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Publication Date

2023-05-01

DOI

10.1016/j.cct.2023.107172

Peer reviewed

HHS Public Access

Author manuscript

Contemp Clin Trials. Author manuscript; available in PMC 2024 May 01.

Published in final edited form as:

Contemp Clin Trials. 2023 May ; 128: 107172. doi:10.1016/j.cct.2023.107172.

Concordance Between Clinical Outcomes in the Systolic Blood Pressure Intervention Trial and in the Electronic Health Record

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Abstract

Background: Randomized trials are the gold standard for generating clinical practice evidence, but follow-up and outcome ascertainment are resource-intensive. Electronic health record (EHR)

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Author Contributions

PED conceptualized the study and was responsible for funding acquisition; PED and KML were responsible for data curation and methodology; KML was responsible for formal analysis; PED and DST provided supervision; CDC wrote the original draft; and all authors reviewed and edited the manuscript.

data from routine care can be a cost-effective means of follow-up, but concordance with trial-ascertained outcomes is less well-studied.

Methods: We linked EHR and trial data for participants of the Systolic Blood Pressure Intervention Trial (SPRINT), a randomized trial comparing intensive and standard blood pressure targets. Among participants with available EHR data concurrent to trial-ascertained outcomes, we calculated sensitivity, specificity, positive predictive value, and negative predictive value for EHR-recorded cardiovascular disease (CVD) events, using the gold standard of SPRINT-adjudicated outcomes (myocardial infarction (MI)/acute coronary syndrome (ACS), heart failure, stroke, and composite CVD events). We additionally compared the incidence of non-CVD adverse events (hyponatremia, hypernatremia, hypokalemia, hyperkalemia, bradycardia, and hypotension) in trial versus EHR data.

Results: 2,468 SPRINT participants were included (mean age 68 (SD 9) years; 26% female). EHR data demonstrated ≥80% sensitivity and specificity, and ≥99% negative predictive value for MI/ACS, heart failure, stroke, and composite CVD events. Positive predictive value ranged from 26% (95% CI; 16%, 38%) for heart failure to 52% (95% CI; 37%, 67%) for MI/ACS. EHR data uniformly identified more non-CVD adverse events and higher incidence rates compared with trial ascertainment.

Conclusions: These results support a role for EHR data collection in clinical trials, particularly for capturing laboratory-based adverse events. EHR data may be an efficient source for CVD outcome ascertainment, though there is clear benefit from adjudication to avoid false positives.

Keywords

cardiovascular outcomes; outcome ascertainment; electronic health record; pragmatic trial

Introduction

Randomized controlled trials are the gold standard for establishing evidence for causal effects, but are costly and resource-intensive. Consequently, there has been growing interest in the complementary role of pragmatic trials, which leverage existing clinical infrastructure and use routinely collected health data for follow-up and outcome assessment.[1–3] Pragmatic trials can achieve a larger scale and capture potentially more representative study populations, while substantially reducing resource requirements compared with a traditional trial infrastructure. The use of data collected in routine health care can also allow for cost-effective long-term follow up, which may be advantageous or even necessary to detect smaller but clinically significant benefits and harms, including rare adverse events.[4,5]

A major concern for pragmatic trials is the reliability of clinical outcome ascertainment using routinely collected health data, due to the lack of expert adjudication and potential for loss to follow-up when care is fragmented across health systems. For cardiovascular events, prior studies have shown variable agreement between routine health data and the gold standard of manual adjudication. These studies, primarily examining claims or registry data, have found that routine health data tended to have very high specificity, with less consistently high sensitivity and positive predictive value (PPV).[6–9] Evidence regarding outcome ascertainment is relatively limited for electronic health record (EHR) data, for

which key concerns include accuracy of diagnostic coding, missing or incomplete data elements, and care fragmentation across health systems.[10] In a validation study using a sample of 225 adjudicated cardiovascular events from a randomized trial of aspirin dosing, Marquis-Gravel et al found that linked EHR data had a 90% and 72% PPV to identify myocardial infarction (MI) and stroke, respectively.[11] In addition, an understudied aspect in studies of routine health data concordance relates to laboratory and vital sign data, which are generally unavailable in claims.[12]

The objective of this study was to examine the concordance of events recorded by protocolized trial procedures and those captured in the EHR using data from the Systolic Blood Pressure Intervention Trial (SPRINT). We leveraged data from an ancillary study that linked trial data with EHR data collected in routine clinical care of study participants.

Methods

Study Data

SPRINT was a randomized clinical trial conducted at 102 clinical sites in the US to test blood pressure treatment targets for hypertension (ClinicalTrials.gov number NCT01206062).[13] Between November 8, 2010 and March 15, 2013, a total of 9,361 participants were randomized to either an intensive treatment arm (goal systolic BP <120 mm Hg) or to a standard treatment arm (goal systolic BP <140 mm Hg). In the SPRINT EHR ancillary study, trial data were linked to participants' EHR data, including diagnosis codes, vital signs, and laboratory results; details of this linkage have been previously described.[14,15] The SPRINT protocol was approved at all participating clinical sites, and informed consent was waived for this ancillary study due to the exclusive involvement of existing trial and EHR data.

