large phase III randomized studies if they tend to enroll homogeneous patient populations. Second, because we wanted to limit the risk of over-fitting models to data, we favored simpler models which generally had modest discriminatory ability. Finally, previously published examples might be "cherry picked" for extreme results and clinical significance. It is also important to recognize that expressing heterogeneity of risk using a finer grouping of predicted risk (e.g. quintiles or deciles) would yield ratios that are much more extreme than the EQRRs reported here.

The observation that indices that describe the distribution of predicted risk distribution are predictable based on the c-statistic and the overall event rate of each trial is as telling as the specific examples in our study. The predictability of the risk distribution derives from the fact that the linear predictor from the risk model conforms fairly closely to a normal distribution [48], yielding distributions of risk that (to a good approximation) conform to log-normal (for risk estimates derived from Cox models) or logistic-normal distributions (for risk estimates derived from logistic regression models). This relationship permits us to anticipate the degree of risk heterogeneity (i.e. EQRR) and the skewness (i.e. MMRR) based on knowledge of the outcome rate and the discrimination (c-statistic) of the model. For example, using our simple linear regression results, we would anticipate that, when the outcome rate is 10% and the c-statistic is 0.8, the EQRR will be approximately 13 and the MMRR will be approximately 0.6. When risk differs 13 fold between large population subsets, the overall treatment effect estimated for the

trial population is not clinically interpretable. When the median risk is 40% lower than that seen in the mean risk, it also seems likely that the average effects may not be easily translated even to typical patients in the same trial. Higher c-statistics and lower outcome prevalence would lead to even more skewed distributions, implying greater risk heterogeneity.

Thus, it does not take extreme assumptions to yield risk distributions that would make overall clinical trial results importantly misleading for many patients. The relationship also implies that a risk stratified approach might be especially important and clinically informative when the outcome is predictable based on easily available clinical information and the overall outcome rate is low. This conclusion is consistent with clinical intuition, because when the outcome is rare and predictable by baseline covariates, it is possible to identify very low risk patients who are unlikely to benefit from therapy. Analyses of HTE over predicted risk are also more likely to be useful for risky or costly therapies, when identifying patients who are unlikely to benefit may be of especially high interest.

Despite the fact that only one trial (DPP) showed a "statistically significant" interaction between the linear predictor of risk and treatment assignment, we would urge caution in interpreting the ostensible consistency of effects on the multiplicative scale. We note that the true relationship between risk and effect is underdetermined by the data. Indeed, trial results may often be statistically consistent with homogenous effects on both additive and multiplicative scales across risk groups—despite the mathematical incompatibility of these models and the potential clinical importance of the different inferences the models may yield. We believe that consistent effects across any of these scales is highly unlikely to represent the "true" relationship between the risk of an outcome and the effect of a therapy, though we

regard the assumption of a constant relative risk reduction (or odds ratio) as a useful convenience.

Our study has several limitations. We acknowledge that the use of quartiles is arbitrary, and tends to underestimate heterogeneity, compared to using finer quantile gradations or smoothed curves. We present our data in quartiles to facilitate comparisons across analyses, based on a previously suggested framework.[18] Heterogeneity may be slightly over-estimated based on model overfitting or underestimated based on underfitting; more careful model building-- exploring non-linearity and interactions--may have increased the estimation of risk heterogeneity. We did not explore non-linear relationships between risk and treatment effects, which may have revealed additional HTE. Additionally, while we tried to standardize our approach to modeling, we used only a single model for each trial. Alternative models may fit the data equally well, yet results regarding HTE may be sensitive to the specific variables included in the models, and whether any of these variables are treatment effect modifiers. While different models may yield different results, the degree to which any particular covariate modifies treatment is typically unknown—and when there is a strong *a priori* reason to believe that a particular covariate is likely to modify a treatment effect (apart from its influence on risk) then the relationship of the covariate with the treatment effect should also be examined separately. Finally, we used a convenience sample of large trials, which do not represent the full spectrum of clinical conditions or, specifically, those conditions for which risk modeling may be most informative. In particular, a risk modeling approach may be especially informative when treatment is associated with both benefit and treatment-related harm on the primary

outcome.[5,6,39,49] In such conditions, the risks of therapy may outweigh the benefits in very low risk patients, and more treatment effect heterogeneity would be anticipated.

Despite these limitations, our results suggest that clinically important differences in effect across risk are likely to be common in trials with statistically significant average effects. While a common assumption (of unclear validity) is consistency of proportional treatment effects across risk groups, the only way of testing this assumption is to actually perform such a risk stratified analysis. Even when analyses fail to reject the null of proportional effects across different risks, the results of risk-stratified analyses can demonstrate clinically important risk differences, which would otherwise be obscured. Nevertheless, risk stratified analyses of clinical trials are still rarely done as part of the initial study design; an expectation on the part of reviewers, editors and regulators may be the best way to promote this approach.[50]

In summary, risk distributions from Cox regression and logistic regression are largely determined based on c-statistic and outcome rates. Clinically significant risk heterogeneity is common even in large "efficacy" trials—particularly when outcome rates are low and c-statistics are high. The median risk in these trials is generally lower than the average risk. Statistically significant HTE on the relative risk scale is unusual, but clinically significant heterogeneity in absolute effects appears to be common. A risk stratified approach to trial analysis is feasible and may be most clinically informative where the outcome is predictable by baseline covariates and uncommon.

