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NatIonal Danish endocarditis stUdieS – Design and objectives of the NIDUS registry

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Aims The NatIonal Danish endocarditis stUdieS (NIDUS) registry aims to investigate the mechanisms contributing to the increasing incidence of infective endocarditis (IE) and to discover risk factors associated to the course, treatment and clinical outcomes of the disease.

Methods The NIDUS registry was created to investigate a nationwide unselected group of patients hospitalized for IE. The National Danish healthcare registries have been queried for validated IE diagnosis codes (International Classification of Disease, 10th edition [ICD-10]: DI33, DI38, and DI398). Subsequently, a team of 28 healthcare professionals, including experts in endocarditis, will systematically review and evaluate all identified patient records using the modified Duke Criteria and the 2015 European Society of Cardiology modified diagnostic criteria. The registry will contain all cases with definite or possible IE found in primary data sources in Denmark between January 1, 2016, and December 31, 2021. We will gather individual patient data, such as clinical, microbiological, and echocardiographic characteristics, treatment regimens, and clinical outcomes. A digital data collection form will be used to the gathering of data. A sample of approximately 4,300 individual patients will be evaluated using primary data sources.

Conclusions and perspectives The NIDUS registry will be the first comprehensive nationwide IE registry, contributing critical knowledge about the course, treatment, and clinical outcomes of the disease. Additionally, it will significantly aid in identifying areas in which future research is needed. (Am Heart J 2024;268:80–93.)

Background

Over the last few decades, several infective endocarditis (IE) registries have contributed with important knowledge on the epidemiological aspects of the disease, revealing increased incidence and changes in microbiological etiology.[1-10] The incidence of IE is estimated at 3.0 to 10.5 per 100,000 person years annually.[11-15] Mortality remains high and almost unchanged over the last few decades.[16,17] Multinational IE registries, such as the International Collaboration on Endocarditis (ICE)[3,4] and the European Society of Cardiology (ESC) EUROpean ENDOcarditis (EURO-ENDO),[1] have set the international standard of reporting epidemiological aspects of the disease

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Abbreviations: AMC, Amsterdam University Medical Centers; ESC, European Society of Cardiology; ESC-EORP EURO-ENDO registry, The European Society of Cardiology EURObservational Research Programme European Endocarditis registry; GAMES, Spanish Collaboration on Endocarditis - Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España; ICD-10, International Classification of Disease, 10th edition; ICE, International Collaboration on Endocarditis; IE, Infective Endocarditis; IRIE, Iranian Registry of Infective Endocarditis; LVEF, Left ventricular ejection fraction; NIDUS, The National Danish endocarditis stUdieS; PET/CT, Positron Emission Tomography/ computer tomography; RIEI, The Italian Registry of Infective endocarditis; SRIE, Swedish National Registry of IE..

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for many years, but both registries are limited by selection bias.[18] In previous IE cohorts, patients were predominantly included at tertiary centers, and data completeness varied substantially among the participating countries because of the limited possibility of follow-up of IE patients after hospital discharge.

Selection bias is evident in the significant disparity observed in the reporting of key measures, such as surgery. Several studies report the occurrence of surgical intervention in 40% to 50% of IE patients,[2,19-21] yet studies from national observational studies have demonstrated significantly lower rates approximating 20%.[12,22] The primary explanation is related to patient selection and reporting.[18] To date, no registries to our knowledge have managed to conduct a nationwide consecutive study. Much of our current knowledge on IE is based on selected cohorts lacking key measurements such as the diagnostic criteria of IE, echocardiographic data, vegetation size and location, complications caused by IE, microbiological data, surgical treatment, antibiotic therapy, and Positron Emission Tomography/ Computer Tomography (PET/CT) imaging, thus limiting population-based studies in the characterization and assessment of potential risk factors for the disease.[11,12,14,15,23-25]

To address these limitations in the IE literature and to offer detailed individual data, our objective is to establish a comprehensive, national, and contemporary IE registry. This registry validates the diagnosis of IE based on the ESC 2015 diagnostic criteria and minimize the loss of patient follow-up in the administrative registries. We will include all available data on patient characteristics, management, and clinical outcomes including mortality, infection relapse, morbidity, activities of daily living after discharge, imaging, surgery, microbiological etiology, and antibiotic regimens during admission. The hypothesis is that the NIDUS study will prospectively provide robust and contemporary information on patient characteristics, treatment, disease courses and short and long-term outcomes of IE in a nationwide consecutive complete cohort of IE patients.

Here, we describe the design and potential use of the NIDUS registry.