Study Population

For the present study, we included SPRINT participants who had linked EHR data that included at least two BP measurements on separate days, one serum creatinine value, and one International Classification of Diseases (ICD) diagnosis code at the site in which they were originally enrolled during the study period. Because our primary outcome was time to an incident cardiovascular disease (CVD) event, we excluded participants who had prevalent CVD at enrollment in our primary analysis (30.7%; n = 1094). Prevalent CVD was defined as a history of MI/acute coronary syndrome (ACS), heart failure, or stroke/cerebrovascular disease upon SPRINT enrollment, based on either the SPRINT baseline questionnaire or the presence of any encounter-based CVD ICD code within EHR data prior to the date of enrollment. Restriction to participants without prevalent CVD reduces the possibility that a CVD event in EHR data would reflect recurrent coding of a past event, rather than a true incident CVD event. For secondary analyses examining non-CVD events as outcomes, we did not exclude participants on the basis of prevalent CVD at baseline.

Outcome Assessment

Outcomes in SPRINT were based on trial reporting of serious adverse events (SAE).[13] The primary outcome was CVD events, defined as a composite of MI/ACS, heart failure, or

stroke/cerebrovascular disease. In SPRINT, CVD events were identified by SAE reports of MI/ACS, heart failure, or stroke, which were then adjudicated according to the trial protocol.[13] In EHR data, CVD events were identified using encounter-based ICD codes.[16–19] In a secondary analysis, we examined non-CVD adverse events, including hyponatremia, hypernatremia, hypokalemia, hyperkalemia, bradycardia, and hypotension. Detailed descriptions of these outcomes as they were defined in SPRINT and EHR data are presented in Supplemental Table 1.

Statistical Analysis

To assess for concordance of outcome ascertainment between SPRINT and EHR data, we first identified all SPRINT SAE occurrences. Because study sites varied in the time at which they began capturing EHR data, we ensured that at the time of each SPRINT SAE, EHR data (defined as having two consecutive days with creatinine values and the presence of any ICD code) was available from the corresponding study site within a window spanning ±14 days of a SPRINT SAE. If EHR data was not available at the time of a SPRINT SAE, then that event was excluded for the concordance analysis. This could occur if the SAE took place at a different health system than the corresponding study site. For each SAE, we assessed diagnosis codes from EHR data within ±14 days to determine concordance in the identification of CVD events. We considered outcomes to be concordant if the EHR data included at least one ICD code for a CVD event of the same type (e.g., MI/ACS, heart failure, or stroke/cerebrovascular disease) within ±14 days of the SPRINT CVD event. Treating SPRINT outcomes as the gold standard, we then calculated sensitivity, specificity, PPV, and negative predictive value (NPV) for EHR-ascertained events. We assessed concordance for the first occurrence of a CVD event, which would align with outcomes for a time-to-event analysis. In a sensitivity analysis, we assessed concordance including both initial and subsequent SAEs occurring during follow up (e.g., one person may have multiple CVD events). Additionally, we repeated our analysis without excluding participants who had CVD at baseline.

In a secondary analysis, we examined the incidence of non-CVD adverse events (hyponatremia, hypernatremia, hypokalemia, hyperkalemia, bradycardia, and hypotension). For each event, we calculated incidence rates and 95% confidence intervals for the intensive treatment and standard treatment arms in SPRINT and EHR data. We used Cox proportional hazard models with a baseline hazard function stratified by site to compute unadjusted hazard ratios for the effect of intensive treatment on each adverse event, censoring participants at the time of death, loss to follow up, or study closeout.

Results

Of 9,361 participants randomized in SPRINT, approximately one-quarter (n=2,468) met our inclusion criteria (Figure 1).

In total, 1206 participants from the standard treatment arm and 1262 participants from the intensive treatment arm were included. Approximately half the study population were from Veterans Affairs (VA) study sites, and nearly three-quarters were male (Table 1).

In both arms, mean age was 68 years (SD 9 years) and approximately one quarter were female. Baseline BP was similar (138/78 mm Hg) in both groups. Baseline characteristics of SPRINT participants who did not meet the inclusion criteria compared to those included in this analysis are shown in Supplemental Table 2.

Concordance of CVD Outcomes between SPRINT and EHR

In total, 865 SPRINT SAE reports had concurrently captured EHR data to assess concordance. Event counts and incidence rates for CVD outcomes in SPRINT and EHR data are shown in Supplemental Figure 1.

