Validating the use of registries and claims data to support randomized trials: Rationale and design of the Extending Trial-Based Evaluations of Medical Therapies Using Novel Sources of Data (EXTEND) Study

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Background Randomized controlled trials are the "gold standard" for comparing the safety and efficacy of therapies but may be limited due to high costs, lack of feasibility, and difficulty enrolling "real-world" patient populations. The Extending Trial-Based Evaluations of Medical Therapies Using Novel Sources of Data (EXTEND) Study seeks to evaluate whether data collected within procedural registries and claims databases can reproduce trial results by substituting surrogate non–trial-based variables for exposures and outcomes.

Methods and results Patient-level data from 2 clinical trial programs—the Dual Antiplatelet Therapy Study and the United States CoreValve Studies—will be linked to a combination of national registry, administrative claims, and health system data. The concordance between baseline and outcomes data collected within nontrial data sets and trial information, including adjudicated end point events, will be assessed. We will compare the study results obtained using these alternative data sources to those derived using trial-ascertained variables and end points using trial-adjudicated end points and covariates.

Conclusions Linkage of trials to registries and claims data represents an opportunity to use alternative data sources in place of and as adjuncts to randomized clinical trial data but requires further validation. The results of this research will help determine how these data sources can be used to improve our present and future understanding of new medical treatments. (Am Heart J 2019;212:64-71.)

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Randomized controlled trials (RCTs) are considered the gold standard for comparing the efficacy and safety of therapies but suffer from a number of important limitations including high costs, limited feasibility, and difficulty enrolling "real-world" patient populations, which limit the generalizability of their findings. Alternatively, observational study designs that harness the large amounts of data routinely collected within disease and procedural registries, health system databases, and payer claims are relatively inexpensive and allow for powerful and efficient long-term evaluation of medical therapies in representative populations. However, these studies are also subject to inherent issues such as miscoding and confounding by unmeasured variables. The combined use of prospectively designed trials that also harness passively collected data in the form of registries or claims databases represents a unique opportunity to leverage the randomization scheme of clinical trials to minimize confounding while gaining the efficiencies of evaluating

outcomes through existing data already collected in the routine course of clinical care. Such data could be used, among other ways, to (1) replace the collection of baseline patient information and subsequent outcomes; (2) augment data collection through filling in gaps of data that were not captured by clinical trials; and (3) assess the generalizability of trial populations through comparisons between trial participants and nonparticipants[1].

Although harnessing existing registries to support trials has been advocated,[2] to date, these approaches have only been used in a small number of trials[3-7] using a limited number of end points. Recently, the use of multistakeholder real-world evidence (eg, clinical registries, electronic health records, and administrative billing claims) for medical device evaluation and regulatory decision making has been advocated by the US Food and Drug Administration, which established the National Evaluation System for Health Technology program to efficiently generate safety and efficacy data to support pre- and postmarketing regulatory decisions.[8] However, in which situations and for what end points these designs may readily be implemented while maintaining validity have not been widely tested in comparison to traditional trial design and data collection.[2,5,9-12]

The linkage of previously conducted clinical trials with registries and claims databases provides the opportunity to more rigorously evaluate pragmatically designed clinical trials. The Extending Trial-Based Evaluations of Medical Therapies Using Novel Sources of Data (EXTEND) Study will seek to address these questions by linking data from claims, procedural registries, and administrative databases with data from 2 separate clinical trial programs (Figure 1). The EXTEND-DAPT substudy will use linkage to the Dual Antiplatelet Therapy (DAPT) Study,[13] a prospective, multicenter, randomized, double-blind trial that assessed the effectiveness and safety of 12 versus 30 months of DAPT in subjects undergoing percutaneous coronary intervention (PCI) with placement of either a drug-eluting stent or bare-metal stent. The EXTEND-CoreValve substudy will use data from the US CoreValve program, a set of prospective trials evaluating the efficacy and safety of transcatheter aortic valve replacement (TAVR) with the CoreValve self-expanding prosthesis in patients with severe aortic stenosis at intermediate, high, or extreme risk of mortality from surgical aortic valve replacement (SAVR).