Objectives of NIDUS registry

1. To examine the associations and relationships between covariates contributing to the increased incidence of IE on a nationwide scale.
2. To identify high risk patients and risk factors for developing IE, and assessment of adverse outcomes such as mortality, embolization, and infection relapse in those who have IE.
3. To gain better understanding of the associations that may be important to prevent the development of the disease or to initiate correct therapeutic treatment at an earlier onset of the disease.
4. To examine prognostic outcomes according to in-hospital treatment regimens and further assess the comparative effectiveness of surgical versus medical treatment of IE.
5. To assess the development and factors associated with microbiological etiology (both blood cultures and tissue) and the description of antibiotic regimes on a national scale.
6. To assess the use of imaging practices in the diagnostic process on a national scale.

METHODS

Data sampling

All Danish patients admitted to the hospital with an ICD-10 diagnosis code of IE between January 1, 2016, and December 31, 2021, will be evaluated for the enrollment criteria, except for patients living in Greenland and the Faroe Islands because of restricted access to their medical records. All hospitals in Denmark will provide a list with unique identification numbers for all patients admitted to the respective hospitals with one of the following ICD-10 diagnostic codes: DI33, DI38, or DI398 (Figure 1). Subsequently, the medical records of all patients will be reviewed using the local electronic medical record software, to ensure the correct diagnosis of IE according to the modified Duke criteria and the ESC 2015 modified diagnostic criteria.[26,27] Thus, we will include almost all recorded episodes of possible or definite IE cases in Denmark between 2016 and 2021, who were registered with a relevant ICD-10 code.

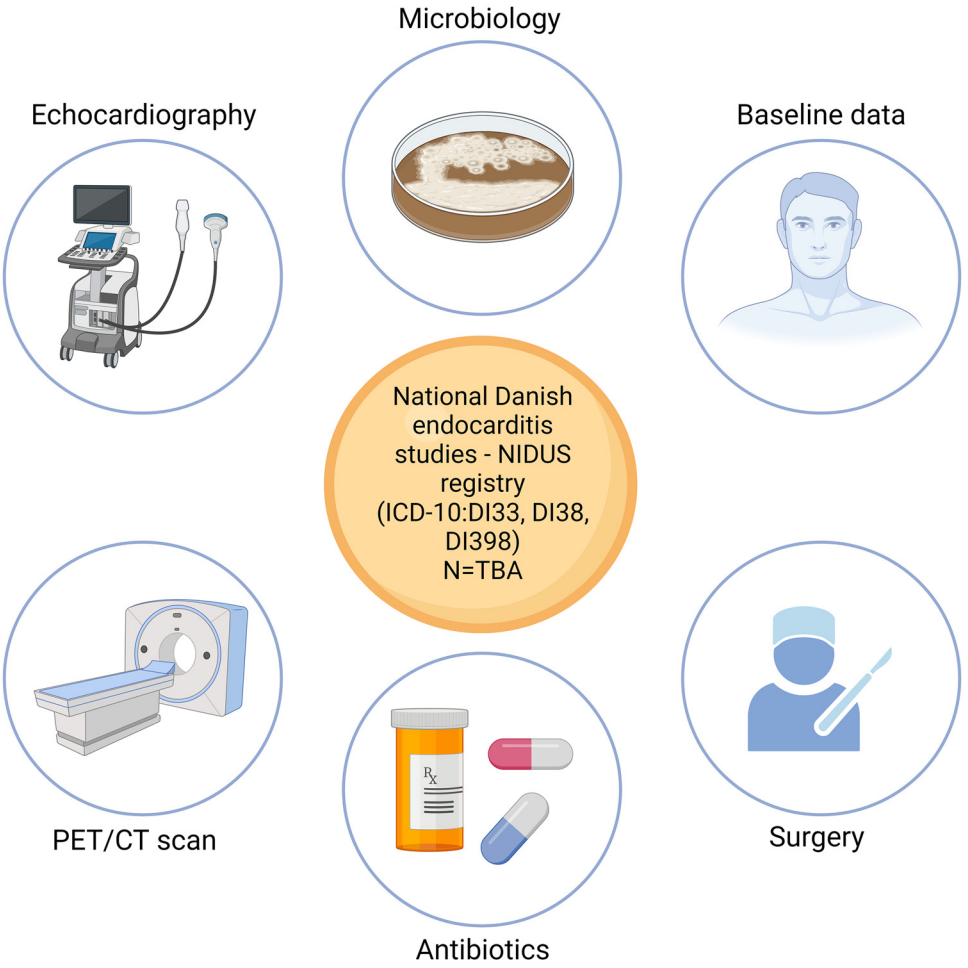
Enrollment criteria

All patients with definite or possible IE, according to the modified Duke criteria and the ESC 2015 modified diagnostic criteria will be included in the NIDUS registry.[26,27] Patients with a diagnosis code of IE that do not fulfill the criteria for either definite or possible IE according to the modified ESC 2015 diagnostic criteria will be excluded. All IE episodes during the study period will be included. Patients will be recorded several times if they have recurrent episodes of possible or definite IE in the study period. IE episodes before 2016 or after 2021 will not be included in the current NIDUS registry. Lastly, foreign citizens admitted to the hospital with IE during the study period will be excluded due to loss of follow-up after discharge.

