Methods Paper

Multitype Events and the Analysis of Heart Failure Readmissions

Illustration of a New Modeling Approach and Comparison With Familiar Composite End Points

Paul M. Brown, PhD; Justin A. Ezekowitz, MBBCh, MSc

Background—Heart failure–related hospital readmissions and mortality are often outcomes in clinical trials. Patients may experience multiple hospital readmissions over time with mortality acting as a dependent terminal event. Univariate composite end points are used for the analysis of readmissions. We may amend these approaches to include emergency department visits as a further outcome. An alternative multivariate modeling approach that categorizes hospital readmissions and emergency department visits as separate event types is proposed.

Methods and Results—We seek to compare the modeling approach which handles event types as separate, correlated end points against composites that amalgamate them to create a unified end point. Using a heart failure data set for illustration, a model with random effects for event types is estimated. The time-to-first event, unmatched win-ratio, and days-alive-and-out-of-hospital composites are derived for comparison. The model provides supplementary statistics such as the correlation among event types and yields considerably more power than the competing composite end points.

Conclusions—The effect on individual outcomes is lost when they are intermingled to form a univariate composite. Simultaneously modeling different outcomes provides an alternative or supplementary analysis that may yield greater statistical power and additional insights. Improvements in software have made the multitype events model easier to implement and thus a useful, more efficient option when analyzing heart failure hospital readmissions and emergency department visits. **(*Circ Cardiovasc Qual Outcomes*. 2017;10:e003382. DOI: 10.1161/CIRCOUTCOMES.116.003382.)**

Key Words: atrial fibrillation ■ disease progression ■ heart failure ■ life ■ software

Urgent heart failure (HF) visits, including emergency department (ED) visits, are important.[1] They do not always result in a hospital admission but are linked to subsequent hospitalizations and death.[2] Since many years may elapse before death and hospital and ED visits are amenable to interventions,[3] these outcomes provide a metric for disease progression and quality of life and more attainable sample sizes. Therefore, how best to analyze HF-related hospital readmissions, ED visits, and death is important for clinical outcome studies and we would like to consider the alternative methods of analysis for these data.

These outcomes are ubiquitous in clinical research which can encourage a conventional approach to analysis.[4] Typically, a Cox regression model is used to analyze time-to-first hospital readmission or a composite of time-to-first readmission and death.[5] However, we ought to incorporate all hospital readmissions in the analysis because doing so entails greater statistical power, or in other words, a smaller sample size.[6,7] Many authors have compared methods for analyzing repeat hospital readmissions.[7–9] However, if our data also include ED visits so that we have multitype events, then we require a method that distinguishes between them.

This becomes even more important when a therapy may have a different effect on the types of events. With multitype event data, the standard approach is to analyze event types separately or combined (ie, not distinguish between them). If analyzed separately, the analysis may be underpowered to show a meaningful difference and would neglect any interdependence among types (ie, if 1 event type affects the risk of another type). On the other hand, if analyzed together, as if the same event, then we ignore the possibility that they reflect different degrees of disease severity. This may lead to a gain in power but a loss of fidelity and the risk of not showing a difference because of a dilution of effect. A more sophisticated approach is needed.

When recurrent events are types, they can be described as multitype recurrent events (MTREs). In many instances, we expect the event types to be correlated, that is, they are not independent processes, and these survival times may be truncated by a dependent terminal event (eg, death). Composite end points are popular in HF clinical trials; however, they merge event types which lead to a loss of information and do not provide event-specific estimates of the effect. MTRE modeling is an alternative which does not require us to mesh

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From the Department of Medicine, University of Alberta, Edmonton, Canada (P.M.B.); and Canadian VIGOUR Centre, Edmonton (P.M.B., J.A.E.).
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Correspondence to Justin A. Ezekowitz, MBBCh, MSc, 2-132 Li Ka Shing Centre for Health Research Innovation, Edmonton, AB T6G 2E1, Canada. E-mail jae2@ualberta.ca

outcomes and has been used elsewhere[10] but not in HF. The objective of this study was to demonstrate the use of MTRE in a patient population with HF, and additionally, qualitatively compare this to popular composite end points which are easily extended to incorporate ED visits.

