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Frequency, Regional Variation, and Predictors of Undetermined Cause of Death in Cardiometabolic Clinical Trials: A Pooled Analysis of 9259 Deaths in 9 Trials

Editorial, see p 874

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BACKGROUND: Modern cardiometabolic clinical trials often include cardiovascular death as a component of a composite primary outcome, requiring central adjudication by a clinical events committee to classify cause of death. However, sometimes the cause of death cannot be determined from available data. The US Food and Drug Administration has indicated that this circumstance should occur only rarely, but its prevalence has not been formally assessed.

METHODS: Data from 9 global clinical trials (2009–2017) with long-term follow-up and blinded, centrally adjudicated cause of death were used to calculate the proportion of deaths attributed to cardiovascular, noncardiovascular, or undetermined causes by therapeutic area (diabetes mellitus/pre–diabetes mellitus, stable atherosclerosis, atrial fibrillation, and acute coronary syndrome), region of patient enrollment, and year of trial manuscript publication. Patient- and trial-level variables associated with undetermined cause of death were identified using a logistic model.

RESULTS: Across 127 049 enrolled participants from 9 trials, there were 9259 centrally adjudicated deaths: 5012 (54.1%) attributable to cardiovascular causes, 2800 (30.2%) attributable to noncardiovascular causes, and 1447 (15.6%) attributable to undetermined causes. There was variability in the proportion of deaths ascribed to undetermined causes by trial therapeutic area, region of enrollment, and year of trial manuscript publication. On multivariable analysis, acute coronary syndrome or atrial fibrillation trial (versus atherosclerotic vascular disease or diabetes mellitus/pre–diabetes mellitus), longer time from enrollment to death, more recent trial manuscript publication year, enrollment in North America (versus Western Europe), female sex, and older age were associated with greater likelihood of death of undetermined cause.

CONCLUSIONS: In 9 cardiometabolic clinical trials with long-term follow-up, approximately 16% of deaths had undetermined causes. This provides a baseline for quality assessment of clinical trials and informs operational efforts to potentially reduce the frequency of undetermined deaths in future clinical research.

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Clinical Perspective

What Is New?

- US Food and Drug Administration guidance indicates that deaths attributable to undetermined causes should be rare in well-run clinical trials.
- Across 9 cardiovascular clinical trials in different therapeutic areas, the proportion of deaths adjudicated as attributable to undetermined causes ranged from 7% to 22% (overall 16%).
- Death attributable to undetermined cause was associated with trial (therapeutic area and year of publication) and patient factors (sex, age, region of enrollment, and time from enrollment to death).

What Are the Clinical Implications?

- Most trials can be expected to have a proportion of deaths attributable to undetermined cause that falls within the range reported in this study.
- Higher rates of deaths attributable to undetermined cause may indicate issues with trial quality and completeness of follow-up, and future trials may pursue lower rates through operational innovation.
- Given the potential importance of cause of death determination to primary trial results and the relatively high proportion of deaths attributable to undetermined cause in modern trials, researchers should publicly report the proportion of deaths where cause was unable to be determined.

Cardiometabolic clinical trials often have a primary composite efficacy end point that includes cardiovascular (CV) death, along with other nonfatal outcomes. As opposed to all-cause mortality, the use of CV death increases the precision of the end point to that which would be targeted by the cardiometabolic intervention under study. Clinical events committees (CECs) are formed to provide systematic, standardized, independent, unbiased, and blinded adjudication of the cause of death from available medical records and documentation of communication with deceased trial participants' family members and friends.

However, sometimes cause of death cannot be determined from available documentation, and the cause of death is formally adjudicated by the CEC as "undetermined." This may occur when there is abundant information, but the proximate cause of death remains unclear. More commonly, it may arise because of inadequate documentation: a participant may not have had contact with family, friends, or investigators in the weeks before death; family members may decline to discuss details of a death with study investigators; and certain countries' conventions and privacy regulations may prevent hospitals from sharing deceased patients' clinical data with researchers. In cardiometabolic trials, deaths of undetermined cause are usually assumed to be CV deaths for the purposes of statistical analyses, and are included in the composite primary outcome. It is for this reason that they warrant attention and review.

In 2014 and 2018, the Standardized Data Collection for Cardiovascular Trials Initiative, in collaboration with the US Food and Drug Administration (FDA), the American College of Cardiology, and the American Heart Association, produced reports defining end points in cardiometabolic clinical trials.[1,2] These documents note that "deaths of undetermined cause should be very few," and that "use of this category is discouraged and should be rare in well-run clinical trials in which adequate source documentation is assiduously sought by participating investigators."[2] Deaths of undetermined cause have subsequently faced stricter scrutiny in FDA evaluations.[3] During the conduct of a well-run clinical trial, the cause of death will inescapably remain undetermined for a certain proportion of deceased participants, but a reasonable target number for those deaths has not yet been determined. To set a benchmark for this proportion, an aggregate review of the number of deaths of undetermined cause in prior clinical trials must be performed. We therefore combined trial- and patient-level data from 9 recent clinical trials across cardiometabolic therapeutic areas to investigate proportions of centrally adjudicated and investigator-reported undetermined cause of death by therapeutic area, region of patient enrollment, and year of trial publication, to evaluate agreement between CEC-adjudicated and investigator-reported cause of death, and to identify baseline patient and trial characteristics associated with undetermined cause of death.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Data were aggregated from 9 recent multinational clinical trials with long-term follow-up and blinded CEC adjudication of cause of death, which enrolled patients with 4 disease states: diabetes mellitus (DM)/pre-DM (TECOS [Trial Evaluating Cardiovascular Outcomes with Sitagliptin][4] and NAVIGATOR [Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research][5]), stable atherosclerotic disease (coronary artery disease [CAD] or peripheral artery disease [PAD]) (EUCLID [Examining Use of Ticagrelor in Peripheral Artery Disease][6] and STABILITY [Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy][7]), atrial fibrillation (ROCKET AF [Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation][8] and ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation][9]), and acute coronary syndrome (ACS) (TRACER