The primary aims of the study are to (1) examine whether outcomes collected in nontrial data sets agree with data collected, cleaned and adjudicated within trials; (2) assess whether the analysis using claims-based outcomes results in the same treatment effect estimates as those observed in trials; and (3) develop measures to assess trial generalizability through the comparison of trial participants and nonparticipants within large real-world data sets.

Study design

The EXTEND study is a National Heart, Lung, and Blood Institute–funded study (1R01HL136708) that will link clinical trial adjudicated data (ie, "actively" acquired data) and administrative claims or registry information obtained on trial participants (ie, "passively" acquired data) to evaluate how nontrial data sets can be used as surrogates or adjuncts to traditional randomized trials. It represents a multi-institutional collaboration involving an academic, federal, and industry partnership between the Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology at Beth Israel Deaconess Medical Center, the Baim Institute for Clinical Research, the American College of Cardiology, and Medtronic.

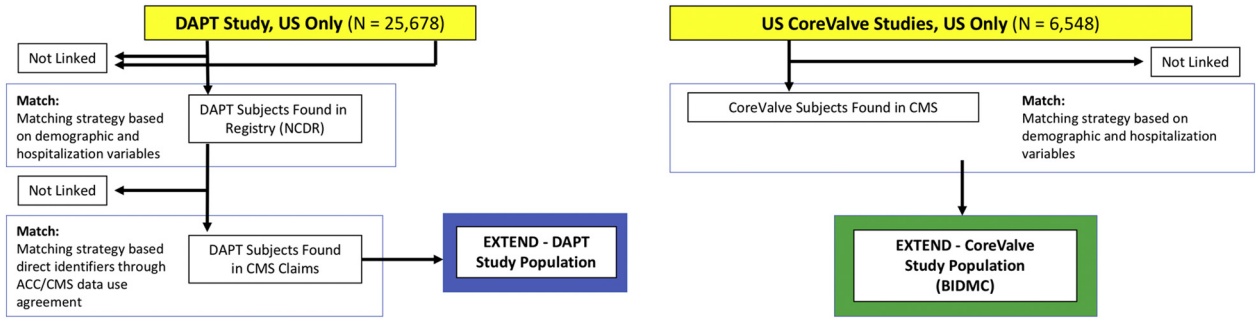
Data sources

Clinical trial data

EXTEND-DAPT. Clinical trial data for EXTEND-DAPT will come from the DAPT Study, a multicenter RCT evaluating long-term dual antiplatelet therapy among patients receiving coronary stents. This was the largest postmarketing study of coronary stent-treated patients to date,[14] enrolling more than 25,000 patients. We will include all US patients enrolled in the DAPT Study (N = 25,678) for this analysis (Table I).[13] Patients undergoing PCI with a bare-metal or drug-eluting coronary stent were enrolled and treated with thienopyridine plus aspirin for 1 year. Thereafter, patients were randomized either to aspirin plus thienopyridine or to aspirin plus placebo for another 18 months. The study, operated by the Baim Institute for Clinical Research, used limited data collection and risk-based site monitoring to reduce trial costs and used a centralized Clinical Events Committee (CEC) for event adjudication.

EXTEND-CoreValve. Clinical trial data for EXTEND-CoreValve will come from the US CoreValve Pivotal Trials database, a set of 3 large studies (N = 3,049) comparing TAVR and SAVR for individuals with severe aortic stenosis: the Surgical or Transcatheter Aortic-Valve Replacement in Intermediate Risk Patients (SURTAVI) study (N = 1660),[15] the US CoreValve High Risk study (N = 750),[16] and the US CoreValve Extreme Risk Study (N = 639)[17] (Table I). The SURTAVI and US CoreValve High Risk studies were randomized comparisons of CoreValve bioprostheses and SAVR, the Extreme Risk Study was a nonrandomized comparison of TAVR to an objective performance measure. Additionally, US TAVR recipients included in the single-arm Continued Access Study (N = 2,732) and Expanded Use Study (N = 767) will be included in EXTEND-CoreValve. The Continued Access Study is a single-arm cohort study of individuals receiving a CoreValve TAVR in the High Risk or Extreme Risk Pivotal Trials, intended for follow-up of outcomes and adverse events. The US CoreValve Expanded Use Study represents a subset of patients excluded from the US CoreValve Extreme Risk Pivotal Trial population due to 1 or more

Figure 1



Linkage of nontrial data sources to trial scheme and rationale.

additional comorbidities. It includes 6 primary cohorts: individuals excluded due to severe mitral valve regurgitation, severe tricuspid valve regurgitation, end-stage renal disease, low-gradient low-output aortic stenosis, or valve in valve with failed bioprosthetic surgical valve, and those with 2 or more of the listed conditions.