Methods

Study Data

We applied the MTRE model and composite end points to study data of 816 patients with HF from the AHF-EM study (Acute Heart Failure Emergency Management). The median follow-up was 39 months. Roughly 30% of patients had at least 1 ED visit and 20% had at least 1 hospital visit during this follow-up; 13% and 6%, respectively, had ≥2 events; and all-cause mortality was 46%.

The analysis data set includes, for each patient, the time to each visit after index discharge and a classification of these visits as ED, or hospital; events occurring on the same day or subsequent days were aggregated (thus, there are no tied survival times within a patient). A selection of the data can be seen in Figure 1. We expect ED and hospital visits to be correlated, but we are not sure of the magnitude of that association and of the association with mortality. To illustrate the difference in outcome, the presence (n=523) or absence (n=293) of atrial fibrillation (AF) was chosen as the comparator. This comparison was prespecified because it was likely to prove instructive.

In addition to analyzing these data, we bootstrapped this study sample (ie, took random samples with replacement) to estimate the statistical power available for event types for a fixed sample size for the various composites and MTRE methods.

Multitype Recurrent Events

The MTRE model is characterized by the use of individual patient random effects for event types. These random effects are often termed frailties because they reflect the proneness of the individual to experience events (a large frailty implies an elevated risk for the event). We assume the frailties are sampled from some distribution—a bivariate Normal distribution in this instance because we have 2 event types (ED and hospital visits). The bivariate distribution implies a potential correlation between these end points, thus linking them.

To handle mortality as a dependent terminal event, we use a joint frailty which yields additional insight on the association between event types and mortality. For the baseline hazard, we assume a Weibull form as per other researchers[10] (alternatively, Liu and Huang[11] consider a piecewise constant). The full model specification can be found in the Data Supplement (with submodels for event types and mortality).

The model is estimated using proc nlmixed in SAS[11] (the code is made available elsewhere[12]). Empirical Bayes estimates of the frailties may be used to evaluate the fit of the MTRE model.[13]

Alternative Analytic Approaches: Composite End Points

Many composites have been proposed that combine readmissions and mortality data, such as time-to-first event,[6] the unmatched win-ratio,[5] and days-alive-and-out-of-hospital (DAOH).[14] These composites have been compared elsewhere.[15,16] Each composite uses a different algorithm for combining outcomes, as follows.

The unmatched win-ratio prioritizes outcomes in a hierarchy to determine whether 1 patient wins (has a favorable response) compared with other patients. For HF readmissions, the ordering of outcomes is mortality, hospital readmission, and repeat ED visit. This implies that a patient with a hospital visit loses against a patient with an ED visit (and no hospital visit) because inpatient visits imply greater cost and a more severe, less subjective outcome. A patient with an early death loses against all patients in the sample and patients with no hospital readmissions or ED visits who remain alive win against most patients in the sample. If the winner/loser cannot be determined on an outcome (because of censored data), then we move to the next outcome in the hierarchy. With the wins (+1), losses (−1), and ties (0) summed for each patient, a test statistic is derived as the sum of these scores for one of the treatment groups (the relevant formulae are given by Pocock et al[5] and Finkelstein and Schoenfeld[17]).

DAOH is the proportion of the total potential follow-up in which a patient is both alive and out of hospital. If a patient dies, then the duration from death to study termination is subtracted from the total potential follow-up (ie, from discharge at the index visit to study termination). If a patient is lost to follow-up, then the total potential follow-up is from discharge to the last available visit. Unlike the win-ratio, DAOH does not distinguish between ED and hospital visits explicitly, only by virtue of their nature, that is, by taking length of stay into account which in a sense accounts for the discrepancy. Both DAOH and the unmatched win-ratio give greater weight to hospital visits (inadvertently and intentionally, respectively). Analysis of the DAOH is by the Wilcoxon rank-sum test.