With SPRINT SAE reports as the gold standard, the sensitivity, specificity, PPV, and NPV of EHR data for ascertaining CVD outcomes are shown in Figure 2. EHR data demonstrated ≥80% sensitivity and specificity, and ≥99% NPV, for MI/ACS, heart failure, stroke, and composite CVD events. Results were largely similar across both intensive treatment and standard treatment arms. Overall specificity was highest for MI/ACS (97%; 95% CI, 96%, 98%) and stroke (98%; 95% CI, 97%, 99%). PPV was lower, ranging from 26% (95% CI; 16%, 38%) for heart failure to 52% (95% CI; 37%, 67%) for MI/ACS. Similar results were observed for evaluating concordance when all events during follow up (not just the first event) were included (Supplemental Table 3). In analyses where participants with prior CVD were included, PPV was notably lower (range 23%−42% across the CVD outcomes) compared with the primary analysis.

Non-CVD Adverse Event Incidence Rates in SPRINT and EHR Data

Event counts, incidence rates, and hazard ratios for non-CVD adverse events are shown in Figure 3. Across different types of adverse events, EHR data uniformly identified more events, resulting in higher incidence rates compared with SPRINT reports. In some cases, EHR data demonstrated several-fold greater event counts and incidence rates: most notably for hypotension, where EHR data identified over 6 times the number of episodes compared with SPRINT (641 events in EHR versus 100 events in SPRINT in the intensive treatment group). For most adverse events, incidence rates were similar between the intensive treatment and standard treatment arms. In regression analyses (Supplemental Table 4), SPRINT and EHR data were mostly concordant in the direction and statistical significance of hazard ratios comparing intensive to standard treatment arms, with two exceptions. For hypernatremia, no events were recorded in SPRINT data for the standard treatment arm, so a hazard ratio was not calculated. The other exception was hypotension, which showed discordant results: in SPRINT data, intensive (versus standard) treatment was associated with increased hypotension events (HR 1.94; 95% CI, 1.38, 2.72), while in EHR data, intensive treatment was associated with fewer hypotension events (HR 0.68; 95% CI, 0.62, 0.76).

Discussion

In this ancillary study of SPRINT examining concordance between linked trial and EHR data, we found that CVD events identified by EHR data demonstrated good sensitivity, excellent specificity and NPV, and relatively poor PPV, when compared with adjudicated

CVD events as the gold standard. These characteristics were similar between intensive and standard treatment arms. For non-CVD adverse events, EHR data consistently captured higher event counts than reported in the trial. These results have a number of implications for the design of clinical trials that involve sourcing EHR data for ascertaining outcomes and adverse events.

The sensitivity ranging 86%−91% for capturing CVD events indicates that most SPRINT-adjudicated CVD events were concordantly captured in EHR data. High sensitivity is important for accurately reporting the risk of events and event rates, and low sensitivity would result in an underestimation of true event rates, independent of the impact of false positives from low specificity. Specificity of EHR data was extremely high or near perfect, indicating that non-CVD SPRINT events virtually never had concurrently recorded CVD conditions in the EHR. High outcome specificity is a useful property that can support use of routine health data for estimating relative measures of treatment effects in clinical trials. As long as sensitivity for the outcome does not differ between arms under comparison, having nearly perfect specificity will result in minimal bias for measures of relative risk.[20] This property may account for the close agreement of treatment effect estimates obtained via analysis of routine health versus trial-collected data in other studies.[8]

In contrast to the sensitivity and specificity results, we found that PPV was notably poorer, ranging 26%−52% across the CVD outcomes, while NPV was close to 1. Low PPV indicates that CVD events recorded in real world data frequently did not represent a true occurrence of a CVD event as assessed by trial adjudication; these false positives would cause a tendency toward inflated CVD event rates when measured by EHR data. Several factors may contribute to false positives and limit the PPV of routine health data. Diagnosis codes may represent historical events, rather than a current active issue; this may account for the worse PPV when participants with prior CVD were included. When patients receive care in multiple health systems, EHR data sourced from one system may be incomplete, and diagnosis codes for a CVD event may lag behind the occurrence of the event itself (e.g., at an outside hospital). This concern may be mitigated by linkage with claims data or using multiple EHR data sources.[21] In addition, initially recorded EHR diagnosis codes may be inaccurate upon further clinical evaluation that changes the ultimate diagnosis, resulting in an excess of false positive CVD events. With the desire for more inter-EHR communication and problem list reconciliation across different EHRs, there is a also potential for more false positives caused by inaccurate or outdated information being reconciled. The pattern we observed of low PPV with high NPV can also reflect low prevalence, as both predictive values are dependent on the prevalence of true events in the study.[22]

The test characteristics we observed for CVD outcomes in EHR data compared to adjudicated SPRINT outcomes are similar to those found in studies examining claims or registry data sources.[6–9] Consistent features include very high or near perfect specificity, with sensitivity that is good but not as high. Meanwhile, PPV was much lower for CVD outcomes in our study, which assessed concordance with EHR data, as well as in other studies that examined concordance with claims and registry data. For example, in a study comparing claims with trial-ascertained CVD outcomes of MI, stroke, and composite CVD events, Faridi et al found near perfect specificity, sensitivity ranging from 62–73%, and