Registry Data

Registry data for EXTEND-DAPT will come from the American College of Cardiology National Cardiovascular Data Registry CathPCI Registry.[18] This is a national quality improvement registry of patients undergoing cardiac catheterization and PCI and includes data from more than 1,700 hospitals drawn from all 50 states in the United States.[19] The registry collects detailed sociodemographic, clinical, and procedural information for more than 600,000 patients at participating centers each year, along with in-hospital outcomes. Vital status will be obtained from the National Death Index, a centralized registry of death record information maintained by the National Center for Health Statistics and made available for research purposes. EXTEND-CoreValve will not involve linkage to registry data.

Claims data

Payer claims data for linkage to trial data in EXTEND-DAPT and EXTEND-CoreValve will come from Medicare fee-for-service beneficiary claims. Research files will be obtained from the Centers for Medicare and Medicaid Services (CMS) for the years 2003-2014 (2009-2014 for EXTEND-DAPT), consisting of a 100% sample of patient- and hospital-level inpatient billing data for Medicare fee-for-service beneficiaries in the Medicare Provider and Analysis Review (MedPAR data set) and Inpatient Standard Analytical Files (SAF; Part A claims).

Data management

To permit the exchange of data across multiple platforms, data use agreements were obtained between the Smith Center and CMS, the Smith Center and Medtronic (for CoreValve data), the Baim Institute and CMS, and the Baim Institute and the American College of Cardiology (for registry data in EXTEND-DAPT). Whereas EXTEND-CoreValve data will be located behind a secure firewall at the Smith Center and analyzed by Smith Center biostatisticians, EXTEND-DAPT data will be located behind a secure firewall at the Baim Institute and analyzed by Baim Institute biostatisticians. As contacting individual trial participants was infeasible and the study was thought to present minimal risk to participants, a waiver of informed consent was obtained in addition to institutional review board approval from the BIDMC Committee on Clinical investigations for EXTEND-CoreValve (obtained via the Smith Center). Approval is pending for EXTEND-DAPT. Data linkage and analyses will be performed with SAS v 9.4 (SAS Institute, Cary, NC). Per the data use agreements, a deidentified EXTEND data set cannot be made publicly available.

Covariates, outcomes, and statistical considerations

Linkage strategy

We will use deterministic linkage methods to perform multiple distinct linkages between data sets based on presence or absence of direct identifiers (Figure 1). As direct patient identifiers are not available in the DAPT Study and US CoreValve Pivotal Trials, a deterministic matching algorithm will be applied, similar to previously described methods.[18,20] Specifically, we will link records from different data sources using age or date of birth, sex, admission and discharge dates, procedure date and type, and hospital identifier. In cases where multiple records are linked (more likely for EXTEND-DAPT), additional variables including stent type, stent brand, number of stents, and myocardial infarction during index hospitalization may be used. This general strategy has been found to effectively match 86% of CMS patients undergoing PCI at National Cardiovascular Data Registry–CMS linkable

Table I. Summary of studies included in the EXTEND Study

Trial name	Subjects	Sites	STS-PROM score	Comparison	Randomization strategy
DAPT	25,678	452	N/A	12 vs 30 months DAPT	Randomized
SURTAVI	1,660	87	3%-15%	CoreValve bioprosthesis vs SAVR	Randomized (Bayesian)
US CoreValve High Risk Study	750	45	>15%	CoreValve bioprosthesis vs SAVR	Randomized
US Pivotal Extreme Risk Study	639	41	>50%	CoreValve bioprosthesis vs objective performance goal	Nonrandomized
US CoreValve Continued Access Study	2,732	44	3% to >50%	CoreValve bioprosthesis	Nonrandomized
US CoreValve Expanded Use Study	767	41	>50%	CoreValve bioprosthesis	Nonrandomized

STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality Score.
*Arm A = 30 months of DAPT (EXTEND-DAPT) or TAVR (EXTEND-CoreValve). Arm B = 12 months of DAPT (EXTEND-DAPT) or SAVR (EXTEND-CoreValve).

hospitals, and 75% of patients aged 65 or older within the CathPCI Registry.[18] For linkage of claims to CathPCI registry data, patient identifiers are available and will be submitted securely to CMS to match individuals included in both data sets.

