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Review

Considerations for analysis of time-to-event outcomes subject to competing risks in veterinary clinical studies☆

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Abstract In veterinary medicine, prospective clinical trials are increasingly utilized to address questions regarding effectiveness of therapies and patient prognosis. A large number of these trials involve time-to-event (TTE) endpoints, which require special methods of analysis to handle data in which not all subjects are observed to have the event of interest. Analyses and interpretation of the results can be further complicated when an endpoint of interest is not observed in some patients because they incur a competing risk, such as death from an unrelated cause. Competing risks have been the source of confusion in many epidemiologic analyses leading to the potential for misinterpretation. In this article, we review

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key considerations for the TTE analysis in the setting of competing risks. We briefly review standard TTE tools, namely Kaplan—Meier survival curves and Cox regression. In the setting of outcomes with competing risks, we provide guidance on the appropriate analysis techniques, such as cumulative incidence curves, to estimate the risk of an event of interest. We also describe a common pitfall of treating competing risks as censoring in Kaplan—Meier survival curve analysis, which can overestimate the event rate of interest. We describe two common regression methods that examine associated risk factors in the presence of competing risks and highlight the different research questions these methods address. This article provides an introductory overview and illustrates concepts with examples from veterinary trials and with example data sets.

Abbreviations

CHF	congestive heart failure
HR	hazard ratio
KM	Kaplan—Meier
SHR	subdistribution hazard ratio
TTE	time to event

Randomized clinical studies provide an important basis for evidence-based practice. As such, the proper design, analysis, and reporting of clinical trials is a subject of increasing interest to consumers of these data, including practitioners, researchers, governmental regulators, and industry. Many clinical cardiovascular studies [1—10] involve time-to-event (TTE) analysis, in which the duration of time from study enrollment to the first occurrence of a clinically meaningful event is studied. This outcome is often referred to as the 'survival' time whether or not the event involves death. TTE or survival analysis generally requires statistical approaches different from those used for other types of outcome data, such as continuous variables (e.g. blood pressure) or dichotomous variables (e.g. the number of patients experiencing disease recurrence within 30 days). Over the course of TTE studies, patients either will have experienced the event, in which case one utilizes the time at which the event occurred, or patients will not have experienced the event, in which case one utilizes the length of time the patient was observed event free. For certain types of TTE analysis, patients not experiencing the event of interest are all treated similarly, regardless of the reason. For instance, in a study of cardiac-related sudden death in dogs with dilated cardiomyopathy [3], patients who were alive at the end of the study, lost to follow-up, or were euthanized or died from non-cardiac causes were all accounted for in a similar fashion; however, these patients differ in an important respect. Patients who are still alive or lost to follow-up still could theoretically experience cardiac-related death at some point in the future, whereas patients dying from another disease cannot. The latter is an example of an intervening event that precludes always observing the event of interest and is termed a *competing risk*. To accurately estimate the probability of the event of interest within a given time period, one must account for the probability of any competing risks.

Competing risks are commonly overlooked, even in highly visible studies. A review [11] of 50 human clinical studies that were published in high-impact medical journals found 35 of 50 (70%) inadequately addressed competing risks. In veterinary medicine, competing risks are rarely, if ever, accounted for. In this article, we review key considerations for TTE analysis in the setting of competing risks. We briefly review standard tools for TTE analysis, namely Kaplan—Meier (KM) survival curves and Cox regression. In the setting of TTE outcomes with competing risks, we provide the reader with guidance on the appropriate analysis techniques, such as cumulative incidence curves, to estimate the risk of an event of interest. We also describe a less familiar regression method that appropriately examines risk factors in the presence of competing risks and highlight how the research question of interest guides the choice of which particular regression method to use. This article provides an introductory overview of these topics and illustrates concepts with examples from veterinary clinical studies and with example data sets. We refer readers interested in further detail to a several excellent references on the topic [12,13].

Time-to-event analysis and censoring

A distinguishing feature of TTE analyses is that some individuals will not have an observed event time. Instead, the last time known without the event, otherwise known as the censoring time, is observed. For all individuals, this time should be relative to a well-defined start time (e.g. time from diagnosis) and a defined end time (e.g. the end of the planned follow-up period for clinical study). The advantage of TTE analysis is that rather than simply comparing the proportions that experienced the event by the end of the study, such analysis considers the length of time an at-risk individual was observed to be event free and not just whether the event occurred [14]. Thus, TTE analysis incorporates more information about the patient's clinical outcome and can be more precise than simply analyzing the proportion with an event, for example, the percentage that survived or died.

