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Exploring the epidemiology of disseminated intravascular coagulation: protocol for the DANish Disseminated Intravascular Coagulation (DANDIC) Cohort Study

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ABSTRACT

Introduction Since disseminated intravascular coagulation (DIC) was first described, it has been considered a serious disease of the coagulation system and a major challenge to clinicians. Currently, several important knowledge gaps remain. The DANish Disseminated Intravascular Coagulation (DANDIC) Cohort Study will aim to answer questions regarding the incidence and mortality of patients with DIC including time trends. The study will also identify prognostic factors that may guide personalised prevention and treatment. Furthermore, the study will describe treatment patterns and the safety and effectiveness of various treatment modalities.

Methods and analysis We will establish the DANDIC Cohort using data collected in daily clinical practice from the Central Denmark Region, which covers approximately 1.3 million residents. The study period will encompass 1 January 2011 through 1 July 2021. Potential DIC cases will be identified from the hospital laboratory database, based on coagulation biomarkers, and diagnoses will be adjudicated by medical experts. The dataset will be enriched with detailed clinical data from electronic medical charts on aetiologies, bleeding, microthrombus formation, organ failure, thrombosis, treatments and comorbidities. The dataset will also take advantage of in-hospital data with longitudinal information on laboratory records, transfusions, microbiology and treatments. It will be possible to merge this dataset with other unique Danish health registries with more than 10 years of virtually complete follow-up. The project will use state-of-the-art epidemiological and biostatistical methods.

Ethics and dissemination The project has been approved by the Danish Patient Safety Authority (31-1521-452), the Central Denmark Region (1-45-70-83-21), the Danish Data Protection Agency (1-16-02-258-21) and all the hospital chairs. Register-based studies require no ethical approval in Denmark. The results will be disseminated in international peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The DANish Disseminated Intravascular Coagulation (DANDIC) Cohort will be a population-based study with longitudinal data and virtually complete long-term follow-up.
⇒ Multiple sources of healthcare data will be merged to provide a comprehensive dataset with detailed information on disseminated intravascular coagulation (DIC) aetiology, bleeding, microthrombosis, organ failure, thrombosis, treatment and comorbidity.
⇒ The data from the DANDIC Cohort will constitute a unique resource, providing new insights into the clinical epidemiology of DIC.
⇒ A study limitation is the retrospective inclusion of patients with DIC based on information from medical charts.

INTRODUCTION

Disseminated intravascular coagulation (DIC) is a complication of severe infection; malignant disorders; serious obstetric conditions; other medical events including trauma and cardiac arrest; and less common conditions.[1] It is characterised by activation of the coagulation system with loss of inhibitory anticoagulant proteins, resulting in widespread clotting in the microvasculature leading to organ failure. Consumption of platelets and endothelial dysfunction may lead to significant bleeding.[1] The condition is known for its poor prognosis and limited treatment options.[1 2]

Despite the devastating prognosis of DIC, specific knowledge about its epidemiology remains limited. The few studies that have investigated the clinical epidemiology of DIC have been limited to selected patients, for example, patients in the intensive care unit (ICU) at university hospitals[3 4]; were mainly conducted in Japan[3 5]; were more than 10 years old[3 4]; were unable to track patients across transitions in sites of care, for example, transfer between hospitals[4 6]; and did not include rich clinical data on symptoms/signs,

laboratory records, microbiology and in-hospital treatment, for example, transfusions or use of haemostatic drugs.[3 4] Moreover, most existing studies did not have population-based case ascertainment covering multiple DIC aetiologies.[6] Prior studies that relied on diagnosis codes from administrative registries to identify patients with DIC[5] did not capture mild, subclinical and transient DIC episodes, and thus were unable to account for disease severity in their analyses.

Currently, only a few DIC registries and other data sources exist. The Japan Septic Disseminated Intravascular Coagulation study was conducted between 2011 and 2013.[7] It focused on sepsis patients treated in the ICU, with data collected only within the first week of ICU admission. Recently, the International Prospective Registry for the Diagnosis and Management of Disseminated Intravascular Coagulation in the Intensive Care Unit was initiated.[8] It is expected to enrol approximately 1000 critically ill patients and follow them for 28 days to track development of subsequent DIC. Another registry, the Global Registry of DIC in Pregnancy,[9] launched by the International Society on Thrombosis and Haemostasis (ISTH), is currently enrolling patients with obstetric complications and DIC.

Denmark has a long tradition of register-based research and is recognised internationally for its unique network of electronic healthcare registries.[10] Individual-level data can be linked easily among registers, combining high-quality data from electronic medical charts with longitudinal routine registry data, including laboratory records, discharge diagnoses and prescription data with long-term and virtually complete follow-up.[10] A cohort of patients with DIC thus will be established in Denmark to support a series of studies on DIC and to provide sufficient evidence for guidelines on DIC diagnosis, prognosis and treatment. Here, we describe the protocol for the DANish Disseminated Intravascular Coagulation (DANDIC) Cohort Study.