PPV ranging from 47% (for stroke) to 86% (MI).[9] Additionally, we did not find substantive differences in test characteristics by randomization arm, a reassuring finding as differential ascertainment according to exposure status may be a source of bias in treatment effect estimation.[23]

In addition to the primary outcomes, assessment of adverse events is a critical aspect of clinical trials. We found that for adverse events, EHR data uniformly identified a greater number of events than reported in the SPRINT follow-up procedures. Greater event capture by EHR data was similarly noted in a study examining acute kidney injury outcomes in EHR and SPRINT data.[15] Ascertainment of these adverse events relies on laboratory or vital sign data, which can be collected at a greater frequency in routine health data compared with the trial setting, where these data are collected in study visits at prespecified follow up intervals. For outcomes based on commonly obtained laboratory data, collection of EHR data could be a useful adjunct for outcome ascertainment that is more sensitive compared to study visit testing. This may be especially beneficial for identifying safety signals in rare adverse events. However, such findings may require confirmation because routine health data can be subject to differential ascertainment by other patient charcteristics (detection bias).[24,25] For example, one group may have more observed hypokalemia if they experience a greater frequency of emergency visits with laboratory testing—and thus more opportunity for hypokalemia to be detected—for unrelated reasons, even if the true incidence of hypokalemia is the same between groups. Nevertheless, our study found that EHR and SPRINT data demonstrated largely concordant findings with respect to direction and statistical significance for the intervention effect on electrolyte disturbances.

With respect to hypotension, however, we noted discordance in the direction of event associations: intensive BP control was associated with more hypotension in SPRINT follow up visits, but less hypotension in EHR data. This discordance may relate to the inability to replicate ascertainment of hypotension in SPRINT, which was identified by site investigators. Hypotension in EHR data was defined as a >20% decline in an outpatient systolic BP relative to a baseline value (the previous SPRINT study visit BP, or in cases where antihypertensive medications had been adjusted, the average of the previous and following SPRINT study visit BP). Thus, greater EHR hypotension incidence rate in the standard treatment arm may be explained by the higher baseline BP values in SPRINT visits,[13] from which a 20% decline is more easily achievable upon repeated BP measures. It is also worth noting that SPRINT BP measures used a standardized protocol,[26] whereas the circumstances of BP measures recorded in EHR data may come from a variety of care settings and are less well specified, with an inconsistent correlation to standardized BP measurements from SPRINT.[14]

Strengths of our study included the linkage of EHR data to rigorously collected and adjudicated clinical trial data across a geographically diverse multicenter setting and assessment of concordance between trial and EHR based incidence of laboratory and vital sign based adverse events. Limitations included EHR data being available for a subset of the SPRINT population, thus lacking power to replicate SPRINT results or estimate treatment effects in EHR data for comparison. EHR data may not be comprehensive if participants receive care across multiple health systems, although this is also representative of a

pragmatic trial scenario. We restricted our analysis to participants having concurrent EHR and trial data to focus on concordance of event ascertainment. Thus, generalizability may be limited in settings with greater EHR data "leakage", i.e., missingness due to fragmentation of care across multiple health systems with incomplete interoperability. Nearly half the study population came from VA systems, where data leakage is less common; thus the applicability of results to different health system settings is less certain. These limitations depict and highlight broader challenges in the use of EHR data for pragmatic trial follow up, particularly in large scale multicenter settings. For example, the 26% of SPRINT participants with EHR linkage in this study were not necessarily representative of the overall SPRINT study population. This was most notable in that VA health systems comprised 47% the present study cohort compared with 21% of the overall SPRINT study; consequently, nearly 75% of the present study cohort were male. Thus, the design of large scale pragmatic trials should consider that selection of study sites based on availability of EHR data, the extent of data fragmentation, or other data quality parameters may have important implications for representativeness and generalizability.

In conclusion, we found that for SPRINT participants, EHR data had high specificity and NPV, good sensitivity, and relatively poor PPV for CVD outcomes. In addition, EHR data identified a greater number of non-CVD adverse events than recorded in SPRINT follow up study visits and could be a powerful tool for identification of adverse events. Both pragmatic and explanatory clinical trials could benefit from incorporating linkage with EHR data for ascertainment of laboratory-based events. For CVD outcomes, it may be ideal to combine EHR with other data sources (e.g., claims) or use manual validation for a sample of outcomes to attain the most reliable and effective scaling for pragmatic trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures

CDC receives research support from Bayer Healthcare, Inc. outside the submitted work. AM reports ownership interest in iEnroll, LLC. The remaining authors have nothing to disclose.