TTE data are routinely summarized using KM survival curves [15]. Survival curves from different treatment groups can be compared using a log-rank test [15]. For example, Figure 1 shows the KM survival curves in critically ill cats with and without hyperlactatemia reported in the study by Shea et al. [5] In this study, the survival of cats with hyperlactatemia was significantly different (log-rank p-value was 0.03) from that of those without hyperlactatemia. Standard survival analysis also uses the Cox proportional hazards model, which evaluates the effect of one or more variables on the survival time. The Cox regression model estimates the hazard ratio (HR) of the event in the treatment arm vs. the control arm at any given point in time during the study [15]. The HR can be thought of as a relative probability of an impending event; that is, it represents the instantaneous risk ratio between two patient groups in the next small time interval, among those still at risk. The individual hazard rates may be varying over time, but the commonly used Cox proportional hazards model assumes that their ratio is constant over time.

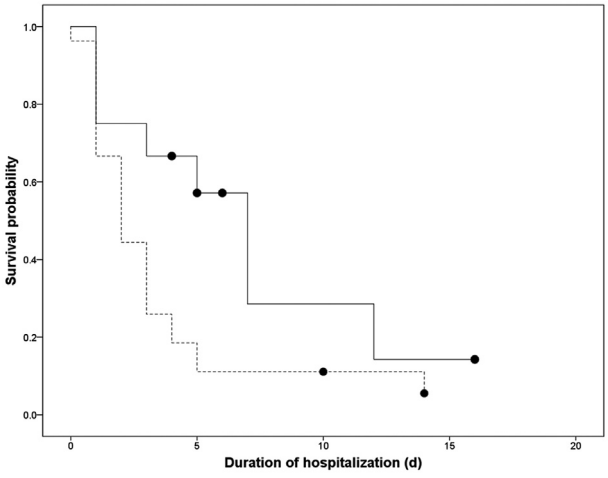

Figure 1 Kaplan—Meier (KM) survival curves of critically ill cats with (dashed line) and without (solid line) hyperlactatemia. At the beginning of hospitalization, all cats were alive. Over the course of follow-up, the survival curve stair steps downward as cats die. Cats that survived and were discharged from the hospital are represented by a solid circle. The survival curves between cats with and without hyperlactatemia were significantly different by the log-rank test with a p-value of 0.03 (From the study by Shea et al. [5]).

As previously stated, an important advantage of TTE analysis is that study participants not reaching the primary endpoint (i.e. the 'censored' observations) can be included in the analysis up to the point when their observation is discontinued or the study ends [14]. Examples of censoring include individuals withdrawn early from the study before an event was observed, perhaps due to a change in location that made visits no longer feasible, or those who remain free from the event of interest by the end of the study. A key assumption in the conventional survival analysis is that the *probability of experiencing the outcome of interest is independent of the reason for censoring* [16]. This type of censoring is referred to as 'independent censoring' and permits analysis of the data in hand without concern that dropouts or non-related deaths are potentially biasing the results. As will be seen later, this assumption is violated in the case of a competing risk.

Competing risks and analysis pitfalls

Survival analysis methods, such as KM analysis, were originally developed to evaluate the probability of *all-cause* mortality [14]. Kaplan—Meier analysis assumes that regardless of the reason for censoring, a censored individual is still at risk for the outcome (i.e. death for any reason). The assumption is that within each treatment cohort, censored individuals would eventually have died at the same rate as the individuals remaining in the study, thereby preserving the independent nature of the censoring. Kaplan—Meier analysis subsequently has been widely used to estimate the probability of non-fatal clinical outcomes, for instance, hospitalization, disease recrudescence, or 'treatment failure' or the probability of cause-specific mortality, such as death due to heart

failure or cardiovascular disease. When applied in this manner, the key assumption of independent censoring can break down. For instance, consider a study [3] that used KM analysis to evaluate the time to the first onset of congestive heart failure (CHF) or sudden cardiac death in dogs with preclinical cardiomyopathy. Dogs that died from unrelated causes were treated as censored observations. Thus, for the purposes of the KM analysis, they were considered to still be at risk for CHF or sudden death despite being dead. Said differently, by treating deaths from other causes as a censoring event, the KM survival curve estimated the risk of CHF or sudden death recurrence in a world where death from other causes did not occur. Depending on the specific circumstances, such as the incidence of death from other causes, the impact of the reported treatment benefit on 'real-world' animals that are, in fact, subject to death from other causes can be clouded. We further illustrate this below by examining how the KM curve is calculated and describe an alternate way to calculate incidence rates that account for interceding events, namely we describe something called the cumulative incidence curve.

