

ORIGINAL ARTICLE

Reproducibility of clinical events adjudications in a trial of venous thromboembolism prevention

P. GIRARD,* A. PENALOZA,† F. PARENT,‡ B. GABLE,§ O. SANCHEZ,¶ P. DURIEUX,** P. HAUSFATER,†† S. DAMBRINE,§ G. MEYER¶¶ and P.-M. ROY‡‡‡

*Département Thoracique, L'Institut Mutualiste Montsouris, Paris, France; †Service des Urgences, Cliniques Universitaires St Luc, Université Catholique de Louvain, Brussels, Belgium; ‡Service de Pneumologie, Centre de Référence de l'Hypertension Pulmonaire Sévère, Hôpital de Bicêtre, AP-HP; Université Paris-Sud, INSERM UMRS 999, Le Kremlin Bicêtre; §Département de Médecine d'Urgence, CHU d'Angers, Angers; ¶Service de Pneumologie, Hôpital Européen Georges Pompidou, AP-HP; Université Paris Descartes, Sorbonne Paris Cité, INSERM UMRS 970 and CIC 1418; **Département de Santé Publique et Informatique Médicale, Hôpital Européen Georges Pompidou, AP-HP; Université Paris Descartes, Sorbonne Paris Cité, INSERM UMRS 872, Centre de recherche des Cordeliers; ††Département des Urgences, Hôpital Pitié-Salpêtrière, AP-HP; Sorbonne Universités UPMC-Univ Paris 6, INSERM UMRS 1166, IHUC ICAN, GRC-UPMC BIOSFAST, Paris; and ‡‡‡Département de Médecine d'Urgence, Centre Vasculaire et de la Coagulation, CHU d'Angers; Institut MITOVASC, EA3860, Université d'Angers, Angers, France

To cite this article: Girard P, Penaloza A, Parent F, Gable B, Sanchez O, Durieux P, Hausfater P, Dambrine S, Meyer G, Roy P-M. Reproducibility of clinical events adjudications in a trial of venous thromboembolism prevention. *J Thromb Haemost* 2017; **15**: 662–9.

Essentials

- The reproducibility of Clinical Events Committee (CEC) adjudications is almost unexplored.
- A random selection of events from a venous thromboembolism trial was blindly re-adjudicated.
- 'Unexplained sudden deaths' (possible fatal embolism) explained most discordant adjudications.
- A precise definition for CEC adjudication of this type of events is needed and proposed.

Summary. *Background:* When clinical trials use clinical endpoints, establishing independent Clinical Events Committees (CECs) is recommended to homogenize the interpretation of investigators' data. However, the reproducibility of CEC adjudications is almost unexplored. *Objectives:* To assess the reproducibility of CEC adjudications in a trial of venous thromboembolism (VTE) prevention. *Methods:* The PREVENU trial, a multicenter trial of VTE prevention, included 15 351 hospitalized medical patients. The primary endpoint was the composite of symptomatic VTE, major bleeding or unexplained sudden death (interpreted as possible fatal pulmonary embolism [PE]) at 3 months. The CEC comprised

a chairman and four pairs of adjudicators. Of 2970 adjudicated clinical events, a random selection of 179 events (121 deaths, 40 bleeding events, and 18 VTE events) was blindly resubmitted to the CEC. Kappa values and their 95% confidence intervals (CIs) were calculated to measure adjudication agreement. *Results:* Overall, 18 of 179 (10.1%, 95% CI 6.5–15.3%) adjudications proved discordant. Agreement for the PREVENU composite primary endpoint was good (kappa = 0.73, 95% CI 0.61–0.85). When analyzed separately, agreements were very good for non-fatal VTE events (1, 95% CI not applicable), moderate for all (fatal and non-fatal) VTE events (0.58, 95% CI 0.34–0.82), good for fatal and non-fatal major bleeding events (0.71, 95% CI 0.55–0.88), and moderate for all fatal events (0.60, 95% CI 0.40–0.81). Unexplained sudden death interpreted as possible fatal PE was responsible for nine of 18 (50%) discordant adjudications. *Conclusion:* The reproducibility of CEC adjudications was good or very good for non-fatal VTE and bleeding events, but insufficient for VTE-related deaths, for which more precise and widely accepted definitions are needed.