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Table 1. Description of trials

Trial Acronym	Year of Publication	Patients Randomized (n)	Patient Population/ Index Condition	Intervention	Comparator	Primary Outcome*	Secondary Outcome*
ACCORD[§23]	2008	10,251	Type 2 Diabetes Mellitus	intensive strategy	standard treatment	first occurrence of a major CVD event	all-cause mortality (-)
AFFIRM[51]	2002	4,060	Atrial Fibrillation / Risk of Stroke or Death	rate-control therapy	rhythm-control therapy	all-cause mortality	not assessed
ALLHAT HTN[†§24]	2002	33,357	Hypertension	amlodipine or Lisinopril	chlorthalidone	fatal CHD or nonfatal MI combined	combined CVD events (-)
ALLHAT LLT[52]	2002	10,355	Hypercholesterolemia / Hypertension	pravastatin	usual care	all-cause mortality	not assessed
AMIS[30]	1980	4,524	Myocardial Infarction	aspirin	placebo	all-cause mortality	not assessed
ATN[29]	2008	1,124	Acute Kidney Failure / Sepsis	intensive renal-replacement therapy	less intensive renal-replacement therapy	all-cause mortality (60 day)	not assessed
BARI[53]	1996	1,829	Coronary Artery Disease / Severe Angina	percutaneous transluminal coronary balloon angioplasty	coronary artery bypass grafting	cardiac mortality	not assessed
BEST[§25]	2001	2,708	Advanced Heart Failure / Congestive Heart Failure	bucindolol hydrocholoride	placebo	all-cause mortality	death due to cardiovascular causes (+)
BHAT[54]	1982	3,837	Acute Myocardial Infarction	propranolol	placebo	all-cause mortality (+)	not assessed
CAST[55]	1991	1498	Myocardial Infarction	class I and Ib antiarrhythmic agents	placebo	all-cause mortality or cardiac arrest (-)	not assessed
CPPT[56]	1984	3,806	Hypercholesterolemia	cholestyramine	placebo	cHD death and/or definite nonfatal myocardial infarction (+)	not assessed
DCCT[§21]	1993	prevention: 726, intervention: 715	Type 1 Diabetes Mellitus	intensive diabetes therapy	conventional diabetes therapy	appearance and/or progression of retinopathy and other complications (+)	not assessed
DIG[§26]	1997	6,800	Heart Failure	digoxin	placebo	all-cause mortality	hospitalization for worsening heart failure (+)
DPP[†33]	2002	3,234	At Risk for Diabetes Mellitus	1) metformin 2)intensive lifestyle intervention	placebo	development of diabetes (+)	not assessed
ENRICHD[57]	2003	2,481	Acute Myocardial Infarction	cognitive behavior therapy - based intervention	usual medical care	All-cause mortality or recurrent myocardial infarction	not assessed
FAVORIT[58]	2011	4,110	Stable Kidney Transplant	multivitamin plus folic acid, vitamin B12, and vitamin B6	Treatment with an identical multivitamin alone	arteriosclerotic cardiovascular disease outcome	not assessed
FUTURA[59]	2010	2,026	Unstable Angina/ non–STEMI	low dose unfractionated heparin	standard dose unfractionated heparin	peri-PCI major bleeding, minor	not assessed

