

**Uniform data collection in routine clinical practice in cardiovascular patients
for optimal care, quality control and research:
The Utrecht Cardiovascular Cohort**

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ABSTRACT (word count 242)

Background: Cardiovascular disease remains the major contributor to morbidity and mortality. In routine care for patients with an elevated cardiovascular risk or with symptomatic cardiovascular disease information is mostly collected in an unstructured manner, making the data of limited use for structural feedback, quality control, learning and scientific research.

Objective: The Utrecht Cardiovascular Cohort (UCC) initiative aims to create an infrastructure for uniform registration of cardiovascular information in routine clinical practice for patients referred for cardiovascular care at the University Medical Center Utrecht. This infrastructure will promote optimal care according to guidelines, continuous quality control in a learning health care system and creation of a research database.

Methods: The UCC comprises three parts. UCC-1 comprises enrolment of all eligible cardiovascular patients in whom the same information will be collected, based on the Dutch cardiovascular management guideline. A sample of UCC-1 will be invited for UCC-2. UCC-2 involves an enrichment through extensive clinical measurements with emphasis on heart failure, cerebral ischemia, arterial aneurysms, diabetes mellitus and elevated blood pressure. UCC-3 comprises on-top studies, with in depth measurements in smaller groups of participants typically based on dedicated project grants. All participants are followed up for morbidity and mortality through linkage with national registries.

Conclusion: In a multidisciplinary effort with physicians, patients and researchers the UCC sets a benchmark for a learning cardiovascular health care system. UCC offers an invaluable resource for future high quality care as well as for first class research for investigators.

Introduction

Patients with increased risk of cardiovascular disease (CVD), or those with symptoms potentially related to presence of cardiovascular abnormalities are commonly referred to various specialists, including cardiologists, endocrinologists, geriatricians, nephrologists, neurologists, internists, or vascular surgeons. Guidelines exist as to what should be recorded as a minimum in those patients.(1,2) Yet, compliance to these recommendations varies considerably across specialties(3) as each specialty collects a specific set of patient data, depending on signs and symptoms and the suspected condition. Furthermore, definitions and coding of data vary and location of information in the electronic health records shows marked variability. In specialist care, patients are followed only if the condition demands repeat visits. If it does not, patients return to the referring physician in another hospital or their general practitioner. Complete short and long term follow-up information is of major importance to determine quality and outcome of care but is often lacking.(4). It is well established that a steady flow of reliable data collected in routine clinical practice are the lifeblood of a continuous learning health care system. A learning healthcare system is one designed to generate and apply the best evidence for the collaborative healthcare choices of each patient and provider; to drive the process of discovery as a natural outgrowth of patient care; and to ensure innovation, quality, safety, and value in health care.(5). Data are needed to coordinate and monitor patient care, analyze and improve systems of care and its quality, conduct scientific research to develop new products and approaches, assess the effectiveness of medical interventions, and advance population health.(5)

In 2010 the University Medical Center Utrecht (UMC Utrecht) formulated a new strategy for academic patient care and research with a main focus on a selected number of major disease areas in which the UMC Utrecht has particular strengths and interests. This led to the establishment of the Center for Circulatory Health in which all departments taking care for cardiovascular patients unite to integrate their patient care, research and educational activities. To enable continuous monitoring of clinical performance and quality of care, and to promote high quality research across all domains of CVD, the Utrecht Cardiovascular Cohort (UCC) was initiated. UCC provides an infrastructure for uniform registration of cardiovascular information embedded in routine care and for systematic follow-up of these patients. UCC builds on the experience of the Second Manifestations of ARterial disease cohort at the UMC Utrecht(6,7), an initiative that started in 1996 and enrolled over 12,000 patients.

The UCC infrastructure is meant to improve care and enable the collection of data to address diagnostic, etiologic, prognostic and therapeutic research questions. The UCC is governed and run by the Center for Circulatory Health at the UMC Utrecht.

