Correction methods for measurement error in epidemiologic research

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Guidance for reporting of studies on incidence of venous thromboembolism in COVID-19 patients

Coagulation abnormalities and coagulopathy are recognised as consequences of Coronavirus disease (COVID-19) and venous thromboembolism (VTE) has been reported as a frequent complication. By 27 May 2021, at least 93 original studies and 25 meta-analyses investigating VTE incidence in COVID-19 patients had been published, showing large heterogeneity in reported VTE incidence ranging from 0–85%. This large variation complicates interpretation of individual study results as well as comparisons across studies, e.g., to investigate changes in incidence over time, compare subgroups, and perform meta-analyses. We identified different sources of heterogeneity in VTE incidence studies and classified these as clinical sources and methodologic sources. Clinical sources of heterogeneity include differences between studies regarding patient characteristics which affect baseline VTE risk and protocols used for VTE testing. Methodologic sources of heterogeneity include differences in VTE inclusion types, data quality and the methods used for data analysis. Each of these issues is discussed and illustrated using examples of VTE incidence studies in COVID-19 patients. To appreciate reported estimates of VTE incidence in COVID-19 patients in relation to its aetiology, prevention, and treatment, researchers should unambiguously report about possible clinical and methodological sources of heterogeneity in those estimates. This chapter provides guidance for that.

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6.1. Introduction

Coronavirus disease (COVID-19), caused by the virus SARS-CoV-2, primarily affects the respiratory system, but coagulation abnormalities and coagulopathy are also recognised as consequences [1]. In particular, venous thromboembolism (VTE) has been reported as a major complication, with VTE incidences up to 50% in intensive care unit (ICU) admitted patients [2]. By 27 May 2021, already 25 systematic reviews investigating VTE incidence in COVID-19 patients had been published [3–27], of which the most recent meta-analysis by Kollias et al. identified 93 unique studies on VTE incidence [13].

Systematic reviews of VTE incidence in COVID-19 patients show large heterogeneity [13], [20], [12]. For instance, Nopp et al. described VTE incidences in hospital admitted patients ranging from 0% – 40.3% [20], while Jiménez et al. even reported VTE incidences between 0% – 85% [12]. Kollias et al. restricted their systematic review to studies that performed "screening/assessment in the total sample for DVT (lower limb ultrasonography) or were focused on patients with suspicion for PE (whole study population subjected to tomography pulmonary angiogram)", but despite this restriction, they found heterogenous VTE incidences ranging between 0% – 85% [13]. Possible explanations for this heterogeneity in VTE incidence include differences in design of the study, clinical setting, and local practice (e.g., thromboprophylaxis strategy) [20], differences in endpoint definition, testing strategies, and patients' characteristics [12].

The wide variation in VTE incidence not only raises questions about the interpretation of individual study results, but, more importantly, complicates comparisons between studies to investigate e.g., changes over time, difference among subgroups, and to perform meta-analyses. To appreciate reported VTE incidences and to diminish their heterogeneity, it is important to understand different sources of this heterogeneity across studies. Therefore, we provide an overview of such sources of heterogeneity in VTE incidence studies on COVID-19 and illustrate this using various examples. Conclusively, we add a list of essential information to report, in order to improve consistency and hence the relevance of studies on VTE incidence in COVID-19 patients.

6.2. Methods

The large heterogeneity in VTE incidence across studies found in the meta-analyses by Jiménez et al. [12] and Nopp et al. [20] incentivised this project. On 27 May 2021, a pragmatic search on PubMed using the search string "meta-analysis covid-19 venous thromboembolism" was performed resulting in a rough estimate of the number of meta-analyses published. Twenty-five meta-analyses were identified. The most recent meta-analysis was published on April 4, 2021 by Kollias et al. [13]. The individual VTE incidence studies included in the meta-analyses by Jiménez et al., Nopp et al. and Kollias et al. were screened, and an initial list of potential sources of heterogeneity was created through discussions by LN, RHHG and SCC. The initial list was discussed in meetings with FAK, BSB and MJHAK, and revised until consensus was reached. For educational purposes, an example was sought for each listed source of heterogeneity by identifying two heterogenous studies also showing heterogeneity in their estimated VTE incidence, without taking other explanations into account. For consistency, incidences of all VTE incidence studies reported in this study were calculated as "number of cases during the entire study follow up divided by the size of the study population" and accompanied by a

95% Wald based confidence interval (CI).