METHODS AND ANALYSIS

Setting

The Danish National Health Service is divided into five regions (Capital Region of Denmark, Central Denmark Region, Region of Northern Denmark, Region of Southern Denmark and Region Zealand) that are considered relatively homogenous with regard to patient characteristics and healthcare utilisation.[11] The Central Denmark Region contains approximately 1.3 million residents and covers 20% of the entire Danish population.[11]

The Danish National Health Service provides free universal tax-supported healthcare guaranteeing free access to general practitioners and hospitals. The unique Danish Civil Registration System (CPR) number makes it possible to merge data across Danish data sources.[12]

Study population

We will establish the DANDIC Cohort using routinely collected healthcare data from the Central Denmark Region. Data will be obtained from six regional hospitals (Herning, Holstebro, Horsens, Randers, Silkeborg and Viborg) and one university hospital (Aarhus) (figure 1). The cohort will comprise patients with a first-time episode of DIC during the period 1 January 2011 through 1 July 2021. As a DIC diagnosis is based mainly on specific laboratory findings, we will identify potential DIC patients through the hospital laboratory information system database and the diagnosis will be verified by medical chart review. In clinical practice, several scoring algorithms solely based on routine coagulation biomarkers are used to diagnose DIC. The most common are the ISTH[2] and the Japanese Association for Acute Medicine (JAAM)[13] DIC scores. In the presence of an aetiology compatible with DIC, DIC is diagnosed with an ISTH score≥5 or a JAAM score≥4. In the present project, we will focus on the ISTH DIC Score and JAAM DIC Score with antithrombin, as these scoring systems can be calculated solely on the basis of laboratory database records, which represent our main data source. We used the revised JAAM DIC Score to identify potential DIC patients. This score differs from the original JAAM DIC Score, which incorporates the systemic inflammatory response syndrome (SIRS) criteria. For patients with infection as the aetiology of DIC, we will collect data on SIRS criteria. This will allow us to calculate the original JAAM DIC Score for this subset of patients and to perform additional analyses.

The ISTH score was developed in 2001 as an 8-point scale, assigning 1 point for a platelet count level between 50×10^9 and 100×10^9/L, an international normalised ratio (INR) between 1.3 and 1.6, and fibrinogen below 2.9 µmol/L; two points each for a platelet count level below 50×10^9/L, INR over 1.6, and elevated fibrin D-dimer up to 10 times higher than the upper limit of the reference interval; and 3 points for a fibrin D-dimer elevation more than or equal to 10 times the upper limit of the reference interval (table 1).

While the ISTH score was developed for all potential DIC aetiologies, the JAAM DIC Score was specifically validated in a population of patients with sepsis.[13] The JAAM score incorporates antithrombin activity instead of fibrinogen and accounts for dropping platelet count levels that may occur within 24 hours. It is an 8-point scale that assigns 1 point each for a platelet count level between 80×10^9 and 120×10^9/L or more than a 30% drop within 24 hours, INR over 1.2, a fibrin D-dimer level between 10 and 20 times the upper limit of the reference interval and antithrombin activity below the reference interval (0.80×10^3 IU/L). It assigns 3 points each for a platelet count level below 80×10^9/L or more than a 50% decrease within 24 hours and fibrin D-dimer over 20 times the upper limit of the reference interval (table 2). The weight and ranges of specific point assignments used in this study were selected based on prior studies.[2 14 15]