Methods

Setting

UCC is designed as a prospective cohort study and comprises three parts. UCC-1 comprises enrolment of all eligible CVD patients in whom information will be collected in routine clinical care. From UCC-1 participants, a large sample will be invited for UCC-2, which involves an enrichment of the information through more extensive measurements. Finally, UCC-3 involves specific measurements in selected samples of UCC participants, typically based on project grants. Broad informed consent is obtained in UCC-1 for storage of blood samples, follow-up procedures, and for contacting participants in the future. For the UCC-2 and UCC-3, study specific informed consents are obtained. (Flow chart figure 1). UCC has been approved by the Institutional Review Board of the UMC Utrecht.

Study population

All patients who come for a first-time visit to one of the departments of the Center for Circulatory Health at the UMC Utrecht for the evaluation of a symptomatic vascular disease or an asymptomatic vascular condition, are enrolled (departments listed in table 1). Minimum set of data, according to the Dutch Cardiovascular Risk Management Guidelines,(1) is collected in all patients at all departments. Annual number of eligible patients is 6,500 patients (UCC-1 population).

In UCC-2 measurements will be performed that are in part based on existing guidelines for clinical care (2,8-16), and in part driven by science. These measurements will be done in a sample of UCC-1 participants who are at “very high CVD risk” as defined by the 2016 European Guidelines on cardiovascular disease prevention in clinical practice (2). The very high risk population comprises patients with documented CVD (including previous acute myocardial infarction, acute coronary syndrome, coronary revascularization and other arterial revascularization procedures, heart failure, stroke and TIA, aortic aneurysm and peripheral arterial disease); patients with documented CVD on imaging (including plaque on coronary imaging or carotid ultrasound); patients with diabetes mellitus and signs of end organ damage (proteinuria) or with a major risk factor such as smoking or marked hypercholesterolemia or marked hypertension; patients with severe renal impairment (eGFR <30 mL/min/1.73 m²); or patients with a calculated HEART SCORE of 10% or above.(2) To expand the distribution of risk and risk factors into non-disease or non-referred range, addition of a population sample is needed to allow studying the complete cardiovascular spectrum and follow individuals that move into care. Therefore, we include an age- and sex stratified sample from the general population, i.e., 2000 participants from the Utrecht Health Project(17), an ongoing cohort in a new suburb of the city of Utrecht where in all new inhabitants that participate information is collected similar to that of UCC-1 participants. Over 10,000 individuals have been enrolled.

UCC-1 measurements

A questionnaire is completed which includes demographic data, medical history, family history of premature CVD, physical activity, smoking, alcohol consumption, obstetric history and medication use (table 2). New patients referred for elective non-acute care receive the questionnaire at home in advance to be completed on-line through a secure patient portal or on paper. In case of the latter, data are entered into the electronic health record during the hospital visit assisted by a staff member if needed. A same approach is used for patients admitted with an acute vascular problem (figure 1). Relevant questionnaire information is directly accessible to the treating physician.

Measurements taken during the first visit in the hospital include body weight, height, systolic and diastolic blood pressure, serum lipids (total cholesterol, HDL cholesterol, triglycerides), glycosylated haemoglobin (Hb1Ac), renal function (serum creatinine with glomerular filtration rate (eGFR) estimated using the Chronic Kidney Disease-Epidemiology (CKD-EPI) formula), and haemoglobin. Spare blood samples (heparin, full blood) are taken and stored at -80 degrees Celsius.

Ethnic minority is considered if when at least one of the parents was born abroad.(18)
Socioeconomic status (SES) is defined based on an area-level indicator by four-digit postal code, constructed by the Netherlands Institute for Social Research.(18)

UCC-2 measurements

The measurements reflect the main research priorities of the Center for Circulatory Health of the UMC Utrecht: heart failure, cerebral ischemia, arterial aneurysms, diabetes mellitus and elevated blood pressure.