Data collection and data quality

Primary data will be collected from the patients' medical records. All data will be recorded in an electronic database (REDCap) enabled by dynamic data, allowing for continuous monitoring of data validity, such as "typing" errors, expected data ranges, and mandatory fields.[28,29] The electronic data collection form will be comparable to that of the ICE registry.[3,4]

Figure 1



Overview of data collected in the NIDUS registry. TBA, To be announced. Created with BioRender.com.

Data will be collected by a team of 23 medical students, 2 research nurses, and 2 PhD fellows under the supervision of an IE specialist. In case of uncertainties concerning the diagnosis of IE, the medical students and research nurses will first consult the 2 PhD fellows. If the diagnosis of IE remains unclear, the IE specialist will be consulted. In addition, all personnel will be trained by one of the PhD fellows and have at least 2 days of supervision before they independently record data into the NIDUS registry. To assess the inter-rater agreement, we will use duplicated IE cases that have been randomly entered twice in the NIDUS registry. We will calculate inter-rater agreement as a percentage of identical values out of all possible combinations in the following selected key variables: microbiological etiology, surgery (yes/no), left ventricular ejection fraction (LVEF) categories ("<30%," "30%-44%," "45%-54%," and "55%+"), relapse of IE (defined as recurrence of IE with same bacteria within 6 months) (yes/no), and death (yes/no). To further evaluate the quality of data collection, we plan to conduct a blinded inter-rater reliability trial in which 5 medical students or research nurses will be asked to enter information regarding several key variables in 20 randomly selected IE cases blinded to each other and the existing collected data. The data collected in the NIDUS registry will be critically revised continuously by the PhD fellows using assisting tools such as calculated fields and logical syntax to reveal some typing errors resulting in outliers for instance time of admission or antibiotic treatment below 10 or above 100 days. If typing errors are found these will be corrected immediately. Regular meetings will be scheduled to address any doubts regarding the data collection process for the NIDUS registry in order to maintain a high quality in the database and to ensure agreement among all the healthcare professionals entering data into the NIDUS registry. We will collect data

Table 1. Overview of items of interest in the data collection.

Baseline data	Demographic data
	Medical history
	Cardiovascular history
	Prior cardiovascular surgery
	Medication 3 months prior to admission
	IE-related complications prior to admission (emboli, vascular/immunological phenomena, heart failure, sepsis, severe arrhythmia).
	Symptoms at admission (fever, myalgia, dyspnea, weight loss, vascular/immunological phenomena, duration)
	Length of hospital stay
	Smoking status, alcohol consumption, iv-abuse.
	Work status and self-reliance.
	Assistance to activities of daily living (ADL)
Echocardiographic data	Diagnostic echocardiography
	Valve/valves affected, pacemaker cord or other locations
	Valve insufficiencies
	Other valve pathologies
	Vegetation size (both numerical and categorical)
	Signs of complicated infections (ie, valve abscess or aortic root abscess)
	Left ventricular systolic function, LVEF (both numerical and categorical)
	Echocardiography at discharge
	Residual vegetations both numerical and categorical
	Valve insufficiencies
	LVEF
Microbiology	Most likely microbiological cause based on blood cultures and tissue samples.
	Polymerase chain reaction (PCR) analysis on extracted tissue samples.
	Antimicrobial susceptibility testing from the Danish Microbiology Database (MiBa)
Surgical treatment during admission	Indication for surgery and date of surgery
	The American Society of Anesthesiologists (ASA)-score
	Reasoning for refraining from surgery
	Type of surgery isolated or combined
	Timing of surgery
	Post-operative complications
	Planned future surgical procedures
Antibiotic treatment	Intravenous or tablet
	Start and end of antibiotic treatment
	Reason for terminating antibiotic treatment
Focus of infection	Clinical assessment of point of entry Positron Emission Tomography/ Computer Tomography (PET-CT)
Discharge	Acquisition of infection
	Antibiotic prophylaxis
	IE-related complications developed or worsened during admission
	Other complications during admission
Events	Date of death.
	Date IE relapse or date of new IE episode.
	Date of unplanned surgery
	Date of embolization and localization.

on the following items: baseline information including demographic data, medical history, comorbidities, symptoms at admission, complications related to IE at admission including immunological and vascular phenomena, prior cardiovascular diseases and surgery, prior medication, echocardiographic data, microbiology (blood cultures and tissue), treatment (surgical and antibiotic treatment including shift to oral treatment), focus of infection (including imaging), and discharge information (including assistance in activities of daily living and self-reliance). The NIDUS registry contains a total of 480 variables categorized in 8 instruments, for a more detailed overview of the data in the NIDUS registry, see Table 1.