Funding

Research reported in this publication was supported by the Agency for Healthcare Research and Quality under award number K12HS026383, the National Center for Advancing Translational Sciences of the NIH under award number KL2TR001870, and the National Heart Lung and Blood Institute under award number R01HL136679. The content is solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

References

1. Sepehrvand N, Alemayehu W, Das D, Gupta AK, Gouda P, Ghimire A, et al. Trends in the Explanatory or Pragmatic Nature of Cardiovascular Clinical Trials Over 2 Decades. JAMA Cardiol 4: 1122–1128, 2019 [PubMed: 31473763]
2. Rodriguez F, Califf RM, Harrington RA. Consequences of Slow Progress Toward Pragmatism in Randomized Clinical Trials: It Is Time to Get Practical. JAMA Cardiol 4: 1129–1130, 2019 [PubMed: 31473764]

3. Usman MS, Van Spall HGC, Greene SJ, Pandey A, McGuire DK, Ali ZA, et al. The need for increased pragmatism in cardiovascular clinical trials. Nat Rev Cardiol 19: 737–750, 2022 [PubMed: 35581337]
4. Fitzpatrick T, Perrier L, Shakik S, Cairncross Z, Tricco AC, Lix L, et al. Assessment of Long-term Follow-up of Randomized Trial Participants by Linkage to Routinely Collected Data: A Scoping Review and Analysis. JAMA Netw Open 1: e186019, 2018 [PubMed: 30646311]
5. Kwakkenbos L, Imran M, McCord KA, Sampson M, Fröbert O, Gale C, et al. Protocol for a scoping review to support development of a CONSORT extension for randomised controlled trials using cohorts and routinely collected health data. BMJ Open 8: e025266, 2018
6. Rubbo B, Fitzpatrick NK, Denaxas S, Daskalopoulou M, Yu N, Patel RS, et al. Use of electronic health records to ascertain, validate and phenotype acute myocardial infarction: A systematic review and recommendations. Int J Cardiol 187: 705–711, 2015 [PubMed: 25966015]
7. Harper C, Mafham M, Herrington W, Staplin N, Stevens W, Wallendszus K, et al. Comparison of the Accuracy and Completeness of Records of Serious Vascular Events in Routinely Collected Data vs Clinical Trial–Adjudicated Direct Follow-up Data in the UK. JAMA Netw Open 4: e2139748, 2021 [PubMed: 34962561]
8. Rodrigues C, Odutayo A, Patel S, Agarwal A, da Costa BR, Lin E, et al. Accuracy of Cardiovascular Trial Outcome Ascertainment and Treatment Effect Estimates from Routine Health Data: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes 14: e007903, 2021 [PubMed: 33993728]
9. Faridi KF, Tamez H, Butala NM, Song Y, Shen C, Secemsky EA, et al. Comparability of Event Adjudication Versus Administrative Billing Claims for Outcome Ascertainment in the Dual Antiplatelet Therapy (DAPT) Study: Findings from the EXTEND-DAPT Study. Circ Cardiovasc Qual Outcomes 14: e006589, 2021 [PubMed: 33435731]
10. Raman SR, O'Brien EC, Hammill BG, Nelson AJ, Fish LJ, Curtis LH, et al. Evaluating fitness-for-use of electronic health records in pragmatic clinical trials: reported practices and recommendations. J Am Med Inform Assoc 29: 798–804, 2022 [PubMed: 35171985]
11. Marquis-Gravel G, Hammill BG, Mulder H, Roe MT, Robertson HR, Wruck LM, et al. Validation of Cardiovascular End Points Ascertainment Leveraging Multisource Electronic Health Records Harmonized Into a Common Data Model in the ADAPTABLE Randomized Clinical Trial. Circ Cardiovasc Qual Outcomes 14: e008190, 2021 [PubMed: 34886680]
12. Sarrazin MSV, Rosenthal GE. Finding pure and simple truths with administrative data. JAMA 307: 1433–1435, 2012 [PubMed: 22474208]
13. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 373: 2103–2116, 2015 [PubMed: 26551272]
14. Drawz PE, Agarwal A, Dwyer JP, Horwitz E, Lash J, Lenoir K, et al. Concordance Between Blood Pressure in the Systolic Blood Pressure Intervention Trial and in Routine Clinical Practice. JAMA Intern Med 180: 1655–1663, 2020 [PubMed: 33044494]
15. Drawz PE, Rai NK, Lenoir KM, Suarez M, Powell JR, Raj DS, et al. Effect of Intensive versus Standard BP Control on AKI and Subsequent Cardiovascular Outcomes and Mortality: Findings from the SPRINT EHR Study. Kidney360 3: 1253–1262, 2022 [PubMed: 35919535]
16. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi J-C, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 43: 1130–1139, 2005 [PubMed: 16224307]
17. Tonelli M, Wiebe N, Fortin M, Guthrie B, Hemmelgarn BR, James MT, et al. Methods for identifying 30 chronic conditions: application to administrative data. BMC Med Inform Decis Mak 15: 31, 2015 [PubMed: 25886580]
18. Yasaitis LC, Berkman LF, Chandra A. Comparison of self-reported and Medicare claims-identified acute myocardial infarction. Circulation 131: 1477–1485; discussion 1485, 2015 [PubMed: 25747935]
19. Dawwas GK, Dietrich E, Winchester DE, Winterstein AG, Segal R, Park H. Comparative Effectiveness and Safety of Ticagrelor versus Prasugrel in Patients with Acute Coronary Syndrome: A Retrospective Cohort Analysis. Pharmacotherapy 39: 912–920, 2019 [PubMed: 31332815]