6.3. Sources of heterogeneity of VTE incidence studies

Figures 6.1–6.2 provide an overview of the identified sources of variation in VTE incidence studies. A distinction was made between clinical (Figure 6.1) and methodologic sources (Figure 6.2). Clinical sources of heterogeneity include differences related to study characteristics affecting VTE risk and VTE testing. Methodologic sources of heterogeneity refer to differences in VTE manifestation inclusion types (e.g., inclusion of DVT, PE or both), data quality and the analytical methods used, i.e., what method was used to estimate VTE incidence and how limitations of the data were handled. These clinical and methodologic sources are explained in more detail below.

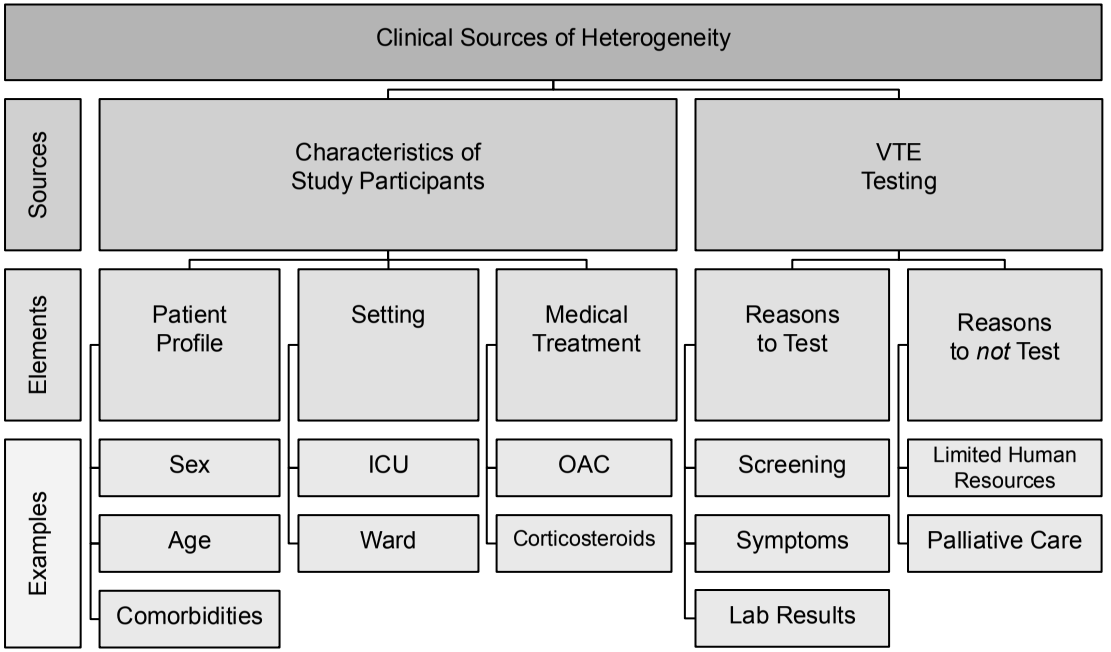

Figure 6.1: Clinical sources of heterogeneity in venous thromboembolism incidence studies that may explain observed heterogeneity across studies. ICU : Intensive Care Unit; OAC: oral anticoagulation.

