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Design and rationale of the NetherLands registry of invasive Coronary vasomotor Function Testing (NL-CFT)

C. Crooijmans [a,1,2], T.P.J. Jansen [a,1,2], R.E. Konst [a,1], J. Woudstra [b,1], Y. Appelman [b,1], H.M. den Ruijter [c,1], N.C. Onland-Moret [c,1], J.G. Meeder [d,1], A.M.J. de Vos [e,1], V. Paradies [f,1], P. Woudstra [g,1], K.D. Sjauw [g,1], A. van 't Hof [h,j,k,1], M. Meuwissen [i,1], P. Winkler [j,1], E. Boersma [l], T.P. van de Hoef [c,1], A.H.E.M. Maas [a,1], A.C. Dimitriu-Leen [a,1], N. van Royen [a,1], S.E. Elias-Smale [a,1], P. Damman [a,*,1], for NL-CFT[3]

[a] Dept. of Cardiology, Radboudumc, Nijmegen, the Netherlands
[b] Dept. of Cardiology, Amsterdam UMC, location Vrije Universiteit Amsterdam, Amsterdam Cardiovascular Sciences, Amsterdam, the Netherlands
[c] Laboratory of Experimental Cardiology, UMC Utrecht, Utrecht University, Utrecht, the Netherlands
[d] Dept. of Cardiology, Viecuri Medical Center, Venlo, the Netherlands
[e] Dept. of Cardiology, Catharina Hospital, Eindhoven, the Netherlands
[f] Dept. of Cardiology, Maasstad Hospital, Rotterdam, the Netherlands
[g] Dept. of Cardiology, Medical Center Leeuwarden, Leeuwarden, the Netherlands
[h] Dept. of Cardiology, MUMC, Maastricht, the Netherlands
[i] Dept. of Cardiology, Amphia Hospital, Breda, the Netherlands
[j] Dept. of Cardiology, Zuyderland, Heerlen, the Netherlands
[k] CArdiovascular Research Institute Maastricht (CARIM), Maastricht, the Netherlands
[l] Dept. of Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands

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ABSTRACT

Background: Angina without angiographic evidence of obstructive coronary artery disease (ANOCA) is a highly prevalent condition with insufficient pathophysiological knowledge and lack of evidence-based medical therapies. This affects ANOCA patients prognosis, their healthcare utilization and quality of life. In current guidelines, performing a coronary function test (CFT) is recommended to identify a specific vasomotor dysfunction endotype. The NetherLands registry of invasive Coronary vasomotor Function testing (NL-CFT) has been designed to collect data on ANOCA patients undergoing CFT in the Netherlands.

Abbreviations: ACH, acetylcholine; ANOCA, angina with no obstructive coronary artery disease; APV, average peak Doppler flow velocity; BMI, body mass index; CAD, coronary artery disease; CBS, statistics Netherlands (centraal bureau voor de statistiek); CFR, coronary flow reserve; CFT, coronary function test; DRE, digital research environment; ECG, electrocardiogram; EDC, electronic data capture; FAIR, findable, accessible, interoperable, reusable; FFR, fractional flow reserve; GDPR, general data protection regulation; HMR, hyperemic microvascular resistance; IMR, index of microvascular resistance; MRR, microvascular resistance reserve; NL-CFT, the NetherLands registry of invasive Coronary vasomotor Function Testing; Q, flow; R, resistance; RRCT, registry based randomized clinical trials; SAQ, Seattle Angina Questionnaire; WMO, Medical Research Involving Human Subjects Act (wet medisch- wetenschappelijk onderzoek met mensen).

* Corresponding author at: Dept. of Cardiology, route 616, Radboud University Medical Center, Geert Grooteplein Zuid 10, 6525, GA, Nijmegen, the Netherlands.
E-mail address: Peter.Damman@radboudumc.nl (P. Damman).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

[2] Contributed equally.