Outcomes

The primary clinical outcomes for future studies in the registry will be all-cause mortality, bacteremia with the same micro-organism, relapse of IE with the same micro-organism within 6 months, new IE events (with a different micro-organism or after 6 months with the same micro-organism), embolization, and unplanned heart surgery at discharge. All outcomes will be assessed through review of medical records at the time of data entry. All clinical outcomes will be reassessed in 2026. Loss to follow-up can occur if patients emigrate from Denmark. To increase the quality and validity, we will cross-link the NIDUS registry with the validated Danish health-

care registries to assess key outcomes, such as death and rehospitalizations. Furthermore, to assess the association of other outcomes of interest. The National Danish registries will ensure continuous longitudinal follow-up data including all blood cultures, prescriptions, and hospital contacts.

Statistical analyses

Statistical considerations will vary depending on the time of study conducted. However, there will be several common considerations in all the analyses of the NIDUS registry. Adjustment methodologies will be considered when attempting to compare patients; these may include multivariable adjustment, such as logistic regression or survival analyses, including competing risk models. Furthermore, propensity score matching, inverse probability weighting, or other methods will be applied when we compare heterogeneous groups in an attempt to make the groups more comparable according to the baseline characteristics. Missing data will be imputed whenever it is feasible using methods specific to individual analyses. The inter-rater agreement analyses were performed using the SAS Enterprise software version 8.3.

New projects using data from the NIDUS registry

Future studies with data from the NIDUS registry will need to formulate specific research questions using the PECO statement in which, the authors must perform a statistical analysis plan as well as a description of the aim and novelty of the study and what the study adds. Subsequently, all the research questions will be evaluated internally by the steering committee, potentially followed by cycles of revisions and resubmissions before the final study can be approved and the study can begin the data management and analysis phase. The steering committee will ensure that the aim, novelty, and statistical analysis plan of the new studies are valid and not protruding or overlapping. Members of the steering committee will review the final manuscript before the submission to medical journals.

Ethics

The study follows all national ethical principles regarding register-based studies issued by the National Ethics Committee in Denmark. Informed consent is waivered, and the Danish Data Protection Agency has approved data acquisition (P-2020-92).

Results

IE population in the NIDUS registry

We will be evaluating more than 4,300 distinct patients between 2016 and 2021 from the primary data sources. To assess the current inter-rater agreement, we used a temporary sample of 47 cases who were randomly entered twice in the NIDUS registry by different healthcare professionals. The inter-rater agreement was reasonable for some of the selected key variables. An agreement of 98% was found in the assessment of surgical treatment followed by 98% for death, 96% for IE relapse, 87% for microbiological etiology, and 87% for categorical assessment of left ventricular ejection fraction.

Discussion

The NIDUS registry will be a nationwide and complete sample of patients registered with definite or possible IE between 2016 and 2021. The NIDUS registry will be an unselected clinical registry with extensive comprehensive clinical information that will be comparable to contemporary existing IE registries. The NIDUS registry will provide unique opportunities to study the unbiased epidemiology and practice patterns of IE in Denmark.

Overview of current clinical IE registries

To our knowledge, 9 larger IE registries exist, the first of which was initiated in 1995. A timeline of the clinical registries can be seen in Figure 2, several registries have been terminated; however, 3 registries are prospective and still include IE patients.[5,6,10] The registries range in size from 390 to 10,841 patients. The largest registries are the Swedish registry of IE (SRIE) containing data on 10,841 adults (>18 years of age) with possible or definite IE according to modified Duke criteria,[5] and the ICE-cohorts (ICE-PCS and ICE-PLUS) comprises 5,676 and 2,124 patients, respectively with definite IE.[30–32]

Followed by GAMES including 5,590 patients with possible or definite IE according to the modified Duke criteria,[6] the French National Observatory on Infective Endocarditis including 3,473 (initial surveys included patients according to Reyn IE criteria and the rest of the population according to modified Duke criteria),[10,33–35] and the European Infective Endocarditis (ESC-EORP EURO-ENDO) registry comprises 3,116 adults with possible or definite IE according 2015 ESC diagnostic criteria.[1] The smaller registries comprise of the following 4 registries: The East Danish Database on Endocarditis including 977 patients with possible or definite IE according to modified Duke criteria.[36,37] The Italian Registry of Infective endocarditis (RIEI) including 677 adults with definite IE or highly possible according to modified Duke criteria.[7,38] The Iranian Registry of Infective Endocarditis (IRIE) including 612 adults with possible or definite IE according to modified Duke criteria.[8] Last, the Amsterdam University Medical Centers (UMC) registry including 597 patients discussed within the endocarditis team, of those 390 patients were classified as having definite IE according to modified Duke Criteria.[9] A detailed overview of all the registries and their study designs, inclusion criteria, population sizes, participating sites/countries, and clinical data is presented in Table 2.