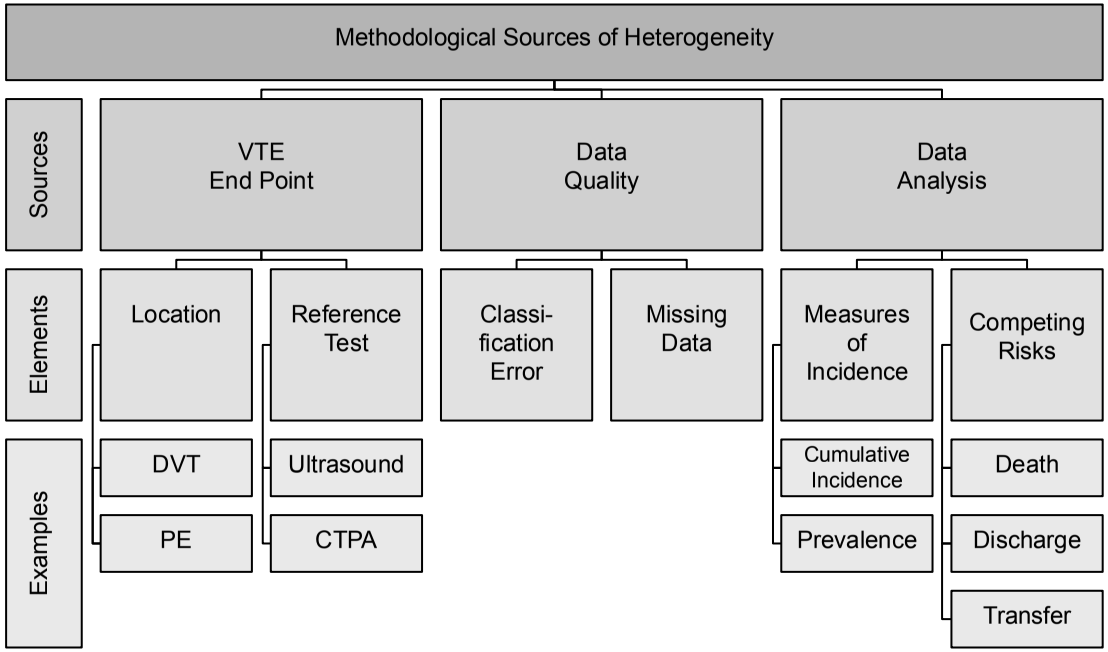

Figure 6.2: Methodological sources of heterogeneity in venous thromboembolism incidence studies that may explain observed heterogeneity across studies. DVT: deep vein thrombosis; PE: pulmonary embolism; CTPA: computed tomography pulmonary angiogram.

6.3.1. Clinical sources of heterogeneity

Patient characteristics

One potential source of heterogeneity in VTE incidence studies are differences in patient characteristics across studies. These patient characteristics are factors that increase or decrease the risk of VTE, i.e., established risk factors such as age and comorbidities [28] or ethnicity [29]. For example, Mei et al. performed a study among subjects with a mean age of 55.5 years (range 0.5-87), of whom 0.8% had a history of VTE. They reported a VTE incidence of 2.0% (95% CI 0.3;3.6).[30] In contrast, Middeldorp et al. reported a VTE incidence of 19.7% (95% CI 14.2;25.2) in a patient group that was older (mean age 61 years (standard deviation (SD) 4)) and in whom a history of VTE was more frequent (5.6%). [31] Hence, the underlying VTE risk may have been higher in the latter study, which may be one of the factors explaining the higher VTE incidence found in that study.