Using these linkage rules, we have already successfully linked 80% of patients in the US CoreValve Pivotal Trials and Continued Access Study to the Medicare Current Beneficiary Summary File (eg, the "denominator" file) (Figure 2). To do so, we evaluated 6,548 patients in the CoreValve Pivotal Trials data set. After excluding patients under age 65 and those patients who underwent the index procedure at Veterans Affairs or European hospitals, a total of 5,936 patients were identified for potential linkage (High Risk Study, n = 735; Extreme Risk Study, n = 620; SURTAVI, n = 1305; Expanded Use Study, n = 634; Continued Access Registry for the Extreme Risk Study, n = 1568; Continued Access Registry for the High Risk Study, n = 1074). As a given health care facility could have multiple names in the trial or CMS data sets, sites were matched based on CMS hospital provider number. The frequency of occurrence of the provider number in the CMS data was used to check that the provider number identified corresponded to the most likely hospital match. Using procedure date, birthdate, and physician provider number as merging criteria and hospital provider number as the checking criterion, we were able to uniquely match 3225 patients (3225/3997 [80.7%]) of those in the High Risk and Extreme Risk Pivotal Studies and the Continued Access Study.

As the SURTAVI trial lacked birthdate information, the procedure date, admission date, discharge date, and physician provider number were used as merging criteria, and both hospital provider number and difference in age between the trial and CMS were used as checking criteria. Only those with a listed age in CMS within 1 year of the age listed in the trial were considered a true match. Using these criteria, we matched 1005 (1005/1305 [77.0%]) unique patients in SURTAVI to CMS data. For the Expanded Use Study, procedure date and birthdate were used as merging criteria and gender and procedure date as checking criteria, resulting in 505 (505/634 [79.7%]) individuals being successfully matched to CMS data. A comparison of linked and nonlinked trial participants will be done for EXTEND-DAPT to evaluate their differences. A similar comparison has already been conducted for EXTEND-CoreValve and showed minimal differences between linked and nonlinked populations (Table II). As Medicare Advantage Health Maintenance Organizations represented 13%-30% of overall Medicare enrollees during the time period evaluated,[21] we consider the majority of nonmatched individuals likely to be Medicare Advantage enrolled.

Validation of outcomes

Linkage of clinical trials and administrative data permits the validation of outcomes determined from Medicare and non-Medicare claims against rigorously adjudicated clinical trial variables. As it is unknown if CEC-adjudicated exposure and outcome variables will record certain information as well as claims, we will evaluate agreement in the aggregated outcomes between claims data and trial data. To do this, we will specify a 14-day time window before and after a trial adjudicated event in which a claim submitted for a trial participant for a similar event during this time will be considered a "match." Specifically, as each individual may have multiple possible "event matches," the difference between the index procedure date and the event date will be determined for both CMS and trial populations. The difference between these 2 values represents the discrepancy between dates. The event with the lowest discrepancy in dates, following the index procedure, within the 14-day window, will be considered the matched event. For those with multiple events in a given hospitalization, only the first event will be considered. As time latency for reporting of trial events could result in mismatched event dates, a 14-day window before and after the event dates will be applied as above to identify the most likely possible match.