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[Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome],[10] TRILOGY ACS [Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes],[11] and PLATO [Study of Platelet Inhibition and Patient Outcomes][12]). CECs for all trials, except NAVIGATOR and STABILITY, were coordinated by the Duke Clinical Research Institute; NAVIGATOR's CEC was coordinated by the Cleveland Clinic Coordinating Center for Clinical Research, and STABILITY's CEC was coordinated by the Uppsala Clinical Research Center. Individual studies were approved by institutional review boards at participating institutions, and all patients provided written informed consent.

In all trials, cause of death was reported by site investigators, and available documentation was transferred to an independent, blinded CEC that adjudicated cause of death based on trial-specific definitions. In each trial, the CEC adjudicated deaths as attributable to CV, non-CV, or undetermined cause. In all trials except TRACER, investigators also signified whether death was attributable to CV, non-CV, or undetermined causes. In TRACER, investigators did not have the option to select "undetermined" as a cause of death, but did describe the circumstances of the death in free text; for this trial, any deaths for which the free text indicated the cause was "unknown" were classified as undetermined. All trials included a category of sudden cardiac death or presumed CV death, and reviewers were instructed to select this option when available records indicated that the patient was known to be well within 24 hours of death, with undetermined cause of death reserved for instances where circumstances of death were totally unknown (see Table I in the online-only Data Supplement for specific definitions in each trial).

In the primary results article for several trials, deaths occurring after a prespecified date were not included in the primary analysis. The causes of these deaths were centrally adjudicated by CECs, and they were included in our analysis. In other trials, patients who were enrolled at sites that committed major protocol violations were excluded from the analysis; deaths occurring in these patients were not included in our analysis.

Statistical Analysis

Trial and patient characteristics are presented for patients with undetermined, CV, or non-CV cause of death. Categorical variables are presented as frequencies (percentages), and continuous variables are presented as medians (interquartile range). Pearson χ^2 tests and Kruskal-Wallis tests were used for comparing categorical and continuous variables, respectively. A *P*-value threshold of <0.05 was used to define statistical significance.

The proportions of deaths characterized by the CEC and by site investigators as attributable to CV, non-CV, and undetermined cause were calculated by therapeutic area (DM/pre-DM, CAD/PAD, atrial fibrillation, ACS), region of patient enrollment, and year of trial publication. The world was subdivided into regions based on United Nations regional groups, modified to avoid regions including only 1 or 2 countries. Countries included in each region are defined in Appendix I of the online-only Data Supplement. Pearson χ^2 tests were used to compare the proportion of deaths attributable to undetermined cause across therapeutic area, region of patient enrollment, and year of trial publication subgroups. The agreement between CEC-adjudicated and investigator-reported cause of death was also evaluated with Cohen's κ.

To determine the multivariable association of patient- and trial-level characteristics with undetermined cause of death, a logistic model was created. Stepwise methods were used to select covariates from among the following trial and patient characteristics: region of enrollment, therapeutic area, year of trial publication, time from enrollment to death, age, sex, prior myocardial infarction, prior stroke, hypertension, and history of heart failure. The threshold for inclusion in the final model was $P \leq 0.10$. Multivariable modeling was conducted using complete cases only, including factors that were considered important and available across all studies.

RESULTS

Across the 9 trials, there were a total of 9259 CEC-adjudicated deaths. CECs adjudicated 5012 CV deaths (54.1%), 2800 non-CV deaths (30.2%), and 1447 undetermined deaths (15.6%). Of CEC-adjudicated deaths, 28 were not reported by investigators, leaving 9231 investigator-reported deaths: 4929 (53.4%) from CV causes, 3087 (33.4%) from non-CV causes, and 1215 (13.2%) from undetermined causes. The proportion of CEC-adjudicated deaths of undetermined cause ranged from 7.0% to 21.7% across trials (Table 1); the proportion of investigator-reported deaths of undetermined cause ranged from 8.5% to 19.2%.