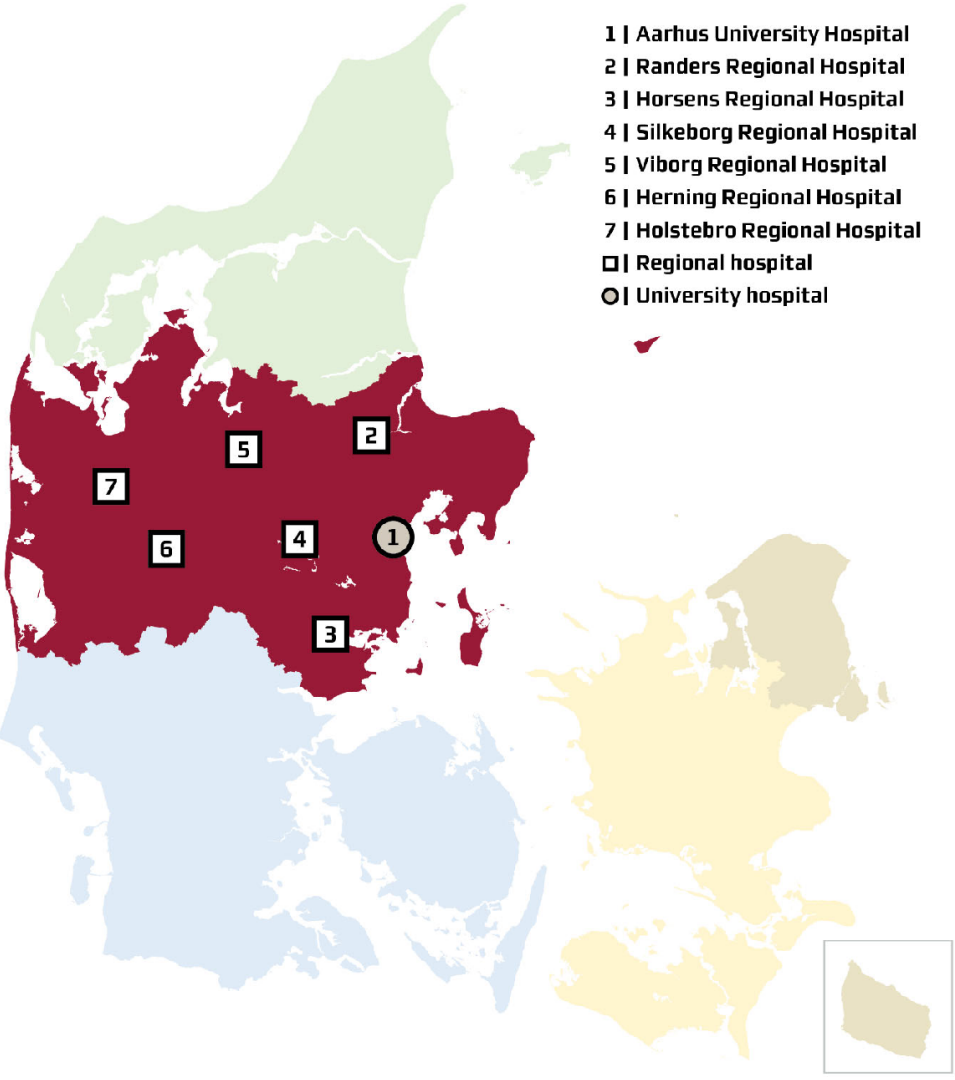

Figure 1 Map showing the Central Denmark Region and the hospitals in the region.

Biomarkers measured in daily clinical practice are available from Denmark's electronic hospital laboratory information system. In Denmark, hospital laboratories are part of the public hospital system and private medical laboratories accounts for a negligible number of test results and consist mainly of highly specialised biomarkers.[16] The biomarkers are registered using the International System of Nomenclature, Properties, and Units system (online supplemental data, etable 1). In the Central Denmark Region, data from the hospital laboratory system (labka II) is considered complete since 2011.[16]

During the study period, the laboratory methods were largely comparable, and the reference intervals were unchanged within the Central Denmark Region. Analytic methods included automatic haematology analysers for platelet count levels, the standardised clot-based method for INR, immunochemical methods for fibrin D-dimer, clot-based methods for fibrinogen and chromogenic assays for determination of antithrombin activity. The quality of the biomarker results in the laboratory information system database is high, and all hospital laboratories are accredited and comply with international standards for medical laboratory testing specified by the International Organization for Standardization (ISO15189).[16]

Inclusion criteria, exclusion criteria and medical chart review

Patients identified from the hospital laboratory system with an ISTH DIC Score≥5 and/or JAAM DIC Score≥4 (with all the coagulation biomarkers of the respective scoring systems measured on the same date) will be selected for medical chart review by trained adjudicators (SF, KA). If the patients' medical chart is unavailable, the patient will not be eligible for inclusion. Furthermore, inclusion will be dependent on the presence of an aetiology relevant to DIC.[1 17] The aetiologies are defined as follows: suspected or verified infection 1 week before or after a score consistent with DIC; active or suspected activity in malignant disease 3 months before or after a score consistent with DIC; obstetrical complications or other aetiologies including trauma and cardiac arrest 1 week prior to a score consistent with DIC. The medical charts of the first 50 patients will be reviewed and discussed between KA

Table 1 International Society on Thrombosis and Haemostasis disseminated intravascular coagulation score algorithm

	Value	Score
Platelet count (×10^9/L) Reference range: 145–350 (males), 165–390 (females)	>100	0
	≥50 and ≤100	1
	<50	2
INR Reference range: <1.3	<1.3	0
	≥1.3 and ≤1.6	1
	>1.6	2
Fibrin D-dimer (mg/L) Reference range: age specific*	<1	0
	≥1 and <10	2
	≥10	3
Fibrinogen (µmol/L) Reference range: 5.5–12	≥2.94	0
	<2.94	1

*0–55 years: <0.50; 55–65 years: <0.60; 65–75 years: <0.70; 75–85 years: <0.80; 85–95 years: <0.90; 95–105 years: <1.00; 105–115 years: <1.10.
INR, international normalised ratio.

and SF to ensure that inclusion and exclusion criteria are standardised and to minimise interobserver variability. Only the first-time episode will be included for patients with more than one episode consistent with DIC, but all potential DIC episodes will be reviewed by the adjudicators according to the ISTH and JAAM criteria.

Exclusion criteria are differential diagnoses causing coagulation abnormalities diagnosed 1 month before or after a score consistent with DIC. Differential diagnoses include idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura (defined as a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13) activity below 10%), haemolytic uremic syndrome, a positive screen test for heparin-induced thrombocytopenia, vaccine-induced immune thrombotic thrombocytopenia[18] and presence of a coagulation factor inhibitor diagnostic for acquired haemophilia. Furthermore, patients receiving chemotherapy within 3 months before a score consistent with DIC will be excluded unless they have a platelet count>120×10^9/L more than 1 month after end of treatment. Patients treated with a vitamin K antagonist or direct oral anticoagulants within the previous week will also be excluded. For patients receiving chemotherapy and for patients receiving anticoagulant therapy, it is almost impossible to determine whether their biochemical findings are related to a specific treatment or to DIC itself. Thus, in line with recommendations on tradeoffs between accuracy measures for electronic health data algorithms, we prioritised a high positive predictive value of the DIC diagnosis. A high positive predictive value is particularly important for identifying a cohort of persons with a condition of interest.[19] However, we will perform full medical chart review of patients excluded from the study at the time of their first potential DIC episode if they later have an episode consistent with DIC. Thus, patients initially excluded based on a first episode potentially consistent with DIC can be included in the cohort if they develop DIC at a later point in time (eg, 4 months following chemotherapy). Patients with haematological malignancies and liver disease have been excluded from several prior studies on DIC,[2 4 6] because it can be difficult to disentangle whether coagulation abnormalities are caused by the underlying condition or represent new-onset DIC. At the same time, these patients may represent a group at particularly high risk of DIC. As such, we will not exclude these patients a priori. If a patient suffers from a haematological malignancy (online supplemental data, etable 2) with prevalent thrombocytopenia (<120×10^9/L) or has no platelet counts within 3 months prior to a DIC Score consistent with DIC, the patients' medical chart will be subject to expert review. The medical charts of patients with disseminated carcinomatosis of the bone marrow will also be subject to expert review, although the effect on the bone marrow is caused by a solid tumour and not a haematological malignancy. Similarly, patients with liver disease (online supplemental data, etable 3) and prevalent thrombocytopenia (<120×10^9/L) and/or prolonged INR (>1.2) or no measurements of these biomarkers within the last 3 months will also be subject to expert review. Expert review will consist of case discussion among the first and last author (SF, KA). If the authors are unable to reach consensus, a third author will be consulted. If DIC is considered the cause of the coagulation changes, the patient will be included in the cohort. If the abnormality in the