A food frequency questionnaire will be used to measure dietary intake. Cognitive function, dyspnea, anxiety, depression, quality of life will be assessed. Questionnaires can be completed through an on-line a secure patient portal or on paper. Next to regular office blood pressure measurements, we include a 30 minute supine automated blood pressure measurement as a good approximation for 24 hour ambulatory measurements (19). A spot urine sample is taken to assess (micro)albuminuria, proteinuria and sodium and potassium creatinine ratio. As part of an in depth diagnostic work-up in patients with difficult to control elevated blood pressure, 24 hour urine sample is collected.(20).

A twelve lead resting electrocardiogram is made. An echocardiogram is performed for ventricular dimensions and cardiac function and to diagnose (subclinical) heart failure including heart failure with preserved left ventricular ejection fraction.(21-23) An ankle-brachial index is measured.(24) Data on arterial calcifications and arterial dimensions (aneurysms) will come from a low dose thoracic and abdominal CT scan.(25-27) For young information on atherosclerosis will be obtained

using ultrasound: Common carotid intima-media thickness, arterial wall density and presence and extent of carotid plaques using established techniques.(28,29) In a selected set of participants, cerebral magnetic resonance imaging is performed to assess intracranial atherosclerosis and aneurysms. Information on intra-abdominal adiposity will be extracted from CT imaging.

A limited set of laboratory measurements will be done including high-sensitivity C- reactive protein, thyroid stimulating hormone, amino-terminal B-type natriuretic peptide (NTproBNP), lipoprotein and high sensitivity troponin.(2,8-16) Also an additional venous blood sample will be stored in -80 Celsius in the UMC Utrecht Biobank for future research.

UCC- follow-up

UCC participants are followed for the occurrence of non-fatal and fatal events. To track patients the Dutch population register is used which contains information on all individuals living in the Netherlands, including date of birth, sex, current address, postal code, nationality, native country (both of registered person and his/her parents), date of death or date of emigration.(30) Routinely performed clinical follow-up measurements and treatment in the UMC Utrecht will be obtained from the electronic health records. In addition, information on hospital admissions will be obtained through linkage with the national Dutch Hospital Data (DHD) registry which provides hospital discharge data including primary and secondary diagnoses, dates of hospital admission and discharge, and has a 90% coverage. Data are coded according to the WHO International Classification of Diseases version 10 (ICD-10).(31). Primary and secondary cause of death will be obtained through linkage with the National Cause of Death Registry.(30) Prescribed drugs during follow-up will be derived from the Foundation on Pharmaceutical Statistics that covers over 95 % of the community pharmacies in The Netherlands.(32) Data on dialysis and kidney transplantation will be obtained from the RENINE registers.(33) Information on cancer incidence will be obtained through the Netherlands Cancer Registry.(34) Furthermore, information will be obtained through contacts with the Utrecht General Practitioners Network.(35) Finally, UCC-2 participants regularly receive questionnaires on clinical outcome, including new onset diabetes and hypertension, and quality of life and lifestyle changes.(6,7)

To facilitate linkage of databases , the Mondriaan system, sponsored by the Dutch Ministry of Health, is important. Mondriaan uses privacy enhancing technologies such as the use of datashields and Trusted Third Parties for linkage of data sources and allows access to various healthcare and research data.(36) Furthermore, the system allows selection and approach of subjects for additional clinical research like clinical trials and pharmacogenetic studies and includes a data catalogue for simple queries over the integrated databases.

Privacy issues

A written informed consent is needed for individual personalized deterministic linkage with regional and national registries in agreement with the privacy legislation in the Netherlands using established procedures.(36) In case of informed consent there are no privacy issues and linkage occurs using a deterministic approach. In case of no informed consent, a trusted third party (TTP) interference may be needed to apply probability based linkage algorithms for regional and national registries to obtain follow-up information on events (hospitalisation, various disease incidence (e.g. cancer), use of general practitioners care, mortality, and prescribed medicine).