						bleeding, major vascular access site complications	
HALTC[60]	2008	1,050	Chronic Hepatitis C	indefinite pegylated interferon alfa-2a (beyond 3.5 years)	pegylated interferon alfa-2a discontinue use after 3.5 years	progression to cirrhosis	not assessed
HDFP[61]	1979	10,940	Hypertension	stepped care-antihypertensive therapy	referred care	all-cause mortality (+)	not assessed
HEMO[†][62]	2002	1,846	Hemodialysis	high dose/high-flux dialysis	standard dose/low flux dialysis	all-cause mortality	not assessed
IST[§][22]	1997	19,435	Acute stroke	unfractionated heparin, aspirin	placebo	death within 14 days, death/dependency at 6 months	not assessed
MAGIC[63]	2002	6,213	Acute Myocardial Infarction	intravenous magnesium sulphate	placebo	all-cause mortality	not assessed
MRFIT[64]	1982	12,866	At Risk for Coronary Heart Disease	stepped-care treatment, counseling, dietary advice	usual care	death from coronary heart disease	not assessed
MTOPS[‡][32]	2003	3,047	Benign prostatic hyperplasia	1)doxazosin, 2) finasteride, or 3) combination therapy	placebo	clinical progression of benign prostatic hyperplasia (+)	not assessed
OAT[65]	2006	2,166	Congestive Heart Failure	routine PCI and stenting with optimal medical therapy	optimal medical therapy alone	mortality, recurrent MI, and hospitalization for CHF	not assessed
PEACE[66]	2004	8,290	Coronary Artery Disease	trandolapril	placebo	death from cardiovascular causes or nonfatal MI	not assessed
ROC[†§][67,68]	HS: 2011 TBI: 2010	HS:895, TBI: 1331	Hypovolemic Shock Traumatic Brain Injury	hypertonic saline solution	normal saline solution	28-day survival six-month neurologic outcome based on the Extended Glasgow Outcome Scale	not assessed
SHEP[69]	1991	4,736	Hypertension	Chlorthalidone/ atenolol antihypertensive drug regimen	placebo	nonfatal and fatal stroke (+)	not assessed
SOLVD[‖][27,28]	prevention: 1992 intervention: 1991	prevention: 4,228, intervention: 2,569	Congestive Heart Failure	enalapril	placebo	all-cause mortality (T+)	death or hospitalization for heart failure (P+)
TIMI-II[70]	1989	3,262	Acute Myocardial Infarction	invasive strategy	conservative strategy	All-cause mortality or non-fatal MI	not assessed
32 trials (33 cohorts[¶])		180,291					18 positive treatment effects from 14 trials

*Summary treatment effect on outcome is statistically insignificant unless indicated by sign: (+) indicates positive treatment effect, (-) indicates treatment harm.

[†]indicates 2 treatment arms; [‡] indicates 3 treatment arms

Summary results are from 39 risk distributions: [§]indicates 2 risk distributions; [||]indicates 3 risk distributions (if not specified, assume 1 risk distribution).

[¶] DCCT has 2 cohorts whereas all other trials have 1 cohort.

Notations: ALLHAT HTN = antihypertensive trial, ALLHAT LLT = lipid lowering trial; HEMO used 2-by-2 factorial design; IST investigated two primary outcomes; Primary outcome treatment effect for SOLVD was significant for the left ventricular dysfunction cohort (T) and the secondary outcome treatment effect was positive for the asymptomatic cohort (P).

Table 2. Summary of results for 39 risk distributions

	Median	IQR	Mean	Range
Overall event rate	0.15	0.09-0.29	0.20	0.03-0.63
Model risk predictors	10	7-16	10.9	4-20
Events per variable	51.3	32.3-84.7	107.0	12.5-907.1
c-statistic	0.69	0.65-0.71	0.70	0.59-0.89
EQRR predicted	4.0	3.1-5.4	5.3	1.9-35.2
EQRR observed	4.3	3.0-6.1	6.1	1.8-50.7
MMRR	0.86	0.80-0.92	0.84	0.42-1.04
PMSC	0.74	0.60-0.86	0.70	-0.24-1.56

EQRR = extreme quartile risk ratio; MMRR = median-to-mean risk ratio;

PMSC = Pearson's median skewness coefficient; IQR = inter-quartile range

Table 3. Regression model results

	log EQRR predicted				MMRR		
	Estimate (SE)	t Value	p value		Estimate (SE)	t Value	p value
Intercept	-3.88 (0.39)	-10.05	<.0001		1.80 (0.12)	15.47	<.0001
Overall event rate	-1.94 (0.24)	-7.98	<.0001		0.66 (0.07)	9.06	<.0001
c-statistic	8.27 (0.57)	14.41	<.0001		-1.57 (0.17)	-9.05	<.0001
R-square	0.86				0.78		

EQRR = extreme quartile risk ratio; MMRR = median-to-mean risk ratio; SE = standard error

Table 4. Summary of results for 18 positive treatment comparisons (14 trials).

	Median	IQR	Mean	Range
Hazard (or odds) ratio Q1	0.63	0.52-0.87	0.66	0.16-1.10
Hazard (or odds) ratio Q4	0.69	0.44-0.90	0.64	0.27-0.96
Extreme quartile relative hazard ratio (Q4/Q1)	1.02	0.70-1.21	1.05	0.41-1.82
Absolute risk reduction Q1 (%)	4.73	0.83-6.06	4.50	-1.43-18.27
Absolute risk reduction Q4 (%)	9.04	3.25-19.84	12.01	0.77-34.99
Extreme quartile absolute risk reduction difference (Q4-Q1)	5.10	0.33-10.91	7.51	-3.23-28.33

IQR = inter-quartile range

Figure 1. Risk Distributions

The histograms show the distribution of the predicted risk for the outcome of interest. Curves shown in red are fitted to the distribution of predictions generated by Cox models; curves shown in blue are fitted to the distribution of predictions generated by logistic models. Fitted log normal curves and fitted logistic normal curves are also shown for the Cox and logistic regression generated curves, respectively. As can be seen, these log normal and logistic normal curves approximate very well the red and blue fitted curves. Note: FUTURA Trial is not included in this figure since we could not export individual level patient predictions from the site the data was housed.

