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The use of echocardiography in observational clinical trials: the EURECA-m registry

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Abstract

Echocardiography is the most widely used non-invasive imaging technique due to its availability, low cost, transportability and lack of ionizing radiations. However, it suffers from the main limitation of being highly subjective and operator-dependent. Furthermore, specifically, population or disease-dependent issues exist which should be addressed when this technique is applied in multicenter studies. As to the population of patients with end-stage renal disease (ESRD) maintained on chronic dialysis, indexation of echocardiographic parameters and timing of echocardiography in relationship to dialysis represent a specific, main issue that needs to be carefully considered and standardized. Scientific societies recommend the set-up of core laboratories in order to reduce inter- and intra-observer variability when an echocardiographic parameter is considered as an end-point in clinical research. Several studies have shown the superiority of interpretation given by echocardiography core-lab reading. These advantages are counterbalanced by higher costs and complexity. The EURECA-m registry by the EURECA-m working group, an ERA-EDTA initiative, aimed at promoting the scientific collaboration among professionals in the field of cardiovascular and renal medicine. The registry involves several centers in Europe and one of its aims is to measure conventional echocardiographic parameters in ESRD patients on chronic dialysis. A central reading protocol has been set up for the registry in order to give robustness to the echo studies.

Keywords: clinical trials; core lab; echocardiography

Alterations of left ventricular parameters in chronic kidney disease: methodological issues specific to dialysis patients

One of the aims of the EURECA-m registry is to assess a number of circulating and echocardiographic parameters in end-stage renal disease (ESRD) patients (aged >18 years) on dialysis (either on haemodialysis or on peritoneal dialysis). In these patients, echocardiography should take into account several factors that may exhibit changes before, after and in-between dialytic treatments, such as volumes and, consequently, ejection fraction. Ideally, echocardiographic studies in this population should be performed in the phase where body fluid volume status is more likely to be at equilibrium, i.e. in the midweek dialysis interval. Logistic problems much often prevent echocardiographic studies at this time, and both in clinical practice and in clinical studies measurements are generally

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performed before or sometimes after dialysis. These limitations may be overcome by standardizing image acquisition timing (whenever possible) and centralizing image analysis and measurements. Such an approach may provide insights into the variation of echo parameters in relation to fluid loading conditions of the patient, and minimize its effect in interpreting echo exams. In fact, in routine clinical practice, caution is needed when interpreting the echo results without taking into consideration fluid shifts. It is also true that many echo parameters are totally load-independent and will not be influenced by the condition of the patient. For instance, left ventricular (LV) mass may show a low reproducibility if some conditions are not respected for its assessment. It is well established that LV hypertrophy is an independent predictor of morbidity and mortality in the general population (Figure 1). All calculations/measurements (M-mode, 2D, 3D) are based upon the subtraction of LV cavity volume from the volume enclosed by the LV epicardium to obtain LV muscle or shell volume, which is then multiplied by myocardium-specific weight (1.05 g/mL). LV mass calculations can be performed using linear measurements from the 2D-guided M-mode or direct 2D views. The American Society of Echocardiography (ASE) formula [1] is appropriate for patients with normal LV geometry, but its accuracy is suboptimal when compared with postmortem LV mass. This parameter has a large inter-observer variability and a poor inter-study (test–retest) reproducibility, with standard deviations of the differences between the successive measurements from 22 to 40 g (95% CI 45–78 g) [2]. By using anatomically corrected 2D echocardiographic (2DE) linear measurements, the reproducibility of LV mass was similar in the echo core lab of the PRESERVE trial: between-study LV mass change of ±34 and 18 g in single patients had a likelihood of being true changes ≥90 and ≥80%, respectively [3]. The 2DE method of LV mass calculation is based on the truncated ellipsoid model and the area–length formula [1], relying on myocardial area measurements at the mid-papillary levels and excluding the papillary muscles in the endocardial tracings. Accuracy and reproducibility are slightly better than calculations derived from linear measurements. The calculation of LV mass from 3D removes geometric assumptions and reduces errors due to foreshortening [4]. 3D LV mass assessment has a very high reproducibility, and it could reduce the samples' size to assess LV mass changes when compared with M-mode and 2DE, being also highly competitive with magnetic resonance imaging. The methodological assumptions for LV assessment make the standardization and the setting up of a core lab mandatory for clinical trials that would otherwise give inconclusive or, even worse, unreliable results.

