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Use of Medicare Data to Identify Coronary Heart Disease Outcomes In the Women's Health Initiative (WHI)

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Abstract

Background—Data collected as part of routine clinical practice could be used to detect cardiovascular outcomes in pragmatic clinical trials, or in clinical registry studies. The reliability of claims data for documenting outcomes is unknown.

Methods and Results—We linked records of Women's Health Initiative (WHI) participants aged 65 years and older to Medicare claims data, and compared hospitalizations that had diagnosis codes for acute myocardial infarction (MI) or coronary revascularization with WHI outcomes adjudicated by study physicians. We then compared the hazard ratios for active versus placebo hormone therapy based solely on WHI adjudicated events with corresponding hazard ratios based solely on claims data for the same hormone trial participants.

Agreement between WHI adjudicated outcomes and Medicare claims was good for the diagnosis for MI (kappa = 0.71 to 0.74), and excellent for coronary revascularization (kappa=0.88 to 0.91). The hormone:placebo hazard ratio for clinical MI was 1.31 (95% confidence interval (CI) 1.03 to

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1.67) based on WHI outcomes, and 1.29 (CI 1.00 to 1.68) based on Medicare data. The hazard ratio for coronary revascularization was 1.09 (CI 0.88 to 1.35) based on WHI outcomes and 1.10 (CI 0.89 to 1.35) based on Medicare data. The differences between hazard ratios derived from WHI and Medicare data were not significant in 1,000 bootstrap replications.

Conclusion—Medicare claims may provide useful data on coronary heart disease outcomes among patients aged 65 years and older in clinical research studies.

Clinical Trials Registration Information—www.clinicaltrials.gov, Trial Number NCT00000611

Keywords

outcomes research; research design; randomized controlled trials

Randomized clinical trials (RCTs) are the reference standard for clinical research studies, but are expensive and challenging to conduct. Methods to improve the efficiency of RCTs, while maintaining their validity, are therefore of considerable interest. A potential way to streamline RCTs would be to capitalize on electronic databases of health insurers or integrated health care systems to capture data about clinical events among trial participants. Medicare, for instance, provides health insurance coverage for Americans aged 65 years and older, as well as younger individuals with disability or end-stage renal disease, and collects electronic data on hospitalizations, outpatient visits, and other health care utilization for billing purposes. Medicare claims data are commonly used for health services research studies, and have increasingly been linked to clinical registries to obtain follow-up data (1-4). In contrast, claims data have been infrequently linked to RCTs (5-7), which usually include prospective follow-up and validation of endpoints. As such, the potential value of using claims data to document clinical outcomes in RCTs has been largely unexplored; if such an approach were feasible, it might simplify and improve the efficiency of RCTs.

The Women's Health Initiative (WHI) included two RCTs of hormone therapy (one using combination estrogen plus progestin [E+P] versus placebo, and the other using estrogen alone [E-only] versus placebo), with baseline enrollment between 1993 and 1998 and ongoing post-intervention follow-up (8, 9), as well as a dietary modification trial and an observational study. Data from WHI have been linked to Medicare files from the Centers for Medicare & Medicaid Services (CMS), expanding the data available on WHI participants. The purpose of the current study was to compare major coronary disease outcomes ascertained from Medicare files with physician adjudicated outcomes in the WHI hormone therapy trials.

Methods

The nationwide study population for these analyses consisted of women aged 65 years and older at study entry who were continuously enrolled in traditional fee-for-service Medicare Part A coverage. WHI participants were linked with CMS data using social security number, date of birth and, in some cases, date of death or residential zip code.