Cause of Death by Therapeutic Area, Region of Enrollment, and Year of Publication

There was variability in the proportion of CEC-adjudicated deaths of undetermined cause by therapeutic area: in DM/pre-DM trials, 16.0% of deaths were of undetermined cause, compared with 20.0% in CAD/PAD trials, 14.1% in atrial fibrillation trials, and 12.5% in ACS trials ($P<0.001$, Figure 1A). There was marked difference in the proportion of deaths attributed to non-CV causes by therapeutic area, with non-CV death accounting for 19.5% of deaths in trials enrolling patients with ACS and 38.7% of deaths in DM/pre-DM trials. Investigator-reported deaths of undetermined cause similarly varied across therapeutic areas, as did the proportion of deaths attributed to CV and non-CV causes (Figure 1B).

When the frequency of death of undetermined cause was analyzed by region, CEC-adjudicated undetermined cause of death ranged from 10.0% in Australia, Oceania, and South Africa to 18.5% in East/South Asia, although there was a relatively small number of deaths in these regions (n = 1260 in East/South Asia, and 310 in Australia/Oceania/South Africa) (Figure I in the online-only Data Supplement). In Europe and the Americas, where the majority of deaths occurred, differences in the proportion of deaths attributable to

Table 1. CEC-Adjudicated Undetermined Cause of Death in Included Clinical Trials

Trial	Clinical Condition	Compound	Year of Publication	Median Follow-up (mo)	Did Not Complete Study (%)*	Total Deaths	CV Deaths	Non-CV Deaths	Undetermined Deaths	Undetermined Death (%)
TECOS[4]	DM	Sitagliptin	2015	36	5.4	1084	530	338	216	19.9
NAVIGATOR[5]	DM	Nateglinide, valsartan	2010	78	13.0	622	243	322	57	9.2
EUCLID[6]	CAD/PAD	Ticagrelor	2017	30	1.7	1331	493	549	289	21.7
STABILITY[7]	CAD/PAD	Darapladib	2014	44	3.5	1159	592	358	209	18.0
ROCKET AF[8]	AF	Rivaroxaban	2011	23	3.4	1297	826	329	142	11.0
ARISTOTLE[9]	AF	Apixaban	2011	22	4.9	1373	700	438	235	17.1
TRILOGY ACS[11]	ACS	Prasugrel	2012	17	6.1	795	467	156	172	21.6
PLATO[12]	ACS	Ticagrelor	2009	9	—†	937	740	116	81	8.6
TRACER[10]	ACS	Vorapaxar	2016	17	5.9	661	421	194	46	7.0

All trials enrolled patients from Australia/Oceania/South Africa, South/Central America, East/South Asia, Eastern Europe, Eastern Mediterranean, North America, and Western Europe, except for STABILITY, which did not enroll patients from the Eastern Mediterranean. ACS indicates acute coronary syndrome; AF, atrial fibrillation; ARISTOTLE; Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CAD, coronary artery disease; CEC, clinical events committee; CV, cardiovascular; DM, diabetes mellitus; EUCLID, Examining Use of Ticagrelor in Peripheral Artery Disease; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; PAD, peripheral artery disease; PLATO, Study of Platelet Inhibition and Patient Outcomes; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; STABILITY; Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; TRACER, Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome; TRILOGY ACS, Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes.

*Patients that did not complete the study were either lost to follow-up or withdrew consent. Data gathered from each study's primary manuscript, when available, or from Food and Drug Administration medical reviews when not included in the primary study manuscript.

†PLATO did not report the proportion of patients completing the trial, and this information was not available publicly.

undetermined causes were smaller: 17.2% of deaths in North America were attributable to undetermined causes, compared with 13.0% in Western Europe.

When the frequency of undetermined death designation was analyzed by year of trial results publication, both CEC-adjudicated and investigator-reported death of undetermined causes were greater in trials with later publication year (Figure II in the online-only Data Supplement). CEC-adjudicated undetermined cause of death was 8.9% in the 2 trials from 2009 to 2010, 14.4% in the 4 trials from 2011 to 2012, and 20.0% in the 3 trials from 2013 to 2017 ($P<0.001$).