[3] **NL-CFT investigators**Crooijmans C, Jansen TPJ, Konst RE, Maas AHEM, Dimitriu-Leen AC, van Royen N, Elias-Smale SE, Damman P (Radboudumc, Nijmegen); Appelman Y (Amsterdam UMC, Amsterdam); den Ruijter HM, Onland-Moret NC, van de Hoef TP, Rittersma ZH (UMC Utrecht, Utrecht); Boersma E (Erasmus MC, Rotterdam); Meeder JG (Viecurie, Venlo); de Vos AMJ (Catharina ziekenhuis, Eindhoven); Paradies V, Smits PC (Maasstadziekenhuis, Rotterdam); Woudstra P, Sjauw KD, Vossenberg TN (MCL, Leeuwarden); van 't Hof A (MUMC, Maastricht); Meuwissen M (Amphia, Breda); Winkler P (Zuyderland, Heerlen); van der Werf HW, Lipsic E (UMCG, Groningen); van den Oord SCH (Rijnstate, Arnhem); Oemrawsingh RM, Weevers A (Albert Schweitzer Ziekenhuis, Dordrecht); van Kuijk JP (Antonius, Nieuwegein); Widdershoven JWGM (Elisabeth Tweesteden, Tilburg), Lemmert ME, Arts I (Isala, Zwolle); Olde Bijvank E, van der Heijden D (Haaglanden MC, Den Haag); Arkenbout KE, Madera M (TerGooi, Hilversum); Vos NS, Herrman JPR (OLVG, Amsterdam); Stoel M (MST, Enschede).

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Methods: The NL-CFT is a web-based, prospective, observational registry including all consecutive ANOCA patients undergoing clinically indicated CFT in participating centers throughout the Netherlands. Data on medical history, procedural data and (patient reported) outcomes are gathered.
The implementation of a common CFT protocol in all participating hospitals promotes an equal diagnostic strategy and ensures representation of the entire ANOCA population. A CFT is performed after ruling out obstructive coronary artery disease. It comprises of both acetylcholine vasoreactivity testing as well as bolus thermodilution assessment of microvascular function. Optionally, continuous thermodilution or Doppler flow measurements can be performed. Participating centers can perform research using own data, or pooled data will be made available upon specific request via a secure digital research environment, after approval of a steering committee.
Conclusion: NL-CFT will be an important registry by enabling both observational and registry based (randomized) clinical trials in ANOCA patients undergoing CFT.

1. Introduction

Angina without angiographic evidence of obstructive coronary artery disease (ANOCA) is a highly prevalent condition that is increasingly being recognized. [1] No obstructive coronary artery disease (CAD) is found in about 65% of females and 30% of males with angina undergoing a first-time coronary angiography. [2] Moreover, even with positive non-invasive testing prior to angiography, 50% of patients do not have obstructive coronary artery disease. [3–7] A large proportion of ANOCA patients, more commonly the female than male, have underlying coronary vasomotor dysfunction consisting of abnormal epicardial or microvascular constriction (spasm), and/or impaired vasodilatation. Vasomotor dysfunction is not benign, and previous studies have shown these patients have a worse prognosis. [8–10] The heterogeneity of this population combined with insufficient pathophysiological knowledge and lack of evidence-based medical therapies lead to a high angina burden, resulting in impaired quality of life and repeated healthcare utilization. [11]

A coronary function test (CFT) enables diagnosis and objective classification of different pathophysiological mechanisms or endotypes of coronary vasomotor dysfunction. Endotyping is done according to standardized diagnostic criteria for microvascular dysfunction and vasospastic angina. [12,13] Coronary function testing can potentially be performed routinely after ruling out obstructive CAD by coronary angiography (CAG). Stratified pharmacological treatment based on CFT confirmed endotype leads to a reduction in angina and improvement in quality of life. [14] This has resulted in a class IIa recommendation for coronary function testing in ANOCA patients in both the American and European guidelines for patients with chronic angina, and is also recommended in a recent expert consensus document. [1,11,15]

To facilitate future research, the NetherLands registry of invasive Coronary vasomotor Function testing (NL-CFT) was initiated for easy but extensive data collection on patient and procedural characteristics as well as their treatment and outcomes in patients with suspected and established coronary vasomotor dysfunction. The registry will provide a base to conduct registry based (randomized) diagnostic, therapeutic and outcome trials. With these trials, NL-CFT will provide more insight into the pathophysiology, diagnostic process, prognosis and treatment of ANOCA patients.