The primary outcome for this analysis was incident acute MI, and the secondary outcome was coronary revascularization. We identified outcomes In the CMS Medicare Provider Analysis and Review data by using the International Classification of Diseases (9th Revision, Clinical Modification [ICD-9-CM]) principal diagnosis code, secondary diagnoses codes (up to nine), and the procedure codes of hospital discharges. We defined acute MI in the CMS data as hospitalizations with ICD-9-CM discharge diagnosis codes of 410.×0 or 410.×1, and coronary revascularization by an ICD-9-CM procedure code for coronary artery bypass graft surgery (36.1×, 36.2) or percutaneous coronary intervention (00.66, 36.0, 36.00, 36.01, 36.02, 36.05, 36.06, or 36.07). In the WHI, diagnoses of MI and coronary revascularization were established by physician adjudicators based on review of medical records using standardized forms and definitions (10, 11). Diagnosis of an acute MI was based on chart review findings of three standard factors: chest pain, diagnostic or suggestive ECG changes, and abnormal cardiac markers. We excluded the few (3%) silent, ECG-only MIs found in WHI clinical trial participants, as these events were, by definition, clinically unrecognized and would not be expected to appear in the CMS hospital data. Results were essentially unchanged when ECG-only MIs were included (Online Appendix).

We compared the agreement between outcomes identified in the CMS data and WHI adjudicated outcomes through December 31, 2007, the last date for which CMS data were available. We examined only first occurrences of these events, because WHI did not adjudicate recurrent events. Women were censored when they no longer had Medicare fee-for-service coverage, or if they were lost to follow-up in WHI.

Agreement beyond chance between WHI and CMS data was evaluated with a kappa statistic.

First-Stage Analysis

To determine the optimal definition for an acute MI in the CMS data, we conducted a first stage analysis among women who were enrolled in the WHI observational study or the diet trial and were not participants in the hormone therapy trials. In a second stage analysis, we applied the operational definition of acute MI developed in the first stage to the independent sample of women in the two WHI hormone therapy trials (i.e., E+P and E-only).

Intention-to-Treat Analysis

Using the WHI hormone trial participants, we performed an intention-to-treat analysis based solely on Medicare determined outcomes among women 65 years of age and older, and calculated the hormone:placebo hazard ratios using Cox proportional hazards models. In order to maximize the number of events and narrow the confidence intervals for the hazard ratios, the primary analysis combined data from both hormone trials. We compared the incidence of MI among the women allocated randomly to hormone therapy or placebo during the period of active intervention, namely through July 7, 2002 in the E+P trial (8), and through February 29, 2004 in the E-only trial (9). Participants were censored when they were no longer enrolled in fee-for-service Medicare Part A.

We then compared the hazard ratios from the Medicare-based intention-to-treat analysis with the corresponding risk ratios derived from WHI adjudicated outcomes. To determine if

these hazard ratios differed significantly, we calculated the confidence interval around the difference between these two point estimates using the bootstrap technique (1000 resamplings, with recomputation of the difference between the two hazard ratios in each bootstrap sample).

All participants gave written informed consent to participate in the WHI. The linkage of WHI and CMS data was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, which granted a waiver of additional consent for the linkage study.

Results

Agreement of MI Diagnosis

The WHI observational study and diet trial included 58,793 women aged 65 years and older nationwide at the time of study entry, 215 of whom were not followed for outcomes in WHI; 52,735 of the remaining women (90%) were successfully linked to CMS records. The study population for the first stage analysis consisted of 37,397 women aged 65 years and older at entry who had traditional fee-for-service Medicare coverage at WHI enrollment. In this population, 1,345 women had a clinically evident MI adjudicated by WHI, 1,195 had a hospitalization with a principal diagnosis of acute MI in the CMS data and an additional 306 women had a hospitalization with a secondary diagnosis code for an acute MI in the CMS data.

The agreement between WHI and CMS diagnoses of acute MI was good (kappa 0.71, $p<0.0001$). A total of 914 women had an MI in both data sets, with exact agreement on the date of the event in 82%, and agreement within 30 days in 94% (Table 1). However, 281 women with an MI in the CMS data did not have an MI in the WHI data, and 431 women with an MI in the WHI data did not have an MI in the CMS data (Table 1).

There were several reasons for disagreement between the WHI and CMS data sources for an acute MI. Almost half of the women with an MI in the CMS data but not in the WHI data had not reported a hospitalization to the WHI staff, and an additional 12% reported a possible clinical event that was not adjudicated, either because the WHI staff could not obtain sufficient hospital records, or because the reported reason for admission did not meet WHI criteria for adjudication. In most of the remaining cases, another cardiovascular outcome was adjudicated by WHI after review of records. Restricting the analyses to those cases with adequate documentation would improve the kappa to 0.76 for the diagnosis of MI (Supplemental Material, Supplemental Table 1).