Keywords: anticoagulants; cause of death; clinical trial; reproducibility of results; venous thromboembolism.

Correspondence: Philippe Girard, Département Thoracique, L'Institut Mutualiste Montsouris, 42 boulevard Jourdan, 75014 Paris, France. Tel.: +33 15 661 6208; fax +33 15 661 6247. E-mail: philippe.girard@imm.fr

Received 6 September 2016

Manuscript handled by: M. Carrier

Final decision: F. R. Rosendaal, 31 December 2016

Introduction

In clinical trials, when the endpoints are 'complex to assess and/or include subjective components and/or the study cannot be blinded', the European Medicines Agency (EMA) and the Food and Drug Administration recommend establishing independent Clinical Events

Committees (CECs) [1–3]. The EMEA defines such CECs as committees of clinical experts in a specific clinical area whose aim is to standardize and harmonize endpoint assessment. Indeed, changes in the classification of events between local investigators and CEC interpretations have been reported to occur in 20–30% of cases, with potential significant impacts on trial results [4–6]. However, according to a systematic review published in 2009, only 33.4% of 314 clinical trials reported using a CEC [3]. The authors of this review recommended the systematic planning and reporting of CEC processes, including a systematic assessment of the reliability of CEC adjudications [3].

In trials of venous thromboembolism (VTE), the usual clinical endpoints of thromboembolic and bleeding events, fatal and non-fatal, fulfill the complexity and subjectivity criteria that support their adjudication by a CEC. However, only 111 of 161 (68.9%) VTE trials in a systematic review reported the use of a CEC, only five (3%) trials reported or described a method to assess the reliability of CEC adjudications [7], and none reported the results of such assessments.

The PREVENU trial included 15 351 patients during the intervention period in a randomized multicenter trial of VTE prevention whose main study endpoint was the composite of symptomatic VTE and major bleeding events at 3 months [8]. The large number of expected clinical events provided an opportunity to assess the reproducibility of the trial's CEC adjudications.

Materials and methods

The PREVENU trial

The PREVENU trial (NCT01212393) is a multicenter clinical trial that tested 'the impact of a multifaceted intervention to prevent VTE in patients admitted to emergency wards and hospitalized for acute medical illness', whose results were recently published [8]. This trial included 16 753 patients at 27 centers in France: 1402 during the pre-intervention period, and 15 351 during the intervention period. The primary endpoint was the composite of thromboembolic events (symptomatic deep vein thrombosis [DVT], pulmonary embolism [PE]), unexplained sudden death (interpreted as possible fatal PE), and major bleeding at 3 months.

The detailed definitions of these events, as they appeared in the study protocol and as they were used by the CEC, are as follows: (i) symptomatic VTE, comprising symptomatic proximal DVT confirmed by compression ultrasound or venography or computed tomography (CT) venography, symptomatic PE confirmed by CT pulmonary angiography, pulmonary angiography, high-probability V/Q lung scan, or proximal DVT or autopsy, and 'possible' fatal PE, defined as sudden death without an obvious cause according to the adjudication committee;

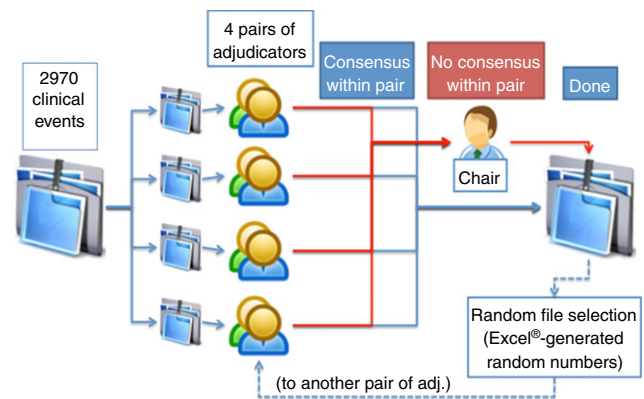


Fig. 1. Workflow of the PREVENU Clinical Events Committee, and blinded re-adjudication of randomly selected files. [Color figure can be viewed at wileyonlinelibrary.com]

(ii) major bleeding (ISTH definition in non-surgical patients [9]), comprising fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red blood cells.