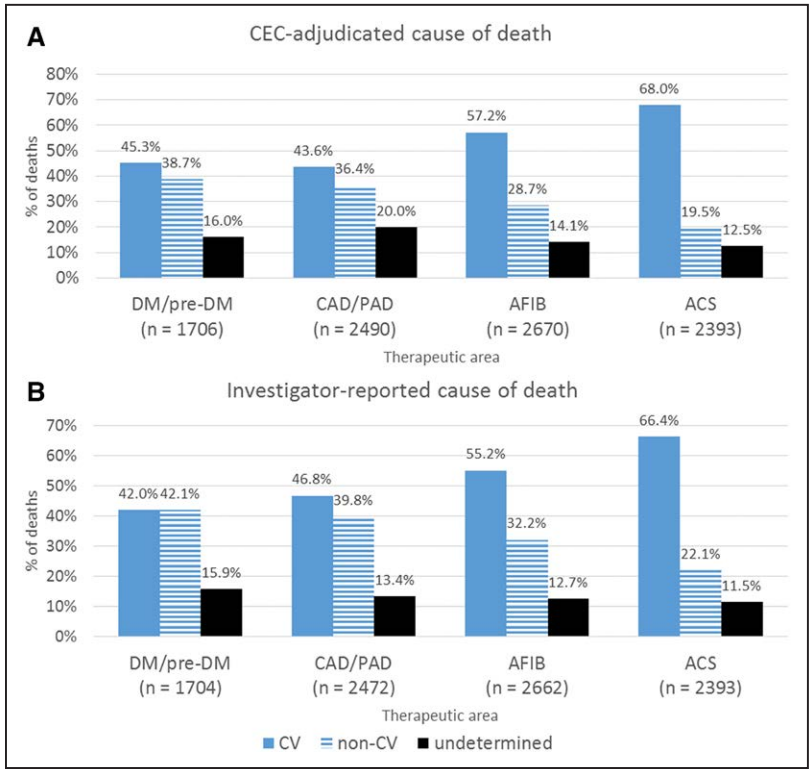

Figure 1. Deaths of undetermined cause by trial therapeutic area.
Bar graphs show the proportion of cardiovascular (CV), non-CV, and undetermined deaths by trial therapeutic area as adjudicated by the clinical events committees (CEC) (**A**), and as reported by investigators (**B**). ACS indicates acute coronary syndromes; AFIB, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; and PAD, peripheral artery disease. DM/pre-DM trials were TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) and NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research); CAD/PAD trials were EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) and STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy); AFIB trials were ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation); ACS trials were PLATO (Study of Platelet Inhibition and Patient Outcomes), TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes), and TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome).

Agreement Between Investigators and CEC on Cause of Death

Agreement between CEC-adjudicated and investigator-reported cause of death was moderate (κ=0.66). The CEC agreed with investigators' CV death determination 84.8% of the time, non-CV death determination 80.3% of the time, and unknown cause-of-death determination 57.9% of the time (Table II in the online-only Data Supplement). In cases where the CEC attributed a death to undetermined causes and investigators did not, 69.0% of deaths were attributed to CV causes by investigators.

Characteristics of Patients With Undetermined Death

Preenrollment characteristics of patients with an undetermined cause of death were generally similar to those of patients with CV and non-CV death (Table 2). Patients with undetermined cause of death had a lower baseline prevalence of prior myocardial infarction, prior stroke, congestive heart failure, and atrial fibrillation than patients with CV death, but a lower prevalence of these comorbidities than patients with non-CV death. Patients with undetermined cause of death had a longer interval from randomization to death than those with CV death (median 521 versus 323 days; $P<0.001$).

When CV and non-CV death were pooled to define a cohort of patients with "determined" cause of death, patients with determined and undetermined cause of death were largely similar with respect to baseline characteristics (Table III in the online-only Data Supplement). Patients with undetermined cause of death had a longer interval from randomization to death than those with "determined" cause of death (median 521 versus 396 days; $P<0.001$).

On multivariable modeling, time from randomization to death remained strongly associated with undetermined cause of death (odds ratio, 1.21; 95% CI, 1.14–1.29; per 1-year increase) compared with "determined" cause of death. Other patient and trial features associated with greater odds of undetermined cause of death included older age at enrollment, later publication year, and female sex (Figure 2). Enrollment in Australia/Oceania/South Africa, Central/South America, or Western Europe was associated with lower odds of an undetermined cause of death, compared with enrollment in North America. Compared with patients who enrolled in ACS trials and died, patients enrolled in DM/pre-DM and CAD/PAD trials had lower odds of undetermined cause of death.

Only EUCLID asked adjudicators whether deaths of undetermined cause had adequate source documentation to determine cause of death. In that trial, of 209 CEC-adjudicated deaths of undetermined cause, 197 (94.3%) were coded as having "limited or no source documents," and 12 (5.7%) were coded as having "adequate source documents."

DISCUSSION

In 9 cardiometabolic clinical trials conducted between 2009 and 2017, 15.7% of deaths were adjudicated by the CEC as attributable to undetermined causes, with a range from 7.0% to 21.7% in individual trials. On multivariable analysis, patient- and trial-level variables independently associated with greater likelihood of death attributable to undetermined causes were ACS or atrial fibrillation trial (versus atherosclerotic vascular disease or DM/pre-DM), longer time from enrollment to death, more recent trial manuscript publication year, enrollment in North America (versus Western Europe), female sex, and older age. Moreover, there was considerable between-trial variability in non-CV deaths among deaths that had an adjudicated cause. The relatively high proportion of deaths attributable to undetermined cause should alert researchers that reporting cause of death—CV, non-CV, and undetermined—is important to help clinicians, patients, regulatory authorities, and guideline-writing committees understand trial results and the quality of trial conduct. Furthermore, investigators should consider reporting sensitivity analyses that address the impact of deaths attributable to undetermined causes on efficacy analyses.

Despite the FDA's indication that few deaths in well-run clinical trials should be attributed to undetermined causes,[1] the meaning of "few" is uncertain, as no study has previously reported the proportion of CEC-adjudicated (or investigator-reported) deaths of undetermined cause in a series of clinical trials across therapeutic areas. Because of the nature of the CEC process, some deaths in a well-run clinical trial will be attributable to undetermined causes, and therefore a "lower is better" approach may not necessarily be the correct evaluative framework. Our study sets a data-driven range for the expected proportion of deaths attributable to undetermined causes in clinical trials with long-term follow-up.