20. Yland JJ, Wesselink AK, Lash TL, Fox MP. Misconceptions About the Direction of Bias From Nondifferential Misclassification. Am J Epidemiol 191: 1485–1495, 2022 [PubMed: 35231925]

21. Ishani A, Cushman WC, Leatherman SM, Lew RA, Woods P, Glassman PA, et al. Chlorthalidone vs. Hydrochlorothiazide for Hypertension–Cardiovascular Events. N Engl J Med 2022

22. Sensitivity Trevethan R., Specificity, and Predictive Values: Foundations, Pliabilities, and Pitfalls in Research and Practice. Front Public Health 5: 307, 2017 [PubMed: 29209603]

23. Copeland KT, Checkoway H, McMichael AJ, Holbrook RH. Bias due to misclassification in the estimation of relative risk. Am J Epidemiol 105: 488–495, 1977 [PubMed: 871121]

24. Kennes LN. Methodological Aspects in Studies Based on Clinical Routine Data. Adv Ther 34: 2199–2209, 2017 [PubMed: 28900858]

25. Wirtz HS, Calip GS, Buist DSM, Gralow JR, Barlow WE, Gray S, et al. Evidence for Detection Bias by Medication Use in a Cohort Study of Breast Cancer Survivors. Am J Epidemiol 185: 661–672, 2017 [PubMed: 28338879]

26. The SPRINT Study Research Group. The design and rationale of a multi-center clinical trial comparing two strategies for control of systolic blood pressure: The Systolic Blood Pressure Intervention Trial (SPRINT). Clin Trials 11: 532–546, 2014 [PubMed: 24902920]

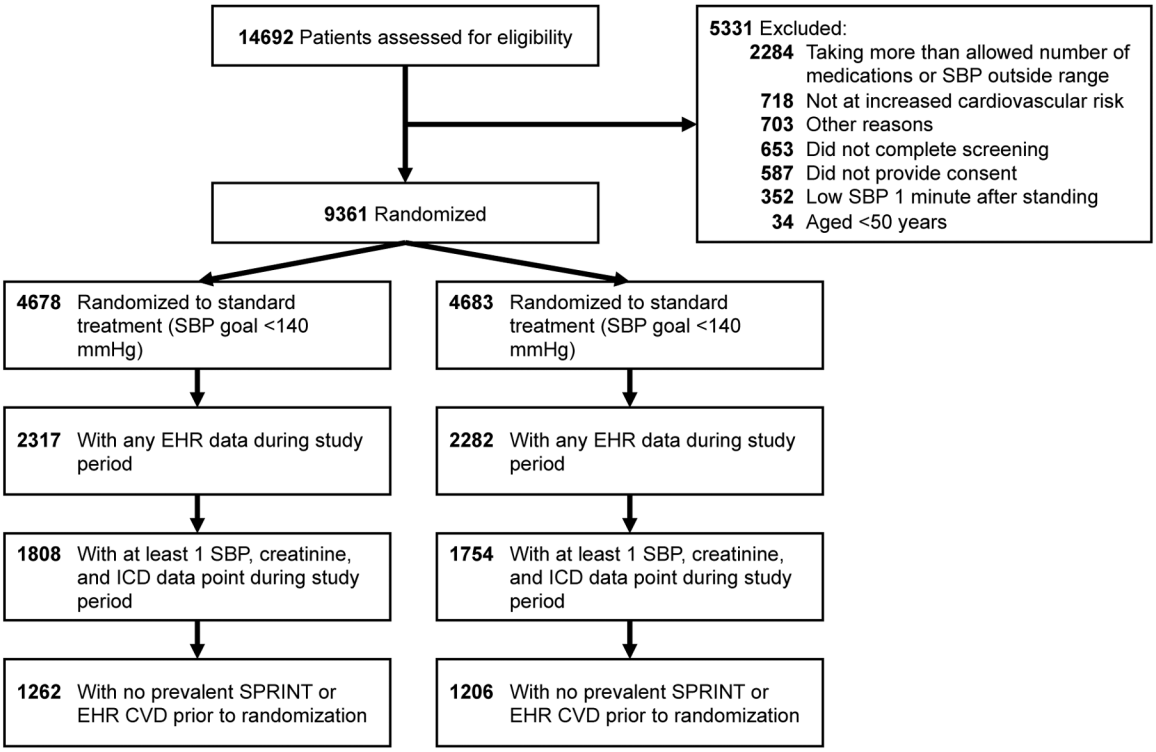

Figure 1. Study Flow Diagram

Abbreviations: CVD = cardiovascular disease; EHR = electronic health record; ICD = International Classification of Diseases; SBP = systolic blood pressure; SPRINT = Systolic Blood Pressure Intervention Trial.