Table I. Summary of studies included in the EXTEND-Study

Primary end point	Primary analysis	Rate of primary end point in Arm A*	Rate of primary end point in Arm B*	*P* value for primary end point
All-cause mortality or stent-thrombosis at 30 m post-PCI	Intention to treat	4.3% (Death) 0.4% (Stent thrombosis)	5.9% (Death) 1.4% (Stent thrombosis)	$P < .001$ for both outcomes (superiority)
All-cause 2-y mortality or disabling stroke	Modified intention to treat	12.6%	14.0%	Posterior probability $> .99$ (noninferiority)
All-cause 1-y mortality	Per protocol	14.2%	19.1%	$P < .001$ (noninferiority), $P = .04$ (superiority)
All-cause 1-y mortality or major stroke	Intention to treat	26.0%	43.0%	$P < .001$
All-cause mortality (High Risk)	Intention to treat	34.2% (Death)	N/A	N/A
All-cause mortality or major stroke (Extreme Risk)		40.3% (MACCE)		
All-cause mortality or major stroke at 1 y	Intention to treat	N/A	N/A	N/A

Figure 2

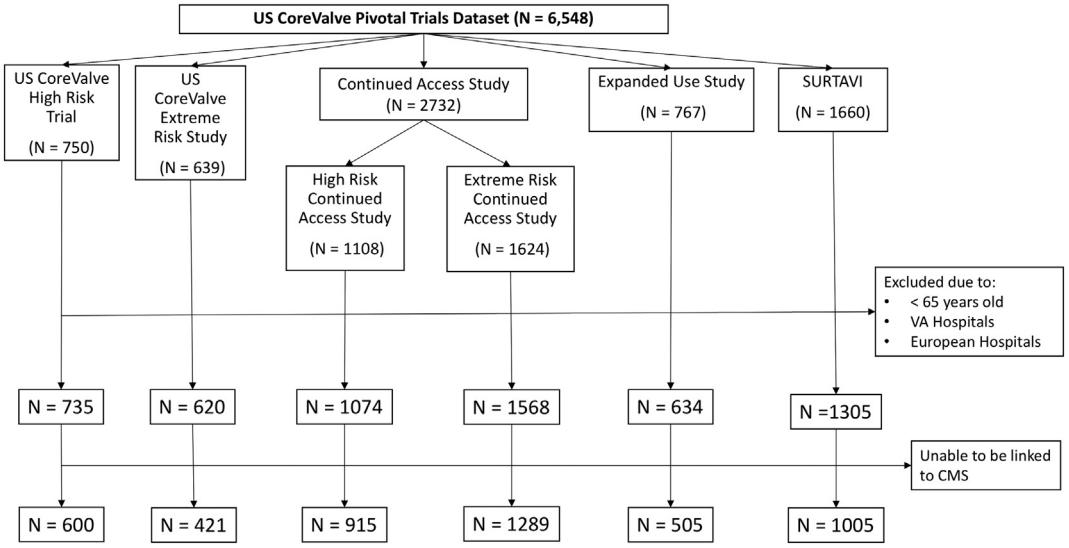


Diagram illustrating linkage strategy and results for the EXTEND-CoreValve study.

We will conduct a number of validation analyses for each outcome using a hierarchical algorithm as follows. First, codes representing a given outcome and matched to trial events will be ranked based on the frequency of occurrence. If multiple codes are used to represent a trial event, only the code most frequently used overall will be considered. Kappa statistics will be determined for each code and outcome pair. Additionally, assuming trials as the criterion standard, the sensitivity, specificity, and positive and negative predictive values for the most commonly used codes will be determined for each outcome subtype (eg, for neurologic events, we will consider hemorrhagic stroke, ischemic stroke, and transient ischemic attack separately). Additionally, recursive partitioning will be used in sensitivity analysis to assure that this hierarchical algorithm identifies a similar parsimonious list of claims corresponding to each outcome, with N-fold cross-validation used to evaluate the extent of overfitting. Both procedural codes (eg, transfusion) and diagnosis codes (eg, gastrointestinal hemorrhage) will be considered in the event matching. No medication information is available in the proposed data sets.

Additionally, we will construct Kaplan-Meier plots to assess the agreement in time to events between trial and claims data over the study period using the censoring dates from the trial. As codes during trial follow-up could represent individuals with a history of a given outcome in some cases, we will construct separate Kaplan-Meier estimates for individuals without a code for that outcome in the year prior to the date of their index procedure. An exhaustive list of claims (eTables 1-4) will be considered for each event to identify those codes which best agree with trial variables and outcomes.