In addition to these patient profiles, also relevant are characteristics of the research setting, related to COVID-19 disease severity or VTE risk. For example, critically ill patients are at higher risk of developing VTE compared to non-ICU patients [32], so inclusion of patients from the ICU, the general ward or both, affects VTE incidence. In the study by Al-Samkari et al., patients from both the general ward and ICU were included. In their study, a VTE incidence was found of 3.1% in ward patients (95% CI 1.0;5.3) and of 7.6% in ICU patients (95% CI 3.3-12.0).[33] Of note, the case mix of COVID-19 ICU patients may differ between countries, due to national-level differences in accessibility of intensive care beds [34]. What is more, VTE incidence in COVID-19 outpatients is different from VTE incidence in hospitalised COVID-19 patients [35]. Limiting or not limiting the research setting to patients with e.g. an elevated D-dimer level may affect VTE incidence, because patients with an elevated D-dimer level are at high risk of developing VTE [36]. For example, Demelo-Rodríguez et al. only included patients with a D-dimer level >1000 ng/ml and reported a VTE incidence of 14.7% (95% CI 9.2;20.3) [37]. In comparison, Whyte et al. did not use a D-dimer level threshold to restrict patient inclusion and included all hospitalised COVID-19 patients and found a VTE incidence of 5.4% (95% CI 4.3;6.6) [38]. The research setting and VTE risk may also be affected by the way in which patient selection was performed. For example, in a study by Hill et al., a VTE incidence of 1.4% (95% CI 1.1;1.7) was found. In this study, patients were included retrospectively, by screening electronic health records and including all patients positive for Sars-CoV-2 on polymerase chain reaction-based testing. Patients were included after a visit to an emergency department and/or admission to an inpatient unit.[39] In comparison, in a study by Trimaille et al., a VTE incidence of 17.0% (95% CI 12.6;21.3) was found. In this study, all consecutive patients who were hospitalised for COVID-19 were included.[40] In these two studies, the clinical characteristics of the underlying populations where the study populations were sampled from were different, which may have affected baseline risk for VTE.

A third characteristic that requires attention is the local medical strategy, such as the use of anticoagulation treatment or COVID-19 treatment, which may influence the risk of VTE. A patient group that is treated with full dose anticoagulation may show a lower VTE incidence compared to patient groups receiving no or prophylactic anticoagulation. Cattaneao et al. reported a VTE incidence of 0.0% (95% CI 0.000;0.008). In this study, all patients had been treated with standard dose thromboprophylaxis.[41] In comparison, Zhang et al. reported a VTE incidence of 46.2% (95% CI 38.0;54.3). In this study, 90 patients out of 143 patients (63%) received no anticoagulation at all. [42] The difference in VTE

incidence between these two studies could be partly explained by the difference in use of anticoagulation. Additionally, as of 2 September 2020, the WHO recommended the use of systemic corticosteroids in patients with severe or critical COVID-19 [43–45]. For example, a meta-analysis showed an increased risk of 1.39 (95% CI 1.10-1.77) of VTE in COVID-19 patients when being administered corticosteroids [46]. The use of corticosteroids may therefore also be a source of heterogeneity in VTE incidence.

VTE testing

An additional clinical source of heterogeneity in VTE incidence is variation in VTE diagnostic practices. In particular, reasons to test for VTE and reasons to *not* test for VTE differed across studies. For example, diagnostic tests for PE or DVT may have been conducted at the occurrence of symptoms. Alternatively, a patient may have been tested for VTE independent of symptoms (i.e., screening), detecting both symptomatic and asymptomatic cases. For example, Cattaneao et al. found no symptomatic DVT cases in their study, resulting in a VTE incidence of 0.0% (95% CI 0.000;0.008) [41]. In comparison, Demelo-Rodríguez et al. screened for asymptomatic DVT and found an incidence of 14.7% (95% CI 9.2;20.3) [37]. Furthermore, studies may use a decision rule (e.g., based on lab results) before undertaking imaging. For example, Whyte et al. found a VTE incidence of 5.4% (95% CI 4.3;6.6). In this study, imaging was not undertaken "for those considered 'PE unlikely' by the Wells score (score <4) in conjunction with a D-dimer result below 500 ng/ml".[38] In comparison, Voicu et al. performed ultrasound imaging in all patients 3 days after intubation and found a VTE incidence of 35.7% (95% CI 23.2;48.3) [47]. Studies using a decision rule for VTE imaging, may miss cases of VTE [48], but are a closer resemblance of clinical practice. What is more, despite a VTE testing protocol in place, VTE testing may not be reasonable or feasible in some patients and studies may therefore deviate from their testing protocol in these cases. For example, VTE testing may not be reasonable in patients hospitalised for palliative care and VTE testing may not be feasible due to limitations in (human) resources in a health crisis setting, since performing a computed tomographic pulmonary angiogram (CTPA) in an ICU patient with mechanical ventilation can be laborious. For instance, Koleilat et al. reported a VTE incidence of 0.5% (95% CI 0.3;0.8). In this study, only "those patients with significant clinical concern for DVT or in those in whom the results were deemed to impact management were tested for DVT (e.g., patients who were mechanically ventilated and placed prone for persistently poor oxygenation were deemed too unstable, and those already on anticoagulation for other reasons such as cardiac arrhythmias or a prior history of thrombotic episodes requiring lifelong anticoagulation were unlikely to undergo venous duplex testing)".[49] In comparison, Ren et al. reported a (both a- and symptomatic) VTE incidence of 85.4% (95% CI 75.4;95.4). In the latter study, all patients were tested for DVT at least twice.[50]

