THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2016, Vol. 71, No. 8, 1113–1116
doi:10.1093/gerona/glv223
Advance Access publication January 8, 2016

OXFORD

Brief Report

Methodology to Estimate the Longitudinal Average Attributable Fraction of Guideline-recommended Medications for Death in Older Adults With Multiple Chronic Conditions

Heather G. Allore,[1,2] Yilei Zhan,[2,3] Andrew B. Cohen,[1] Mary E. Tinetti,[1] Mark Trentalange,[1] and Gail McAvay[1]

[1]Department of Medicine, Yale School of Medicine, New Haven, Connecticut. [2]Department of Biostatistics, Yale School of Public Health, New Haven, Connecticut. [3]Department of Statistics and Biostatistics, Rutgers University, New Brunswick, New Jersey.

Address correspondence to Heather Allore, PhD, Department of Internal Medicine, Yale School of Medicine, 300 George Street, Suite 775, New Haven, CT 06511-6624. E-mail: Heather.Allore@yale.edu

Received September 1, 2015; Accepted November 30, 2015

Decision Editor: Stephen Kritchevsky, PhD

Abstract

Background: Persons with multiple chronic conditions receive multiple guideline-recommended medications to improve outcomes such as mortality. Our objective was to estimate the longitudinal average attributable fraction for 3-year survival of medications for cardiovascular conditions in persons with multiple chronic conditions and to determine whether heterogeneity occurred by age.

Methods: Medicare Current Beneficiary Survey participants (N = 8,578) with two or more chronic conditions, enrolled from 2005 to 2009 with follow-up through 2011, were analyzed. We calculated the longitudinal extension of the average attributable fraction for oral medications (beta blockers, renin–angiotensin system blockers, and thiazide diuretics) indicated for cardiovascular conditions (atrial fibrillation, coronary artery disease, heart failure, and hypertension), on survival adjusted for 18 participant characteristics. Models stratified by age (≤80 and >80 years) were analyzed to determine heterogeneity of both cardiovascular conditions and medications.

Results: Heart failure had the greatest average attributable fraction (39%) for mortality. The fractional contributions of beta blockers, renin–angiotensin system blockers, and thiazides to improve survival were 10.4%, 9.3%, and 7.2% respectively. In age-stratified models, of these medications thiazides had a significant contribution to survival only for those aged 80 years or younger. The effects of the remaining medications were similar in both age strata.

Conclusions: Most cardiovascular medications were attributed independently to survival. The two cardiovascular conditions contributing independently to death were heart failure and atrial fibrillation. The medication effects were similar by age except for thiazides that had a significant contribution to survival in persons younger than 80 years.

Keywords: Chronic disease—Medications—Multimorbidity—Mortality—Longitudinal study—Average attributable fraction

Clinical practice guidelines for cardiovascular diseases include recommendations about indicated medications based on evidence, of varying quality, that these medications reduce mortality or improve other health outcomes (1). Persons with multiple chronic diseases or conditions (MCCs), however, who represent the majority of adults older than 65 years, are routinely excluded from the clinical trials on which this evidence is based. The benefits of medications for common cardiovascular diseases remain uncertain in older adults with MCCs.

Determining the harms and benefits of medications is inherently complex in individuals with MCCs. Research has been hampered by a lack of methods for handling the dauntingly complex combinations of conditions, medications, and outcomes among patients with MCCs. Recently, we estimated the relative associations between

guideline-recommended medications and death in older adults with MCCs (2). We extend that work to determine longitudinal average attributable fractions to death which provide population-level absolute values.

Our objective was to estimate longitudinal average attributable fractions to death of four common cardiovascular conditions in persons with MCCs, as well as the effect of three oral medications recommended by national guidelines for these conditions. We also explored whether heterogeneity occurs by age. We present a methodology called the longitudinal extension of the average attributable fraction (LE-AAF) (3,4) that can be applied to dichotomous outcomes, such as mortality, and overcomes many analytic challenges including attributable fractions adding to more than 100%.