The time-to-first composite treats recurrent events as if they were nonrecurring events (ie, terminal events) and we analyze this outcome using Cox regression. In the case of readmissions data, this composite must either combine ED and hospital events together (ie, the time from discharge to either an ED or hospital visit) or analyze them separately. The time-to-first composite has been criticized[6] but remains a recent choice for the primary outcome of HF readmissions.[18]

Results

The results for the 3 composites, the individual outcomes (displayed under time-to-first), and the MTRE model are displayed in Figure 2. The MTRE and the time-to-first analyses are displayed by event type; DAOH and the win-ratio combine outcome data and thus yield a single overall result. The wider 95% confidence intervals for the MTRE are to be expected (owing to the random effects, ie, patient heterogeneity). The MTRE produces a P value below the threshold for statistical significance allowing us to conclude that patients with AF at the index visit have a higher rate of repeat ED visits than those without AF (hazard ratio, 1.47; P=0.018). Hospital readmissions are more similar between these groups however (hazard ratio, 1.24; P=0.259). The combined ED/hospital MTRE analysis (assuming a common effect across outcomes) also

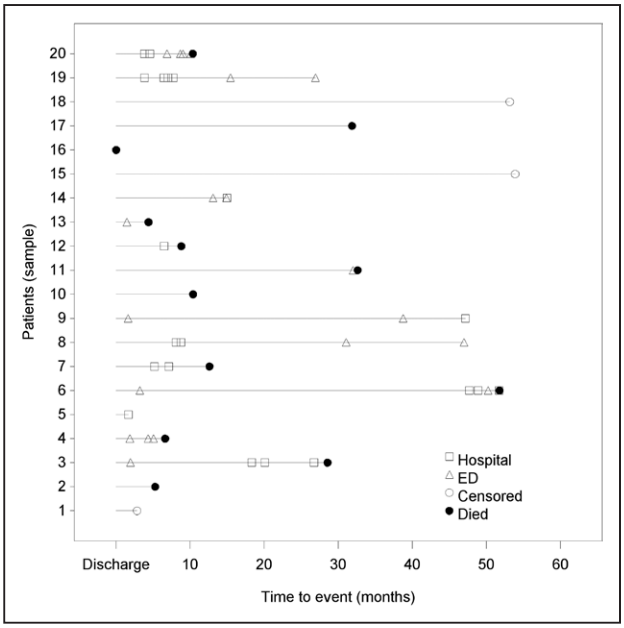

Figure 1. Sample of heart failure readmissions data. ED indicates emergency department.

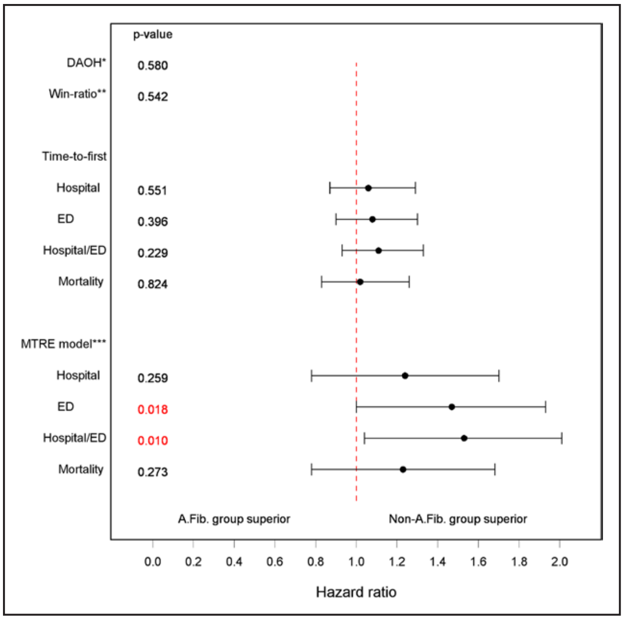

Figure 2. Comparison of results: *P* values and hazard ratios with 95% confidence intervals. *Days-alive-and-out-of-hospital (DAOH). **Three-tier unmatched win-ratio. Wilcoxon rank-sum test. ***Multitypes recurrent events model with multivariate normal random effects. The correlation for bivariate frailties is 0.88 (0.80–0.97). The model includes atrial fibrillation. covariate only. ED indicates emergency department; MTRE, multitype recurrent event; and Win-ratio, unmatched win-ratio.

produces a statistically significant result (*P*=0.010), despite the absence of an effect for hospital visits.