Feedback to treating physicians

Abnormal UCC-1 findings are reported back to the treating physician as part of routine care. UCC-2 results for each patient are discussed at a weekly multidisciplinary team meeting (internist, vascular surgeon, cardiologist, neurologist, radiologist, nurse practitioner) to arrive at an individualized treatment advice regarding vascular risk management. Subsequently, treatment is started and the patient is scheduled for two visits at the UMC Utrecht, after which UCC-2 results joined with treatment advice and its findings are reported in writing to the treating specialist and the general practitioner. Recommendations comply to Dutch guidelines which are broadly in agreement with the recent ESC prevention guidelines (1,2).

Data management and access

The data management group of the Center for Circulatory Health ensures privacy, security and traceability and is ISO 9000 certified. Investigators from the participating departments of Center for Circulatory Health have free access to the UCC database. Researchers can request existing data and samples for analysis of new markers. Tailor made datasets will be distributed to the investigator upon approval of request by the UCC Steering Committee. Approval mainly involves checking feasibility, potential overlap with previous requests, material availability, and need for involvement of specific disciplines. After data distribution, automated checks on progress will be made at regular intervals. For investigators outside these departments or from outside the UMC Utrecht, a similar procedure is available. When new variables are measured in stored samples these must be added the UCC database. A copy of the distributed dataset remains at the UMC Utrecht for long term storage. Details on available data, the application form and procedure can be found on our website. For researchers outside participating departments we charge a data access fee per dataset to cover our costs for inclusion, maintenance, quality control and management.

Current status

As of December 12, 2016, over 1000 patients have been invited for UCC-1. Of those, overall 53% gave a written informed consent, but varied across departments (e.g., 34% at the geriatrics outpatient clinic (mean age 80 years), 65% at the diabetes outpatient clinic, or 77% at the neurology ward (patients admitted for a stroke). Response rates are weekly given to the research group to be discussed with the health care workers responsible for the enrolment. UCC-2 shall start in 2017.

Discussion

The UCC is set up to provide an infrastructure and a set of governing principles for uniform registration of essential data for patient care and research in all patients referred for cardiovascular evaluation to the Center for Circulatory Health at the UMC Utrecht. UCC promotes guideline based optimal care, creates a continuous database for multidisciplinary cardiovascular research and provides a quality control system with structured analysis and reporting of clinical information and advice to specialist working in the hospital and referring physicians. Based on the registered information in usual care physicians get predefined feedback on their performance (feedback prioritized by the physicians), have regular discussions on the feedback findings (with management, colleagues, researchers), may modify behaviour and potentially treatment approaches. This circle is developed bottom-up in close collaboration with the nurses and physicians, the data management and IT people to see what the options for improvement are within the electronic health record software. The learning cardiovascular health system will be further be optimized in detail during the next years. UCC sets a benchmark for a learning cardiovascular health care system. Our previous experience has shown that a structured program indeed improves health.(37)

In addition to an invaluable resource for high quality care and prevention, UCC offers first class research opportunities. The necessity of studies as the UCC were strongly advocated in a recently published series on the future of cardiovascular medicine.(38,39) The potential for research is multiple, including generation of clinical evidence for health care, like clinical trials and effectiveness. The concept of embedding clinical trials within pre-enrolled cohorts has gained enthusiasm.(40) The availability of a procedure of routinely collecting patient data greatly speeds up the assessment process for interventions. Structured databases can be queried for specific in- and exclusion criteria to identify and screen patients for clinical trials, and can be used to ascertain potential end points in trials. Since data are already in place, conducting clinical research does not require building new infrastructure nor collecting new data. The UCC approach is combined in the electronic health record with unstructured clinical information (clinical notes, physical notes or discharge summaries) and test results (radiology reports). That structure also allows for application and evaluation of various of text mining strategies to for example identify individual risks for personalized treatment approaches, and,

when combined with genetic information, be of use for pharmacogenomics research and patient care.(41)