CEC description

The CEC held six formal (in person) 1-day meetings over a period of 2 years. The CEC consisted of nine members, including a chairman (G.M.). All members were active clinicians with expertise in VTE, including five pulmonologists (P.G., F.P., O.S., P.D., and G.M.) and four emergency physicians (P.H., A.P., S.D., and P.M.R.). All CEC members had participated in previous VTE trials as investigators, and seven members had previously participated in CEC adjudications.

The CEC workflow and the process of blinded file resubmission are shown in Fig. 1. Briefly, the study coordinator collected data on a total of 2970 clinical events, reported by the investigators or identified during on-site monitoring of participating centers by clinical research assistants. All available information for each event, blinded for study arm, was submitted to one of four pairs of adjudicators, each pair adjudicating approximately one-quarter of the 2970 events. If, after discussion, a consensus was reached within the pair at this stage, there was no further adjudication. If a consensus could not be reached within the pair for a given event, the event was discussed with the chairman so that a majority decision (two to one) could be reached.

Adjudications were reported on specific adjudication forms for non-fatal VTE events (VTE according to protocol definition versus no VTE) and non-fatal major

bleeding (major bleeding according to protocol definition versus no major bleeding). For deaths, adjudicators had to choose one among several causes of death: fatal VTE, unexplained sudden death (interpreted as possible PE), fatal bleeding, and an open list of other causes of death, including 'unknown cause of death' when sufficient information was unavailable.

Blinded resubmission

The adjudicators were left unaware that 183 randomly selected events (representing ~ 10% of the events already adjudicated at the time of selection) were re-injected into the adjudication circuit, with attention being paid into the fact that a given event should not be adjudicated twice by the same pair of adjudicators (Fig. 1). For this exploratory study, the number of events submitted for re-adjudication was only a pragmatic compromise between feasibility (additional workload for the CEC) and reliability (narrow confidence intervals [CIs]). Only the initial adjudication was kept for the final results of the PREVENU trial.

Statistics

Agreement between the two adjudications was measured by calculating kappa values and their 95% CIs, with MEDCALC Version 11.4.2.0 (www.medcalc.org). Other CIs were calculated with OPENEPI (Open Source Epidemiologic Statistics for Public Health; www.OpenEpi.com, updated 6 April 2013).

Additional data from the literature and simulation

To explore the effects of variations in the definition and/or rate of fatal VTE events on the results of clinical trials, we compared the main characteristics of six studies (one outcome study and five randomized controlled trials of VTE prevention or treatment, including the PREVENU trial) in which VTE events, fatal and non-fatal, formed part of the study primary endpoint. As PE is the cause of < 20% of syncope and only ~ 5% of sudden deaths [10,11], we included a simple simulation to assess whether the results of these studies would have differed if only 20% of all VTE events were fatal.

Results

Of the 2970 events submitted to the CEC (371 non-fatal VTE events, 895 non-fatal bleeding events, and 1704 deaths), 183 events were randomly selected for resubmission. Of these, 179 events could be analyzed (because of missing information on four second adjudication forms), consisting of 18 non-fatal VTE events, 40 non-fatal bleeding events, and 121 deaths.

A summary of all adjudications is shown in Table 1. Overall agreement for the PREVENU primary (composite) endpoint was good (kappa = 0.73, 95% CI 0.61–0.85; Table 1). Each component of the composite endpoint (non-fatal VTE, non-fatal major bleeding, and causes of death including possible fatal PE and fatal bleeding) was then analyzed separately. Agreement for non-fatal VTE was very good (kappa = 1), but became only moderate (kappa = 0.58) when fatal VTE events were included in the comparison (Table 1). Agreement for fatal and non-fatal major bleeding was good (kappa = 0.71). Agreement for the causes of death (fatal PE versus fatal bleeding versus possible fatal PE versus other causes) was only moderate (kappa = 0.60, 95% CI 0.40–0.81; Table 1).

Overall, there were 18 discordant adjudications (10.1%, 95% CI 6.5–15.3%; Table 1); unexplained sudden deaths interpreted as possible fatal PEs accounted for nine of the discordant adjudications (50%, 95% CI 29–71%). It is of note that, among the 1704 patients who died in the PREVENU trial, only three (0.2%) had a postmortem examination, and none had PE.