Table II. Characteristics of linked and nonlinked individuals included in EXTEND-CoreValve

Characteristic	Linked group (N = 4230)	Nonlinked group (N = 1072)	*P* value
Age, y ± SD	83.0 ± 6.7	82.4 ± 7.1	.02
Female sex, n (%)	1939 (45.8)	478 (44.6)	.47
Body mass index, kg/m^2 ± SD	28.2 ± 6.2	28.3 ± 6.4	.14
New York Heart Association class, n (%)			.69
Class II	811 (19.2)	218 (20.3)	
Class III	2781 (65.7)	696 (20.0)	
Class IV	638 (15.1)	158 (19.9)	
Society of Thoracic Surgeons Risk Score, % ± SD	7.9 ± 4.5	7.5 ± 4.4	.02
Logistic EuroSCORE, % ± SD	19.5 ± 14.6	20.0 ± 15.7	.0011
Diabetes mellitus, n (%)			
All	1585 (37.5)	400 (37.3)	.94
Controlled by insulin	545 (12.9)	143 (13.3)	.68
History of hypertension, n (%)	3955 (93.5)	1000 (93.3)	.80
Peripheral vascular disease, n/total N (%)	1787 (42.4)	474 (44.2)	.28
Prior stroke, n/total N (%)	496 (11.7)	113 (10.6)	.28
Prior transient ischemic attack, n/total N (%)	425 (10.1)	93 (8.7)	.19
Cardiac risk factors, n/total N (%)			
Coronary artery disease	3189 (75.4)	813 (75.8)	.76
Prior coronary artery bypass surgery	1315 (31.1)	320 (29.9)	.46
Prior percutaneous coronary intervention	1468 (34.7)	364 (34.0)	.65
Balloon valvuloplasty	417 (9.9)	98 (9.1)	.53
Preexisting pacemaker of implantable cardioverter-defibrillator	818 (19.3)	234 (21.8)	.07
Prior myocardial infarction	1025 (24.2)	252 (23.5)	.63
Congestive heart failure	4126 (97.5)	1033 (96.4)	.04
Prior atrial fibrillation or atrial flutter	1711 (40.5)	427 (39.9)	.73

Baseline characteristics of individuals whose trial data could and could not be linked to Medicare claims.

For EXTEND-DAPT, we will include all patients who underwent PCI with a Food and Drug Administration–approved stent between August 13, 2009, and July 1, 2011. Baseline characteristics of patients will be determined based on *International Classification of Diseases, Ninth Revision, Clinical Modification* and Current Procedural Terminology codes (eTable 1). Clinical and comorbidity variables will be determined for individuals using claims available up to 1 year prior to the admission date of hospitalization for PCI. The co-primary outcomes include definite or probable stent thrombosis or major adverse cardiovascular or cerebrovascular events (MACCE) (eg, death, myocardial infarction, or stroke) during the period of 12-30 months postenrollment, similar to those in the DAPT study (eTable 2).

For EXTEND-CoreValve, adults (≥18 years) in the CMS database hospitalized from January 1, 2003, to December 31, 2016, with the *International Classification of Diseases, Ninth Revision, Clinical Modification* procedure codes for TAVR and SAVR will be included if successfully linked to the US CoreValve Pivotal data. Clinical and comorbidity variables will be determined for individuals undergoing aortic valve replacement (AVR) using claims available up to 1 year prior to the admission date of hospitalization for AVR (eTable 3). Mirroring the trials, the primary outcomes will include all-cause mortality at 1 year (High Risk trial) and all-cause mortality or stroke at 12 months (Extreme Risk trial). As outcome data were incomplete beyond 1 year in SURTAVI, all-cause mortality and stroke at 1 year will be used as the primary outcome for this comparison. Additional outcomes will include rates of major vascular complications, major bleeding, hospitalization for acute kidney injury, cardiogenic shock, permanent pacemaker implantation, new-onset atrial fibrillation, or mechanical complications from heart valve prosthesis placement (eTable 4).[5,10,22-37]

As both the DAPT and CoreValve trials relied on individual site reporting to identify hospitalization events, it is possible that claims may identify adverse events not otherwise reported for trial adjudication. By contrast, codes for adverse events may not be included in hospitalization discharge billing records if they were not the primary reason for hospitalization. As such, all coding positions will be used to identify potential events.