Among the 431 women who had a WHI adjudicated MI but no hospitalization with a principal diagnosis of MI in the CMS data, 32% had a secondary diagnosis of an acute MI, many of which were adjudicated by WHI as a procedure-related MI. (Only 3.7% of admissions with a principal diagnosis of MI in the CMS data were adjudicated as procedure-related MIs.) Most of the remaining women (39%) were hospitalized with another principal cardiovascular diagnosis, 15% had a non-cardiovascular principal diagnosis, and 14% had no CMS record of a hospital admission within 30 days of the date of MI recorded by WHI.

Based on the reasons for disagreement between CMS and WHI diagnoses, we examined an alternative definition of MI in CMS data that included either a principal or secondary diagnosis of acute MI, which we compared with the WHI diagnosis of clinically evident MI (Table 1). This definition modestly improved the agreement between the two data sources, with a kappa of 0.74 ($p<0.0001$). The kappa statistic for agreement between a WHI diagnosis of non-procedure related MI and a CMS primary diagnosis of acute MI was 0.73 (Table 1). Based on these results, we decided a priori that the second stage analysis would compare the WHI diagnosis of clinical MI with a CMS principal or secondary diagnosis of acute MI, and compare the WHI diagnosis of non-procedure-related MI with a CMS principal diagnosis of acute MI.

Agreement between CMS data and WHI data was quite high for coronary revascularization procedures, with a kappa statistic of 0.91 for coronary artery bypass graft surgery, and a kappa of 0.88 for percutaneous coronary intervention (Table 1).

Intention-to-Treat Analysis

In the WHI, 10,739 women were randomized in the E-only trial and an additional 16,608 women were randomized in the E+P trial. At the time of study entry, 12,705 hormone trial participants were aged 65 years or older, and 11,963 (94%) were linked successfully to CMS records. The baseline clinical characteristics of the 8,375 women with Medicare fee-for-service coverage at study entry were generally similar to those of the remaining women aged 65 and over, but the women with fee-for-service coverage were slightly younger and less likely to have had prior hormone therapy (Table 2).

Over a mean follow-up of 73.9 months, 270 women with fee-for-service Medicare coverage in the combined hormone trial populations had a clinically evident MI adjudicated by the WHI; in comparison, 228 women had a hospitalization documented in Medicare data with a principal or secondary diagnosis of acute MI over a mean follow-up of 65.2 months. In the intention-to-treat analysis of the combined trials, the hazard ratio of 1.29 for hormone therapy compared with placebo based on a CMS principal or secondary diagnosis of MI agreed well with the hazard ratio of 1.31 based on WHI adjudicated clinical MI (Figure 1). The difference of 0.02 between these hazard ratios had 95% confidence limits of -0.22 to +0.25 based on 1,000 bootstrap replications. Comparing the more restrictive definition of non-procedure related MI in the WHI data with a principal diagnosis of acute MI in the CMS data, the hazard ratio of 1.38 based on CMS data also agreed well with the hazard ratio of 1.28 based on WHI adjudicated outcomes (Figure 1). The confidence limits on the difference of -0.10 between these hazard ratios ranged from -0.40 to +0.18. Intention-to-treat comparisons in the E+P trial and E-alone trial are presented separately in the Supplemental Material, Supplemental Table 5.

A total of 352 women had a coronary revascularization procedure adjudicated by WHI, compared with 374 women with a procedure recorded in the CMS data (Table 2). In the intention-to-treat comparison using coronary revascularization as an outcome, the hazard ratio for hormone therapy of 1.10 based on CMS data agreed well with the hazard ratio of 1.09 based on WHI data (Figure 1). The confidence limits on the -0.01 difference in these hazard ratios ranged from -0.16 to +0.15.

Discussion

This study demonstrates that administrative data may be reliable and useful in assessing coronary heart disease outcomes among patients aged 65 years and older in clinical research studies. Furthermore, our data suggest that treatment comparisons based on outcomes ascertained in CMS claims yield hazard ratios similar to those determined by standard clinical trial outcome ascertainment and adjudication procedures. The use of claims data to detect outcomes may be particularly attractive in conducting large “pragmatic” clinical trials that assess the comparative effectiveness of alternative treatments, and in extending follow-up of trial participants.