Patient events that preclude the observation of the primary study endpoint are called 'competing events,' and these types of events produce '*competing risks*' [17,18]. A competing risk that could be risk of death or a major health event from another cause that once observed would make it impossible for the individual to experience the event of interest [11]. For example, in a study [7] investigating the effect of tricuspid valve annular motion on cardiac-related death in dogs, death from a non-cardiac cause is a competing risk in that the dog cannot subsequently die again for cardiac reasons. Whereas the time to either of these two events or overall survival can be examined using usual methods, the specific probability of cardiovascular death must be analyzed using a technique that accounts for the competing risk of death.

Not all censored observations are competing events. Censored individuals who are still event free at the end of the study or were lost to follow-up for reasons unrelated to the health outcome under study can reasonably be assumed to have the same subsequent risk for the study endpoint as those who remain under study, but for a patient who has truly experienced a competing event, the subsequent risk for the outcome of interest is now zero. As a result of how the KM analysis uniformly treats all censored individuals as still at risk, it overestimates the probability of an outcome subject to competing risks, as shown below.

Effect of competing risks on survival analysis

When analyzing survival data, we identify a group of individuals who have not experienced the outcome of interest before an observed event time and those who are about to experience the event at that time. This population serves as the denominator in calculating the instantaneous baseline hazard, which is then used to derive the KM survival curve. The numerator of the hazard is the number of individuals who have experienced the outcome at the time in question. Standard KM analysis uniformly treats competing events as censored observations, and in doing so, it removes them from the denominator. This effectively assumes that they are still at risk for having the primary outcome, implying that the event rate is the same in those still under observation as those no longer under observation. In the absence of competing risks, KM analysis estimates the survival function. The log-rank test is used to test for a difference in survival between two or more groups, and Cox regression can be used to estimate associations between covariates and the hazard rate [13,15]. In the presence of competing risks, KM analysis no longer estimates the survival function because the risk of events in the censored individuals (i.e. 0) is different from the risk in those not censored [12,17]. Despite the presence of competing risks, Cox regression can still be used to estimate the efficacy of an intervention, such as the effect of a drug or placebo on the hazard or risk of an outcome at a given time [18]. In this scenario, the event indicator for the analysis is whether or not the event of interest occurred and the regression model estimates a 'cause-specific' hazard, for instance, the risk of experiencing the outcome if receiving the drug [17].

In addition to the survival time and cause-specific HR, another important characteristic of disease is the proportion of subjects experiencing an event of interest by a given time, otherwise known as the *cumulative incidence*. When determining the cumulative incidence of specific events such as cardiovascular-related death, those who died from other reasons can be specifically accounted for. For instance, dogs dying for other reasons are subsequently no longer considered as at risk for cardiovascular death, whereas dogs having been censored for non-fatal reasons (e.g. alive at the end of study, lost to follow-up, protocol violations, etc.) remain at risk. Thus, analysis and regression methods designed to specifically assess the cumulative incidence function take competing risks into account.

Analysis based on cumulative incidence

Unlike the KM method, the cumulative incidence function for an event of interest considers three possible event types at any given time as follows: those who experienced the event of interest, those who experienced a competing risk, and those who were censored. The resultant calculation estimates the risk of the primary event in individuals who have not yet experienced any event. Individuals who are censored are treated as still at risk at the time of censoring; those who experience a competing risk are not. In this way, one correctly estimates the cumulative incidence of observing an event at a given time.

Analysis based on the cumulative incidence function is similar to KM analysis in that two different cumulative incidence curves can be compared using techniques [19] analogous to the log-rank test. Similarly, the association of various covariates with the cumulative incidence can be determined using techniques developed by Fine and Gray [12,17,20,21] which are analogous to Cox regression. A full discussion of the mathematical and epidemiological attributes of these calculations is outside the scope of this review, but in general, cause-specific HRs based on Cox regression can be thought of as measures of the relative risk of incurring an event among those still at risk, whereas regression methods for the cumulative incidence produce a relative measure of the absolute risk known as the 'subdistribution' hazard ratio (SHR) [17,22]. This SHR estimates the covariate effects on the rate of the event in the individuals either still at risk or having already succumbed to a competing risk. Note that this makes the SHR harder to interpret as it does not correspond to a rate for a population of interest, but it does provide information on the relative cumulative incidence (or probability) for that event. For this reason, we will refer to the SHR as a comparative measure of the absolute (cumulative) risk. The interested reader is referred to the On-line Supplemental Tables A, B and Fig. I for more details regarding the calculation of KM survival and cumulative incidence curves.