Echocardiography-derived outcome measures in observational and experimental studies

Echocardiography is part of the core curriculum of cardiologists, with its wide applications for risk and disease assessment on several subsets of patients. However, echocardiography suffers from a major limitation related to its high operator dependence and experience. Scientific bodies have tried to overcome this limitation by two main strategies: appropriate training and standardization in parameter measurements [5, 6], and the set-up of core laboratories with the aim of reducing arbitrariness and variability [7, 8]. It is, therefore, reasonable and critical when echocardiographic parameters are end-points in clinical studies to ascertain the quality of operators in enrolling centers and have a centralized re-reading of all the exams performed in centers. When designing a clinical trial using echocardiography, there are several steps that should be taken into action in order to provide robustness to the study results, with the involvement of the core lab responsible for the study design and a close relation in the

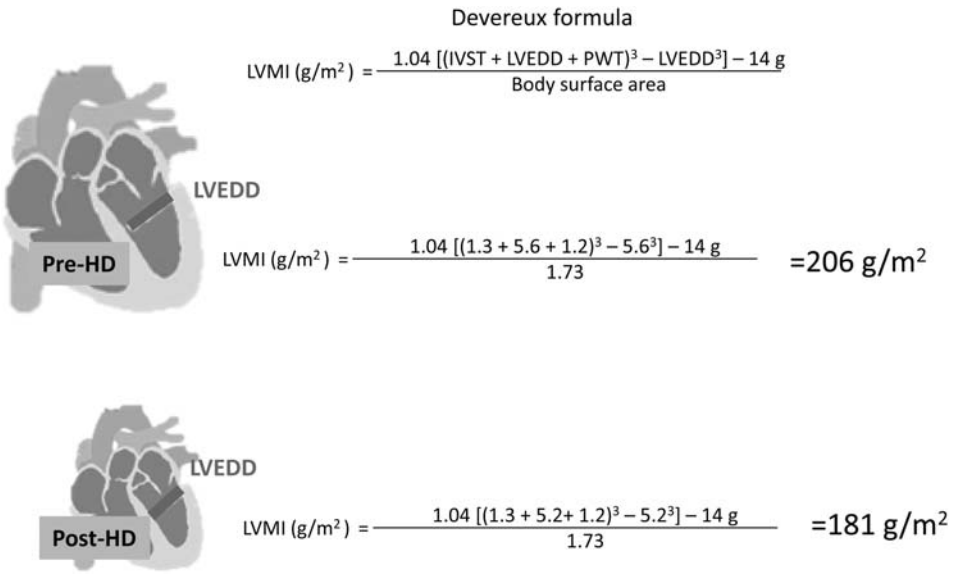

Fig. 1. Tricks and pitfalls of assessing LV mass in patients with ESRF.

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process of the setting of the trial structure. The use of core lab has many advantages as it has been demonstrated in several other studies, showing the superiority of core-lab interpretation to reduce variability and enhance the precision of study results [9–11]. However, the potential downside of core labs setting is the increase of costs of clinical studies.

The ASE has classified into three categories the use of echo in clinical trials: (i) any study that includes Food and Drug Administration (FDA) or other regulatory body oversight or is performed for registration. Although specific guidance for imaging is lacking, the FDA's general requirements for regulatory compliance mandate the highest level of best practices. (ii) Studies that do not involve FDA or other regulatory body oversight but involve complex imaging or include echocardiographic measures as primary or secondary efficacy or safety end-points. (iii) Studies that do not involve regulatory oversight, complex imaging or echocardiographic end-points [12].

Both ASE and the European Association of Echocardiography (EAE) have described the importance of high-quality imaging in research [7, 8]. Therefore, we will refer to those documents that recommend methods for common applications of echocardiography, such as LV ejection fraction and mass. EURECA-m is a registry, not a clinical trial, in which echocardiography at several time points is performed in a network of European ESRD patients. Nonetheless, to standardize and homogenize echo results, a core lab has been set up and actions have been taken in order to increase agreement and guarantee imaging quality.

Installation of central database and echo core lab

Table 1 summarizes the 10 main actions to ensure quality control in clinical trials and multicenter clinical studies.

EURECA-m will aim at using modern Information and Communications Technology infrastructure to implement the dataflow of the study. Wherever possible, open source implementations will be adopted. At the imaging core facilities, all required infrastructures for the image processing will be installed and tested. Figure 2 summarizes the overall design of core lab and image flow.

Definition of the imaging protocol

Echo-Doppler parameters to be included will be chosen taking into account their accuracy [mainly by validation with a reference imaging modality such as cardiac magnetic resonance, reliability, reading variability (intra- and inter-observer), biological variability (day-to-day or test-re-test) and instrumentation variability (machine-to-machine)].