The comparison with other published trials is shown in Table 2. Establishing an upper limit of 20% for the rate of fatal VTE events among all VTE events could have transformed the results of one trial from non-significant to significant (Table 2).

Discussion

Although planning of methods to assess the reliability of CEC adjudications in clinical trials is recommended [3], such assessments are unavailable or non-existent in the VTE literature [7]. The PREVENU trial, with its high number of clinical events, provided a unique opportunity to assess the reproducibility of CEC adjudications through a blind re-adjudication of ~ 6% of the 2970 events. The reassuring findings of this study regarding non-fatal events probably reflect the use of well-defined and well-known criteria for diagnosing non-fatal VTE events, and the availability of a clear definition for major bleeding events in medical patients [9]. On the other hand, the poor performance of CEC reproducibility for 'unexplained sudden deaths', interpreted as possible fatal PEs, is concerning.

In VTE trials, whatever the clinical context (diagnosis, prevention, or treatment), it is usual to consider that deaths 'for which PE cannot be ruled out', especially 'sudden deaths' without autopsy, will be interpreted in the study results as deaths from PE, in so-called 'worst-case scenarios'. Table 2 shows some recent VTE trials, including the PREVENU trial, in which fatal PE formed part of the study primary endpoint. The studies were chosen to represent trials of diagnostic strategies in suspected PE [12], VTE primary prevention [8,13,14], and treatment of acute VTE [15,16]. Except for autopsy-diagnosed PEs, the definitions of fatal PE vary across studies, from vague

Table 1 (a) Results for all adjudications and overall discordance rate. Initial adjudications appear in columns, and second adjudications in lines. (b) Discordances, kappa values and corresponding agreements between adjudications for various endpoints

(a)									
	Suspected VTE event				Suspected major bleeding				Discordances, <i>n/N</i> (%; 95% CI)
	Non-fatal VTE event (A)	Fatal PE (B)	Possible fatal PE (C)	Not VTE event (D)	Non-fatal major bleeding (E)	Fatal bleeding (F)	Not major bleeding (G)	Other causes of death (H)	
Suspected VTE event									
Non-fatal VTE event (A)	9	–	–	–	–	–	–	–	0/9
Fatal PE (B)	–	1	–	–	–	–	–	–	0/1
Possible fatal PE (C)	–	–	4	–	–	–	–	4	4/8
Not VTE event (D)	–	–	–	9	–	–	–	–	0/9
Suspected major bleeding									
Non-fatal major bleeding (E)	–	–	–	–	14	–	4	–	4/18
Fatal bleeding (F)	–	–	–	–	–	7	–	3	3/10
Not major bleeding (G)	–	–	–	–	1	–	21	–	1/22
Other causes of death (H)	–	–	5	–	–	1	–	96	6/102
Discordances, <i>n/N</i> (%; 95% CI)	0/9	0/1	5/9	0/9	1/15	1/8	4/25	7/103	18/179 (10.1; 6.5–15.3)

(b)			
	Discordances, <i>n/N</i> (%; 95% CI)	Kappa values (95% CI)	Agreement
Overall (A, B, C, D, E, F, G, H)	18/179 (10.1; 6.5–15.3)	0.84 (0.77–0.91)	Very good
PREVENU composite endpoint ([A + B + C + E + F], [D + G + H])	18/179 (10.1; 6.5–15.3)	0.73 (0.61–0.85)	Good
Suspected VTE events			
Non-fatal VTE events (A, D)	0/18 (0; 0–17.6)	1 (NA)	Very good
All VTE events (A, B, C, D)	9/32 (28.1, 15.6–45.4)	0.58 (0.34–0.82)	Moderate
Suspected major bleeding			
Non-fatal bleeding (E, G)	5/40 (12.5; 5.5–26.1)	0.74 (0.53–0.95)	Good
All bleeding events (E, F, G)	9/51 (17.6; 9.6–30.3)	0.71 (0.55–0.88)	Good
Deaths (fatal PE, possible fatal PE, fatal bleeding, other causes) (B, C, F, H)	13/121 (10.7; 6.4–17.5)	0.60 (0.40–0.81)	Moderate

CI, confidence interval; NA, not applicable; PE, pulmonary embolism; VTE, venous thromboembolism.