Table 2 Japanese Association for Acute Medicine disseminated intravascular coagulation score algorithm

	Value	Score
Platelet count (×10^9/L) Reference range: 145–350 (males), 165–390 (females)	≥120	0
	≥80 and <120 or >30% decrease within 24 hours	1
	<80 or >50% decrease within 24 hours	3
INR Reference range: <1.3	>1.2	1
Fibrin D-dimer (mg/L) Reference range: age specific*	<10	0
	≥10 and <20	1
	≥20	3
Antithrombin (IU/L) Reference range: 0.80–1.20×10^3	≥0.80	0
	<0.80	1

*0–55 years: <0.50; 55–65 years: <0.60; 65–75 years: <0.70; 75–85 years: <0.80; 85–95 years: <0.90; 95–105 years: <1.00; 105–115 years: <1.10
INR, international normalised ratio.

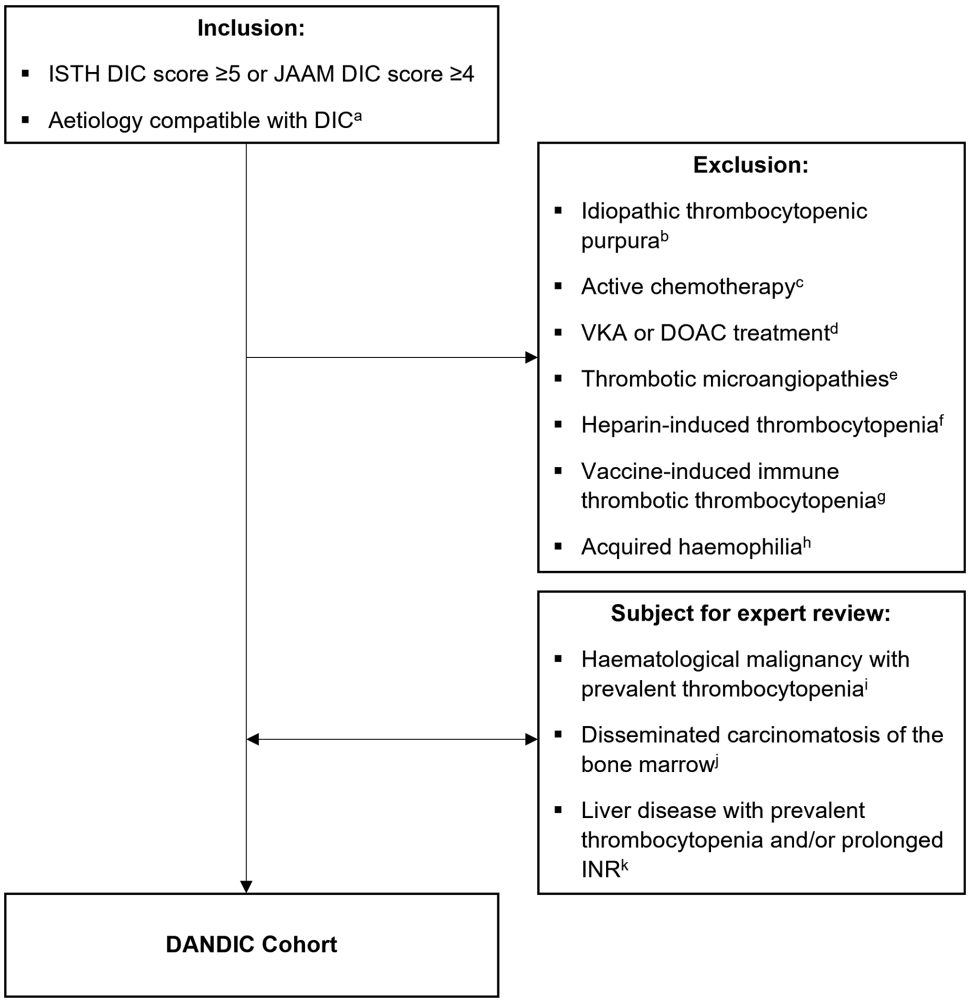

Figure 2 Flowchart for inclusion and exclusion in the DANish Disseminated Intravascular Coagulation (DANDIC) Cohort. [a]Underlying conditions are infection, malignancy, obstetrical complications and others including trauma and cardiac arrest. If electronic medical charts are unavailable, the patient is excluded. [b]Diagnosis DD693 or described as very likely in the medical chart 1 month before or after ISTH or JAAM scoring consistent with DIC. [c]Treatment received within the last 3 months. However, patients can be included if they have a platelet count>120×10^9/L measured more than 1 month after end of treatment. [d]Treatment received within the last week. [e]Thrombotic thrombocytopenic purpura (ADAMTS 13 activity<10%) or haemolytic uremic syndrome (diagnosis DD593 or described as very likely in the medical chart) 1 month before or after ISTH or JAAM scoring consistent with DIC. [f]Positive screen test 1 month before or after ISTH or JAAM scoring consistent with DIC. [g]Vaccine-induced immune thrombotic thrombocytopenia 1 month before or after ISTH or JAAM scoring consistent with DIC. [h]Inhibitor present 1 month before or after ISTH or JAAM scoring consistent with DIC. [i]Expert review of medical chart if there is a record of thrombocytopenia or no platelet count within 3 months prior to ISTH or JAAM scoring consistent with DIC. [j]Expert review of medical chart if the patient has disseminated carcinomatosis of the bone marrow prior to or 1 month after ISTH or JAAM scoring consistent with DIC. [k]Expert review of medical chart if there is a record of thrombocytopenia and/or prolonged INR or no measurement of these biomarkers within 3 months prior to ISTH or JAAM scoring consistent with DIC. ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; DIC, disseminated intravascular coagulation; DOAC, direct oral anticoagulant; INR, international normalised ratio; ISTH, International Society on Thrombosis and Haemostasis; JAAM: Japanese Association for Acute Medicine; VKA: vitamin K antagonist.

biomarkers is caused by the underlying haematological malignancy, disseminated carcinomatosis of the bone marrow or liver disease and therefore not compatible with DIC, the patient will be excluded. A flowchart for the inclusion and exclusion is provided in figure 2.

Research questions

We will use the registry for the DANDIC Cohort for several purposes: to ascertain incidence and mortality of DIC, including time trends, overall and in subgroups of patients; to identify prognostic factors that could be useful in determining the prognosis of DIC and thus in guiding treatment decisions; to evaluate treatment patterns; and to study the effectiveness and safety of various treatment strategies, including antithrombin substitution.