Figure 2. Risk quartile (A) hazard ratios and (B) absolute risk reduction.

Red markers indicate that the treatment arms were switched (intervention was harmful). In Figure 2A, the scale for hazard ratio axis is different for DCCT and MTOPS. In Figure 2B, the scale for absolute risk reduction is different for DPP, MTOPS, and DCCT.

Predicted risk

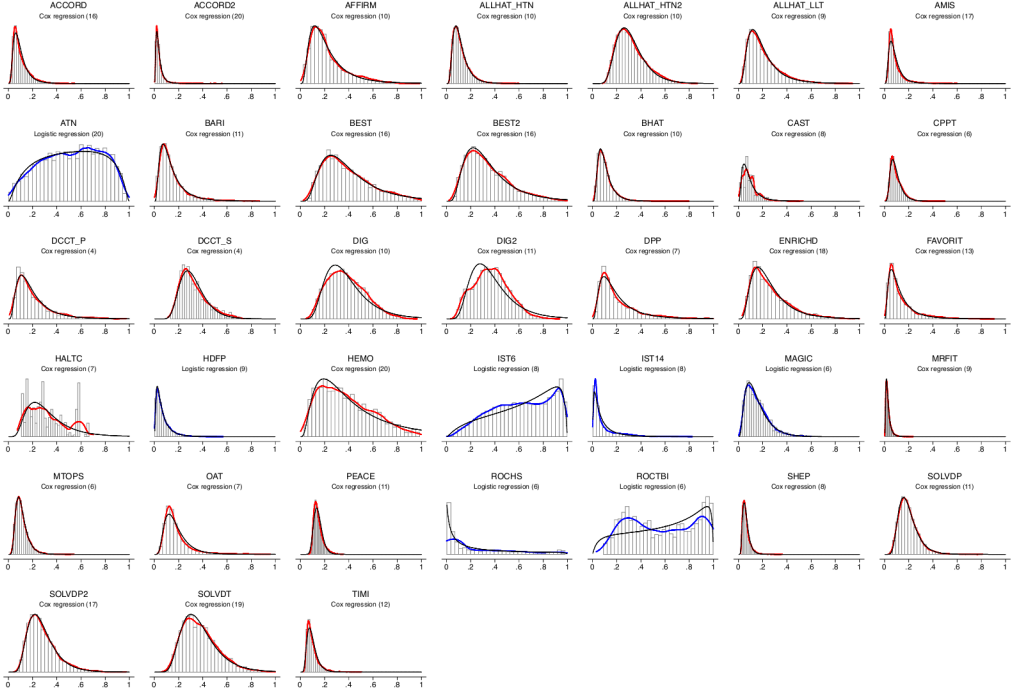
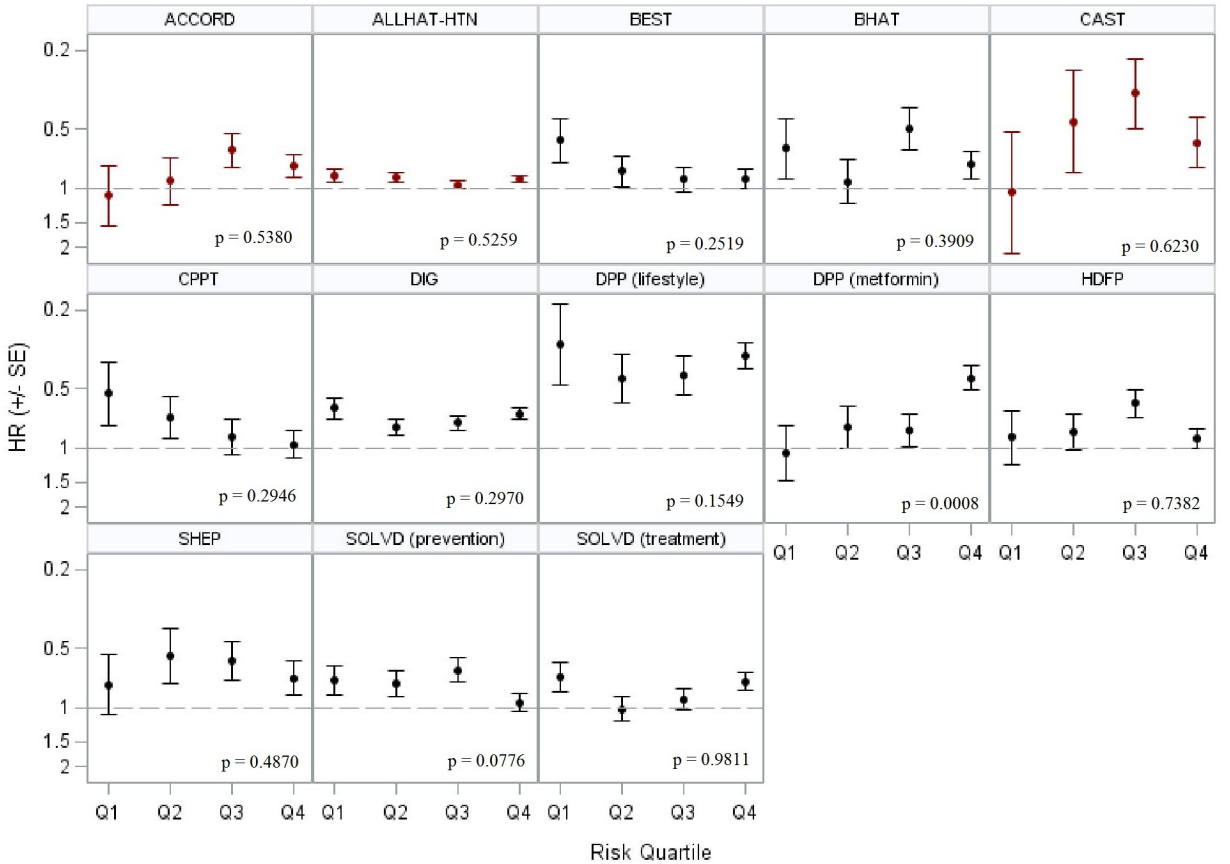
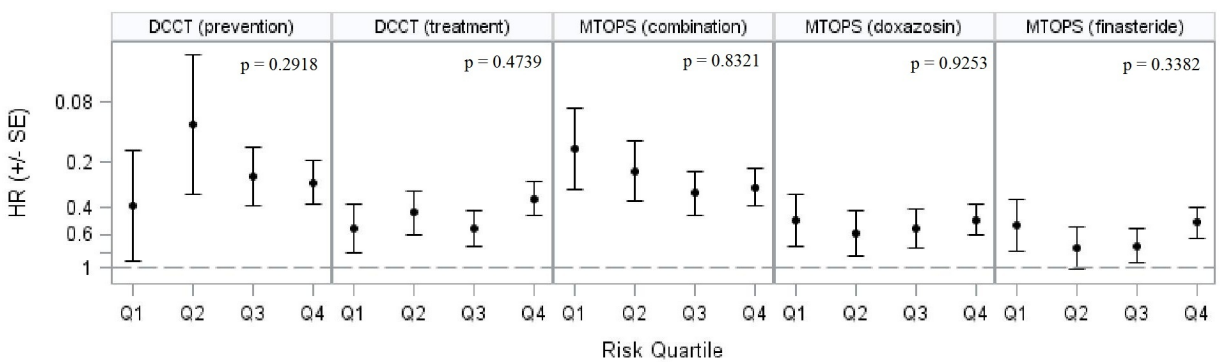