Illustrative example 1: estimating incidence in the presence of competing risks

Previous authors have illustrated the clinical features of a competing risk using examples from human medical clinical trials [20,23,24] and through the use of computer simulations [20,24—26], and we have adapted some of the latter [20,25,26] in the following illustrative example. By using a computer-simulated clinical trial, we can examine the value of different statistics, such as the probability of observing various events of interest, and compare them with the underlying true values determined by the parameters used to generate the data. Using statistical software,[d] we modified published code [25] to create a hypothetical data set consisting of information on 125 Doberman Pinschers with dilated cardiomyopathy. Previous veterinary studies have shown that affected dogs are at high risk for cardiac-related death due to ventricular arrhythmias or CHF [27,28]. Thus, if one specifically considers sudden death as the primary endpoint, death due to CHF represents a competing risk. We then simulated a 2-year follow-up period during which dogs had an equal chance of dying either suddenly or from CHF, and follow-up data were generated for all dogs.

Cumulative incidence is overestimated by KM analysis

According to our simulation, at the end of 2 years, 65 dogs had died suddenly, 53 dogs had died from CHF, and 7 dogs were still alive. We then calculated a KM survival curve of dogs that died suddenly (Fig. 2A). The KM analysis treats dogs that either died from CHF or remained alive as censored observations and assumes all censored observations are still at risk for sudden death. The complement of the KM survival curve (1-KM) represents a naïve estimate of the cumulative incidence of the outcome, in this case, sudden death (Fig. 2B). In studies that ignore the competing risk, the 1-KM curve is routinely cited as the cumulative incidence of the primary event [17]. Thus, based on the KM analysis of our simulated data, the 2-year probability of sudden death is ~78% (Fig. 2B). However, this probability is substantially overestimated. When considering the cumulative incidence function, which accounts for competing risks, the estimate of sudden death at 2 years is only 52% (Fig. 2C). The overestimation of sudden death based on the KM estimator arises from imputing sudden death events in the individuals who had already died from CHF and therefore were no longer at risk of sudden death.

Median survival is underestimated by KM analysis

A standard reporting practice in TTE studies is to use the KM or 1-KM curve to report the median TTE

[d] STATA 14.2, STATA Corp., College Station, TX.