2. Methods

2.1. Registry design

The NL-CFT is a prospective, observational registry of all consecutive ANOCA patients undergoing clinically indicated CFT in participating cardiac interventional centers throughout the Netherlands (Fig. 1). Data are collected in a web-based electronic data capture system (EDC, Castor, The Netherlands). Since all data are pseudonymized and patients will not be subjected to (additional) procedures, the Dutch Medical Research Involving Human subjects act (WMO) does not apply. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Study population and informed consent

All patients planned for CFT are informed about the registry before performing the CFT, for example when visiting the outpatient clinic. Informed consent is asked for participation in the registry and optionally to contact treating physicians regarding clinical events, sharing data with third parties, or to be contacted for future research. Consent can be withdrawn at any time.

2.3. The coronary function test

Before detailed physiological characterization by CFT, significant epicardial obstructive coronary artery disease always needs to be ruled out by angiography including, if indicated, intracoronary physiology (e.

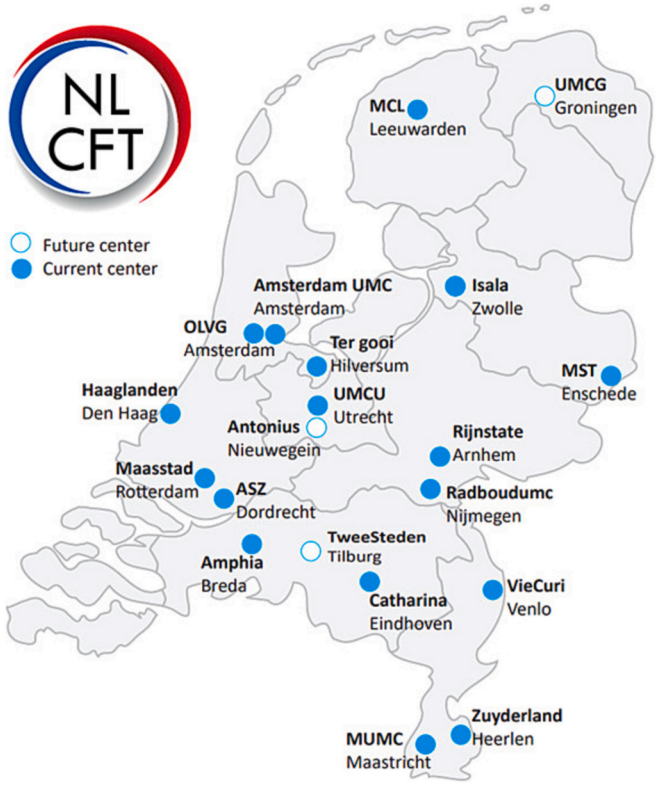

Fig. 1. Participating centers.
Caption All current and future participating hospitals at time of submission. ASZ Albert Schweitzer Ziekenhuis; MCL Medisch Centrum Leeuwarden; MST Medisch Spectrum Twente; MUMC Maastricht University Medical Centre; OLVG Onze Lieve Vrouwe Gasthuis; UMCG University Medical Centre Groningen.

g. fractional flow reserve). CFT can be planned in patients with previously established nonobstructive CAD (by coronary CT or CAG) or performed adhoc following coronary angiography demonstrating nonobstructive CAD for anginal complaints. Any coronary abnormalities are categorized per vessel: either no abnormalities or the extent of atherosclerosis, categorized by number of vessels, percentage of stenosis and physiological significance (FFR/RFR/iFR). Usually, the left anterior descending artery is chosen to perform CFT. For a visual of all measurements see Fig. 2.