In this study, the agreement was quite good between WHI adjudicated outcomes and hospitalized events documented in CMS data (Table 1). Many of the instances of “disagreement” between the two data sources arose from a lack of hospital records needed for outcome adjudication. As such, the kappa statistics would have been higher (0.76 for acute MI) had we analyzed only events with adequate documentation (Supplemental Material, Supplemental Table1). The level of agreement between WHI adjudicated outcomes and CMS determined events in this study was close to the level of agreement between WHI local and central adjudicators who reviewed the same cases: kappa statistics were 0.80 for acute MI, 0.94 for coronary bypass surgery, and 0.89 for percutaneous coronary intervention (11).

Since some disagreement is expected whenever two different methods are used to document outcomes in a clinical trial, the key question is whether the comparative effectiveness of randomized treatments is similar based on outcomes identified by the alternative approaches. In this study, we found the hazard ratios for hormone therapy relative to placebo were quite similar whether they were based on the WHI adjudicated events or the CMS documented outcomes. The bootstrap confidence limits around the difference in hazard ratios included zero, suggesting there was no significant bias in the estimated treatment effect based on CMS data.

In previous studies, a discharge diagnosis of acute MI in administrative data has generally been confirmed by review of hospital records. Burwen and associates confirmed the principal diagnosis of acute MI in 87% of 270,467 hospital discharges in Medicare data nationwide (12). Yeh and coworkers found 97% of hospitalizations in Kaiser Permanente of Northern California with a primary discharge diagnosis of acute MI met standard diagnostic criteria for MI (13). Kiyota and coworkers confirmed on record review 94% of 1,851 admissions in Pennsylvania with a principal or first-listed secondary diagnosis of acute MI (14). In the Atherosclerosis Risk in Communities Study, 75% of 17,900 discharges with a 410.xx discharge code in any position (principal or secondary) had a definite or probable MI upon record review, 12% had a suspected MI, and 13% had no MI (15). The literature therefore supports a discharge diagnosis of acute MI as having high positive predictive value, consistent with the findings in this study.

While a discharge diagnosis of acute MI has high positive predictive value, not all MIs will be detected using claims data. An acute MI that was a consequence of a procedure or

medical illness was less frequently coded in Medicare claims. In the WHI, an acute MI was actively sought and found by WHI adjudicators in some records that lacked either an ICD-9 code for acute MI, or a participant self-report of an MI, or both (11). Consequently, some acute MIs would be missed if administrative claims were the only source of data. Conversely, in this study the CMS data captured some acute MIs that were not identified by the standard WHI outcome surveillance procedures. Similar to other clinical trials, outcomes ascertainment in WHI was based on contacts by study personnel with the participant or her family. Although complete loss to follow-up was uncommon in WHI, participants who had a recent illness may have been less likely to respond to attempts to contact them, and medical records may not have been released. Respondents' recall of possible outcome events is also imperfect, so ascertainment of outcomes may be incomplete. Hospital claims do not depend on the recall of the participant or family, and hence provide an independent method of identifying potential clinical outcome events. Silent, ECG-only MIs would not be detected in claims, since they do not result in a hospital admission; but only 3% of MIs in WHI were detected by ECG only, and our results were essentially unchanged when they were included in the analysis (Supplemental Material, Supplemental Table 1).

Depending on the type of event, claims data alone may be sufficiently accurate for purposes of the clinical trial. Hospital discharge codes in this study were quite accurate, for instance, in identifying coronary revascularization procedures, particularly coronary bypass surgery. Arguably, trials might not need to investigate such events further, and could accept discharge codes as adequate documentation. The recent trend towards performing percutaneous coronary interventions in the outpatient setting would, however, require use of Part B codes to identify all procedures. The ICD-9CM codes might be used to identify other clinical events, or to document health care utilization and cost. Claims data would not, however, be useful in early phase studies of new therapies, since clinical records of suspected outcome events are important for regulatory review. Nor would claims data be useful in assessing MIs after initial treatment for acute coronary syndrome, since the timing of these events requires careful review of serial cardiac markers and ECGs (16, 17). Claims data could be very useful, however, for long-term follow-up in pragmatic clinical trials (or registry studies) of approved therapies.