6.3.2. Methodologic sources

VTE endpoint

Heterogeneity in VTE incidence studies may be caused by inconsistent inclusion of types of VTE across studies. For example, Mazzaccora et al. reported a VTE incidence of 65.6% (95% CI 49.2%;82.1%), where VTE included pulmonary embolism, diagnosed using a CT pulmonary angiogram, or DVT, which was diagnosed with an ultrasound of the veins of the upper and lower limbs.[51] In contrast, the study by Criel et al. reported a VTE incidence

of 7.3% (95% CI 1.7;13.0). Here, VTE included DVT only. [52] Furthermore, thrombosis in other venous compartments may be included (e.g., upper extremity, splanchnic veins). In the above mentioned study by Mazzaccaro et al. all patients underwent a duplex scan of the veins and arteries of the upper and lower limbs to investigate the presence of peripheral thrombosis.[51] In contrast, Santoliquido et al. reported a VTE incidence of 11.9% (95% CI 5.0;18.8).[53] Here, all patients were screened for DVT with lower-limb venous compression ultrasound. Another example is the study by Llitjos et al., that found a VTE incidence of 69.2% (95% CI 51.5;87.0) in which 4 of 18 (22%) reported DVTs were superficial. In comparison, the study by Desborough et al. did not include superficial DVTs and found a VTE incidence of 15.2% (95% CI 6.5;23.8). In addition, a distinction can be made between central, segmental and subsegmental PEs, based on the location of thrombi in the pulmonary vascular tree. Longchamp et al. "did not record subsegmental PEs" and reported a VTE incidence of 56.0% (95% CI 36.5;75.5) [54]. In comparison, Mazzaccaro et al. found a VTE incidence of 65.6% (95% CI 49.2;82.1), based on 21 cases of 'pulmonary vessel thrombosis', including 7 (33.3%) cases of subsegmental thrombi [51]. Additionally, DVT may be associated with indwelling lines and these DVTs could be included or not. For example, in the study by Desborough et al. [55], 10 of the 66 patients were diagnosed with VTE, resulting in a VTE incidence of 15.2% (95% CI 6.5;23.8). However, 6 of the DVTs were found to be associated with a line and one patient had a both a DVT and a PE. Consequently, 5 patients had a none line associated VTE, changing VTE incidence to 7.6% (95% CI 1.2;14.0).

VTE endpoint classification may also differ across studies in terms of the protocol that was used for the interpretation of the CT or ultrasound test by radiologists for a VTE diagnosis. Chen et al. reported a VTE incidence of 1% (95% CI 0.4;1.6). In this study, "all CT and CTPA image analyses were performed by 2 radiologists experienced in thoracic radiology [...], who were blinded to the clinical information. Disagreements were resolved through discussion until consensus was reached".[56] Conversely, Artifoni et al. reported a VTE incidence of 22.5% (95% CI 12.8;32.3) in a study where "chest angio-CT scan was performed in case of suspicion of pulmonary embolism" [57]. In the study by Chen et al., classification error in VTE diagnosis is less likely, while the study by Artifoni et al. more closely resembles clinical practice.