Figure 2. Risk quartile (A) hazard ratios and (B) absolute risk reduction.

(A) Hazard ratios

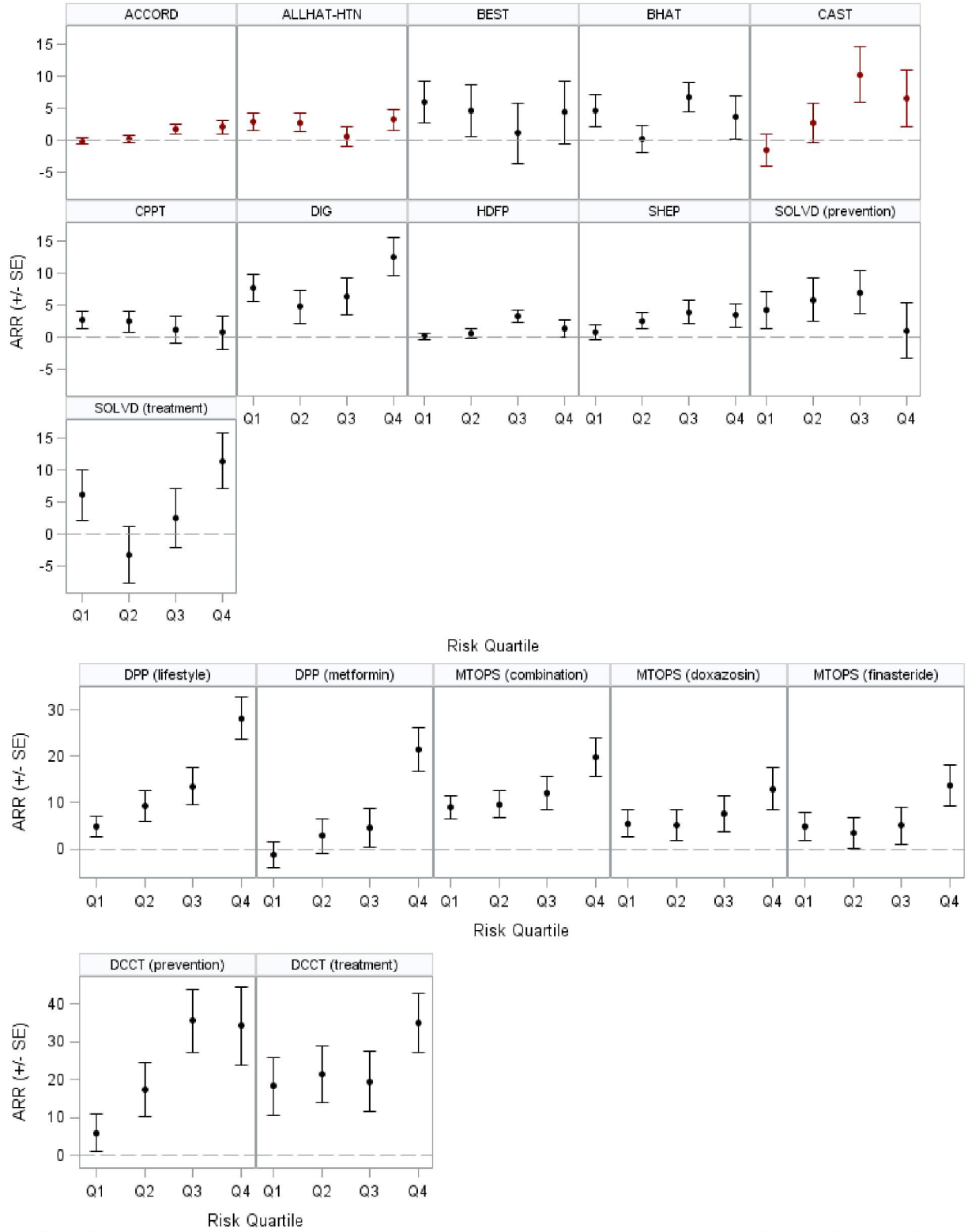




Note: p-values correspond to the test for interaction of the linear predictor with treatment assignment.

*Red markers indicate that the treatment arms were switched (intervention was harmful). Scale for hazard ratio axis is different for DCCT and MTOPS.

(B) Absolute risk reduction



* Red markers indicate that the treatment arms were switched (intervention was harmful). Scale for absolute risk reduction is different for DPP, MTOPS, and DCCT.

APPENDIX

RCT	Published models (PMID)	Regression method	Risk factors included
ACCORD	16732001,[1] 18591403,[2] 21719139,[3] 11724655[4]	Cox	age, duration with diabetes, sex, race, current smoking status, body weight, BMI, HbA1c, SBP, total cholesterol, HDL cholesterol, antihypertensive therapy, lipid lowering medication, atrial fibrillation, microalbuminuria or macroalbuminuria within 2 years, history of cardiovascular disease
ACCORD2	18809629,[5] 18332288[6]	Cox	age, duration with diabetes, sex, race, current smoking status, HbA1c, SBP, DBP, triglycerides, BMI, albumin-creatinine ratio, GFR, history of congestive heart failure, thiazolidinedione therapy, insulin therapy, ACE-inhibitor therapy, ARB therapy, anticoagulant therapy, aspirin therapy, statin therapy
AFFIRM	21962993,[7] 21247518,[8] 12941677[9]	Cox	history of congestive heart failure, age, history of diabetes, history of stroke or TIA, history of MI, SBP, sex, race, current smoking status, history of coronary artery disease
ALLHATHTN	11451781,[10] 20001655[11]	Cox	age, sex, current smoking status, history of diabetes, antihypertensive therapy, SBP, total cholesterol, height, history of stroke or MI, left ventricular hypertrophy
ALLHATHTN2	11451781,[10] 20001655[11]	Cox	age, sex, current smoking status, history of diabetes, antihypertensive therapy, SBP, total cholesterol, height, history of stroke or MI, left ventricular hypertrophy
ALLHATLLT	17299196,[12] 18997194,[13] 9603539,[14] 14505774[15]	Cox	age, sex, race, total cholesterol, HDL cholesterol, history of diabetes, antihypertensive therapy, current smoking status, SBP
AMIS	11686666,[16] 15187054,[17] 16824842[18]	Cox	age, sex, ventricular tachycardia, history of intermittent claudication, current smoking status, history of diabetes, antihypertensive therapy, heart rate, history of MI, history of congestive heart failure, SBP, ST-segment depression, peripheral arterial occlusion, history of stroke, pulmonary congestion, history of renal disease, nitroglycerin or long-acting nitrate therapy
ATN	3928249,[19] 8254858,[20] 10990106[21]	Logistic	age, body temperature, mean arterial pressure, arterial pH, heart rate, potassium, creatinine, bilirubin, albumin, platelet count, on sedation, eye response, motor response, urine output, ischemic etiology, post open surgical procedure, malignancy, chronic hypoxemia, immune suppressed, history of cardiovascular disease
BARI	15117846,[22] 22547673,[23] 10456395,[24] 23439103,[25] 22361329[26]	Cox	age, history of diabetes, diabetes therapy, proximal left anterior descending disease, history of congestive heart failure, sex, unstable angina, history of MI, race, current smoking status, history of hypertension, number of diseased vessels