In WHI, acute MI was one component of the composite coronary heart disease (CHD) endpoint, which consisted of CHD death, non-fatal MI, and silent MI. We did not attempt to assess the broader outcome of CHD death in this study, but focused on the more specific outcome of acute MI. While most CHD deaths would be expected to have had a preceding hospitalization for an acute MI or a coronary revascularization procedure, some deaths due to coronary disease occur out of hospital, or have hospital diagnosis codes other than MI. Algorithms to identify CHD deaths accurately from claims data and death records are needed.

Most of the women aged 65 years and older in the WHI hormone trials were linked successfully to the CMS database, but only 69% had traditional fee-for-service Medicare coverage, with complete billing data to document their subsequent hospitalizations. CMS data, as currently collected, would provide outcome data for most, but not all, of the participants aged 65 and older in a clinical trial. Supplementing CMS data with the

administrative records of integrated health care systems in the United States (e.g., health maintenance organizations or the Department of Veteran Affairs), or using universal health insurance plans in other countries, would provide data for a larger proportion of participants in a clinical trial, and thus might be able to document most clinical outcomes based on data collected as part of the routine delivery of care. Another practical limitation of using claims to assess outcomes is that CMS data are available only after some delay. Traditional event identification and adjudication also take time, however, so that it is difficult to assess the degree of delay that would be added by relying on claims data.

While women aged 65 years and older differed in many baseline characteristics from younger women, there were relatively minor differences between older women with or without fee-for-service Medicare coverage (Table 2). In a previous study of the National Health and Nutrition Examination participants aged 65 years and older, the clinical characteristics of 1,472 Medicare fee-for-service were quite similar to those of the 603 Medicare Advantage enrollees (18). The present study included four times as many participants, so our findings confirm and extend their results. Nevertheless, Medicare fee-for-service beneficiaries may differ in other ways from Medicare Advantage participants, and so may not be fully representative of the entire population aged 65 and older.

In summary, this study suggests that Medicare claims data can provide useful data about coronary disease outcomes of older participants in a clinical research study, even though not all participants can be followed using these data. The linkage of administrative data with clinical trial (or registry) databases should be evaluated further, as it has the potential to extend the length of follow-up, expand the range of outcomes studied, and identify outcomes that might otherwise be unobtainable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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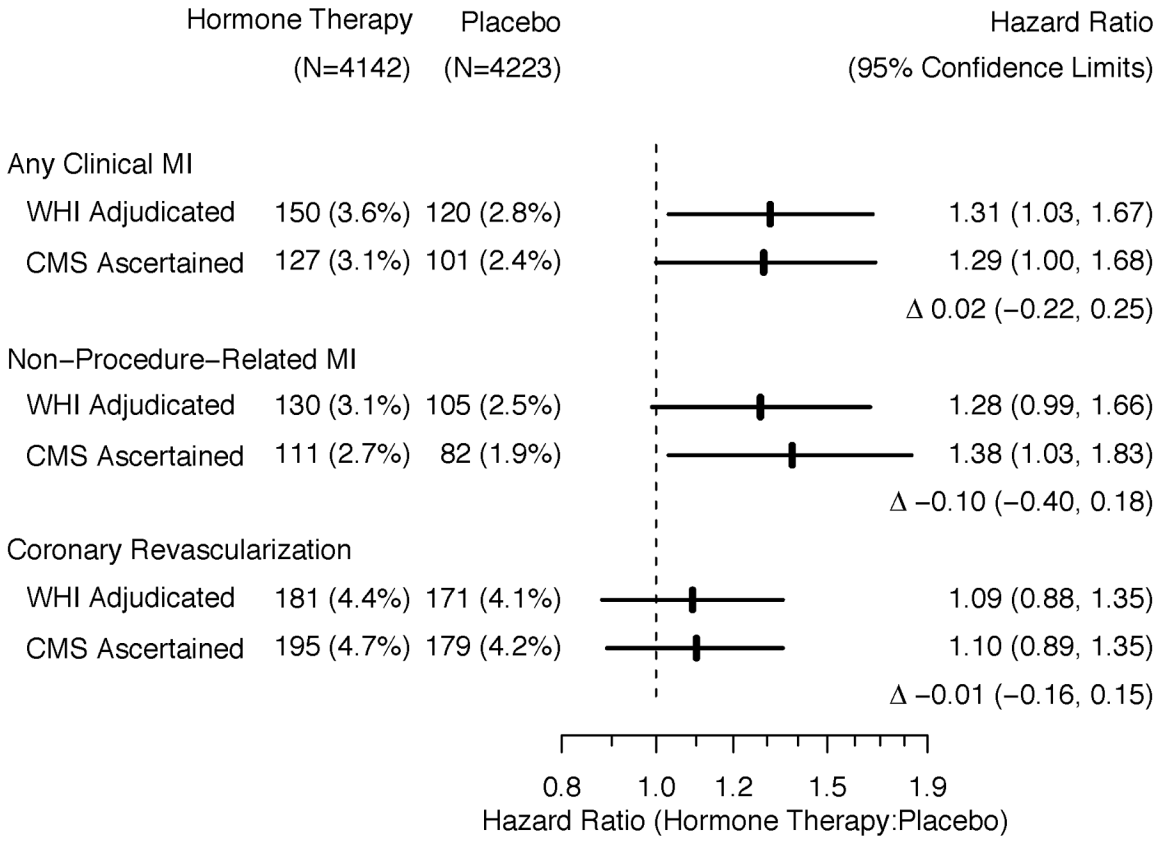