The effect for repeat ED visits is diluted by the weaker effect observed for hospital readmissions, producing no effect overall (DAOH *P*=0.580, unmatched win-ratio *P*=0.542). For the time-to-first composite, the differential ED visit rates for AF and non-AF groups are diminished by neglecting recurrent events and intermingling the effect on ED visits with a smaller or indifferent effect on mortality (the *P* value for mortality from the MTRE model is 0.273; hazard ratio, 1.23). Unlike the MTRE, the time-to-first composite does not show an effect for the combined ED/hospital outcome (which treats ED and hospital event types as the same).

The MTRE model provides additional insights on the association between outcomes (not presented in the figure). For example, there is a significant relationship between mortality and hospital readmissions (*P*=0.011), although there is no evidence of such a relationship between mortality and ED visits (*P*=0.814). Also, the MTRE reveals a high correlation between ED and hospital visits (0.88; with 95% confidence interval, 0.80–0.97), indicating that the risk of event types is interdependent, for example, patients with a high risk for ED visits tend to have a correspondingly high risk for hospital readmission. Incidentally, the Weibull shape parameter for the baseline hazards is <1.1, indicating that event times are highly skewed right.

The martingale residuals of the model seem adequate with the mean close to zero for both event types (Figure I in the Data Supplement). The full results can be seen in Table I in the Data Supplement.

The AHF-EM study sample was bootstrapped to obtain estimates of the statistical power for the various methods for a fixed sample size of n=800 (Figure 3). There is a considerable gain in power for the MTRE approach (for the combined effect ED/hospital, a weighted average is used). The different methods answer slightly different research questions which partly explain the difference in power obtained. In particular, the win-ratio and DAOH emphasize mortality and hospital readmissions over repeat ED visits, whereas the time-to-first analysis does not make any distinction between ED and hospital visits for the combined ED/hospital analysis. With the hospital outcome less sensitive to the effect, the difference on

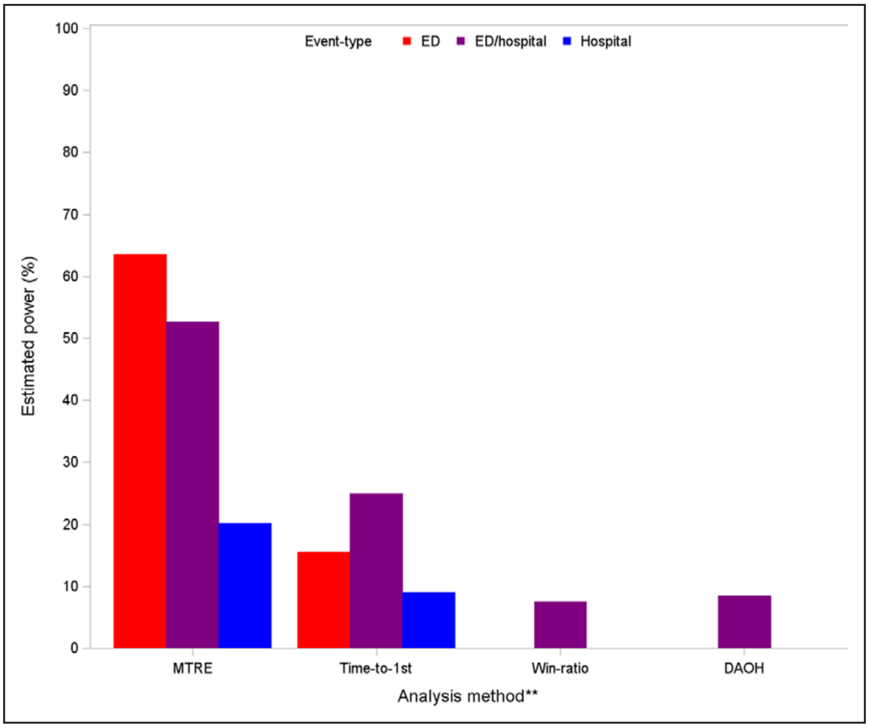

Figure 3. Estimated power for n=800*: multivariate modeling vs composite end points. *Based on AHF-EM (Acute Heart Failure Emergency Management): bootstrapping, sampling with replacement. **Time-to-first: Cox regression. DAOH indicates days-alive-and-out-of-hospital; ED, emergency department; MTRE, multitype recurrent event; and Win-ratio, unmatched win-ratio.