All participating centers were trained to perform CFT according to a standardized protocol. This includes both pharmacological spasm provocation testing with acetylcholine (ACH) and assessment of

Fig. 2. Coronary function test.
Caption A visual summary of a complete coronary function test. Both Doppler flow velocity method and continuous thermodilution method are optional. ACH acetylcholine; CFR coronary flow reserve; IMR index of microcirculatory resistance; HMR hyperemic microvascular resistance; R resistance; MRR microvascular resistance reserve.

microvascular function by either bolus thermodilution (using adenosine) or Doppler flow velocity, and optionally by additional continuous thermodilution. [11,16]. The sequence in which to perform different components of the protocol, and method to assess microvascular dysfunction (bolus thermodilution, Doppler flow velocity, continuous thermodilution) is performed according to local standards. Specific treatment advise for patients can be provided when physicians apply for the regularly planned national (digital) multidisciplinary consultation.

2.3.1. Acetylcholine vasoreactivity testing

Intracoronary acetylcholine (ACH) promotes vasodilation in patients with healthy endothelium and normal smooth-muscle cell function. In patients with vasomotor dysfunction spasm can be elicited. As acetylcholine always acts on both endothelial (vasodilation) and smooth-muscle cells (vasoconstriction), the observed effect is the sum of the two opposite effects. Usually, the vasodilatory effect of acetylcholine is larger than the vasoconstrictive effect of acetylcholine on the smooth-muscle cell. However, when endothelial damage/dysfunction is present, the vasoconstrictive effect of the of the smooth-muscle cell overrules the vasodilative effect, leading to spasm. [17]

Vasoreactivity is tested by administration of incremental doses of ACH, namely 2, 20, 100 and a maximal dose of 200 μg in approximately 1 to 3 minutes per dose with the speed limited by atrioventricular conduction disorders. After each ACH dose, angiography is performed to evaluate the presence of epicardial vasoconstriction. [5] The diagnosis of epicardial and/or microvascular spasm is made according to the presence of vasospasm, anginal complaints and ECG abnormalities. [12] After provocation of epicardial spasm or the highest ACH dose, whichever comes first, 200–300 μg of intracoronary nitroglycerin is administered and repeated if necessary. In the event of nitroglycerin refractory spasm or hemodynamic instability 0.5 mg atropine should be administered intravenously. If clinically indicated, an acetylcholine rechallenge can be considered.

In centers using Doppler technology, endothelial function is assessed with the administration of ACH as well. An increase in coronary blood flow of >50% from baseline after administration of low dose acetylcholine (20-100μg) is considered indicative of preserved endothelial function. [18] While we comply with the term endothelial function as used in previous literature, we note the effect of ACH on blood flow is based on the net effect of endothelial and smooth muscle cells. Coronary blood flow is calculated with the change in epicardial coronary artery diameter and average peak velocity, derived from dedicated Doppler software (ComboMAP, Philips-Volcano, San Diego, CA).

2.3.2. Assessment of microvascular function using bolus thermodilution

Microvascular function is assessed using repeated 3 mL intracoronary saline boluses both in rest and during hyperemia induced by intravenous adenosine 140 μg/kg/min. [19,20] Coronary flow reserve (CFR) is the ratio between hyperemic mean transit time (Tmn_{hyp}) and resting mean transit time (Tmn_{rest}) of the bolus in a coronary vessel.

The index of microvascular resistance (IMR) is calculated by multiplying mean distal aortic pressure (Pd) with mean Tmn_{hyp}. IMR_{corr} corrects for epicardial collateral flow contribution (IMRcorr = Pa x Tmn x ([1.35 x Pd/Pa] – 0.32). [9,13] Measurements are done by positioning a guidewire with pressure and temperature sensors into the distal part of the coronary artery (PressureWire X, Abbott Vascular, Santa Clara, CA, USA). Calculations require use of dedicated software (Coroventis Coroflow, Uppsala, Sweden).