Table 2. Detailed overview of the larger clinical IE registries.

Endocarditis cohorts	Study design	Inclusion criteria	Population	Participating sites / countries	Data included	Limitations
French National Observatory on Infective Endocarditis	Consists of 3 IE surveys (October 1990 to November 1991, 1999, 2008) and a prospective cohort initiated 01 January 2009	All patients with possible and definite IE cases according to modified Duke-criteria were included Adults (>18 years of age). The first survey from 1990 was based on Reyn et al. IE criteria: definite, probable, or possible	3,473 IE patients†	From 21 centers in France	Demographic data Medical history Clinical data Microbiological data Echocardiographic data Imaging data (PET-CT) from 2009 and forward Treatment -Surgery -Antibiotics Outcomes only mortality	- Selection bias: only 21 centers in France. Observational study from surveys. - Lack of discharge information - Data entered on volunteer basis - the data from the early survey differs in regard to IE definition. - Lack of data on daily activities. - Lack of data on outcomes besides mortality
SRIE (Swedish national Registry of IE)	Prospective cohort initiated in 1995 – status at the end of 2021. Coverage of estimated 85% of all hospital-treated episodes in Sweden	Definite or possible IE according to modified Duke criteria. Adults (age > 18 years)	10,841 IE patients‡ (76% with definite IE)	All 30 departments of infectious diseases in Sweden have participated since its inception	Demographic dataMedical historyClinical dataPrevious cardiac surgeryMicrobiological dataEchocardiographic dataTreatment - Surgery - Antibiotics Discharge informationEvents/outcomes	- Reporting from all infectious department in Sweden – reporting on volunteer basis. - Data on TEE from 88% of patients. - >50 % had missing information on vegetation size. - Lack of data on complications - Limited data on PET/CT scan (only 8 cases) - Lack of data on daily activities.
ICE (International Collaboration of Endocarditis)*	ICE-MD comprised of merged databases from 7 sites in 5 countries. (Retrospective database). ICE-PCS (prospective cohort) was initiated 01 June 2000 and terminated the 31 of December 2006 ICE-PLUS was initiated September 2008 and ended on 31 December 2012 (prospective cohort)	Definite IE according to Duke criteria. Adults (age > 18 years). *ICE-MD also included possible IE cases	ICE-MD: 2,212 IE patients ICE-PCS: 5,676 IE patients ICE-PLUS: 2124 IE patients		Demographic data,Medical historyClinical dataPrevious cardiac surgeryMicrobiological data Echocardiographic dataComplications during admissionTreatment - Surgery - Antibiotics Discharge informationEvents/outcomes	- Selection bias: primary recruitment from tertiary hospitals from many different countries. - No data on PET/CT scan.

(continued on next page)

Table 2. (*continued*)

Endocarditis cohorts	Study design	Inclusion criteria	Population	Participating sites / countries	Data included	Limitations
The East Danish Database on Endocarditis	Prospective cohort of IE patients with consecutive enrollment from October 1st, 2002, to December 31st, 2012	Definite IE or possible (only if they received similar treatment as definite cases) IE according to modified Duke criteria	977 IE patients.	Two tertiary referral heart centers in Copenhagen, Denmark	Demographic dataMedical historyClinical dataPrevious cardiac surgeryMicrobiological dataEchocardiographic dataComplication during admissionTreatment - Surgery - Antibiotics Discharge informationEvents/outcomes	- Selection bias: only including IE patients from 2 referral centers. - No data on PET/CT scan.
IRIE (Iranian Registry of Infective Endocarditis)	Retrospective cohort study between 2006 and 2016. Prospective cohort between January 2016 and 2018	Definite or possible IE according to modified Duke criteria. Adults (age > 18 years)	602 IE patients	Tertiary referral center in Iran	Demographic dataMedical historyClinical dataPrevious cardiac surgeryMicrobiological dataEchocardiographic dataComplication during admissionTreatment - Surgery - Antibiotics Discharge informationEvents/outcomes	- Selection bias, only including IE patients from 1 tertiary referral center - No data on PET/CT scan - Lack of data on daily activities.
RIEI (Italian Registry of Infective Endocarditis - Registro Italiano sull'Endocardite Infettiva)	Prospective cohort from July 2007 to December 2010	Definite IE or highly possible according to modified Duke criteria. Adults (age>18 years)	680 IE patients	From 17 in Italy	Demographic dataMedical historyClinical dataPrevious cardiac surgeryMicrobiological dataEchocardiographic dataComplication during admissionTreatment - Surgery - Antibiotics Discharge informationEvents/outcomes	- Selection bias: only 17 centers in Italy including patients. - Only definite IE or highly possible. - No data on PET/CT scan - Lack of data on daily activities.