Because clinical trials adjudicated by CECs mostly coordinated by a single academic research organization were included, an additional analysis was done by searching the internet for publicly available data on the proportion of deaths attributable to undetermined causes in major clinical trials, and these data were found for 10 trials. In 7 instances, these data were only available in FDA Briefing Documents[3,13–18]; the other 3 trials published the proportion of deaths attributable to undetermined cause in the primary trial manuscript[19,20] or a secondary analysis manuscript.[21] In these trials, the proportion of deaths of undetermined cause ranged from 2.0% to 26.8% (Table 3).[3,13–28]

Overall, the proportion of deaths adjudicated as attributable to undetermined causes was 11.9% across the 10 trials, roughly consistent with our results. The range of proportions of undetermined cause of death across these publicly available trials was broader than in the trials included in our primary analyses; however, without data

Table 2. Baseline and Follow-Up Characteristics of Patient With CV, Non-CV, and Undetermined Cause of Death According to the CEC

	Undetermined Death (n = 1447)	CV Death (n = 5012)	Non-CV Death (n = 2800)	*P* Value (CV vs. Non-CV vs. Undetermined)	*P* Value (CV or Non-CV vs. Undetermined)
Patient characteristics					
Age, y	71 (64, 78)	71 (63, 77)	72 (65, 78)	<0.001	0.08
Female sex	456/1446 (31.5%)	1462/5010 (29.2%)	801/2800 (28.6%)	0.13	0.05
Prior MI	520/1444 (36.0%)	1977/5004 (39.5%)	872/2798 (31.2%)	<0.001	0.71
Prior stroke	217/1445 (15.0%)	788/5005 (15.7%)	355/2798 (12.7%)	0.001	0.72
Hypertension	1222/1445 (84.6%)	4173/5009 (83.3%)	2306/2800 (82.4%)	0.18	0.14
Hyperlipidemia	640/1003 (63.8%)	1883/3221 (58.5%)	1177/1707 (69.0%)	<0.001	0.31
Diabetes	755/1445 (52.2%)	2431/5008 (48.5%)	1312/2800 (46.9%)	0.004	
Chronic kidney disease	545/1146 (47.6%)	1928/4474 (43.1%)	1008/2227 (45.3%)	0.02	0.003
Congestive heart failure	505/1445 (34.9%)	2013/5005 (40.2%)	804/2799 (28.7%)	<0.001	0.40
AF	474/1381 (34.3%)	1805/4746 (38.0%)	922/2472 (37.3%)	0.04	0.02
Cancer	81/1172 (6.9%)	146/3000 (4.9%)	200/2156 (9.3%)	<0.001	0.81
COPD	146/1064 (13.7%)	575/3951 (14.6%)	398/2286 (17.4%)	0.003	0.12
Time from enrollment to death (d)	521 (255, 825)	323 (97, 650)	521 (264, 846)	<0.001	<0.001
Trial characteristics					
Therapeutic area				<0.001	<0.001
DM/pre-DM	273/1447 (18.9%)	773/5012 (15.4%)	660/2800 (23.6%)		
CAD/PAD	498/1447 (34.4%)	1085/5012 (21.6%)	907/2800 (32.4%)		
AF	377/1447 (26.1%)	1526/5012 (30.4%)	767/2800 (27.4%)		
ACS	299/1447 (20.7%)	1628/5012 (32.5%)	466/2800 (16.6%)		
Region of enrollment				<0.001	<0.001
Australia/Oceania/South Africa	31/1390 (2.2%)	166/4856 (3.4%)	113/2687 (4.2%)		
Central/South America	231/1390 (16.6%)	875/4856 (18.0%)	507/2687 (18.9%)		
East/South Asia	233/1390 (16.8%)	710/4856 (14.6%)	317/2687 (11.8%)		
Eastern Europe	368/1390 (26.5%)	1414/4856 (29.1%)	503/2687 (18.7%)		
Eastern Mediterranean	33/1390 (2.4%)	105/4856 (2.2%)	57/2687 (2.1%)		
North America	281/1390 (20.2%)	764/4856 (15.7%)	588/2687 (21.9%)		
Western Europe	213/1390 (15.3%)	822/4856 (16.9%)	602/2687 (22.4%)		
Per capita GNI of enrolling country (US dollars)	12 450 (7850, 43 280)	11 620 (7850, 42 190)	19 720 (8910, 45 850)	<0.001	0.03
Year of trial publication				<0.001	<0.001
2009–2010	138/1447 (9.5%)	983/5012 (19.6%)	438/2800 (15.6%)		
2011–2012	595/1447 (41.1%)	2414/5012 (48.2%)	1117/2800 (39.9%)		
2013–2017	714/1447 (49.3%)	1615/5012 (32.2%)	1245/2800 (44.5%)		
Median trial follow-up				<0.001	<0.001
0–1 y	81/1447 (5.6%)	740/5012 (14.8%)	116/2800 (4.1%)		
1–2 y	595/1447 (41.1%)	2414/5012 (48.2%)	1117/2800 (39.9%)		
2–3 y	505/1447 (34.9%)	1023/5012 (20.4%)	887/2800 (31.7%)		
3–4 y	209/1447 (14.4%)	592/5012 (11.8%)	358/2800 (12.8%)		
>4 y	57/1447 (3.9%)	243/5012 (4.8%)	322/2800 (11.5%)		