BEST	18652942,[27] 18926148,[28] 16534009[29]	Cox	ACE inhibitor therapy, age, sodium, implanted cardiovascular defibrillator or pacemaker), left ventricular ejection fraction, sex, heart rate, hemoglobin, ischemic etiology, white blood cell count, NYHA heart failure class, serum creatinine, SBP, total cholesterol, uric acid, body weight
BEST2	18652942,[27] 18926148,[28] 16534009[29]	Cox	ACE inhibitor therapy, age, sodium, implanted cardiovascular defibrillator or pacemaker), left ventricular ejection fraction, sex, heart rate, hemoglobin, ischemic etiology, white blood cell count, NYHA heart failure class, serum creatinine, SBP, total cholesterol, uric acid, body weight
BHAT	11686666,[16] 15187054,[17] 17032691,[30] 16824842[18]	Cox	age, intermittent claudication, current smoking status, history of diabetes, heart rate, total cholesterol, SBP, serum creatinine, history of MI, coronary vasodilators
CAST	15862409,[31] 20932590,[32] 17868806[33]	Cox	left ventricular ejection fraction, history of renal disease or diabetes, age, mitral regurgitation, CABG or other cardiac surgery, thrombolytic therapy, history of neoplasm or chronic pulmonary disease, intraventricular conduction delay or left bundle branch block
CPPT	17299196,[12] 18997194,[13] 9603539,[14] 14505774[15]	Cox	age, race, total cholesterol, HDL cholesterol, current smoking status, SBP
DCCTP	19068374[34]	Cox	HbA1c, albuminuria, SBP, BMI
DCCTS	19068374[34]	Cox	HbA1c, BMI, sex, severity of retinopathy
DIG	18652942,[27] 18926148,[28] 16534009[29]	Cox	age, left ventricular ejection fraction, sex, BMI, heart rate, SBP, NYHA heart failure class, ischemic etiology, potassium-sparing diuretic therapy, ACE inhibitor therapy
DIG2	22683041,[35] 22819429[36]	Cox	age, BMI, NYHA heart failure class, sex, race, SBP, DBP, heart rate, potassium-sparing diuretic therapy, ACE inhibitor or ARB therapy, nitrate therapy
DPP	21902820[37] (review)	Cox	fasting plasma glucose, HbA1c, history of high blood glucose, triglycerides, waist circumference, height, waist to hip ratio
ENRICHD	20691304,[38] 2144989,[39] 23568781,[40] 2013140[41]	Cox	sustained ventricular tachycardia or fibrillation, cardiogenic shock, sex, age, BMI, history of hypertension, history of diabetes, ACE inhibitor therapy, beta blocker therapy, heart rate, SBP, creatinine, Killip class, history of MI, cardiac enzymes > 2 times upper limit, ST-T changes or new Q waves on ECG, treatment with PTCA, antiplatelet therapy
FAVORIT	17299196,[12] 18997194,[13] 9603539,[14] 14505774,[15] 17088464,[42] 23407372,[43]	Cox	age, sex, race, current smoking status, history of diabetes, HDL cholesterol, total cholesterol, history of hypertension, DBP, SBP, creatinine, BMI, history of 2 or more comorbid conditions (e.g., MI, coronary artery revascularization, stroke, carotid arterial revascularization, aortic aneurysm repair, renal arterial