Data collection process

We will enrich the DANDIC Cohort dataset with detailed clinical information. A summary of the case report form (CRF) is provided in table 3, an overview of the data levels

Table 3 Overview of the multiple data sources and variables included in the DANish Disseminated Intravascular Coagulation (DANDIC) Cohort Study

Data from electronic medical charts in Central Denmark Region, health record database*	
Aetiology	Infection/sepsis
	► Primary site of infection
	► SIRS and qSOFA
	► Septic shock
	► Travel history
	► Animal exposure
	Active malignancy
	► Solid tumour – Histology
	► Haematological
	Obstetric complications
	► Type of complication
	► Parity
	► Gestational age
	Others
	► Cardiac arrest
	► Trauma
	► Less common (eg, snake bite)
Symptoms and signs of DIC	Bleeding
	► WHO bleeding scale
	► ISTH's criteria for major bleeding
	Microthrombosis
	► Visible signs
	► Organ failure – SAPS II or III – SOFA
	Thrombosis
	► Arterial cardiovascular events
	► Venous thromboembolism
Treatment	Anticoagulant, haemostatic and antifibrinolytic
	► Type
	► Dose
	► Administration time
	Intensive care
	► Ventilation
	► ECMO
	► Dialysis
	► Inotrope/vasopressor
	Surgery
	► Amputation
	► Bowel removal
Risk factors for bleeding and cardiovascular events†	Recent surgery
	Prior major bleeding
	Alcohol consumption and smoking history
	BMI
	Hypertension
	Diabetes
	► Type
	► Complications
	Hypercholesterolemia
In-hospital data	
Laboratory data	Biomarkers
	► Coagulation
	► Organ function (eg, kidney, liver)
	► Haematological quantities
Transfusions	Red blood cells, fresh frozen plasma, platelets and cryoprecipitate
Microbiology	Microbiologic agent (eg, Gram-negative and Gram-positive bacteria, fungi, viruses, parasites)
	Culture site
	Resistance patterns
In-hospital treatment	All treatments provided in hospital (eg, anticoagulant treatment, haemostatic treatment, antibiotics)
Register-based	
Data from the Danish National Patient Registry, administrative registry since 1977	Inpatient and outpatient discharge diagnoses (eg, diagnoses of cancer, comorbidity, cardiovascular outcomes)
	Procedure, treatment, and surgery codes
Data on all persons residing in Denmark from the Danish Civil Registration System‡ since 1968	Vital status

*Randers Regional Hospital implemented electronic medical charts in 2010, Silkeborg, Herning and Holstebro Regional Hospitals in 2011, Aarhus University Hospital, Horsens Regional Hospital and psychiatric departments across the Central Denmark Region in 2012, and Viborg Regional Hospital in 2013.
†The list will be supplemented with information from other registries regarding additional comorbidities and medication usage predisposing to bleeding.
‡The Danish Civil Registration System is updated daily with information on vital status.
BMI, body mass index; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; ISTH, International Society on Thrombosis and Haemostasis; qSOFA, quick Sequential Organ Failure Assessment Score; SAPS, Simplified Acute Physiology Score; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment Score.

is provided in figure 3, and the full CRF is provided in online supplemental data 2. The clinical information will be used to characterise the cohort, define exposures, perform subgroup analyses, investigate effect measure modification and as covariates in multivariable regression analyses.