2.3.3. Assessment of microvascular function using Doppler method

When using Doppler velocity measurements, CFR is the ratio between hyperemic and resting averaged peak Doppler flow velocity (APV). Doppler flow velocity-derived hyperemic microvascular resistance (HMR) is defined as the ratio of (drift-corrected) distal coronary pressure to APV in hyperemic conditions [21,32]. A doppler flow velocity tipped sensor guidewire (ComboWire or FloWire; Philips Volcano, San Diego, California) as well as a dedicated device (ComboMap; Philips Volcano, San Diego, California) and software are needed.

2.3.4. Assessment of microvascular function using continuous thermodilution

Absolute flow is determined by continuous thermodilution both in resting state with intracoronary saline infusion of 10 mL/min [23], and after inducing hyperemia with 20 mL/min of saline infusion. [24] Direct measurement of flow (Q, in L/min) enables calculation of absolute CFR, determined by dividing Q in rest by Q in hyperemia. [25–28] Additionally, by using continuous thermodilution to measure resistance (R, in WU) and fractional flow reserve (FFR), microvascular resistance reserve (MRR) can be calculated by dividing CFR by FFR corrected for driving pressures. MRR has been proposed as an operator-independent, quantitative metric for coronary microvascular dysfunction. [29] For continuous thermodilution measurements, a monorail infusion catheter (Rayflow™, Hexacath, Paris) and dedicated software (Coroventis Coroflow, Uppsala, Sweden) are needed. Since absolute resistance values depend on the amount of myocardial mass subtended to the location in the coronary artery where measurements are performed, no normal values for continuous thermodilution-derived microvascular resistance have been established. Since routine assessment of the left anterior descending territory is proposed in CFT protocols, $Q > 200$ mL/min and $R < 500$ WU are proposed as thresholds for abnormal absolute maximal flow and absolute microvascular resistance, respectively. [30]

2.3.5. Endotype definitions

A complete CFT consists of both spasm provocation testing with acetylcholine and microvascular function assessment using thermodilution or Doppler. With regards to microvascular function, normal is defined as bolus thermodilution CFR ≥ 2.0 and IMR < 25 or Doppler CFR ≥ 2.0 and HMR ≤ 1.9. [11] While these cut-offs are according to the recent consensus document, we note that a CFR and HMR of 2.0–2.5 can be considered a grey zone that could reflect disease as shown by recent data [22,31].

As multiple mechanisms of vasomotor dysfunction can co-exist in a patient, six different endotypes are shown in Table 1.

2.4. Data

Data are entered by study teams at local sites. In the EDC, data are categorized as follows.

Table 1
Endotype definitions according to CFT results.

	Epicardial spasm[a]	Microvascular spasm[b]	No spasm[c]
Normal microvascular function[d]	Epicardial spasm (focal/diffuse)	Microvascular spasm	Normal
Abnormal microvascular function[e]	Mixed epicardial and microvascular vasomotor dysfunction	Mixed microvascular vasomotor dysfunction	Microvascular dysfunction (CMD)

CFR coronary flow reserve; COVADIS Coronary Vasomotion Disorders International Study Group; CMD coronary microvascular dysfunction; IMR index of microvascular resistance; ECG electrocardiogram; HMR hyperemic microvascular resistance.

[a] defined according to COVADIS criteria (recognizable complaints, ischemic ECG changes and ≥ 90% luminal reduction). [12]

[b] defined according to COVADIS criteria (recognizable complaints, ischemic ECG changes but no or < 90% luminal reduction). [13]

[c] any other spasm provocation test result.