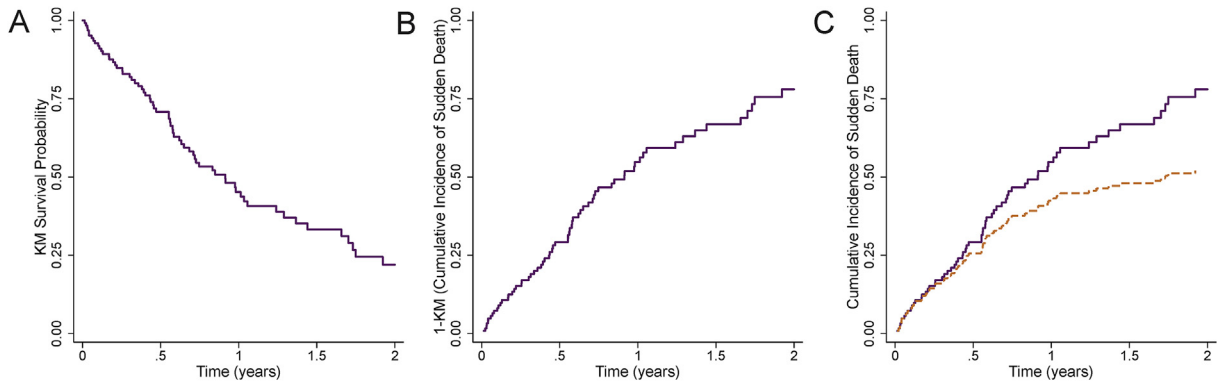

Figure 2 Kaplan—Meier (KM) and cumulative incidence function curves from a hypothetical data set of 125 Doberman Pinscher dogs with dilated cardiomyopathy. All dogs were successfully followed for the entirety of the study. A) Two-year KM sudden death-free survival curve showed a progressive decline in the proportion of dogs free from sudden death. The KM analysis treated dogs that died from congestive heart failure (CHF) as independently censored observations (i.e. the future risk of observing sudden death is assumed to be unaffected), thus ignoring the competing nature of this event on the primary outcome. B) The naïve complement (1-KM) of the KM survival curve shown in A estimated the cumulative proportion of dogs experiencing sudden death. The curve indicated that at 2 years, the cumulative incidence of sudden death was 78%. C) The 1-KM curve from B (purple solid line) drawn on the same graph as the cumulative incidence function curve (orange dashed line) of sudden death showed that there was a substantially lower incidence of sudden death at 2 years of 52%. Thus, in the presence of competing risks, the KM analysis overestimated the probability of sudden death.

or median 'survival' time, which is the point in time that half the population has experienced the event in question. As we have demonstrated, in the presence of competing risks, KM analysis upwardly biases the cumulative incidence of the primary event, which will result in shortened cause-specific median survival estimates compared with those derived from the cumulative incidence function [20]. Thus, as a general rule, while Cox regression analysis accurately estimates the relative hazard of the primary event, whenever >10% of study patients experience a competing risk event, the median survival time as determined by KM analysis can be substantially underestimated [17].

Illustrative example 2: risk factor association

We now consider the evaluation of a hypothetical new drug that reduces risk of sudden death in Doberman Pinschers with dilated cardiomyopathy by 35% (equivalent to a HR of 0.65) but does not affect the risk of death due to CHF (HR, 1.0). In this example, we again use our simulation tool so that we can compare empirical results with those predicted by the original conditions, something we would not know in a real-world clinical trial. To simulate this, we created a second cohort of 125 'treated' Doberman Pinschers and simulated outcome over the same 2-year period as the previous 'untreated' cohort. KM curves for sudden death, which treated CHF deaths as censoring, revealed that treatment significantly prolonged time to sudden death in the treated group (Fig. 3). KM

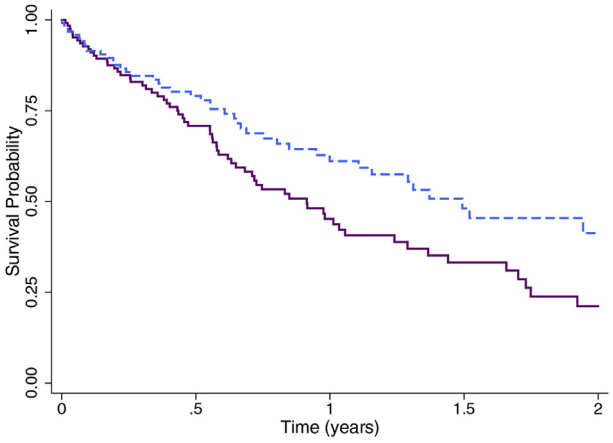

Figure 3 Kaplan—Meier curves of survival from sudden death in a hypothetical study of 250 Doberman Pinscher dogs with dilated cardiomyopathy, where deaths from other causes were treated as censoring. These curves indicate that dogs receiving treatment (blue dashed line) experienced better survival with respect to sudden death vs. dogs not receiving treatment (purple solid line). The median time to sudden death in the treated group was 1.5 years (95% confidence interval [CI], 1.0—∞) compared with 0.9 years (95% CI, 0.6—1.2) in the untreated group (log-rank test, $p = 0.021$). These naïve estimates do not account for competing risks, compared with those obtained by cumulative incidence.

Table 1 Cox-proportional cause-specific hazard ratios (HRs) and 'subdistribution' hazard ratios (SHRs) estimated by Fine—Gray regression from a hypothetical study on Doberman Pinscher dogs receiving a treatment anticipated to reduce the relative risk of sudden death by 35% but with no effect on the relative risk of death due to congestive heart failure (CHF). Results of Cox regression from the simulated data set reflected the ability of treatment to significantly reduce the relative risk of sudden death by ~35%, whereas the HR for death due to CHF was not affected. The cause-specific HRs describe the instantaneous relative risk of the event; here, competing risks are treated as censored events. Results in the second column are derived from the cumulative incidence function and account for competing risk events as events that affect the cumulative incidence. The SHR, although not directly comparable with the Cox-derived cause-specific HRs, are a relative index of absolute, i.e. cumulative, risk. Thus, as treatment reduced both the instantaneous (i.e. Cox-derived) and absolute (i.e., Fine—Gray derived) risk of sudden death, the downstream effect of fewer dogs dying suddenly increased the absolute risk of dying at later times due to CHF despite no effect of treatment on the relative risk of CHF. This is reflected in the SHR for CHF death being significantly greater than 1. See text for more details. CI, confidence interval.