The development, validation, and use of risk prediction models to inform health care, including risk interpretation by individuals, has been singled out as holding great promise.(38,39) The evaluation of risk prediction models that identify which patients benefit most from interventions, from trial results to individualized prediction (42), can be swiftly evaluated and validated. The inclusion of the full spectrum of subjects from healthy to severely diseased allows for life course studies into the development of the various phases of vascular disease, its main drivers and its consequence in terms of morbidity and mortality.(43)

The UCC has obvious challenges and limitations. We aimed to optimally balance the burden and cost associated with its collection (impact on usability) and its value (usefulness of data) through focus, and so had to restrict on availability of measurements and patient groups. Other patient categories with an increased cardiovascular risk may benefit from an approach like UCC, for example those with systemic inflammatory conditions are presently not yet included in UCC. Also, the UCC is limited to patients referred to a tertiary academic center, which is of relevance for generalizability of findings in clinical care and research. However, the UCC approach is certainly transferable to other hospitals , given sufficient effort, dedication, time, and support from all layers of a hospital combined with certain budgets.

In summary, in collaborative effort by physicians, researchers and patients, the UCC sets a benchmark for a learning cardiovascular health care system and offers an invaluable resource for high quality care and prevention as well as cutting edge research for investigators from the UMC Utrecht and other institutions.

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UCC website: www.umcutrecht.nl/UCC (in Dutch).

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Contribution of the authors

Authors order was determined by the executive committee (FA, FV, MB), next alphabetically steering and Center for Circulatory Health committee members, and chairman of the Center for Circulatory Health (DEG).

Contributed to the conception and design: FWA,FLJV,MLB,DEG.

Contributed to the interpretation: FWA,MLB,YMR,FLJV,DEG

Critically revised manuscript: FWA,FJV, MLB, GJdB, MPB, JMD,BGFD,PAD,IEH,MH,PAdJ,SVK,GP, YMR,YTvdS,MCV,DEG.

Drafted the manuscript: FWA,FLJV,MLB,DEG

Approval and agree to be accountable for all aspects of work ensuring integrity and accuracy: FWA,FLJV,MLB,GJdB,MPB,JMD,BGFD,PAD,IEH,MH,PAdJ,SVK,GP,YMR,YTvdS,MCV,DEG.