In addition, a potential source of heterogeneity in the VTE endpoint across studies is the data source used to classify the VTE endpoint. Data quality may differ between data sources, which is discussed in the subsequent subsection.

Data quality

A potential source of heterogeneity in VTE incidence studies is classification error or missing data in the VTE endpoint or in SARS-CoV-2 infection status. Thirty-four out of the 49 VTE incidence studies (69%) included in the meta-analysis by Jiménez et al. were identified as retrospective studies, 11 (22%) were identified as prospective studies, and 4 (8%) as cross-sectional studies [12]. In the 34 retrospective studies, data were often not primarily collected to study VTE incidence, which increases the potential risk for incorrectness of VTE endpoint classification and SARS-CoV-2 infection (i.e., a false-positive or false-negative diagnosis). Misclassification error occurs for example due to an incorrect interpretation of a radiologist or errors in data extraction and entering in databases. Specifically, in the study by Hill et al., reporting a VTE incidence of 3.1% (95% CI 2.5;3.8), electronic health records were queried to identify patients with diagnosis for VTE. Patients

were identified as cases when they received apixaban, rivaroxaban, or dabigatran.[39] Consequently, classification error in the VTE endpoint may be more likely in the study by Hill et al. than in a study using clinical radiology reports for VTE endpoint classification. Radiology reports were for example used in the study by Chen et al., reporting a VTE incidence of 1.0% (95% CI 0.4;1.6).[56]

The consequences of misclassification error and missing data in SARS-CoV-2 infection status is illustrated by the VTE incidence study conducted by Koleilat et al. [49]. In the meta-analysis conducted by Jiménez et al. [12], a VTE incidence of 0.5% (95% CI 0.3;0.8) was reported for the study by Koleilat et al.. This number was calculated by dividing the number of patients with a DVT diagnosis (18) by the number of patients admitted to the hospital with "confirmed COVID-19" (3404). It is unknown what was meant by "confirmed COVID-19" in the original article. The flowchart published in the paper by Koleilat et al. shows that of the 3404 patients with "confirmed COVID-19", 846 patients underwent lower extremity venous duplexes, of whom 145 patients were tested SARS-CoV-2 negative, 135 patients were tested SARS-CoV-2 positive, and 566 were not tested for SARS-CoV-2. Koleilat et al. did not report the SARS-CoV-2 status of the remaining 2558 patients that did not undergo lower extremity venous duplexes. Consequently, due to missing data in SARS-CoV-2 infection status, and potential misclassification error in the "confirmed COVID-19" cases, it is unknown what the correct estimate for VTE incidence was in this study. As an example, if VTE incidence calculation had been restricted to those patients who were known to be tested SARS-CoV-2 positive (135), VTE incidence would change dramatically to (18/135) 13.3% (95% CI 7.6;19.1).

Another example of the consequences of missing data in VTE diagnosis is the VTE incidence study conducted by Chen et al. In this study, 1,008 patients were hospitalised with COVID-19 associated pneumonia.[56] A VTE was diagnosed in 10 patients, and consequently, the meta-analysis by Jiménez et al. reported a VTE incidence of 1.0% (95% CI 0.4;1.6) [12]. In the analysis reported in the original paper, all patients were excluded who did not undergo CTPA examination, since these patients had missing data in VTE diagnosis (yes/no). Restricting the analysis to these 25 patients, would change VTE incidence dramatically to 40.0% (95% CI 20.8;59.2). Including or excluding the patients not undergoing VTE testing, changes the research setting of a study (see also section Patient characteristics). Particularly because, most likely, the odds of a VTE was a priori lower in the group not undergoing a CTPA, compared with the group undergoing a CTPA which was only performed in patients with "elevated D-dimer level or accompanying symptom(s), including chest pain, hemoptysis, and dyspnea" [56].