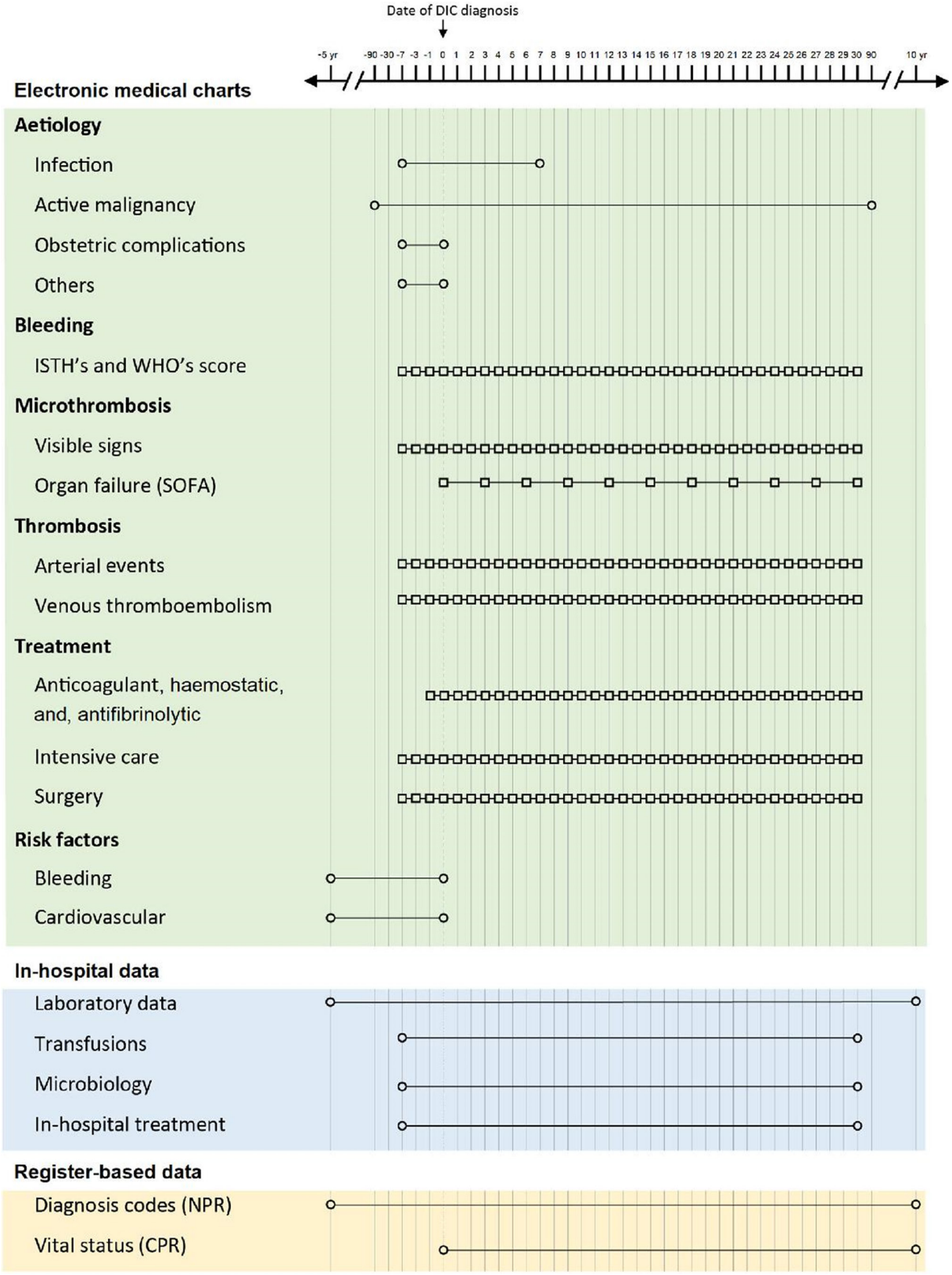

Figure 3 Data levels in the case report form for the DANish Disseminated Intravascular Coagulation (DANDIC) Cohort. Lines between circles indicate recording of data during the given period. Squares indicate individual records of data at the given times. CPR, Civil Registration System; DIC, disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Haemostasis; NPR, National Patient Register; SAPS, Simplified Acute Physiology Score; SIRS, systemic inflammatory response syndrome.

Information on aetiology and other specific details will be extracted. For infection, this information will include primary site of infection, SIRS, the quick Sequential Organ Failure Assessment Score (qSOFA), septic shock criteria, and recent travel history and animal exposure.[20 21] Data regarding the presence of solid tumours and haematological malignancies, including histology of solid tumours, will be obtained. Data will be retrieved on type of obstetric complication (miscarriage, preterm labour, preterm labour rupture of membrane, intrauterine growth retardation, stillbirth, pre-eclampsia, haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, chorioamnionitis, placental abruption, acute fatty liver, amniotic fluid embolism and other complications).

Daily data on bleeding, according to the WHO Bleeding Assessment Scale and ISTH major bleeding criteria, will be collected.[22 23] In brief, the WHO Bleeding Assessment Scale categorises the severity of bleeding into localised minor bleeding (eg, epistaxis), bleeding at invasive sites, bleeding requiring red blood cell transfusion, bleeding associated with haemodynamic instability and fatal bleeding. In addition, information on occurrence of the ISTH criteria for major bleeding, that is, symptomatic presentation of (1) a fatal bleed and/or (2) bleeding in an organ or a critical area (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome) and/or (3) bleeding leading to a fall in haemoglobin level of 1.24 mmol/L or more or requiring transfusion of two or more units of red blood cells within 24 hours.