Table. Benefits of Random Effects Modeling Over Univariate Composites

Popular alternatives, that is, certain composite end points, have been criticized (see text for references)
Analyses of component outcomes (event types) are a consequence of the model (with the inclusion of an interaction between outcome and treatment)
The model acknowledges correlations among outcomes and may lead to greater power
The model can easily adjust for covariates
Recurrent events are accounted for which some composite end points discard
Provides an estimate of the treatment effect as the familiar hazard ratio (rank-based composites emphasize *P* values)
Mortality (censoring) is handled appropriately
The weighting of outcomes may become irrelevant because outcomes are not amalgamated as they are in composite end points
The model provides additional insights, such as the association between event types and the terminal event (mortality) and the correlation between event types
The model allows an assessment of heterogeneity by testing the consistency of the effect across outcomes
The model simultaneously recognizes various manifestations of the syndrome which may be a motivation for using a composite
Advances in software mean the multitype recurrent events model has become straightforward to implement

ED visits is diluted when events are combined, leading to a loss of power for the MTRE ED/hospital.

Discussion

The main benefit of MTRE is that we can examine associations between the events (in our case, mortality, hospital readmission, and repeat ED visits) and obtain event-specific estimates of the effect in contrast with composite end points which blend individual outcomes in their construction. Focusing on the first event, a single type of event, or combining event types together, limits the analysis and its conclusions on the burden and cost of disease and can mask effects on individual outcomes. Although the potential for an increase in power is also noteworthy, it should be emphasized that statistical power is not the sole consideration when selecting the primary outcome for a trial.[19] Potential advantages of the MTRE approach are summarized in Table.

More appropriate analyses should be encouraged while questioning crude methods such as time-to-first which remains in recent use when event types are not of equal severity.[20,21] The reason often given for combining outcomes to form a composite end point is a hope for gain in statistical power afforded by the increase in events. Likewise, we may speculate on a possible increase in power offered by MTRE modeling (depending on the strength of the correlation between event types, for example) without the need to convert multiple outcomes to a univariate end point. We investigated power using bootstrapping, but future research could investigate how power is affected by the event rate, events per patient, the disparity in event rates between event types, the number of event types, missing data, or the consistency of the group difference across event types. This could inform the design of future trials and extensions to other applications, for example, acute coronary syndrome, or transient ischemic attacks and stroke which may be classified by location.

The popularity of the time-to-first composite as a primary outcome in HF clinical trials may be explained by the ease with which a power calculation can be performed on this end point with other methods, such as the MTRE requiring data simulations. However, with continued improvements in software and estimation,[22] the MTRE model should be more widely adopted for the analysis of multivariate survival data. MTRE may provide an informative secondary analysis with a composite end point designated as the primary outcome. In this case, a composite that handles event types differently (such as the hierarchical win-ratio or DAOH) should be favored over composites that treat event types as the same event (such as time-to-first-event).

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References

1. Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD, Packer M, McMurray JJ; PARADIGM-HF Investigators and Committees. Importance of clinical worsening of heart failure treated in the outpatient setting: evidence from the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF). *Circulation*. 2016;133:2254–2262. doi: 10.1161/CIRCULATIONAHA.115.020729.
2. Ezekowitz JA, Kaul P, Bakal JA, Quan H, McAlister FA. Trends in heart failure care: has the incident diagnosis of heart failure shifted from the hospital to the emergency department and outpatient clinics? *Eur J Heart Fail*. 2011;13:142–147. doi: 10.1093/eurjhf/hfq185.
3. Babayan ZV, McNamara RL, Nagajothi N, Kasper EK, Armenian HK, Powe NR, Baughman KL, Lima JA. Predictors of cause-specific hospital readmission in patients with heart failure. *Clin Cardiol*. 2003;26:411–418.
4. Chun S, Tu JV, Wijeysundera HC, Austin PC, Wang X, Levy D, Lee DS. Lifetime analysis of hospitalizations and survival of patients newly admitted with heart failure. *Circ Heart Fail*. 2012;5:414–421. doi: 10.1161/CIRCHEARTFAILURE.111.964791.
5. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J*. 2012;33:176–182. doi: 10.1093/eurheartj/ehr352.
6. Anker SD, McMurray JJ. Time to move on from 'time-to-first': should all events be included in the analysis of clinical trials? *Eur Heart J*. 2012;33:2764–2765. doi: 10.1093/eurheartj/ehs277.
7. Rogers JK, Pocock SJ, McMurray JJ, Granger CB, Michelson EL, Östergren J, Pfeffer MA, Solomon SD, Swedberg K, Yusuf S. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. *Eur J Heart Fail*. 2014;16:33–40. doi: 10.1002/ejhf.29.
8. Castaneda J, Gerritse B. Appraisal of several methods to model time to multiple events per subject: modelling time to hospitalizations and death. *Revista Colombiana de Estadística*. 2010;33:43–61.