Event	Cox regression cause-specific hazard ratio	Fine—Gray regression subdistribution hazard ratio
Sudden death	0.64	0.59
95% CI	(0.43—0.94)	(0.40—0.87)
p-value	0.022	0.008
Death due to CHF	1.30	1.53
95% CI	(0.91—1.85)	(1.08—2.17)
p-value	0.153	0.018

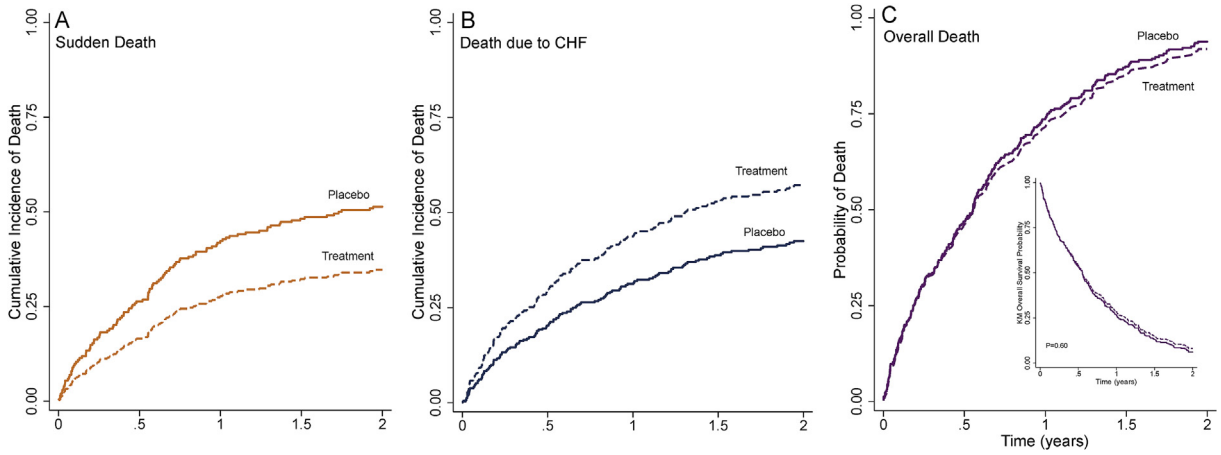

Figure 4 Cumulative incidence curves by cause of death and probability of overall death from a hypothetical study of Doberman Pinscher dogs with dilated cardiomyopathy. A) Cumulative incidence curves for sudden death indicated that dogs receiving treatment (orange dotted line) experienced a reduction in the relative risk of sudden death vs. placebo (orange solid line), consistent with the expected effect of the treatment. Note that there is an approximately 34% absolute risk of sudden death in treated dogs by 2 years. Compare this to the cause-specific Kaplan—Meier (KM) survival curve for sudden death (Fig. 3), which indicated a 43% risk in treated dogs at 2 years. The overestimation by the cause-specific KM estimate as compared with the cumulative incidence curve is due to the failure to account for competing risks. B) Cumulative incidence curves for death due to congestive heart failure (CHF) indicated that the absolute risk of death due to CHF was higher in dogs receiving treatment (blue dotted line) vs. placebo (blue solid line) despite no etiologic effect of the treatment on this mode of death. As fewer dogs receiving treatment died suddenly, the downstream effect was to increase the proportion of treated dogs that died from CHF, such that at the end of the study period, a greater proportion of dogs receiving treatment died from CHF vs. dogs not on treatment. C) KM probability of overall death curve (i.e. 1-KM, where KM is the usual Kaplan—Meier survival curve for death from either cause [inset]) demonstrated that the relative risk of *overall* death is not significantly different in dogs receiving treatment (purple dotted line) relative to dogs receiving placebo (purple solid line) (log-rank test, $p = 0.60$). Thus, the relative risk of sudden death is reduced, but this is offset by a higher probability of dying from CHF than dying suddenly. See text for more details.