[d] defined as bolus thermodilution CFR ≥ 2.0 and IMR < 25 or Doppler CFR ≥ 2.0 and HMR < 1.9. [11]

[e] defined as bolus thermodilution CFR < 2.0 or IMR ≥ 25 or Doppler CFR < 2.0 or HMR ≥1.9. [11]

2.4.1. Informed consent and surveys

When informed consent is obtained, patients are directed to baseline questionnaires regarding quality of life (RAND-36) and angina (Seattle Angina Questionnaire (SAQ)), both translated in Dutch. They are sent every year for a total of 5 years. The questionnaires explore different health concepts, specifically physical limitation, anginal stability and frequency, treatment satisfaction, disease perception, physical functioning, bodily pain, role limitations due to physical health problems, role limitation due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue and general health perceptions. [33,34]

Additional information on healthcare utilization and use of medication is collected through follow-up questionnaires including hospital admissions and emergency department visits.

2.5. Patient characteristics

Data on relevant cardiovascular and general medical history are collected. Additional data regarding demographics (sex, year of birth), body mass index (BMI), classical cardiovascular risk factors, female specific risk factors and previous diagnostics tests are collected.

2.5.1. Use of medication

Use of medication at baseline and follow-up is captured. After CFT, follow-up forms at 1 and 5 years contain both endpoints as well as use of medication.

2.5.2. Coronary function test

The following data are collected: angiography and procedural characteristics, acetylcholine test results, the presence of complaints, ECG (changes), angiographical changes, and intracoronary physiology measurements (acetylcholine provocation and microvascular function assessment).

2.5.3. Follow-up

In this category, data on use of medication and hard end points are collected, e.g. death, myocardial infarction, hospital admissions, revascularization or other cardiac interventions or surgery, heart failure or arrhythmic events.

2.6. Data protection and quality control

To ensure the correctness of data entered, the EDC has error checking routines for range and consistency. Definitions are displayed on the screen when data are entered. There will be at least one study coordinator that has access to all records of all sites in the EDC (study admin role). To reach a high degree of completeness each hospital can monitor their own data completeness in the EDC. Completeness of each participating centers' data is also monitored by the study admin.

Education and support for all users of the registry is provided. Data are subject to the general data protection regulation (GDPR) and are pseudonymized, with patient identification logs created and stored securely at each site separately. The identification log key will be available to specific site investigators only.

Data will be accessible to the involved researchers, who can only add and view patients from their own site unless a request for pooled data via a digital research environment (DRE) is made. This is a cloud-based workspace on a virtual machine that enables data storing, analysis and sharing. DRE complies with laws and regulations such as the FAIR principles, facilitates GDPR and enables collaboration on secured shared data. [35] Participants who withdrew consent will be excluded from this pooled data. In case of a new data request, a new data sharing file will be uploaded. The principal investigator responsibility for safety and costs of the DRE.

2.7. Organization

NL-CFT is led by a steering committee, consisting of the principal investigator, representatives from the initiating centers, representatives from the IMPRESS consortium, and a representative of the Netherlands Society of Cardiology (NVVC) gender working group. The IMPRESS consortium consists of researchers from several university hospitals, who focus on vasomotor dysfunction and early detection of cardiovascular disease in women. Radboudumc designed the NL-CFT protocol and takes responsibility for the project management, monitoring and quality controls, and together with the steering committee the supervision of scientific reports. Participating centers are not reimbursed for participation. All proposals for research questions requiring pooled data are submitted to the steering committee. (Fig. 3).

3. Discussion

3.1. NL-CFT is the first national registry including ANOCA patients undergoing CFT

3.1.1. Strengths

With this national registry of consecutive patients, we enable researchers to gain extensive data on patient characteristics, prevalence, procedural data and outcomes, event rates and patient reported outcomes in a large ANOCA population, which have been identified as gaps in knowledge before. [11]

With NL-CFT we can conduct research on diagnostics, pathophysiological mechanisms and (novel) treatment options. Furthermore, monitoring of long-term outcomes is made possible in patients with invasively confirmed diagnosis of different vasomotor dysfunction endotypes in a large patient population who underwent a CFT. The large patient population enables analyses of endotype subgroups and effects of (new) treatment strategies on different pathophysiological mechanisms of vasomotor dysfunction. This will ultimately improve patient and endotype tailored treatment in ANOCA.