Methods

Study Population

We included Medicare Current Beneficiary Survey participants with a baseline interview from 2005 to 2009 and up to three yearly follow-up interviews. This nationally representative sample of Medicare beneficiaries was obtained using stratified multistage sampling from the Centers for Medicare and Medicaid Services enrollment file. We included all participants aged 65 and older with at least two of nine chronic conditions.

We selected cardiovascular conditions associated with serious morbidity that had a prevalence of at least 5% in the study population and had an oral prescription medication or medication class recommended in recent national disease guidelines that was used by at least 10% of the study population. A participant was determined to have a condition if there was at least one inpatient or two other kinds of claims (outpatient, physician, skilled nursing, home health) during the first 2 years of participation. Cardiovascular conditions that met these criteria were hypertension, coronary artery disease (CAD), heart failure, and atrial fibrillation. Three medications recommended by national guidelines for these cardiovascular conditions had similar prevalences in this population. This allowed us to compare their average attributable fractions, because all forms of attributable fractions use information on both the prevalence of the factor and the size of the effect estimate. The cardiovascular medications were beta blockers (cardioselective or alpha/beta blockers); renin–angiotensin system blockers including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (RAS blockers); and thiazide diuretics. Medications were ascertained through direct observation of the medication containers at annual in-person interviews. Use of prescription medications was updated yearly to account for initiation and discontinuation of treatment.

Other chronic conditions in our study included diabetes mellitus, chronic kidney disease, hyperlipidemia, thromboembolic disease and depression, defined by a claim for depression or anxiety, or self-reported depression or loss of interest. Chronic kidney disease was included because of its effect on several of the study medications and its association with mortality. Other chronic conditions were accounted for in the Elixhauser comorbidity scale, which includes 23 chronic conditions, and was computed based on the International Classification of Diseases-9 codes from claims (5). The scale, excluding the four cardiovascular chronic conditions and depression, diabetes mellitus, chronic kidney disease and thromboembolic disease, was dichotomized at ≥ 2.

Of the 20,026 participants aged 65 years and older, excluded were 2,682 Medicare Advantage participants who lacked claims data, 6,984 who had less than two study conditions, 1,505 who were non-respondents, and 277 who had no medication data, resulting in 8,578 persons in the sample. The study was exempt from review by the Yale University Human Investigation Committee because it used de-identified data available for academic, government, and nonprofit research.

Sociodemographic, behavioral, health, and functional data were obtained at annual in-person interviews. Data included age, gender, race, ethnicity, and income, hearing and vision impairments, use of assistive device, urinary incontinence, smoking status, body mass index, prescription drug insurance coverage, cognitive impairment, and comorbidity. Cognitive impairment or dementia was considered present if there was self-reported memory loss, plus either trouble concentrating or difficulty making decisions that interfered with activities of daily living, or a claim for dementia or cognitive disorder. Finally, we controlled for other medications commonly used to treat the aforementioned conditions, including calcium channel blockers, clopidogrel, metformin, statins, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and warfarin.

All-cause mortality was identified via the Medicare Vital Status file through 2011, with a follow-up period of 3 years assigned to those who completed the study alive. Censoring of individuals prior to 3 years occurred due to drop out or loss to follow-up from Medicare Current Beneficiary Survey or death, with the time to event reflecting the time in the study or the time to death. Baseline characteristics were summarized, overall and by vital status.

Statistical Methods

In this study, the LE-AAF of a condition-indicated medication or condition tells us its population-level fractional contribution to the timed occurrence of death over 3 years in the presence of multiple coexisting medications, conditions, and patient characteristics. Technical details of the LE-AAF method have been previously described (3,4). In brief, it possesses the following properties: additivity—the total average attributable fraction of the medications and conditions equals the sum of individual medications and conditions—and symmetry—the estimate is independent of the order in which the conditions and their indicated medications occur. This is achieved by averaging the estimates in all possible orders and their co-occurrences. The LE-AAF quantifies time-varying medications and conditions (vital status was updated monthly whereas the time-varying conditions and their indicated medications were updated annually). Thus, it models temporal relationships among the cardiovascular conditions and their indicated medications to estimate their population-level average attributable fractions to death or survival.