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Table 2. (*continued*)

Endocarditis cohorts	Study design	Inclusion criteria	Population	Participating sites / countries	Data included	Limitations
GAMES (Spanish Collaboration on Endocarditis - Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España)	Prospective cohort study + literature review. The cohort study was initiated January 2008	Definite or Possible IE according to modified Duke criteria.	5,590 IE patients[§]	From 38 centers/hospitals in Spain	Demographic dataMedical historyClinical dataPrevious cardiac surgeryMicrobiological dataEchocardiographic dataComplication during admissionTreatment - Surgery - Antibiotics Discharge informationEvents/outcomes	- Selection bias, including most IE cases from tertiary centers. - Lack of daily activities
ESC-EORP EURO-ENDO (The European Endocarditis Registry)[*]	Inclusion-period 01 January 2016 to 31 March 2018. Prospective cohort design. Follow-up until 31 March 2019, at least 1-year follow-up	Definite or Possible IE according to ESC 2015 IE diagnostic criteria Patients. Adults (> 18 years of age)	3,116 IE patients	From 156 centers across 40 countries	Demographic dataMedical historyClinical dataPrevious cardiac surgeryMicrobiological dataEchocardiographic dataComplication during admissionImaging data (MRI & PET-CT)Complications during admissionTreatment - Surgery - Antibiotics Events/outcomes	- Selection bias: primary recruitment from tertiary centers -majority of centers contributed with very few IE cases. - Lack of data on daily activities after discharge.

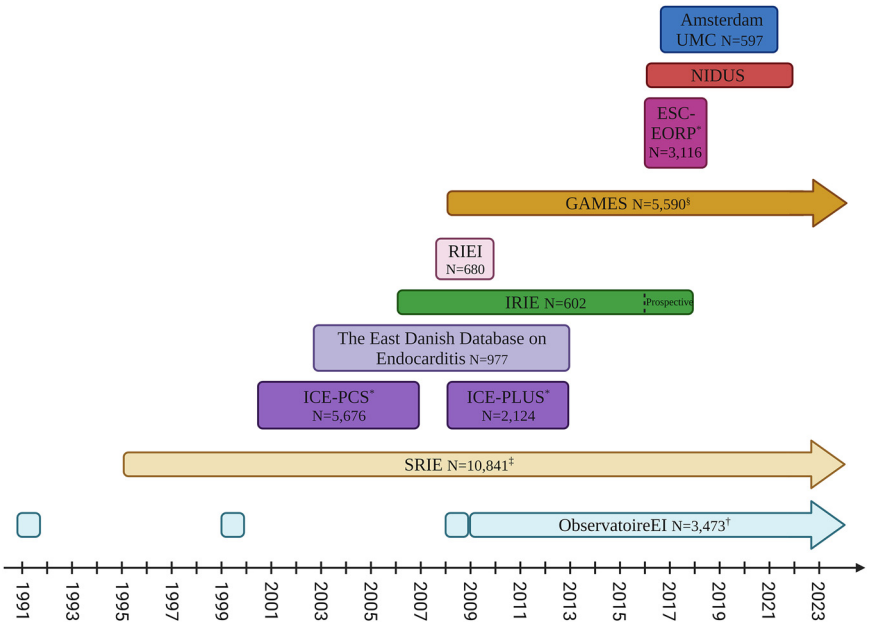
(*continued on next page*)

Table 2. (*continued*)

Endocarditis cohorts	Study design	Inclusion criteria	Population	Participating sites / countries	Data included	Limitations
Amsterdam UMC Registry	Prospective cohort initiated 01 October 2016 and terminated 01 March 2021	All patients discussed in the endocarditis team at the AMC. Definite according to ESC 2015 IE diagnostic criteria Adults (>18 years of age)	597 IE patients, of which 390 patients with definite IE	All patients discussed in the Endocarditis team at UMC Amsterdam	Demographic data Medical history Clinical data Microbiological data Echocardiographic data Imaging data (PET-CT) Treatment - Surgery - Antibiotics Discharge information Events/outcomes	- Selection bias: inclusion of patients discussed on the endocarditis team at the AMC - Lack of data on daily activities.
NIDUS (National Danish endocarditis studies)	Retrospective cohort study / database from January 2016 until 31 December 2021	Definite or possible IE according to ESC 2015 IE diagnostic criteria	*To be determined*	All hospitals and their respective departments involved in the management of IE patients in Denmark were included.	Demographic dataMedical historyClinical dataPrevious cardiac surgeryMicrobiological dataEchocardiographic dataComplications during admissionImaging data (PET-CT)Treatment - Surgery - Antibiotics Daily activitiesDischarge informationEvents/outcomes	Retrospective data collection Data collected from 1 country, which limits generalizability to other countries

* Multinational registries including multiple international sites.
† Number updated at the end of 2019.
‡ Number updated at the end of 2021.
§ Number updated at the end of 2020.