We will also obtain daily data on signs and symptoms of microthrombus formation and organ failure: coldness of extremities, blue skin and visible acral thrombosis and necrosis. On the date of ICU admission, the Simplified Acute Physiology Score (SAPS) II or III will be obtained and the SOFA Score will be calculated on the date of cohort inclusion and every third day until day 30 or hospital discharge. Similarly, arterial events (acute coronary syndrome, ischaemic stroke, peripheral arterial and splanchnic artery thrombosis) and venous thrombotic events (deep venous thrombosis, lung embolus, splanchnic venous thrombosis and cerebral venous thrombosis) will also be recorded on a daily basis.

Furthermore, daily data will be compiled on anticoagulant treatment, including antithrombin, low-molecular weight heparin, unfractionated heparin. Data on haemostatic drugs comprising fibrinogen concentrate and prothrombin complex concentrate, antifibrinolytic drugs (tranexamic acid), intensive care treatments (ventilation, extracorporeal membrane oxygenation, administration of inotropes, dialysis) and surgery (amputation and bowel removal) will also be collected.

Data on bleeding and cardiovascular risk factors will also be retrieved from the medical charts, including major surgery requiring more than 24 hours hospital admission 3 months before DIC diagnosis, major bleedings requiring hospitalisation and/or transfusions 5 years before DIC diagnosis, alcohol consumption and smoking, body mass index, and specific comorbidities (hypertension, diabetes and its complications and hypercholesterolemia) that are not adequately captured by the administrative health registries, for example, conditions handled primarily by the patients' general practitioner.

Data extracted from the medical charts will be entered manually into REDCap (Research Electronic Data Capture, Vanderbilt University, United States, hosted by Aarhus University).

Additional in-hospital data will be extracted, including information on other routine laboratory records (eg, biomarkers of organ function and other coagulation biomarkers such as those obtained from rotational thromboelastometry), transfusions (red blood cell, cryoprecipitate, fresh frozen plasma and platelet transfusions), microbiology (cultures from blood, urine and other sites) and treatments dependent on the underlying aetiology (eg, antibiotics or chemotherapy).[16]

Finally, the dataset will be enriched with information on daily vital statistics (dates of death and emigration) obtained from the Civil Registration System and on somatic (eg, specific cancer diagnoses) and psychiatric comorbidities that will be retrieved from the Danish National Patient Registry.[12 24] This registry contains information on all discharge diagnoses from inpatient hospitalisations starting in 1977, and on all outpatient contacts and emergency room visits since 1995.[24] It is possible to link the dataset with other Danish registries, which contain information as pharmacy-filled prescriptions (eg, antiplatelet treatment), socioeconomical status and causes of death.

Sample size considerations and data management

All patients with DIC during the study period will be included in the cohort and the index date will be defined as the date of DIC diagnosis. In line with the recommendations of epidemiological textbooks,[25] a formal sample size calculation thus will not be performed. Based on data from a feasibility study conducted in three hospitals in the Central Denmark Region (2015–2019), we expect the cohort to include approximately 3500 patients with DIC.[26] The data management and identification of potential DIC cases has already been performed (figure 4). Our dataset from the hospital laboratory database contains 12 209 674 observations, which include 103 201 antithrombin measurements, 330 846 fibrin D-dimer measurements, 154 841 fibrinogen measurements, 2 856 922 INR measurements and 8 763 864 platelet count measurements. Observations that were missing a valid CPR number were excluded. Likewise, patients under 18 or over 100 years of age at the sampling date and observations lacking a numerical number were also excluded. Observations stated as larger or lesser than the measuring interval were assigned the stated value, for example, fibrin D-dimer>20 mg/L was assigned a value of 20 mg/L. We limited the observations to patients who had measurements of the respective biomarkers for each scoring algorithm on the same date. If a patient