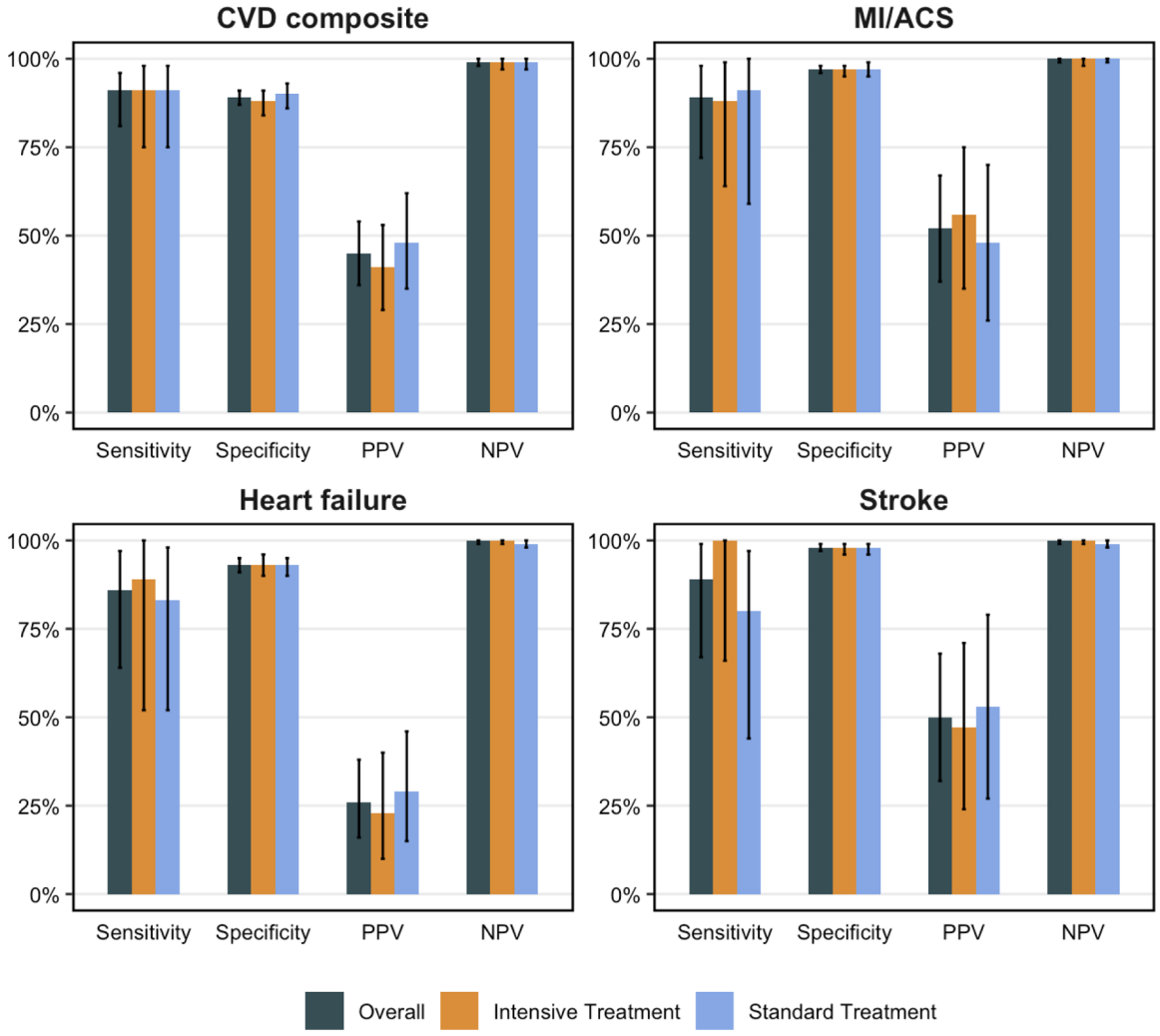

Figure 2. Concordance of Electronic Health Records with Serious Adverse Event Reports for Cardiovascular Events in the Systolic Blood Pressure Intervention Trial

Error bars indicate 95% confidence intervals.

Abbreviations: CVD = cardiovascular disease; MI/ACS = myocardial infarction/acute coronary syndrome; NPV = negative predictive value; PPV = positive predictive value.