The first analytic step of a pooled logistic model based on monthly observations with year-specific terms was estimated including the cardiovascular conditions, the co-occurring chronic conditions, and the interactions between conditions and their indicated medications. This interaction allowed us to estimate the indicated medication effect among those with the condition. To control for confounding variables, age (≤80 or >80 years) and sex were included, and forward selection of race (White or non-White), ethnicity (Hispanic or non-Hispanic), and time-varying characteristics updated at each year of study participation (income, smoking, obesity, prescription drug insurance, incontinence, use of assistive device, hearing impairment, vision impairment, cognitive impairment, and Elixhauser comorbidity score (≥ 2) was performed. In this approach, each observation represented a person-month while each person's follow-up time was divided into yearly intervals, assuming that the baseline hazard is constant within a year (3).

Coefficients from these adjusted models were used to calculate the LE-AAFs as the weighted average of the year-specific attributable fractions, with person-years as the weights. The design matrix

without covariates contains 5,925 rows of unique combinations; the design matrix with covariates increased to 15,177 rows of unique combinations because a participant could contribute up to three unique combinations given the time-varying characteristics. Variability of the LE-AAFs was estimated by 95% bias-corrected and accelerated confidence intervals from 300 bootstrap samples, which satisfied normality assumptions by the Shapiro–Wilks test. Calculating the LE-AAFs from the adjusted model with multiple covariates increased the computational burden; thus, a data-centric approach reduced computation time (4). In order to explore the heterogeneity by age (≤80 versus >80 years at baseline), the same procedures were undertaken with age-stratified models.

The pooled logistic regression models were estimated using SAS, version 9.4 (SAS Institute, Inc., Cary, NC), whereas the LE-AAFs were calculated using the MATLAB, version R2014a (MathWorks, Natick, MA). A 95% confidence interval that does not include zero for the proportional contribution denotes statistical significance.

Results

Approximately 15% of the study sample died. Their baseline cardiovascular characteristics by vital status are given in Table 1. Overall prevalence of the cardiovascular conditions at baseline ranged 92.2% for hypertension to 19.2% for atrial fibrillation. Only 3.4% of participants reported no studied cardiovascular condition during follow-up. Prevalence of study medications ranged from 46.5% for beta blockers to 53.5% for RAS blockers at baseline. Overall longitudinal average attributable fractions of mortality for the unadjusted and adjusted models are presented in Table 2. Positive values indicate that the factor contributed to death and negative values indicate that the factor contributed to survival. Heart failure was the largest contributor to mortality (39%) followed by atrial fibrillation, whereas CAD and hypertension were not significant contributors based on adjusted results. Of the cardiovascular medications, beta blockers made the largest contribution to survival (10.4%) followed by RAS blockers (9.3%) and thiazides (7.2%).

Table 1. Baseline Cardiovascular Characteristics by Vital Status (*N* = 8,578)

	Alive		Deceased	
	(*N* = 7,291)		(*N* = 1,287)	
	n	%	*n*	%
Age >80 years	2,278	31.2	795	61.8
Female gender	4,284	58.8	742	57.7
Cardiovascular chronic conditions				
Atrial fibrillation	1,207	16.6	442	34.3
Coronary artery disease	2,742	37.6	641	49.8
Heart failure	1,144	15.7	599	46.5
Hypertension	6,718	92.1	1,193	92.7
Number of cardiovascular chronic conditions				
0	270	3.7	20	1.6
1	3,657	50.2	362	28.1
2	2,216	30.4	395	30.7
3	870	11.9	317	24.6
4	278	3.8	193	15.0
Cardiovascular medications				
Beta blocker	3,373	46.3	614	47.7
Renin–angiotensin system blockers	3,977	54.6	615	47.8
Thiazide	3,282	45.0	725	56.3
Number of cardiovascular medications				
0	1,260	17.3	214	16.6
1	2,563	35.2	418	32.5
2	2,335	32.0	429	33.3
3	1,133	15.5	226	17.6
Comorbidity score ≥ 2[a]	2,896	39.7	942	73.2

Note: [a]Comorbidity ≥ 2 indicates two or more comorbid conditions from the Elixhauser scale excluding the study conditions (3).