With NL-CFT, cooperation within a large network of partners that combine forces in collecting data enables performance of large (randomized) registry-based trials. The adoption and implementation of a common CFT protocol forms the basis for an increase in scale and joining of expertise and skills in both peripheral and academic hospitals, thereby representing the entire ANOCA population. Data collection on all CFTs executed in the Netherlands combined with follow-up data, use of medications and patient reported outcomes enables patient centered research and sharing of knowledge and thereby will hopefully improve quality of care and outcomes, including soft endpoints such as angina burden and quality of life.

As all follow-up questionnaires are by email, participation in the registry does not require extra visits to the hospital. Willingness to participate in the registry is high, as are the response rates to questionnaires in the pilot version of NL-CFT.

NL-CFT will be a source of observational research and registry based randomized clinical trials (RRCT). With regards to RRCT, unselected large patient cohorts and rapid consecutive enrollment are possible advantages. This becomes even more interesting when the research population has a low overall event rate and thus requires a large sample size to detect outcome differences. Another advantage of registry-based trials are their relatively low costs. Also noticeable is that in general, patients suitable for randomized trials might not represent real-world practice. A registry-based trial enhances generalizability of findings. [36,37] EDIT-CMD is a recent RCT in ANOCA in NL-CFT centers, demonstrating the value of the current data collecting structure. [38] EDIT-CMD was a randomized controlled trial testing diltiazem versus placebo in ANOCA patients. No improvements in coronary microvascular dysfunction, symptoms or quality of life were found after 6 weeks of treatment. However, diltiazem is currently one of the recommended treatments in ANOCA, as well as other calcium channel blockers.