Continuous variables reported as median (IQR); categorical variables reported as n/total (%). ACS indicates acute coronary syndrome; AF, atrial fibrillation; CAD, coronary artery disease; CEC, clinical events committee; COPD, chronic obstructive pulmonary disease; CV; cardiovascular; DM, diabetes mellitus; MI, myocardial infarction; GNI, gross national income; and PAD, peripheral artery disease.

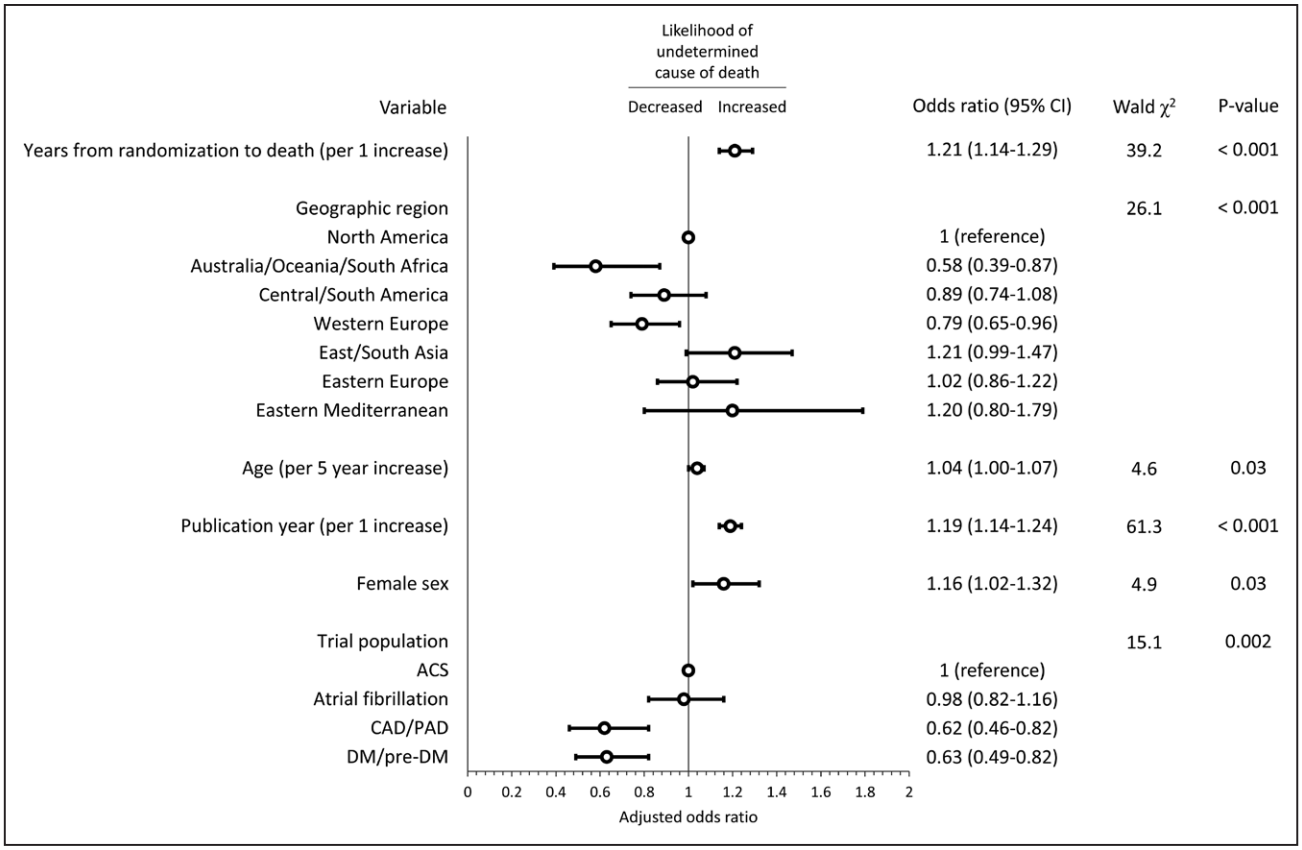

Figure 2. Predictors of undetermined cause of death.
Patient- and trial-level variables associated with clinical events committee–adjudicated undetermined cause of death (versus cardiovascular or noncardiovascular death) on multivariable modeling are shown. C-index = 0.61. ACS indicates acute coronary syndromes; CAD, coronary artery disease; DM, diabetes mellitus; and PAD, peripheral artery disease.

related to how undetermined cause of death was defined in these trials (which is not publicly available), it is difficult to know how to interpret the results. The proportion of deaths attributable to undetermined cause can best be compared across trials with similar definitions.