Reproducing trial results

After validation of end points, we will compare trial results to those obtained from claims data. Specifically, we will assess whether or not claims that have been identified as being the best surrogates of trial variables can reproduce the results observed in the trials when substituted for CEC-adjudicated end points among the linked study populations. As the definitions for each outcome differed by trial, each trial result will be reproduced independently.

Using the linked data sets, we will perform a comparison of the overall results obtained from claims alone versus the

original trial analyses for both the DAPT and CoreValve populations. This will include an assessment of (1) the direction of effect, (2) the magnitude of the hazard ratio, and (3) the differences in absolute event rates (due to differences in sensitivity/specificity of end points) and the corresponding numbers needed to treat/harm. Specifically, in EXTEND-DAPT, only those individuals in the DAPT trial who can be successfully linked to both the CathPCI registry and CMS data will be included in analyses of claims and registry data to reproduce trial results. In the EXTEND-CoreValve study, only those individuals in the US CoreValve Pivotal Trials who can be successfully linked to CMS data will be included.

In the EXTEND-DAPT study, we will use nontrial data to evaluate the primary randomized comparison of 30 versus 12 months of dual antiplatelet therapy in the linked CMS-DAPT-CathPCI data set. Specifically, we will use the stratified log-rank test to compare the cumulative incidence of MACCE and stent thrombosis between treatment arms, with a superiority hypothesis. A comparison of the primary safety end point of claims-defined bleeding between randomized groups will be conducted using a noninferiority analysis and the Farrington-Manning risk difference approach with a noninferiority margin of 0.8%.[13] We will subsequently compare the study results from above to those attained using trial-ascertained variables and end points using the technique for qualitative comparison mentioned above.

In the EXTEND-CoreValve study, we will use claims to reproduce trial results, evaluating 1- and 2-year rates of death using a noninferiority margin of 7.5% between treatment arms for the High-Risk study,[16] and a 12-month rate of death using a "placebo" rate of 43% for the Extreme-Risk study,[17] as used in the trials. Results obtained through analysis of claims data will be compared to trial end points to assess whether results are concordant in direction and magnitude of effect, difference in event rates, consistency of subgroup effects, and number needed to treat/harm.

As the accuracy of coding for an outcome could lead to the conclusion of noninferiority due to type II error, sensitivity analyses will be performed assuming different rates of coding for a given outcome to evaluate how robust the findings are to coding inaccuracies or deficient validation.

Additional aims

Whereas the primary intention of the EXTEND study is to evaluate the agreement of results obtained via trial-collected data and administrative claims or registry-obtained data, linkage of these diverse data sources also permits the study of a number of common questions. First, as trials have been criticized for not enrolling a generalizable population,[18,38] we will evaluate the external validity of these 2 trial populations by directly comparing participants undergoing PCI or aortic valve replacement included in the trials to those not included in the trials but undergoing these procedures within the larger registries or claims data sets. Thus, linkage of trials to registry and claims data may, in the future, permit direct assessment of trial generalizability.

Second, as trials may be limited by financial or personnel resources to acquire certain detailed historical information on their participants,[38] we plan to evaluate whether the addition of historical information obtained from claims data can identify subgroups with differential treatment benefit or harm. By leveraging the randomization of trial participants, we hope to enrich the historical information available for the identification of prognostic and predictive factors. In doing so, we hope to identify individuals with the maximal benefit and minimal harm from the therapies being studied, which may assist in the future in identifying those who benefit most from cardiovascular and noncardiovascular therapies.

Conclusions

The timely and efficient evaluation of new medical treatment strategies, therapies, and devices is critical to improving public health and informing care decisions. Ubiquitous administrative data collected in the routine care of patients remain underused sources of information that could be used to support clinical trial evaluations of novel medical interventions and identify subgroups of particular benefit or harm to these interventions. This approach, although promising, requires testing and validation. Thus, we will link data from several large cardiovascular clinical trials to nontrial data to evaluate whether these data can be used to reproduce trial results, augment information on subgroups with particular benefit or harm, and assess the generalizability to nontrial populations. The information learned has great potential to inform the future conduct of clinical trials while offering novel insights into the efficacy and safety of multiple cardiovascular and noncardiovascular therapies.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.02.007.

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