Approximately 36% of the cohort was older than 80 years at baseline. Figure 1 displays the age-stratified model of the longitudinal average attributable fractions of study conditions to death. The contributions to death from the cardiovascular conditions were similar in the two age groups. The three cardiovascular medications displayed overlapping 95% confidence intervals signifying similar survival effects in older and younger individuals; however, thiazides only significantly contributed to survival for the population aged 80 years and younger.

Discussion

Among studied cardiovascular conditions present in a nationally representative sample of older adults with MCCs, heart failure and atrial fibrillation significantly contributed to mortality. All three classes of cardiovascular medications significantly contributed to survival. Previously, the LE-AAF methodology was applied to Medicare Current Beneficiary Survey data to estimate the contribution of 97 chronic and 36 acute diseases to death (6). The current study extends that work to assess the population-level effect of medications with similar prevalences given for selected cardiovascular conditions on mortality and the heterogeneity by age. It also extends recent work on the effects of medications on mortality for persons with MCCs, which provided relative associations that were similar to those in most randomized clinical trials (2), by providing population-level absolute values.

We present a methodology that can be widely applied to these high-dimensional problems of MCCs and medications. The resultant estimates are additive and account for the multiple ordering of conditions and their medications that can occur. The LE-AAF estimates, at a population level, the proportion of contribution to death from conditions and the medications used to treat them, with respect to that of the total contribution from the coexisting conditions, other medications, and patient characteristics across the entire follow-up time. The estimate is interpreted as an average longitudinal measure of the overall risk attributable to a particular condition or medication during the follow-up period.

As with any attributable fraction, both the prevalence of the risk factor and the conditional probability of having the outcome given the risk factors are important considerations when applying the LE-AAF method. Our results show that although hypertension was highly prevalent, it was not a significant contributor to death—illustrating that prevalence alone does not drive the proportional contribution. We present these findings as exemplary of an innovative methodology for determining medication effects in older adults with multiple coexisting medications and conditions.

Although these population-level estimates are not causal and do not apply to individuals, they provide insight into the average attributable fraction of conditions and their associated medications to death in a nationally representative sample of older adults. Presently, few causal methods can be used to analyze multiple treatments of a single condition (7) and have not been developed for scenarios where individuals have multiple conditions, in which inferences are on multiple condition-specific medications. Future methodology

Table 2. Longitudinal Average Attributable Fractions to 3-Year Mortality of Chronic Conditions and Their Guideline Indicated Medications in the Medicare Current Beneficiary Survey Cohort With Two or More Chronic Conditions (N = 8,578)

	n (%)[a]	Unadjusted LE-AAF[b]	Adjusted LE-AAF[b,c]
Condition			
Atrial fibrillation	1,946 (22.7)	21.21 (13.90, 27.10)	16.88 (10.40, 23.61)
Coronary artery disease	3,780 (44.1)	12.05 (3.17, 21.42)	1.55 (–7.38, 11.08)
Heart failure	2,169 (25.3)	48.11 (36.10, 56.92)	38.98 (26.91, 48.61)
Hypertension	8,074 (94.1)	30.28 (6.18, 49.79)	14.29 (–12.42, 41.96)
Medications			
Beta blockers	4,438 (51.7)	–11.57 (–16.06, –7.51)	–10.35 (–14.78, –5.96)
Renin–angiotensin system blockers	5,109 (59.6)	–13.43 (–18.35, –10.17)	–9.29 (–13.44, –6.21)
Thiazide	4,534 (52.9)	–8.56 (–12.42, –4.61)	–7.21 (–11.36, –2.97)

Notes: [a]Frequency and percentage with condition or medication at any time during the study period.

[b]Estimated using the longitudinal extension of the average attributable fractions (LE-AAF) where positive values indicate that the factor was attributed to mortality and negative values indicate that the factor was attributed to survival. 95% confidence intervals were estimated with 300 bias-corrected and accelerated bootstrapped samples.

[c]Model is adjusted for year, sex, income <$25,000, obesity, prescription drug insurance, incontinence, use of assistive device, hearing impairment, vision impairment, cognitive impairment, diabetes mellitus, chronic kidney disease, hyperlipidemia, thromboembolic disease and depression, Elixhauser comorbidity score ≥ 2 (3), calcium channel blockers, clopidogrel, metformin, statins, selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors, and warfarin.