Importantly, we observed considerable between-trial variability in the proportion of deaths adjudicated as attributable to undetermined cause, both in the trials included in the primary analyses and in trials with publicly available data. Some of this variability is related to factors we did not capture, and the rest is likely attributable to chance. Factors that may affect the proportion of deaths attributable to undetermined cause include details of data collection, and the specific definition of undetermined cause of death. From our experience, variation attributable to data collection processes is most relevant when a patient dies outside of the hospital (or in a hospital where regulations prohibit sharing of information regarding deceased patients), and the site coordinator is unsuccessful in getting detailed information from the patient's family. How well site coordinators are encouraged and trained to try to speak with families after death contributes to the narrative for adjudicators. Though the broad definition of death attributable to undetermined cause was consistent across trials, slightly different wording used is likely to have effects on reviewers' decisions.

CEC-adjudicated deaths of undetermined cause may reflect several different clinical scenarios. In the simplest scenario, one in which cause of death is both undetermined and undeterminable, a patient dies at home without any recent contact with family, friends, study investigators, or the healthcare system. Associations between female sex and older age and undetermined cause of death may reflect women's and older adults' greater likelihood of living alone.[30] Deaths identified by search of public records after a patient has withdrawn from study participation will also necessarily be attributable to undetermined causes, since investigators are not allowed to contact family or friends. Deaths preceded by complex medical illness in which the proximate cause of death cannot be determined, despite adequate documentation, may also be considered attributable to undetermined causes, although this circumstance is rare. These deaths are unavoidably attributable to undetermined cause and do not reflect on trial conduct.

In more complex scenarios, deaths may be of undetermined, but determinable, cause. Most frequently, a patient may die without contact with investigators or the healthcare system, but with recent contact with

Table 3. CEC-Adjudicated Undetermined Cause of Death from Clinical Trials with Publicly Available Cause-of-Death Data

Trial	Clinical Condition	Compound	Year of Publication	Median Follow-up (mo)	Total Deaths	Undetermined Deaths	Undetermined Death (%)
EMPA-REG OUTCOME[3,29]	DM	Empagliflozin	2015	37	463	124	26.8
IMPROVE-IT[21,23]	CAD	Ezetimibe	2015	72	2446	386	15.8
PEGASUS[13,22]	CAD	Ticagrelor	2015	33	961	128	13.3
PARADIGM-HF[14,26]	HF	Sacubitril/ valsartan	2014	27	1546	228	14.7
HPS2-THRIVE[19]	CAD	Niacin/ lapropitant	2014	47	1530	30	2.0
TOPCAT[20]	HF	Spirono-lactone	2014	40	526	111	21.1
SAVOR[15,28]	DM	Saxagliptin	2013	25	798	77	9.7
ATLAS 2-ACS[16,27]	ACS	Rivaroxaban	2012	16	531	14	2.6
RE-LY[17,25]	AF	Dabigatran	2009	24	1371	133	9.7
ATHENA[18,24]	AF	Dronedarone	2009	22	255	12	4.7

All trials enrolled patients from Australia/Oceania/South Africa, South/Central America, East/South Asia, Eastern Europe, Eastern Mediterranean, North America, and Western Europe, except for EMPA-REG OUTCOME, which did not enroll patients from the Eastern Mediterranean, HPS2-THRIVE, which only enrolled in Western Europe and East/South Asia, and TOPCAT, which only enrolled in North America, Central/South America, and Eastern Europe. Case report forms for these trials were not publicly available, and it is unknown whether these case report forms included a category for death of unknown cause. ACS indicates acute coronary syndrome; AF, atrial fibrillation; ATHENA, A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter; ATLAS-2 ACS, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome; CAD, coronary artery disease; CEC, clinical events committee; DM, diabetes mellitus; EMPA-REG OUTCOME, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; HF, heart failure; HPS2-THRIVE, Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; PARADIGM-HF, Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; PEGASUS, Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; SAVOR, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus; and TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist.

family members or friends. If investigators are not persistent in attempts to contact family, or if the family is not willing to provide information about the circumstances surrounding the death to investigators, then the death may ultimately be adjudicated as attributable to undetermined causes. The association between longer time from enrollment to death and greater likelihood of undetermined cause of death may reflect changes in patients' social relationships leading to unfamiliarity between these people and investigators. In other circumstances, country-specific regulations or customs prevent hospitals from releasing deceased patients' information to anyone but family, and investigators may have no way of collecting data about a fatal hospitalization. The association between region of trial enrollment and deaths of undetermined cause may reflect these regulations and customs.

The proportion of deaths that were adjudicated as undetermined but had determinable cause could potentially be reduced with better communication of regulations surrounding data sharing between hospitals and investigators, and by developing strategies to obtain information from family, friends, or facilities after a trial participant dies. Such strategies could include designation of a family member or friend whom investigators could contact in the event of the trial participant's death; affirmative acknowledgment by the participant during the informed consent process that investigators could contact family members, friends, or other hospitals in the event of the participant's death; and/or involvement of family and friends in trial conduct prior to the patient's death.