to very vague (Table 2). Accordingly, the rate of VTE deaths among all VTE events ranges from 13.7% to 54.8%. Of the 289 so-called VTE-related deaths in these six trials, including 139 deaths from the PREVENU trial, < 1% were autopsy-confirmed (data not shown in the table), whereas all other deaths were adjudicated as ‘possible’ fatal PE, or ‘fatal PE cannot be ruled out’, depending on the wording used in each study. In at least one trial, the simple act of limiting the rate of fatal PEs to 20% of all VTE events in both arms would have changed the study results from a non-significant difference to positivity for the primary endpoint [15] (Table 2). Obviously, the introduction of frequent and poorly reproducible components into a composite endpoint may increase the number of events while reducing the differences between groups, and weaken any conclusions drawn from such studies. These data illustrate the need for a clear, widely

accepted and reproducible definition of fatal VTE events, to ensure that all CECs in VTE trials use the same criteria. Finally, the increasing number of meta-analyses and ‘network meta-analyses’, in which this heterogeneity between studies and its potential impact on the results seem to be imprudently neglected, further reinforces the need for such uniform criteria.

Several points should be kept in mind when working on proposals for the adjudication of VTE-related deaths in VTE trials. First, ‘sudden death’ has a clear definition, used by emergency physicians, that includes a time of < 1 h between the onset of new symptoms and death [17]. A ‘probable’ sudden cardiac death is ‘an unexpected death without obvious extracardiac cause that occurred within the previous 24 hours’ [17]. Including such timing criteria for the definition of sudden death would be helpful in VTE trials. Second, PE is a rare cause of sudden

Table 2 Examples of recent clinical trials of venous thromboembolism (VTE) diagnosis, prevention or treatment that included VTE-related deaths in the primary outcome

Category of trial	Diagnosis of PE Outcome study	Primary VTE prevention Medicine	Primary VTE prevention Cancer	Treatment of acute VTE	Treatment of acute VTE Cancer	Primary VTE prevention Emergency medicine
Study acronym (publication year)	ADJUST [12] (2014)	MAGELLAN [13] (2013)	SAVE-ONCO [18] (2012)	EINSTEIN pooled [16] (2013)	CATCH [15] (2015)	PREVENU [8] (2016)
Population	Suspected PE (emergency room)	'Hospitalized for (...) acute medical illness'	Advanced cancer, receiving chemotherapy	Symptomatic DVT and/or PE	Active cancer and acute proximal DVT and/or PE	Emergency room patients admitted in a medical ward
Primary outcome	'Thromboembolic events during 3 months of follow-up'	'Asymptomatic or symptomatic proximal DVT (...), symptomatic non-fatal PE, or death related to VTE (fatal PE or death related to VTE)'	'Symptomatic DVT (...), non-fatal PE, or death related to VTE (fatal PE or death related to VTE)'	'Symptomatic recurrent VTE, i.e. the composite of fatal or non-fatal PE or DVT'	'Symptomatic DVT, symptomatic non-fatal PE, fatal PE, incidental proximal DVT (...), and incidental proximal PE'	Symptomatic DVT, PE, unexplained sudden death and major bleeding
Follow-up	3 months	35 days	3.5 months (median)	Median: ~6 months*	6 months	3 months
Definition of fatal VTE events	PE 'confirmed by autopsy, or if death followed a clinically severe PE' (...)	'Death related to VTE' according to CEC adjudication (no detail available)	'Fatal PE or unexplained death' (no detail available)	'PE with objective documentation (...) or if death could not be attributed to a documented cause and PE could not be confidently ruled out' [19]	'Fatal PE was defined as proven on objective imaging, autopsy, or as the most probable cause of a sudden and unexplained death according to central adjudication'	Fatal PE confirmed by imaging or autopsy; 'sudden death without obvious cause according to the CEC will be considered as possible fatal PE' (see text)
Number of patients	3324 (untreated: 2622)	Rivaroxaban 2967	Semuloparin 1608	Rivaroxaban 4150	Tinzaparin 449	Intervention 8068
Results for primary endpoint, <i>n</i> (%)	9 (0.3)	131 (4.4)	20 (1.2)	86 (2.1)	31 (6.9)	250 (3.1)
VTE deaths, <i>n</i>	4	19	7	15	17†	75 (USD: 72)
% of population	0.1	0.6	0.4	0.4	3.8	0.9
% of all VTEs (95% CI)	44.0 (18.9–73.3)	14.5 (9.5–21.5)	35.0 (18.1–56.7)	17.4 (8.9–28.3)	54.8 (37.8–70.8)	50.0 (41.2–57.9)
Change in study results if only 20% of all VTE events are fatal	No	No	No	No	Possible (17/449 versus 31/451; <i>P</i> = 0.04)	Unlikely (180/8069 versus 154/6692; <i>P</i> = 0.77)