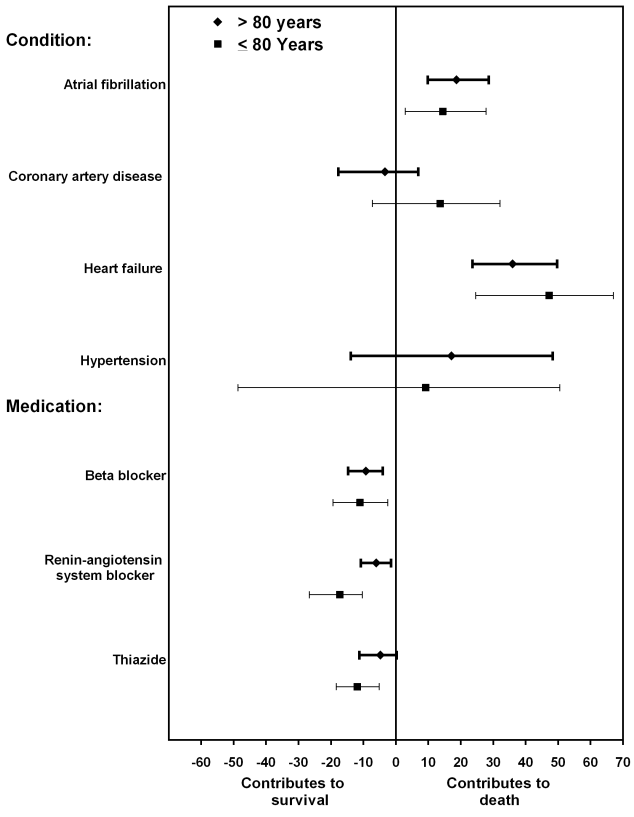

Figure 1. Longitudinal average attributable fraction of conditions and indicated medication in participants ≤80 or >80 years estimated from 8,578 Medicare Current Beneficiary Survey participants with baseline from 2005 to 2009 up to three yearly in-person follow-up interviews with two or more of the conditions. Positive values indicate that the factor was attributed to mortality and negative values indicate that the factor was attributed to survival. 95% confidence intervals were estimated with 300 bias-corrected and accelerated bootstrapped samples.

development should address causal methodology for patient-level inference. We demonstrated a methodology able to accommodate both the contribution and heterogeneity of medications to death in the setting of older adults with MCCs.

Funding

This work was supported by the National Institute of Aging at the National Institutes of Health (R21 AG045148 to M.E.T. and H.G.A., P30 AG021342). Models were run, in part, at the Yale University Biomedical High Performance Computing Center (RR19895 and RR029676-01).

References

1. Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC Jr. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA*. 2009;301:831–841. doi:10.1001/jama.2009.205
2. Tinetti ME, McAvay G, Trentalange M, Cohen AB, Allore HG. Association between guideline-recommended medications and death in older adults with multiple chronic conditions: Population-based cohort study. *BMJ*. 2015;315:h4984. doi:10.1136/bmj.h4984
3. Lin H, Allore HG, McAvay G, Tinetti ME, Gill TM, Gross CP, Murphy TE. A method for portioning the attributable fraction of multiple time-dependent coexisting risk factors for an adverse health outcome. *Amer J Public Health* 2013;103:177–182. doi:10.2105/AJPH.2011.300458
4. Murphy TE, McAvay G, Carriero NJ, Gross CP, Tinetti ME, Allore HG, Lin H. Deaths observed in Medicare beneficiaries: average attributable fraction and its longitudinal extension for many diseases. *Stat Med*. 2012;31:3313–3319. doi:10.1002/sim.5337
5. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD 10 administrative data. *Med Care*. 2005;43:1130–1139.
6. Tinetti ME, McAvay GJ, Murphy TE, Gross CP, Lin H, Allore HG. Contribution of individual diseases to death in older adults with multiple diseases. *J Am Geriatr Soc*. 2012;60:1448–1456. doi:10.1111/j.1532-5415.2012.04077.x
7. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat Med*. 2013;32:3388–3414. doi:10.1002/sim.5753