Data analysis

The frequency measures used to describe VTE incidence may also differ across studies, possibly contributing to heterogeneity in VTE incidence. Commonly used, yet distinct, measures include the cumulative incidence (or risk or incidence proportion), the prevalence and incidence rate.

The risk (or cumulative incidence) is the probability of getting a VTE in a certain period of time and is calculated by dividing the number of subjects who experienced the outcome in a certain time period by the total number of subjects that was observed during that time period. [58] Estimating this measure requires that patients are followed for the entire time period. In addition, interpretation of a risk is only warranted when the length of the time

period over which the risk applies is known, which should therefore be reported. When the time period is small, VTE incidence would approach 0, whereas as the time period becomes longer, VTE incidence will increase [59]. Whyte et al. reported a cumulative incidence at 24 hours of 2.1% (95% CI 1.4;2.8). In comparison, Middeldorp et al. reported cumulative incidences of VTE at 7 days, 14 days and 21 days of 16% (95% CI 10;22), 33% (95% CI 23;43) and 42% (95% CI, 30;54), respectively [31]. Since follow-up duration was highly variable in general, proper interpretation of the reported risks is a challenge and forms a possible explanation for the heterogeneity in VTE incidence.

Prevalence is defined as the proportion of COVID-19 patients with VTE at a particular moment in time [58]. In a cross-sectional study conducted by Criel et al., 82 patients were included and consecutively screened for VTE. In this study, the patients were not followed over time, and consequently, this study estimated VTE prevalence rather than incidence, which was found to be 7.3% (95% CI 1.7;13.0). [52] In comparison, for example, Desborough et al. followed patients for 28 days after admission to critical care (or until death) and, reported a VTE incidence of 15.2% (95% CI 6.5;23.8) [60]. These two estimates are heterogenous since VTE prevalence (Criel et al.) and VTE incidence (Desborough et al.) are incomparable.

Another measure of VTE incidence is the VTE incidence rate, which explicitly takes the duration of follow-up into account. It can be calculated by dividing the number of COVID-19 patients who developed VTE by the total amount of time those patients were followed. For example, Klok et al. reported a VTE incidence rate of 13/patient-year (95% CI 6;27) [2]. This method implicitly takes the length of the follow-up period, and variations between patients, into account.

Another source of heterogeneity across studies is how competing risks are handled in the analysis. In VTE studies of COVID-19, patients can develop a VTE, die, be discharged from the hospital, or be transferred to another hospital. It is often not known whether these patients developed a VTE (or not) after discharge or hospital transfer and it is impossible to know whether these patients would have developed a VTE if they had not died. Moreover, if a patient dies, autopsy should be performed to identify whether the cause of death was a VTE, which usually does not happen. In these patients, the VTE endpoint may, therefore, be misclassified (false-negative). For example, Middeldorp et al. reports "we did not adjudicate deaths to identify fatal PE because almost all deaths were due to hypoxemic respiratory failure, which can be indistinguishable from fatal PE, whereas autopsies were rarely performed in COVID-19 patients".[31] Adjusting or not adjusting for competing risks affects the reported cumulative incidence. Klok et al., reported a crude cumulative incidence of 57% (95% CI 47;67) and a cumulative incidence adjusted for the competing risk of death of 49% (95% CI 41;57). A cumulative incidence adjusted for the competing risk of death and hospital discharge may have decreased the cumulative incidence further since 43% of the patients included in the study were discharged alive.[2]

6.4. Discussion

Studies on VTE incidence in COVID-19 patients show highly heterogeneous results. We identified different sources of this phenomenon, notably, clinical and methodological sources, and illustrated these using various examples. The list of sources of heterogeneity in VTE incidence studies described here (characteristics of study participants, VTE testing,

VTE endpoint, data quality, and data analysis) is not exhaustive and more aspects may be needed to fully comprehend the heterogeneity across studies. Nevertheless, we consider these sources to be important explanations and, therefore, we feel that reporting of these aspects in future VTE incidence studies is required to appreciate and to properly interpret reported VTE incidences. A list of these recommendations is provided in Box 6.1.