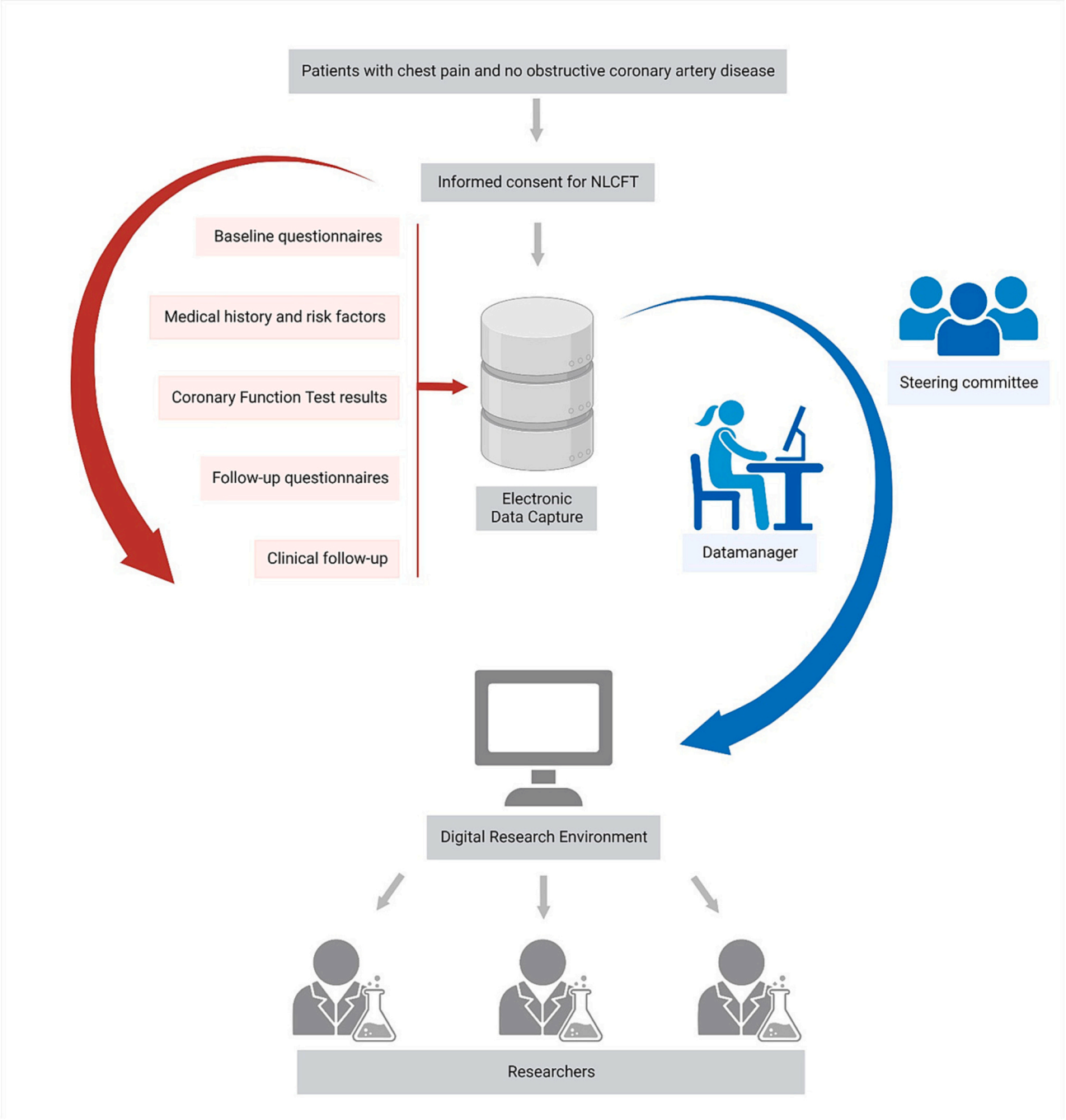

Fig. 3. Data management.
Caption Flowchart representing patients participating in the registry and data management. NLCFT the NetherLands registry of invasive Coronary vasomotor Function Testing.

[1,11,15] This emphasizes the need for additional high-quality trials in ANOCA patients.

3.1.2. *Limitations*

As is inevitable in registry study designs, there are some limitations which deserve to be mentioned. First, as patients are not monitored as extensively as in randomized controlled trials, there is a small risk of underreporting of events. With regards to patient reported outcomes, recall bias is a factor to account for. However, since all clinical outcomes are extracted from the patients' medical records, the risk of underreporting of events is minimalized. Since there are no simultaneous clinical visits or telephone consults, there is a small chance patients might forget or ignore to fill in the questionnaires. To minimize this loss-to-follow up, frequent monitoring of survey progression is done by researchers, and reminders can be sent via the EDC.

Second, since there is only a class IIa recommendation for CFT in current guidelines, selection bias may play a role. Only patients referred for and consenting to CFT will be asked to participate in the registry. There is a possibility we miss an important amount of ANOCA patients. Nevertheless, we believe that with the NL-CFT design, the largest possible patient group with confirmed endotype diagnosis will be included. Notably, patients with vasomotor dysfunction are the population of interest, and by invasively confirming the diagnose we identify exactly those patients.

4. Conclusion and future directions

With the NL-CFT registry we provide opportunity for comparisons and pooled data analysis with sufficient statistical power for different research questions regarding diagnosis, adequate medical therapies and prognosis in a real world registry of patients with ANOCA referred for CFT. By collecting epidemiological, procedural and outcome related data on the largest possible ANOCA patient cohort with and without coronary vasomotor dysfunction we gain extensive data by which we strive to better help patients in the future and to avoid unnecessary healthcare costs. NL-CFT provides a unique platform for both observational and registry based clinical trials, with the ultimate goal to strengthen scientific support for practice guidelines and to develop evidence based best practices in the field of ANOCA.

Declaration of Competing Interest

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Fig. 3 was created with BioRender.com.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.02.043.

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