Figure 1. Outcomes Among Women Aged ≥65 Years Assigned Randomly to Hormone Therapy or to Placebo, According to Source of Outcome Data

CMS = Center for Medicare and Medicaid Services

MI = Myocardial infarction

WHI = Women's Health Initiative

Table 1

Agreement Between WHI Adjudicated MI and CMS Defined MI in the First Stage Analysis of the WHI Observational Study and Diet Trial

Criteria for Acute MI						
CMS	**WHI**	**WHI Yes CMS Yes**	**WHI No CMS Yes**	**WHI Yes CMS No**	**WHI No CMS No**	**Kappa (CL)**
Principal Dx	Clinical Diagnosis	914	281	431	35,771	0.71 (0.69-0.73)
Principal or 2° Dx	Clinical Diagnosis	1062	439	283	35,613	0.74 (0.72-0.75)
Principal Dx	Non-Procedure Related	880	315	293	35,909	0.73 (0.71-0.76)
Coronary Revascularization						
Coronary Bypass Surgery		795	96	53	36,453	0.91 (0.90-0.93)
Percutaneous Coronary Intervention		1369	217	147	35,664	0.88 (0.87-0.89)

CL = 95% Confidence Limit
CMS = Center for Medicare & Medicaid Services
Dx = Diagnosis
MI = Myocardial infarction
WHI = Women's Health Initiative

Table 2

Baseline Clinical Characteristics of Women ≥65 Years of Age at Entry in WHI Hormone Therapy Trials *

	Medicare FFS (n=8375)	Not Medicare FFS (n=3588)
Age	69.8 ± 3.8	70.1 ± 3.9
Years since menopause	21.5 ± 7.5	22.0 ± 7.7
Prior hormone therapy	2626 (31%)	1326 (37%)
E-only trial	3375 (40%)	1425 (40%)
E+P trial	5000 (60%)	2163 (60%)
Diabetes (treated)	506 (6%)	237 (7%)
Hypertension (treated)	2322 (30%)	1027 (30%)
Hypercholesterolemia (treated)	1293 (17%)	625 (17%)
Ever smoked	3815 (46%)	1706 (48%)
Body mass index		
<25 kg/m^2	2441 (29%)	1037 (29%)
25 to <30/Kg/m^2	3066 (37%)	1290 (36%)
>=30 kg/m^2	2822 (34%)	1248 (35%)

* Excludes 742 women not matched to data from the Centers for Medicare & Medicaid Services

E = Estrogen
E+P = Estrogen plus progestin
FFS = Fee-for-service
WHI = Women's Health Initiative