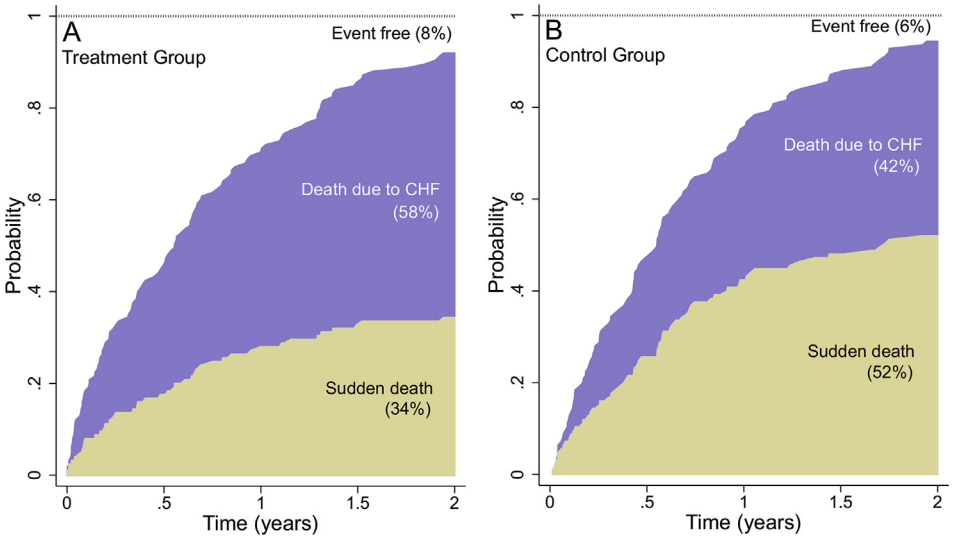

Figure 5 Stacked cumulative incidence function area curves allow for detailed prognostication with regard to probability of various outcomes based on a hypothetical treatment in Doberman Pinscher dogs with dilated cardiomyopathy that reduced risk of sudden death by 35%. The probability of sudden death over the course of the study is shown in gold. The probability of death by congestive heart failure (CHF) is shown as purple, and the area in white is the probability of being event free. Thus, the probability of any of the three outcomes (i.e. sudden death, death by CHF, or event free) will add up to 100%. A) For dogs that received treatment, the probability of experiencing any of the various outcomes by 2 years included a 34% chance of sudden death, 58% chance of death due to CHF, and 8% chance to be free of either. B) For dogs that did not receive treatment, the probability of experiencing any of the various outcomes by 2 years included a 52% chance of sudden death, 42% chance of death due to CHF, and 6% chance to be free of either. These data can facilitate medical decision-making and prognostication. See text for more details.

curves can provide an accurate estimate for probability of all-cause survival, but for estimates of cause-specific survival in both the groups, we will see that KM curves produced incorrect estimates for the reasons we have discussed.

Two separate Cox proportional hazards regression models were used to calculate cause-specific HRs that separately described the relative risk of sudden death and death due to CHF between the treated and untreated cohorts (Table 1). As expected, the cause-specific hazard for sudden death was significantly reduced by ~35% in the treated group, whereas there was no significant change in the relative risk of death due to CHF (HR not significantly different than 1.0). How do these results compare with analyses that account for competing risks?

In the absence of competing risks, there is a direct correspondence between the relative risk of an event and the absolute risk or cumulative incidence of an event such that a lowered relative risk will decrease the cumulative incidence of the event, an elevated relative risk will increase the cumulative incidence, and an unchanged relative risk will neither increase nor decrease the cumulative incidence. In the presence of competing risks, this correspondence might no longer hold, especially when the probability of experiencing the competing event is high. For instance, in our hypothetical study, treatment was associated with a lower instantaneous risk (i.e. HR = 0.64; Table 1) and a lower absolute risk of dying suddenly (SHR = 0.59; Table 1). The 2-year absolute risk (i.e. cumulative incidence) of sudden death in treated vs. untreated dogs was 34% vs. 52%, respectively (Fig. 4A). In contrast, treatment was associated with a neutral effect on the relative risk of death from CHF (HR not significantly different from 1.0, Table 1) but a *higher absolute risk* of dogs dying from CHF (i.e. SHR = 1.53; 2-year cumulative incidence of death from CHF in treated vs. untreated dogs of 58% vs. 42%, respectively, Fig. 4B).