We discussed individual sources of heterogeneity in VTE incidence, but obviously these could occur simultaneously. When two studies differ regarding multiple sources of heterogeneity, the difference in VTE incidence could increase but it could also lead to a cancellation of effects. We do not mean to suggest that the differences in VTE incidence in our examples are caused by the discussed sources of heterogeneity. We solely provide one of the many explanations for a difference in VTE incidence. The example studies referenced in this chapter are merely illustrations and do not reflect our view about their quality.

The heterogeneity in reports of VTE incidence not only complicates interpretation of VTE incidence but may also affect trials using VTE incidence as the primary endpoint or one of the secondary endpoints, such as trials comparing different thromboprophylaxis strategies in COVID-19 patients. Specifically, the sample size of these trials may be based on a reported VTE incidence which may not reflect VTE incidence in the research setting of the trial, leading to an under- or overpowered study. For example, the study by Connors et al., studying the effect of antithrombotic therapy on clinical outcomes in outpatients, "was terminated because of a control event rate lower than anticipated" [35]. It is unclear if sample size calculation was directly affected by studies reporting high VTE incidence in (ambulatory) COVID-19 patients. Connors et al. assumed a placebo event rate of 8% as "previous trials of anticoagulants for prevention of thrombotic events in ambulatory patients have noted similar event rates". What is more, most, if not all, aspects described in this paper translate to trial settings. For example, if no clear and unambiguous description is provided of VTE endpoint assessment in trials, estimates of the treatment effect (e.g., risk difference), or the number needed to treat derived from it, cannot be interpreted.

Standardising VTE research is not limited to COVID-19. Several efforts have already been made to improve the quality and consistency of VTE clinical research data and reporting practices. Examples include, amongst others, the VTE Common Data Elements project launched in November 2018 by the International Society on Thrombosis and Haemostasis [61] and recommendations for standardised reporting and analysis of VTE in oncology trials [62].

Standardising reports of VTE incidence studies is important and allows for comparisons of VTE incidence across groups (e.g., hospitals, countries, regions, sex, or over time), across diseases (e.g., influenza), and for better understanding and comparison of the results of trials on treatments aimed at reducing VTE incidence. Careful description of the elements affecting heterogeneity in future VTE incidence studies may better isolate important differences across groups, diseases and treatments and allow meta-analyses that provide summary results based on more homogeneous studies. Eventually such literature will contribute to improved management of VTE risk in COVID-19 patients.

Box 6.1: Recommendations for reporting of studies of incidence of venous thromboembolism (VTE) in Covid-19 patients

Clinical sources

Characteristics of study participants

- Describe the patient profiles (e.g., sex, age, comorbidities)
- Describe the research setting (e.g., intensive care unit, ward)
- Describe the patients' medical treatments (e.g., anticoagulation, steroids)

VTE testing

- Describe the VTE testing protocol (e.g., screening, symptoms, testing based on lab results)
- Describe the reasons to deviate from the VTE testing protocol (e.g., when testing was not reasonable (e.g., palliative care) or feasible (e.g., limited (human) resources) or when testing had no clinical consequences)

Methodological sources

VTE endpoint

- Describe the types of VTE that were included (e.g., pulmonary embolism, deep vein thrombosis)
- Describe the reference test used (e.g., ultrasound, computed tomographic pulmonary angiogram)

Data quality

- Describe the likelihood of classification error and its consequences (e.g., classification error in VTE diagnosis and SARS-CoV-2 infection)
- Describe missing data and its consequences (e.g., missing data in VTE diagnosis and SARS-CoV-2 infection)

Data analysis

- Describe the measure of incidence used and report its unit (if applicable) (e.g., cumulative incidence, prevalence)
- Describe competing risks (e.g., death, discharge, transfer)

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