9. Lim HJ, Liu J, Melzer-Lange M. Comparison of methods for analyzing recurrent events data: application to the Emergency Department Visits of Pediatric Firearm Victims. *Accid Anal Prev*. 2007;39:290–299. doi: 10.1016/j.aap.2006.07.009.
10. Abu-Libdeh H, Turnbull BW, Clark LC. Analysis of multi-type recurrent events in longitudinal studies; application to a skin cancer prevention trial. *Biometrics*. 1990;46:1017–1034.
11. Liu L, Huang X. The use of Gaussian quadrature for estimation in frailty proportional hazards models. *Stat Med*. 2008;27:2665–2683. doi: 10.1002/sim.3077.
12. Brown PM, Ezekowitz JA. Frailty modelling for multitype recurrent events in clinical trials. *Statistical Modelling*. 2017.
13. Belot A, Rondeau V, Remontet L, Giorgi R; CENSUR Working Survival Group. A joint frailty model to estimate the recurrence process and the disease-specific mortality process without needing the cause of death. *Stat Med*. 2014;33:3147–3166. doi: 10.1002/sim.6140.
14. Ariti CA, Cleland JG, Pocock SJ, Pfeffer MA, Swedberg K, Granger CB, McMurray JJ, Michelson EL, Ostergren J, Yusuf S. Days alive and out of hospital and the patient journey in patients with heart failure: insights from the Candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) program. *Am Heart J*. 2011;162:900–906. doi: 10.1016/j.ahj.2011.08.003.
15. Sun H, Davison BA, Cotter G, Pencina MJ, Koch GG. Evaluating treatment efficacy by multiple end points in phase II acute heart failure clinical trials: analyzing data using a global method. *Circ Heart Fail*. 2012;5:742–749. doi: 10.1161/CIRCHEARTFAILURE.112.969154.
16. Brown PM, Anstrom KJ, Felker GM, Ezekowitz JA. Composite end points in acute heart failure research: data simulations illustrate the limitations. *Can J Cardiol*. 2016;32:1356.e21–1356.e28. doi: 10.1016/j.cjca.2016.02.067.
17. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. *Stat Med*. 1999;18:1341–1354.
18. McGuire DK, Van de Werf F, Armstrong PW, Standl E, Koglin J, Green JB, Bethel MA, Cornel JH, Lopes RD, Halvorsen S, Ambrosio G, Buse JB, Josse RG, Lachin JM, Pencina MJ, Garg J, Lokhnygina Y, Holman RR, Peterson ED. Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus: Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol*. 2016;1:126–135.
19. Senn S. Combining outcome measures: statistical power is irrelevant. *Biometrics*. 1989;45:1027–1028.
20. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322. doi: 10.1056/NEJMoa1603827.
21. Stolker JM, Spertus JA, Cohen DJ, Jones PG, Jain KK, Bamberger E, Lonergan BB, Chan PS. Rethinking composite end points in clinical trials: insights from patients and trialists. *Circulation*. 2014;130:1254–1261. doi: 10.1161/CIRCULATIONAHA.113.006588.
22. Rondeau V, Mazroui Y, Gonzalez JR. frailtypack: an R package for the analysis of correlated survival data with frailty models using penalized likelihood estimation or parametrical estimation. *J Stat Softw*. 2012;47:1–28.

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