The reciprocal relationship between the modes of death resulted in similar longevity in the two treatment arms (Fig. 4C). We see this pattern because as treatment reduces the absolute risk of sudden death, dogs have more chance to experience CHF. Thus, the cumulative incidence of dogs experiencing CHF deaths in the treatment group increases as the study proceeds. This effect can be quantified by regression analysis based on the cumulative incidence curves [22,29]. The increased absolute risk of death due to CHF is indicated by the SHR from the competing risk

regression being significantly >1 (Table 1). The effect of competing risks to produce higher estimates of median survival time for a given event vs. those based on naïve KM analysis is also seen. Based on the naïve KM curves, 50% of dogs with and without treatment were estimated to have died suddenly at 1.5 years and 0.9 years, respectively (Fig. 3), whereas, in fact, only 32% of dogs receiving treatment and 39% of dogs not receiving treatment are expected to experience sudden death at these times based on analysis of the cumulative incidence (Fig. 4A).

Picking an analysis approach in the setting of competing risks

The different analytical approaches presented in our hypothetical studies are best used to address different sets of questions [11,18,21]. Cox regression addresses etiological questions, such as whether or not a specific treatment reduces the relative risk of an event and prolongs the time to that event. Thus, the cause-specific HR is the typical measure of efficacy in a clinical trial comparing the effect of different treatments on a specific event time. Kaplan–Meier survival curves, in presence of competing risks, can only accurately examine overall survival, unless competing risks are rare. Cumulative incidence curves and their associated regression methods better address questions about prognosis by incorporating all risks faced by a patient (Fig. 5). These sorts of analyses can facilitate the presentation of prognostic information to pet owners and subsequent medical decision-making because of their ease of interpretation. In our hypothetical example, despite a significant reduction in the relative risk of sudden death, dogs receiving treatment did not live significantly longer than dogs receiving placebo because of the competing risk of death due to CHF. This is not to say that the treatment somehow had an off-target effect that caused CHF—remember that the Cox-derived cause-specific HR for CHF was not significantly different from 1.0 (Table 1)—it just so happens that preventing sudden death exposed dogs to a competing risk of CHF that was high enough so that overall survival was not significantly improved. From this example, we see that a complete picture of the etiologic effects of a drug and its prognostic implications was only assured after examining all of the following: 1) the cumulative incidence of the primary endpoint and any competing risks, 2) comparative measures of the instantaneous risk (i.e. cause-specific HRs for all event types, 3) comparative measures of the absolute risk (i.e. the subdistribution HRs for all event types), and 4) overall survival.

In special instances—for example, when the incidence of competing events is relatively high, there are strong patient preferences for one form of outcome over another, or there is risk for fatal adverse events associated with treatment—a multi-faceted competing risk analysis should be considered. As an example of the latter, if an effective treatment is associated with important risk of fatal reactions, the reduced number of individuals exposed to the successful treatment might be low enough to overwhelm the etiologic treatment-associated benefit, such that the cumulative incidence of treatment success is actually the same or lower than the incidence of fatal adverse reactions [30]. These types of scenarios demonstrate how KM analysis can be used to assess overall survival and how cumulative incidence analysis can be used to describe the treatment effect on specific outcomes. Analysis based on cumulative incidence is also useful in setting policy and determining allocation of resources based on the cumulative incidence of expected outcomes [24,31,32]. In our hypothetical study, for example, one would need to plan for an increase in the number of CHF cases needing management as the result of treatment. Competing risks are common in both human and veterinary medicine, particularly in studies involving geriatric populations with significant comorbidities [20]. Commercially available statistical software packages readily perform analyses based on either KM or cumulative incidence [25,33–35], and investigators should consider the appropriateness of either or both analyses when performing studies.

Conclusions

In this article, we have highlighted the importance of choosing the right analysis technique for TTE endpoints in the presence of competing risks, so that the resulting statistics and hypothesis tests are aligned with the clinical question of interest. Kaplan–Meier curves provide an appropriate way to describe survival in the presence of rare or non-existing competing risks, whereas cumulative incidence curves accurately describe cumulative incidence rates when competing risks might be substantial. Cox regression addresses questions about relative instantaneous risk, whereas regression based on the cumulative incidence function addresses questions about the ratio of absolute (cumulative) risk for specific

outcomes between groups. The former addresses the etiologic question about the rate of events in those at risk; the latter addresses questions about the probability of certain types of events eventually occurring. Complementary analyses of overall survival and cumulative incidence and use of specialized regression methods in clinical studies with substantial competing risks are likely to provide fuller results that can better guide clinical decision-making and estimation of treatment effects on the multitude of clinical outcomes that are important to the patient.

Conflict of Interest Statement

The authors do not have any conflicts of interest to disclose.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jvc.2018.03.001.

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