Figure 2



Timeline of the current larger IE registries. *Multinational registries including multiple international sites. †Number updated at the end of 2019. ‡Number updated at the end of 2021. §Number updated at the end of 2020. Amsterdam UMC, Amsterdam University Medical Centers; ESC-EORP , ESC-EORP EURO-ENDO (The European Endocarditis Registry); GAMES , Spanish Collaboration on Endocarditis - Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España; ICE , International Collaboration of Endocarditis; IRIE , Iranian Registry of Infective Endocarditis; NIDUS , National Danish endocarditis studies; RIEI , Italian Registry of Infective Endocarditis - Registro Italiano sull'Endocardite Infettiva; ObservatoireEI, the French National Observatory on Infective Endocarditis; SRIE , Swedish National Registry of IE. Created with BioRender.com.

Observational studies on IE

In the last 2 decades, many important observational studies have contributed with important knowledge epidemiological aspects of the disease including temporal trends in the incidence,[14,15,23,39,40] mortality,[24,25] surgery,[22] microbiological characteristics,[13,41,42] and other important factors.[43] The data sources used in these studies originate from national registries, some of which have been validated for IE in a small number of patients. However, all these studies lack important clinical measurements to fully comprehend the true nature of the disease.

Difference between NIDUS and existing registries

The NIDUS registry will contain full coverage of all patients hospitalized with either possible or definite IE in Denmark according to the 2015 ESC diagnostic criteria. In contrast, the ICE registries[3,4,19,30,32] and the ESC-EORP EURO-ENDO registry[1] were international clinical registries including at least 28 countries. However, selection bias was evident in both the registries. The inclusion of patients from referral centers primarily among the active centers in the ESC-EORP EURO-ENDO (120 out of 156 centers, 80%)[20] were high-volume/referral centers with expertise in IE. In addition, all centers were invited to join the EURO-ENDO registry on a voluntary principle, which gave rise to substantial selection bias in the registry, which is also an issue in the French National Observatory on Infective Endocarditis. Furthermore, only a few patients (<10 patients over a 2-year period) were included from many of the centers involved in the ESC-EORP EURO-ENDO registry. In addition, both the ICE and the SRIE registries are limited to definite IE cases in adults. Thus, excluding possible IE cases who might have had the disease. Patients with possible IE are often treated in the clinic, which supports the importance of including all patients with IE in clinical IE registries.

The SRIE registry includes all departments of infectious diseases in Sweden; however, the estimated coverage of all IE cases in Sweden was 85%. Thus, 15% of the patients with IE are not included in the registry, and the remaining patient characteristics may be different.[5] The GAMES registry includes 38 centers in Spain, and the French National Observatory on Infective Endocarditis includes 21 centers, the majority of which are referral centers, leading to potential selection bias in IE patients. In addition, the French National Observatory on Infective Endocarditis is limited because the initial part of the registry, was

based on three 1-year surveys, which gives rise to potential recall bias.[33-35] The East Danish Database on Endocarditis was smaller in size, and the patients were from 2 tertiary heart centers; thus, selection bias was present. Patients diagnosed with IE treated at a local hospital or patients who were transferred for examination at tertiary heart centers but treated at a local hospital were not included.[36,37] The RIEI, IRIE, and Amsterdam UMC registries were all smaller with regard to the number of included patients,[17,18,22] and the Amsterdam UMC have included all patients who were discussed at the endocarditis team.[9]

The NIDUS registry will be a national registry with full coverage of hospitalized IE patients without selection bias, thus allowing for generalizability, which remains an issue for all existing IE registries. Much epidemiological knowledge about IE is currently based on these registries. Thus, more complete data with less selection bias are required to obtain a more comprehensive picture of IE.

The NIDUS registry will include comprehensive data regarding antibiotic regimens, including dosage, administration, time, and duration of each antibiotic treatment as well as the indication for either shifting or discontinuation of antibiotic therapy during hospitalization. Furthermore, we will include microbiological data such as blood cultures, microbiological examination of extracted heart tissue, and polymerase chain reaction analysis. Additionally, the NIDUS registry will contain extensive imaging data to assess the role of PET/CT in the diagnostic process. Furthermore, information regarding surgical indications and the reason for refraining from surgery despite a class I recommendation for surgery according to the current guidelines will also be provided.[21,26] Information on self-reliance at admission, functional level during hospitalization confined to feeding assistance, walking aids, and status at discharge will be collected to assess the impact of this severe disease on the overall functional level of the patients. The NIDUS registry will also contain recurrent IE episodes during the study period. To our knowledge, the NIDUS registry will be the only registry that will contain all the above-mentioned data.