Figure 1. General approach for Utrecht Cardiovascular Cohort

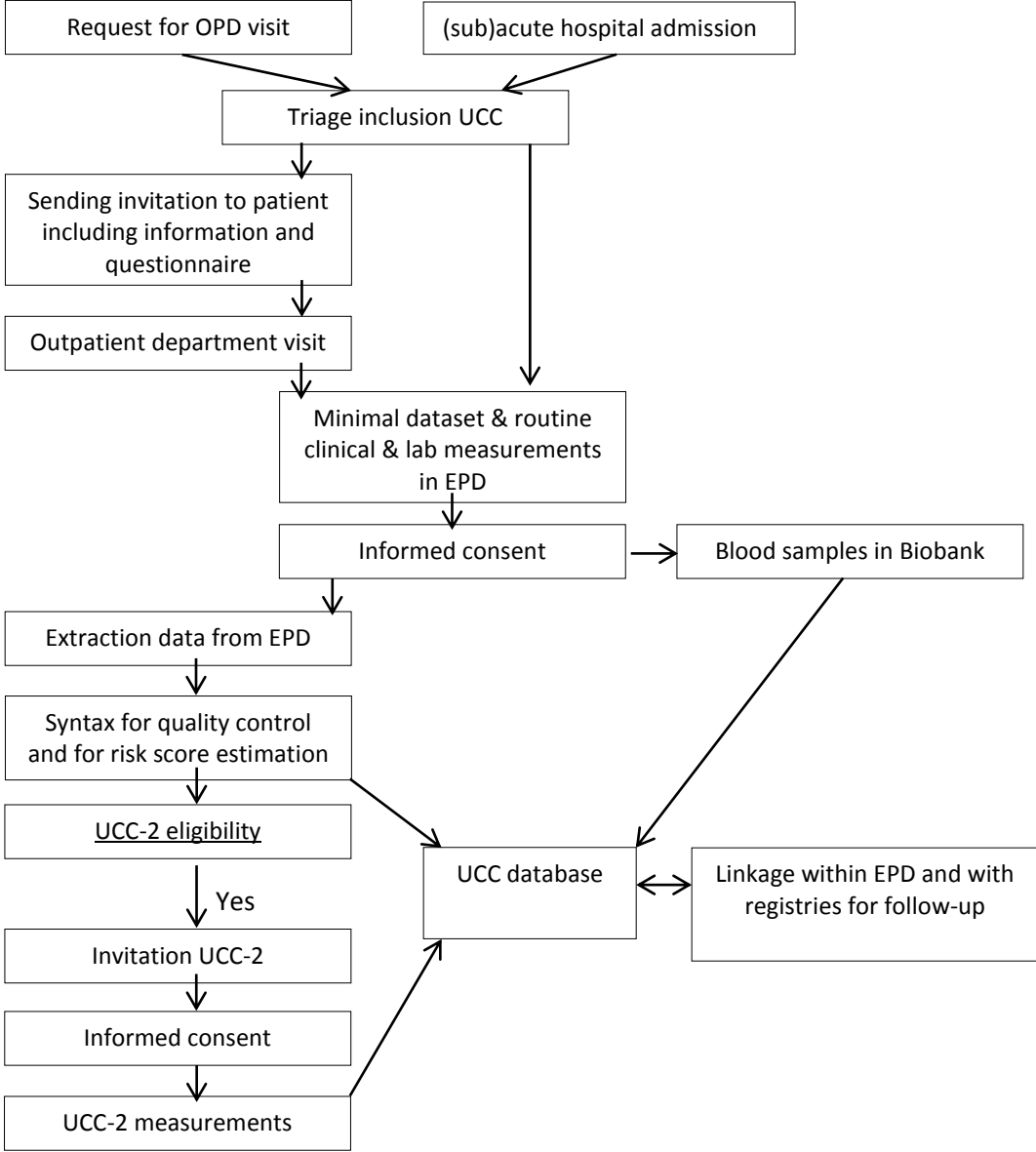


Table 1. Participating divisions and departments in the UMC Utrecht

Division Brain Center Rudolf Magnus

- Neurology and Neurosurgery

Division Heart and Lungs

- Cardiology
- Laboratory for Circulatory Health
- Cardio-Thoracic Surgery

Division Internal Medicine

- Endocrinology
- Geriatric Medicine
- Infectious Disease
- Nephrology and Hypertension
- Vascular Medicine

Division Imaging and Nuclear Medicine

- Radiology

Division Julius Center for Health Sciences and Primary Care

- Clinical Epidemiology
- Primary Care

Division Laboratories and Pharmacy

- Clinical Chemistry and Haematology

Division Surgical Disciplines

- Vascular Surgery

Division Vital Functions

- Anesthesiology and Intensive Care

Division Woman and Baby

- Obstetrics
-

Table 2. Information collected in UCC-1

Demography:	date of enrollment /date of birth/sex/postal code.
General aspects:	treating physician/indication for referral
Medical history:	acute myocardial infarction/CABG/ PTCA/heart failure TIA/stroke/intermittent claudication/Aneurysm Chronic kidney disease/hypertension/hyperlipidemia Family history/Obstetric history
Life style:	Education/smoking/alcohol consumption/physical activity
Physiological measurements:	Height/weight/blood pressure/heart rate
Laboratory measurements:	Total cholesterol/LDL/HDL/Triglycerides/Creatinine/(eGFR)/ HbA1c/Hemoglobin

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