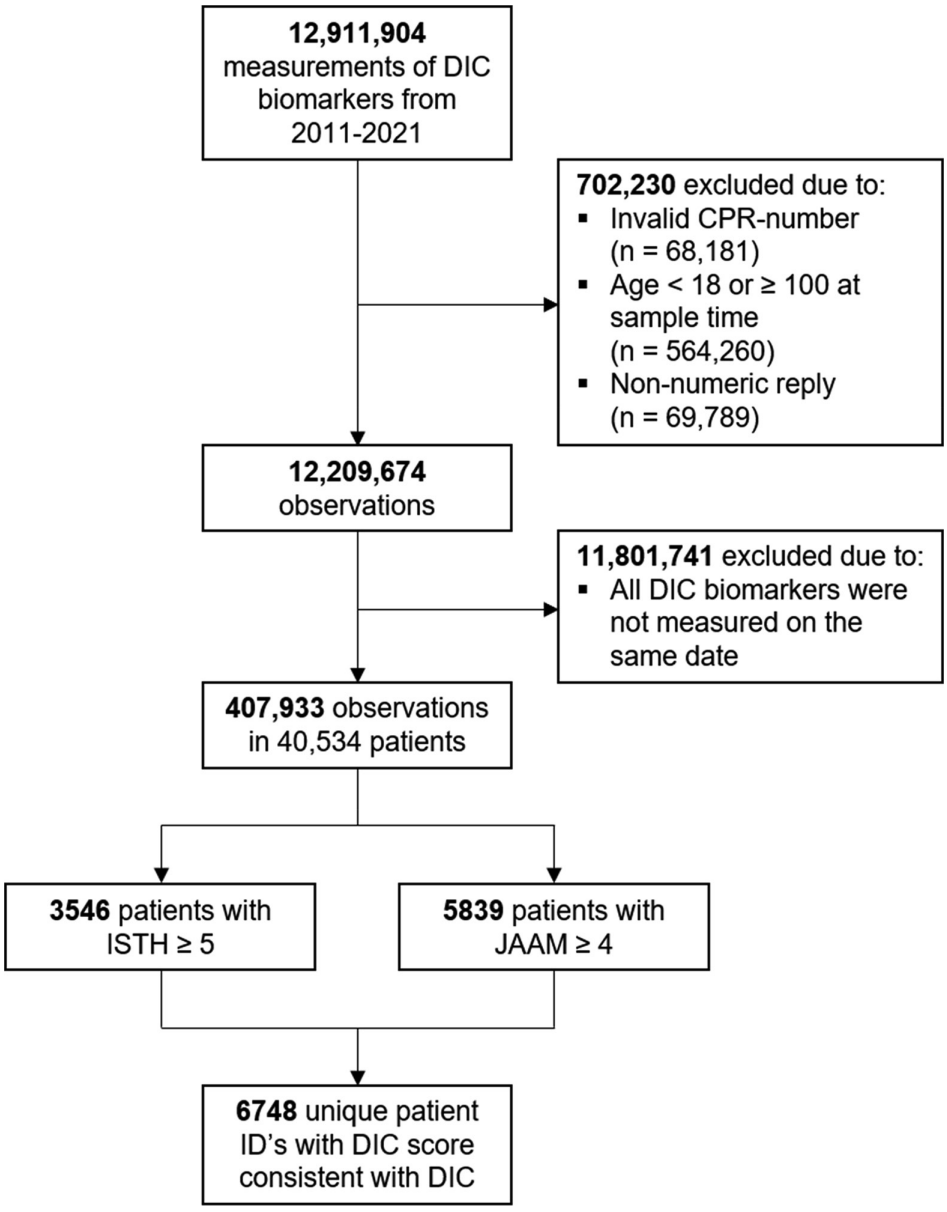

Figure 4 Flowchart for the data management and sampling of patients in the DANish Disseminated Intravascular Coagulation (DANDIC) Cohort. CPR, Civil Registration System; DIC, disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Haemostasis; JAAM, Japanese Association for Acute Medicine.

had multiple measurements of the same biomarker, we used the most extreme value, for example, lowest value of platelet count, fibrinogen and antithrombin, and highest value of INR and fibrin D-dimer. The platelet drop in the JAAM DIC Score was determined by comparing the lowest measured platelet level with the highest measured platelet count level from the day before. Finally, we restricted the patients based on their first-time diagnostic DIC Score.

To ensure that all observations from the hospitals were available in the laboratory database, we tabulated the annual number of observations of each biomarker for the entire region (online supplemental data 3, efigure 1). The number of observations was stable for INR, fibrin D-dimer and platelet count levels, but slightly lower in 2021, reflecting data availability for only 6 months. The number of fibrin D-dimer and INR measurements was highest in 2020, probably because these biomarkers are measured routinely for patients with suspected COVID-19. The number of fibrinogen and antithrombin measurements peaked in 2012 and then slowly declined until 2020, when a new spike occurred. The declining number of observations could be due to the implementation of rotational thromboelastometry after 2008, possibly causing an increase in requests for coagulation analyses in the early years after 2008. Further, there has been a focus on reducing the number of blood samples in the region in recent years, which could have reduced requests for more specialised analyses such as antithrombin and fibrinogen. Although the reference intervals for the biomarkers that defined the ISTH and JAAM scores were unchanged during the study period, we calculated and

plotted the annual median levels for each biomarker to check whether data quality was high and stable over the years. As shown in data online supplemental data 3, efigure 2, the median values remained consistent.

Medical chart review is currently ongoing, and we expect to finalise inclusion of patients by August 2022. The full dataset is expected to be ready for analysis in the beginning of 2023.

Statistical analyses

Descriptive statistics and time-trend statistics will be used. Further, proportions of patients with symptoms and signs of DIC at study inclusion will be tabulated and absolute risk estimates of microthrombosis, organ failure and bleeding during follow-up will be computed, accounting for the competing risk of death.[27] Survival analysis using the Kaplan-Meier method will be used to examine time to death. Measures of relative risk will also be computed to evaluate associations between different exposures and adverse clinical outcomes at study inclusion and during follow-up. Data will be managed using R V.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

Patients and the public were not involved in the development of this research cohort.

Ethics and dissemination

The project has been approved by the Danish Patient Safety Authority (31-1521-452), the Central Denmark Region (1-45-70-83-21), the Danish Data Protection Agency (1-16-02-258-21) and all the hospital chairs. Register-based studies require no ethical approval in Denmark. The results will be disseminated in international peer-reviewed journals.

DISCUSSION

Using electronic medical charts to identify patients with DIC will support future studies on this important complication. The DANDIC Cohort will be one of the most comprehensive datasets of DIC patients in the world, with high completeness, high-quality data[28 29] and virtually complete follow-up obtained through medical chart review and linkage to multiple other data sources. Several limitations should also be mentioned. There may be missing data on such variables as cardiovascular risk factors, and not all information is necessarily recorded in the medical charts (eg, mild bleeding and acute administration of drugs that is not recorded). Although we will only enrol patients with biochemical abnormalities and an aetiology consistent with DIC, we will likely also include some patients with traumatic induced coagulopathy.

Finally, we tried to standardise the inclusion of patients as much as possible, but the diagnosis of DIC may be challenging for some patients, particularly those with haematological malignancy and liver disease.

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