CEC, Clinical Events Committee; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VKA, vitamin K antagonist; USD, unexplained sudden death. *Estimated from the number of patients at risk on Kaplan–Meier curves. †None of these 'VTE deaths' was objectively confirmed.

death. Fewer than 20% of patients with syncope, a symptom associated with high-risk PEs, have PE [11], and, in a large autopsy study, PE was the cause of death in only 4.3% of 668 sudden deaths [10]. Obviously, higher rates can be expected in populations with suspected PE or established VTE, but values reaching 50%, as in some trials (Table 2), are likely to represent a substantial overestimate of the real number of fatal PEs. On these grounds and the lessons learned from the adjudication of the PREVENU clinical events, a proposal for definitions of VTE-related deaths is shown in Table 3. Specifically, we suggest a stricter and slightly different definition of unexpected sudden death interpreted as 'possible fatal PE' between trials of patients with and without established VTE. These proposals could serve as a basis for discussion and eventual ISTH-endorsed guidance for interpreting this type of event. We also suggest that, except for special populations at very high risk of fatal PE (e.g. in the early days following a high-risk PE), the lower limit of the 95% CI for the proportion of fatal PEs among all VTE events should not exceed 20%, a criterion that could be proposed as a marker of the reliability of fatal PE adjudications.

This study has limitations. There are many ways to organize the work of a CEC [3,7], and this study reflects

Table 3 Proposed definitions for fatal pulmonary embolism (PE) in venous thromboembolism (VTE) trials

-
- Confirmed fatal PE:
 - Autopsy-confirmed massive PE
 - Death within 48 h of objectively confirmed high-risk/intermediate high-risk PE (e.g. ESC/ERS criteria [20])
 - Death from the complications of massive PE treatment (e.g. complications of thrombolysis or embolectomy)
 - Possible fatal PE
 - a Patients *without* established VTE*: Unexpected sudden death (< 24 h between onset of symptoms and death) with other signs or symptoms (e.g. signs or symptoms of DVT) or a high clinical probability of PE (ideally, using the Geneva or Wells scores).
 - b Patients *with* established VTE, recent or remote†: Unexpected sudden death (< 24 h between onset of symptoms and death), whatever the clinical probability of PE, unless other causes of death appear more likely
 - Fatal pulmonary embolism NOT confirmed:
 - Any other cause of death more likely than PE
 - PE cannot be ruled out, but is unlikely to be the *main* cause of death (e.g. terminal cancer with performance status > 2)
 - All other circumstances without an obvious cause (e.g. no reliable information from relatives and/or health professionals) should be recorded as 'cause of death: unknown'
-

DVT, deep vein thrombosis; ESC, European Society of Cardiology; ERS, European Respiratory Society. *For example, trials of primary prevention, and outcome studies of diagnostic algorithms for suspected VTE in untreated patient. †For example, trials of new drugs or therapeutic strategies, and duration of treatment.

only one of these ways, which may limit the generalizability of our conclusions. There are no precise guidelines for CEC functioning, except for those 'proposed' by Dechartre *et al.* [3]. The study by Stuck *et al.* describes the reporting of adjudication processes in 111 VTE trials, and only demonstrates the extreme heterogeneity of processes between studies [7]. The PREVENU study and its CEC appear to be in accordance with most propositions by Dechartre *et al.*, but it appears to be unique in reporting the results of an assessment of the reliability of CEC adjudications [3,7]. Such reporting can only be further encouraged. Finally, the poor performance of the CEC in some cases only reflects the limited availability of reliable clinical information, which is key to reliable and reproducible CEC adjudications. The timely collection of all relevant information by the investigators is of utmost importance, and may have been suboptimal in the PREVENU study. However, it is unlikely that the category of 'unknown' cause of death will disappear soon in clinical trials, and CEC members should even resist adjudicating a definite cause of death on fragile bases, especially regarding fatal PE.