	20415903[44]		revascularization, lower extremity arterial revascularization, or lower extremity amputation above the ankle)
FUTURA	12796758[45]	Logistic	age, sex, BMI, history of congestive heart failure, number of lesions treated, ACC lesion type, Clopidogrel therapy, pre- or concurrent procedure GPIIb/IIIa therapy
HALTC	12823595,[46] 22045670[47]	Cox	sex, histological activity index, alcohol consumption, aspartate aminotransferase to alanine aminotransferase ratio, platelet count, total bilirubin, albumin
HDFP	17299196,[12] 18997194,[13] 9603539,[14] 14505774[15]	Logistic	age, sex, race, current smoking status, history of diabetes, family history of MI, total cholesterol, antihypertensive therapy, SBP
HEMO	17699392,[48] 22269655,[49] 22630831[50]	Cox	age, sex, race, body weight, BMI, duration with diabetes, erythropoietin therapy, albumin, sodium, phosphorous, history of coronary artery disease, history of malignancy, history of cardiovascular disease, history of cerebrovascular disease, history of congestive heart failure, history of diabetes, history of hypertension, history of lung disease, history of neurologic disease, history of peripheral vascular disease
IST14	21300951,[51] 22311929,[52] 17068305,[53] 11470384[54]	Logistic	age, sex, stroke subtype (e.g., TACS, PACS, POCS, or LACS), atrial fibrillation, infarct visible on CT, time between stroke and randomization, conscious state, stroke severity (e.g., face deficit, arm/hand deficit, leg/foot deficit, dysphasia, hemianopia, visuospatial disorder, brainstem or cerebellar signs, or other deficit)
IST6	21300951,[51] 22311929,[52] 17068305,[53] 11470384[54]	Logistic	age, sex, stroke subtype (e.g., TACS, PACS, POCS, or LACS), atrial fibrillation, infarct visible on computed tomography, time between stroke and randomization, conscious state, stroke severity (e.g., face deficit, arm/hand deficit, leg/foot deficit, dysphasia, hemianopia, visuospatial disorder, brainstem or cerebellar signs, or other deficit)
MAGIC	14996596,[55] 11044416[56]	Logistic	age, heart rate, anterior MI or left bundle branch block, SBP, history of comorbid conditions (e.g., diabetes, MI chest pain, hypertension), time to thrombolytic therapy
MRFIT	17299196,[12] 18997194,[13] 9603539,[14] 14505774[15]	Cox	age, race, total cholesterol, HDL cholesterol, history of diabetes, parental history of MI, antihypertensive therapy, current smoking status, SBP
MTOPS	19091352,[57] 12814681,[58] 16985924,[59] 15953934[60]	Cox	American Urologic Association (AUA) benign prostatic hyperplasia symptom score, AUA impact index, age, post-void residual urine volume, maximal urinary flow rate, serum prostate specific antigen
OAT	19194534[61]	Cox	history of congestive heart failure, history of peripheral vascular disease, history of diabetes, rales, left ventricular ejection fraction, days from MI to randomization, GFR
PEACE	19962465,[62] 23197169,[63]	Cox	left ventricular ejection fraction, Current Canadian Cardiovascular Society functional classification of angina,

	23200481,[64] 23519584[65]		history of diabetes, history of hypertension, current smoking status, history of angiographic coronary disease, total cholesterol, GFR, age, sex, BMI
ROCHS	22896030,[66] 20009697[67]	Logistic	age, Glasgow coma score, SBP, heart rate, respiratory rate, abnormal shock index (heart rate/SBP > 0.9)
ROCTBI	16238481,[68] 18270239[69]	Logistic	age, pupillary reactivity, hypoxia, hypotension, Marshall Head computed tomography score, Glasgow coma score
SHEP	8266381,[70] 15257999[71]	Cox	age, sex, race, SBP, antihypertensive therapy, current smoking status, history of diabetes, history of cardiovascular disease
SOLVDP	18652942,[27] 18926148,[28] 16534009[29]	Cox	ACE inhibitor therapy, age, beta blocker therapy, diuretic therapy, sodium, left ventricular ejection fraction, sex, heart rate, lymphocytes, NYHA heart failure class, SBP
SOLVDP2	22683041,[35] 22819429[36]	Cox	age, blood urea nitrogen, NYHA heart failure class, diuretic therapy, sex, race, history of CABG or other cardiac surgery, history of chronic obstructive pulmonary disease, history of atrial fibrillation, SBP, DBP, heart rate, ACE inhibitor therapy, beta blocker therapy, creatinine, potassium, white blood cell count
SOLVDT	12748212,[72] 14625335,[73] 16219658,[74] 17027575[75]	Cox	age, sex, body weight, heart rate, current smoking status, history of diabetes, history of MI, history of edema, history of chronic obstructive pulmonary disease, NYHA heart failure class, left ventricular ejection fraction, history of atrial fibrillation ACE inhibitor therapy, beta blocker therapy, creatinine, SBP, DBP, sodium, blood urea nitrogen
TIMI	14996596,[55] 11044416,[56] 17032691,[30] 7882472[76]	Cox	age, heart rate, history of diabetes, history of MI, previous anterior MI, index inferior MI, SBP, time from onset of pain to study entry, body weight, height, history of angina, history or hypertension

BMI = body mass index; HbA1c = hemoglobin A1c; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high density lipoprotein; GFR = glomerular filtration rate; MI = myocardial infarction; ACE = angiotensin-converting-enzyme; ARB = angiotensin receptor blockers; TIA = transient ischemic attack; NYHA = New York Heart Association; CABG = coronary artery bypass graft; ECG = electrocardiogram; PTCA = Percutaneous transluminal coronary angioplasty; ACC = American College of Cardiology; TACS = total anterior circulation syndrome; PACS = partial anterior circulation syndrome; LACS = lacunar syndrome; POCS = posterior circulation syndrome;

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