The trial and regulatory community also needs to consider approaches to analyze the impact of these undetermined deaths in statistical analyses, especially given their reasonably high prevalence. By convention, deaths of undetermined cause are considered CV deaths for the purposes of analysis in nearly all cardiometabolic clinical trials. However, this approach may not be correct in all cases. In the present study, non-CV deaths made up >30% of all adjudicated deaths overall; the majority of patients died of either non-CV or undetermined causes in DM/pre-DM and CAD/PAD clinical trials. Lumping deaths of undetermined cause with CV deaths both inflates trial event rates and can bias trial results toward finding no difference, since including deaths that may be attributable to non-CV causes (which would not be expected to be decreased by a CV medication) in the CV death category increases statistical noise.[2] In the context of a superiority analysis, lumping deaths of undetermined cause with CV deaths is the conservative approach, and can bias toward finding a statistically nonsignificant result. This may result in truly promising treatments failing to demonstrate benefit (type II error). However, in the context of a noninferiority analysis, lumping undetermined and CV deaths together can potentially minimize treatment differences, and may bias toward a significant result (type I error).

Table 4. Proposed Standards for Determining and Reporting Cause of Death in Clinical Trials

1. Cause of death should be collected from site investigators.
2. Cause-of-death information collection should be a part of the informed consent process and site training, including efforts to engage with patients' families throughout the study process and overcome policies limiting clinical data sharing. Families should be asked standardized questions that assist with determining cause of death, such as, "Was the patient known to be alive and well 24 h prior to death?"
3. Operating procedures for contacting the family and friends of deceased patients should be standardized, and attempts at contact should be recorded.
4. Cause of death should be centrally adjudicated by a trained clinical events committee blinded to treatment assignment using prespecified definitions. Ideally, committee members should focus on clinical research and event adjudication as part of their careers, building the experience required to adjudicate difficult cases. For each trial, committee members should be specifically trained on adjudicating cause of death prior to beginning event adjudication, including through the use of examples, and should regularly participate in full committee reviews of difficult to classify cases. In addition, conventions for adjudicating questionable cases should be created before each trial and updated during the trial, with reviewers trained on these conventions continually.
5. Definitions for causes of death should follow US Food and Drug Administration guidance, unless rationale is provided for why this guidance is not followed.
6. When cause of death cannot be determined, clinical trials should prospectively identify whether cause of death was undeterminable (undetermined cause of death due to a complex clinical scenario or inability to contact family/friends) or potentially determinable (undetermined cause of death due to refusal of family/friends to provide information to investigators or strict policies regarding clinical data sharing in certain countries). Reviewers should be prospectively asked whether source documents were adequate to reliably classify the event.
7. Primary study manuscripts should report the proportion of deaths due to undetermined causes and primary reasons cause of death could not be determined.

Investigators should be encouraged to present sensitivity analyses varying the proportion of undetermined deaths that are counted as CV deaths. Alternatively, acknowledging the difficulties inherent in adjudicating cause of death and potential resulting biases, investigators could move toward simpler trial designs that analyze all-cause mortality rather than CV mortality, with increased costs related to the need to enroll more patients potentially offset by a reduction in monitoring and adjudication costs.[31] All-cause mortality is also a more patient-centric outcome than CV mortality, but can introduce statistical noise that overwhelms a signal of treatment effect, as CV therapies would not be expected to reduce the incidence of death because of trauma, suicide, or malignancy, for example. Furthermore, the FDA and other regulatory agencies always require information regarding cause of death at the end of clinical studies, and despite all the potential bias and difficulty in adjudicating cause of death, understanding causes of death in clinical trials can sometimes help researchers, clinicians, and patients interpret clinical trial results. Therefore, cause of death adjudication is likely to remain relevant in clinical trial methodology.

Since trials do not prospectively collect reasons that cause of death could not be determined, it was not possible to determine how many deaths of undetermined cause were truly undeterminable, and the "correct" proportion of deaths attributable to undetermined causes remains uncertain. Based on our results, however, roughly 10% to 20% of deaths in a well-conducted trial will be expected to be attributable to undetermined causes. As some trials achieved even lower rates, these data should continue the conversation regarding best practices for cause-of-death data. Standardizing cause-of-death determination and adjudication across clinical trials would provide needed context for the interpretation of clinical trial results (Table 4).

Limitations

The series of trials included represents a convenience sample from trials coordinated by a single academic research organization; however, the results are broadly consistent with data from other trials that have publicly reported the frequency of undetermined cause of death. We did not perform a systematic review and meta-analysis of the frequency of deaths of undetermined cause across published cardiovascular clinical trials because these data are often not publicly available, and including only trials that reported deaths attributable to undetermined cause may have introduced bias. It was not possible to evaluate all factors that may inform likelihood of undetermined death designation, including the extent of the effort made by sites to contact patients' family members and friends and the content of these conversations.

CONCLUSIONS

In cardiometabolic clinical trials with long-term follow-up, approximately 16% of deaths are centrally adjudicated as being attributable to undetermined causes. These findings provide a baseline for assessment of data adequacy with regard to cause-of-death determination in this setting, and could inform operational efforts to potentially further reduce the frequency of deaths of undetermined cause in future clinical trials.

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