To summarize, the reproducibility of CEC adjudications in the PREVENU study was good or very good for the composite endpoint of non-fatal VTE and bleeding events, but insufficient for sudden deaths interpreted as fatal PEs, which need more precise and widely accepted definitions in future trials. Measuring and reporting of CEC adjudication reproducibility should be encouraged in VTE trials.

Addendum

P.-M. Roy was the investigator of the PREVENU trial, and designed the present study. All authors participated in the work of the PREVENU CEC (chair: G. Meyer; members: P. Girard, F. Parent, A. Penalzoza, P. Hausfater, O. Sanchez, S. Dambrine, P. Durieux, and P.-M. Roy; data management: B. Gable). B. Gable supervised the practical organization of the study, and performed the data analysis with A. Penalzoza. P. Girard drafted the main manuscript, with contributions from all other authors. All authors approved the final version.

Acknowledgements

This study was presented in part at the 2015 ISTH Congress in Toronto (OR192), 20–25 June 2015. The INNNOVTE network and F-CRIN investigators supported the PREVENU trial. Members of the PREVENU study group are listed in the Appendix.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Appendix

The PREVENU Study Group

Steering Committee: P.-M. Roy (Study chair), D. Mottier, J. Schmidt, C. Le Gall, P. Hausfater, G. Le Gal, and P. Durieux.

Statistical analysis: A. Rachas and G. Chatelier.

Data management: J.-M. Chretien.

Research operation team: B. Gable (chair), A. Hamard, G. Durand, M.-L. Pinot, N. Ibrir, and S. Quentin-Georget.

Investigators (by city, all in France): A. Trinh-Duc and A. Buan (Agen), B. Mazet, T. Schotte, and S. Dambrine (Angers), C. Le Gall and P. Peudepièce (Argenteuil), M. Hachelaf and T. Desmesttre (Besançon), A.-E. Dubart (Béthune), F. Adnet and S. Guinemer (Bobigny), D. Elkharrat (Boulogne), M. Jaffrelot and E. L'Her (Brest), G. Bouilleau and L. Soulat (Chateauroux), J. Schmidt and F. Moustafa (Clermont Ferrand), P. Miroux, G. Layani, and Y. Normand (Compiègne), B. Renaud, A. Santin, and A. N'Gako (Créteil), D. Honnart and C. Tissier (Dijon), F. Carpentier and C. Ara Somohano (Grenoble), E. Wiel and P. Williatte (Lilles), M.-L. Alazia and P. Gerbeaux (Marseille), F. Braun (Metz), D. Elkouri and N. Goffinet (Nantes), L. Nace and A. Mercuri (Nancy), J.-E. De La Coussaye and J.-Y. Lefrant (Nîmes), E. Casalino (Paris, Bichat), Y.-E. Claessens and J.-C. Allo (Paris, Cochin), F. Dumas and E. Bloch-Laine (Paris, Hôtel-Dieu), P. Hausfater and S. Delerme (Paris, La Pitié), F. Rayeh-Pelardy, M. Scepti, and J.-Y. Lardeur (Poitiers), J. Bouget (Rennes), F. Staïskowsky (Saint Pierre, La Réunion).