Strict criteria for echo imaging acquisition (e.g. echo views, machine settings), review and storage (e.g. CD-ROM or DVD, non-DICOM format) at the participating peripheral centers, data preparation and collection, labeling and missing data documentation will be clearly stated by the echo core lab in an image review chart in order to ensure standardization and followed by each peripheral center participating into the study.

Table 1. Top 10 procedures recommended from EAE for quality control of echocardiographic studies in clinical research [4]

1	To choose the echo labs on the basis of the head and team experience in both ultrasound technique and clinical trial planning and performance
2	To involve the head and the echo labs in the study design
3	To standardize 'hands on' training of echocardiographers either onsite or at centralized meeting before starting the clinical trial
4	To monitor echocardiographers of the peripheral sites for technical quality (acquisition, storage and processing) of their echo studies
5	To overview quality of the study acquisition at peripheral sites with the head of the core lab
6	To minimize the number of readers in echo labs in order to improve reproducibility of measurements
7	To check the reader variability of echo labs by periodical joint reading sessions with the head
8	To maintain an optimal level of communication between the echo labs and peripheral sites throughout the time course of the study
9	To maintain an optimal level of communication between the echo labs and both the study sponsor and steering committee throughout the time course of the study
10	To involve head and investigators of both echo labs and peripheral sites in data analysis, presentation and publication

The quality of recordings obtained by each peripheral center will be preliminarily tested and validated. This is fundamental for the following reasons: (i) it will spare researchers from collecting data that cannot be utilized properly due to poor image quality or improper data acquisition, adding an unnecessary burden to patient and study costs; (ii) it will prevent unreliable measurements from being entered in the central database of the study, thereby compromising the value of the entire study.

Quality assurance

Quality assurance will be done at two levels: (i) at the level of the clinical sites where data are collected and (ii) at the level of the core lab where data are analysed. In practice, this will be realized by acquiring and processing data in a pilot study. Clinical sites will collect data according to the standard operational procedures previously set out and will send them for analysis (in pre-defined data formats) to the imaging core lab (via the web-based platform). The imaging core lab will verify the data in terms of data format, completeness, appropriateness of the acquisition protocol and data quality. All data will subsequently be analysed and recommendations will be given to the clinical site on how their acquisitions might be optimized when needed. Such recommendations would be formally written in a report that will also be made available to the other partners. If such recommendations were indeed made, a new round of data acquisition/analysis will be started until the analysis core lab has no further comments on the data coming from a particular center. Several iterations might thus take place until the core lab formally approves the data of a particular clinical site (Figure 2). The precise number of patients required in this pilot phase is thus site-specific and undefined. As from this moment, however, the clinical site is allowed to collect data for a particular core lab. Core-lab facilities

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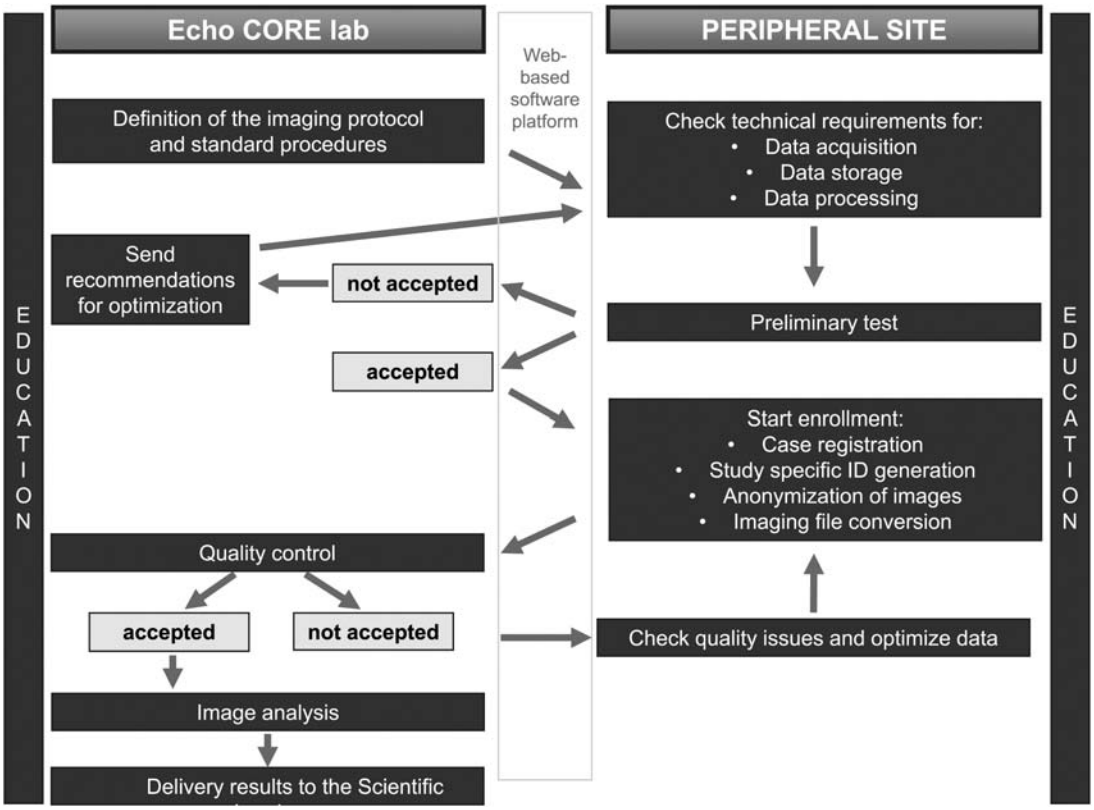