Strengths and limitations

The strength of our registry is the representation of unselected comprehensive clinical data from all hospital admissions for IE in Denmark. Thus, NIDUS will provide a more complete picture of the disease and the associations of risk factors to the disease less biased. No records will be lost to follow-up because each individual living in Denmark for more than 3 months is issued with a unique Danish personal identification number, which allows linkage to national healthcare registries. In addition, all records will be manually verified by qualified healthcare professionals to confirm or reject the IE diagnosis.

Our registry has some limitations. The population in Denmark is very homogeneous; thus, living conditions and population composition may differ from those in other countries, reducing the generalizability of patient characteristics and risk factors associated with IE. For instance, issues of intravenous drug abuse, rheumatic heart disease, and multidrug-resistant bacteria are less prevalent in Denmark than in other countries. Second, data will be evaluated for possible or definite IE cases from all hospital admissions with IE diagnosis codes (DI33, DI38, or DI398). The negative predictive value of ICD-10 codes for IE is not known; thus, we could potentially miss some IE cases for evaluation. For instance, patients with sepsis who die before the diagnosis of IE. However, we believe that the numbers will be few. Third, data collection will be performed by a larger group of healthcare professionals, which likely will lead to interobserver variability. However, all personnel will receive systematic training before independently entering the data and regular meetings will be planned to discuss any doubts in the collection process. Furthermore, 2 PhD fellows taught all the students at least 2 days of data entry to ensure data quality. In addition, we have conducted data quality validation, assessed inter-rater agreement, and found an inter-rater agreement between 87% and 98% for some selected key variables, which we believe is reasonable. The lower inter-rater agreement regarding LVEF, and the primary microbiological agent could reflect the reporting of LVEF in ranges (eg, 40%-45%) and polymicrobial infection with the potential of more than one causative agent.

Data will be collected retrospectively, and inaccurate coding may occur. However, the diagnosis of IE is highly specific; therefore, we suspect that the misclassification bias will be low. Nevertheless, misclassification bias regarding definite or possible IE cannot be excluded, although this will be unlikely in our registry because an endocarditis specialist will be consulted in cases of doubt. Some regional differences in the diagnostic and therapeutic management of IE may occur; however, approved national guidelines regarding the diagnostic and therapeutic management of IE in Denmark have been issued by the Danish Society of Cardiology.[44] Thus, we believe that diagnostics and therapeutic management agree across the regions in Denmark. Missing data could potentially be an issue in some of the variables of interest, however this is also common in other registry studies. Finally, as this is a retrospective observational registry, we will only be able to assess associations and not causality.

Conclusion

The NIDUS registry will provide extensive and comprehensive clinical data from an unselected contemporary nationwide cohort of patients with IE. The NIDUS

registry will expand our knowledge on IE from existing registries.

Perspectives

The NIDUS registry provides the basis for future prospective cohort studies that will continuously enroll patients. We aim to prospectively include IE cases in the NIDUS registry from 2025 and onward. New iterations of data will be performed on a 2-yearly basis until prospective data collection is established. Furthermore, we hope to include other countries, especially countries that have similar registration possibilities.

CRediT authorship contribution statement

Peter L. Graversen: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Katra Hadji-Turdeghal:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jacob Eifer Møller:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Visualization, Writing – review & editing. **Niels Eske Bruun:** Resources, Supervision, Visualization, Writing – review & editing. **Hicham Laghmoch:** Data curation, Investigation, Writing – review & editing. **Andreas Dalsgaard Jensen:** Data curation, Project administration, Writing – review & editing. **Jeppe K. Petersen:** Data curation, Writing – review & editing. **Henning Bundgaard:** Data curation, Methodology, Resources, Writing – review & editing. **Kasper Iversen:** Methodology, Resources, Writing – review & editing. **Jonas A. Povlsen:** Data curation, Investigation, Methodology, Project administration, Writing – review & editing. **Claus Moser:** Resources, Visualization, Writing – review & editing. **Morten Smerup:** Investigation, Methodology, Writing – review & editing. **Hanne Sortsøe Jensen:** Data curation, Project administration, Resources, Writing – review & editing. **Peter Søgaard:** Resources, Writing – review & editing. **Jannik Helweg-Larsen:** Resources, Writing – review & editing. **Daniel Faurholt-Jepsen:** Investigation, Methodology, Resources, Writing – review & editing. **Lauge Østergaard:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Lars Køber:** Conceptualization, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Emil L. Fosbøl:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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