References

- European Medicines Agency. Guideline on data monitoring committees. http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf (last accessed 20 July 2016). 2005.
- Food and Drug Administration. Guidance for clinical trial sponsors. Establishment and Operation of Clinical Trial Data Monitoring Committees. Available at: <http://www.fda.gov/downloads/Regulatoryinformation/Guidances/ucm127073.pdf> (last accessed 20 July 2016). 2006.
- Dechartres A, Boutron I, Roy C, Ravaud P. Inadequate planning and reporting of adjudication committees in clinical trials: recommendation proposal. *J Clin Epidemiol* 2009; **62**: 695–702.
- Arnold DM, Lauzier F, Rabbat C, Zytaruk N, Barlow Cash B, Clarke F, Heels-Ansdell D, Guyatt G, Walter SD, Davies A, Cook DJ; PROTECT Investigators, on behalf of the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Adjudication of bleeding outcomes in an international thromboprophylaxis trial in critical illness. *Thromb Res* 2013; **131**: 204–9.
- Mahaffey KW, Harrington RA, Akkerhuis M, Kleiman NS, Berdan LG, Crenshaw BS, Tardiff BE, Granger CB, DeJong I, Bhapkar M, Widimsky P, Corbalon R, Lee KL, Deckers JW, Simoons ML, Topol EJ, Califf RM; For the PURSUIT Investigators. Disagreements between central clinical events committee and site investigator assessments of myocardial infarction endpoints in an international clinical trial: review of the PURSUIT study. *Curr Control Trials Cardiovasc Med* 2001; **2**: 187–94.
- Petersen JL, Haque G, Hellkamp AS, Flaker GC, Mark Estes NA 3rd, Marchlinski FE, McAnulty JH, Greenspon AJ, Marchak RA, Lee KL, Lamas GA, Mahaffey KW; MOST Clinical Events Committee. Comparing classifications of death in the Mode Selection Trial: agreement and disagreement among site investigators and a clinical events committee. *Contemp Clin Trials* 2006; **27**: 260–8.
- Stuck AK, Fuhrer E, Limacher A, Mean M, Aujesky D. Adjudication-related processes are underreported and lack standardization in clinical trials of venous thromboembolism: a systematic review. *J Clin Epidemiol* 2014; **67**: 278–84.
- Roy PM, Rachas A, Meyer G, Le Gal G, Durieux P, El Kouri D, Honnart D, Schmidt J, Legall C, Hausfater P, Chretien JM, Mottier D; PREVENU Study Group. Multifaceted intervention to prevent venous thromboembolism in patients hospitalized for acute medical illness: a multicenter cluster-randomized trial. *PLoS One* 2016; **11**: e0154832.
- Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; **3**: 692–4.
- Lucena J, Rico A, Vazquez R, Marin R, Martinez C, Salguero M, Miguel L. Pulmonary embolism and sudden-unexpected death: prospective study on 2477 forensic autopsies performed at the Institute of Legal Medicine in Seville. *J Forensic Leg Med* 2009; **16**: 196–201.
- Prandoni P, Lensing AW, Prins MH, Ciammaichella M, Perlati M, Mumoli N, Bucherini E, Visona A, Bova C, Imberti D, Campostri S, Barbar S; PESIT Investigators. Prevalence of pulmonary embolism among patients hospitalized for syncope. *N Engl J Med* 2016; **375**: 1524–31.
- Righini M, van Es J, Den Exter PL, Roy PM, Verschuren F, Ghuyens A, Rutschmann OT, Sanchez O, Jaffrelot M, Trinh-Duc A, Le Gall C, Moustafa F, Principe A, van Houten AA, Ten Wolde M, Douma RA, Hazelaar G, Erkens PM, van Kralingen KW, Grootenboers MJ, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *JAMA* 2014; **311**: 1117–24.
- Cohen AT, Spiro TE, Buller HR, Haskell L, Hu D, Hull R, Mebazaa A, Merli G, Schellong S, Spyropoulos AC, Tapson V; MAGELLAN Investigators. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med* 2013; **368**: 513–23.
- Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. *Br J Surg* 2005; **92**: 1212–20.
- Lee AY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, Khorana AA; CATCH Investigators. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA* 2015; **314**: 677–86.
- Prins MH, Lensing AW, Bauersachs R, van Bellen B, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Raskob GE, Berkowitz SD, Wells PS; EINSTEIN Investigators. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J* 2013; **11**: 21.
- Fishman GI, Chugh SS, Dimarco JP, Albert CM, Anderson ME, Bonow RO, Buxton AE, Chen PS, Estes M, Jouven X, Kwong R, Lathrop DA, Mascette AM, Nerbonne JM, O'Rourke B, Page RL, Roden DM, Rosenbaum DS, Sotoodehnia N, Trayanova NA, et al. Sudden cardiac death prediction and

- prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. *Circulation* 2010; **122**: 2335–48.
- 18 Agnelli G, George DJ, Kakkar AK, Fisher W, Lassen MR, Mismetti P, Mouret P, Chaudhari U, Lawson F, Turpie AG; SAVE-ONCO Investigators. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med* 2012; **366**: 601–9.
- 19 EINSTEIN-PE Investigators, Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; **366**: 1287–97.
- 20 Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, *et al.* 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014; **35**: 3033–69.