Fig. 2. Flow chart of echo core lab and peripheral sites interaction procedures.

will also need validation in order to guarantee appropriate extraction of noninvasive imaging parameters. In order to do so, data sent from the different clinical sites during the pilot phase will be analysed three times to determine the reproducibility of the measurement. These values will be compared with what has been reported in the literature. If reproducibility is significantly below published values, the reason for this discrepancy will be sought (e.g. the use of different software tools, the use of different acquisition protocols, insufficient training of the analyser, etc.) and solved. The intrinsic variability in a particular measurement determined in this phase of the study will subsequently be used to define study end-points. Finally, it should be noted that quality assurance does not stop when all clinical sites/core labs have formally been approved. Quality assurance will be a continuous process in EURECA-m registry and will be part of the study coordination.

Echo core-laboratories implementation

Core-labs distribution and implementation are critical for the use of echocardiography in clinical research. The role of core labs is highly variable in relation to the specific use of echocardiography in an observational study or in a clinical trial, mainly depending on whether the echo data will contribute or not to a primary or secondary efficacy or safety end-point. In any case, the echo core lab will have the responsibility of establishing the imaging protocol and standardizing image acquisition processes and analysis (e.g. definition of suboptimal or unreadable echo imaging, choice of measurements and parameters, decisions regarding number of cardiac cycles to be averaged for measurements) by a proper review chart, organizing and performing education and training programs of both echocardiographers of the peripheral centers involved in the data acquisition and internal readers of the same core lab, as well as managing images and data. The core lab should encourage and assist transmissions of studies and monitor potential deficiencies in data acquisition and analysis.

The main goal of the core lab is to ensure the best data accuracy by reducing measurement variability. This will overcome limitations of the reading in peripheral centers, and in particular limitations due to insufficient expertise for tasks required for a specific clinical study. In this view, the central reading of core labs should involve a practical minimum number of readers with excellent skills and experience, unlike in the peripheral centers where the readers are multiple and can have unverified experience. To further minimize reader variability, the inter-reader variability of core labs should be internally monitored periodically. Obviously, the core lab cannot eradicate all the sources of variability, but it can ensure that acquisition and measurement errors are controlled and do not occur randomly [7]. Core labs will also control and guarantee the data protection in the peripheral centers (Table 2).

Core lab will oversee that accuracy of echo-Doppler measurement and data interpretation complies with recently published ASE and EAE recommendations [8].

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Table 2. Steps to assure quality in echo trials

(i) Definition of imaging protocol	
Indications	Actions
Accuracy	Sample unselected cases from periphery
Reliability	
Reading variability	
Biological variability	
Instrumentation variability	
(ii) Quality assurance	
Standard operating procedures	Validation of facilities
	Verification of data format and quality
	Send recommendations to optimize image acquisition
(iii) Core lab implementation	
Overflow of images (% of uninterpretable images)	Internal reading
	Close interaction with Steering Committee

Conclusion

EURECA-m has the potential to provide relevant clinical information on cardiac disease in patients with ESRD on dialysis (either on haemodialysis or on peritoneal dialysis). The echocardiographic assessment based on a standardized, core lab led approach and the link of echocardiographic parameters to the rich clinical database of the EURECA-m registry represents a novel opportunity for European nephrologists to undertake observational and hopefully intervention studies of the highest standard, and to provide reliable answers to at least some of the many unsolved issues in this high risk population.

Conflict of interest statement. BL is employed by Baxter Healthcare Corporation. Other authors do not declare any conflict of interest.

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