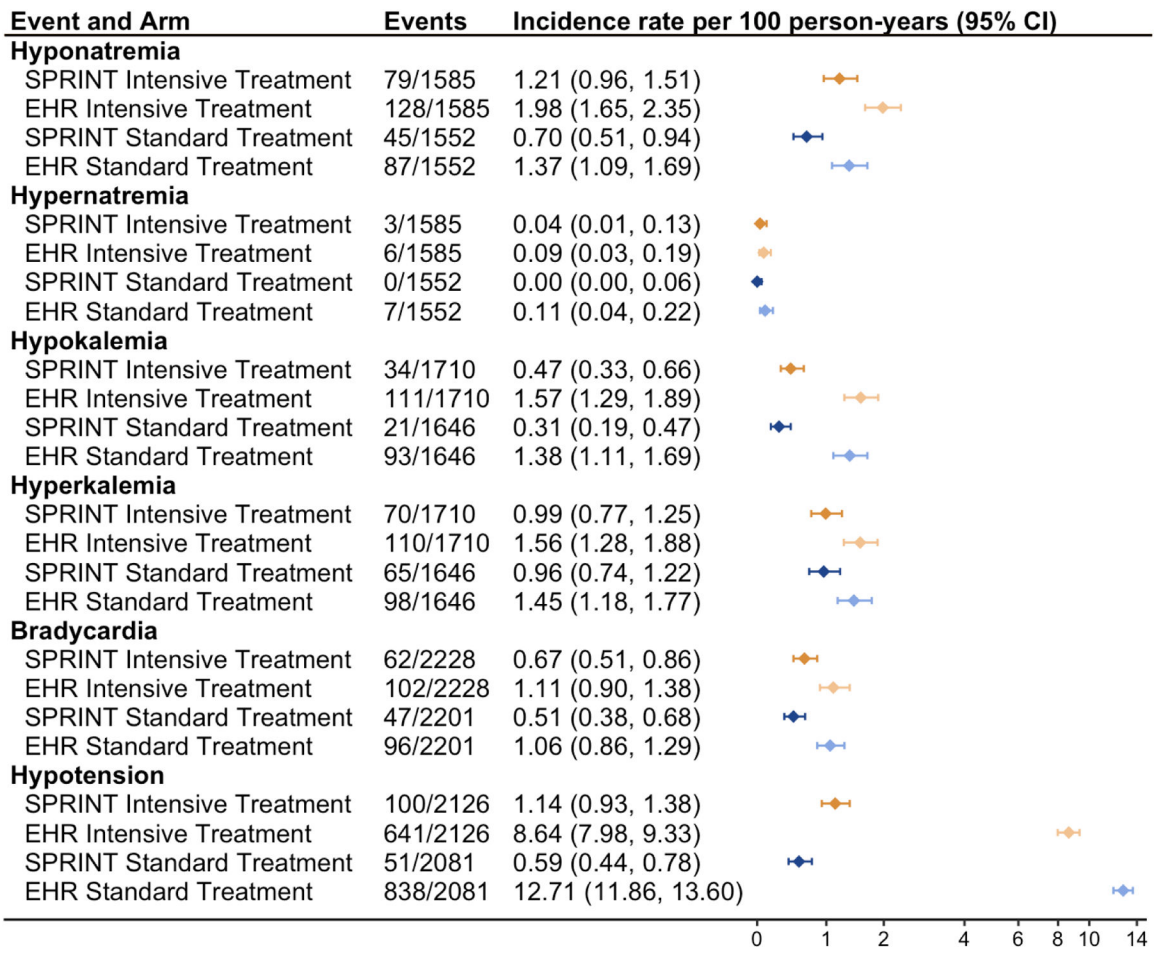

Figure 3. Incidence Rates of Non-CVD Adverse Events Ascertained in SPRINT and EHR Follow Up

Note that denominators differ by adverse event type due to definitions requiring the presence of data in both EHR and trial data (see Supplemental Table 1).

Abbreviations: CI = confidence interval; CVD = cardiovascular disease; EHR = electronic health record; SPRINT = Systolic Blood Pressure Intervention Trial.

Table 1.

Baseline Characteristics of Participants without Prevalent Cardiovascular Disease in the SPRINT EHR Study

Characteristic	Intensive treatment	Standard treatment
N	1262	1206
VA site, n (%)	597 (47.3)	574 (47.6)
Age (years), mean (SD)	67.6 (9.1)	67.6 (9.4)
Female, n (%)	338 (26.8)	305 (25.3)
Race/Ethnicity, n (%)		
Black	429 (34.0)	427 (35.4)
Hispanic	63 (5.0)	43 (3.6)
White	751 (59.5)	725 (60.1)
Other	19 (1.5)	11 (0.9)
Smoking, n (%)		
Never smoker	487 (38.6)	478 (39.6)
Former smoker	589 (46.7)	567 (47.0)
Current smoker	186 (14.7)	161 (13.3)
BMI (kg/m^2), mean (SD)	30.2 (5.8)	30.2 (5.7)
SBP (mm Hg), mean (SD)	138 (15)	138 (15)
DBP (mm Hg), mean (SD)	78 (11)	78 (11)
eGFR <60 ml/min/1.73m^2, n (%)	345 (27.3)	311 (25.8)

Abbreviations: BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; EHR = electronic health record; SBP = systolic blood pressure; SD = standard deviation; SPRINT = Systolic Blood Pressure Intervention Trial; VA = Veterans Affairs.