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Study Protocol:

Comparative Effectiveness Study of Transthoracic and Transesophageal Echocardiography in Stroke (CONTEST)

Version 1.0 (16.01.2016)

Summary:

The Comparative Effectiveness Study of Transthoracic and Transesophageal Echocardiography in Stroke (CONTEST) aims at assessing the diagnostic value of transesophageal echocardiography (TEE) and transthoracic echocardiography (TTE) with regards to treatment consequences in patients with acute ischemic stroke. For this purpose, we will perform a prospective multicenter diagnostic comparative effectiveness study. Patients with acute stroke will be studied by both TTE and TEE. Patients with already defined stroke etiology and determined secondary prevention will be excluded from the trial. Treatment relevant diagnostic findings will be identified by a central endpoint adjudication committee. In order to demonstrate a hypothesized 2% absolute increase in the number of treatment relevant diagnostic findings by TEE as compared to TTE, 880 stroke patients will be enrolled in six German stroke centers. CONTEST will allow answering the question whether and for which group of stroke patients TEE is indicated in addition to TTE. By this, the study will provide evidence to guide justified recommendations for echocardiography in acute stroke patients.

Short Background

Cardioembolism is the second most important cause of stroke following large artery atherosclerosis (Grau et al., 2010). While atrial fibrillation (AF) represents the most frequent

cause of cardiac embolism, there are other cardiac causes of embolic stroke such as akinesia of the ventricular wall following myocardial infarction, left atrial or ventricular thrombus, endocarditis or rare findings like atrial myxoma and non-compaction cardiomyopathy. Thus, a thorough cardiac evaluation is an essential part of the diagnostic work-up of stroke patients. This usually includes echocardiography in a majority of patients, which can be done by either transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) with specific advantages and disadvantages of both techniques. Following expert opinion, it is obvious that TEE is indicated in special situations, e.g. in guiding cardioversion after short-term anticoagulation or in suspected endocarditis if TTE is negative (Pepi et al., 2010). Beyond that the additional diagnostic benefit of TEE in acute stroke is unclear, particularly given the fact that for most of the diagnostic findings that may be better detected by TEE no clear therapeutic recommendation can be given.

In the past years, several studies have tried to evaluate the diagnostic yield of TEE in acute stroke, but results are contradictory. In a sample of 824 stroke patients, in 95% of cases potential sources of cardiac embolism identified by TEE were also detected by TTE (Leung et al., 1995). Moreover, in the subgroup of 211 patients with sinus rhythm and normal TTE, TEE did not provide any findings that provided a clear indication for oral indication. In another study of 1.833 TEE examinations in stroke patients with sinus rhythm, in 3.4% of cases TEE findings leading to changes in treatment strategies for secondary prevention were reported (Cho et al., 2010). In a previous German study, TEE findings indicated oral anticoagulation in 8% of 212 stroke patients with undetermined etiology (Harloff et al., 2006). This, however, included only a single case with positive indication for oral anticoagulation (left atrial thrombus) while for all other cases the indication for oral anticoagulation is debatable (e.g. left atrial spontaneous echo contrast or reduced flow velocity).

National and international guidelines on acute stroke management do not provide clear recommendations as to the use of echocardiography in stroke patients. The latest guidelines form the European Stroke Organization (ESO) state that “Echocardiography is recommended in selected patients” (ESO, 2008). However, they do not provide any recommendation as to the choice of TTE or TEE. Guidelines on acute stroke management by the American Heart Association (AHA) do not mention echocardiography at all (Jauch et al., 2013).

To summarize, based on the currently available evidence it is completely unclear in which stroke patients, if at all, TEE is indicated. It is particularly unclear in how many cases TEE will yield diagnostic findings that result in a change in the treatment regimen for acute treatment or secondary prevention.

Aims and hypotheses

CONTEST aims at assessing the diagnostic value of TEE and TTE with regards to treatment consequences in patients with acute ischemic stroke. By this, CONTEST will allow answering the question whether and for which group of stroke patients TEE is indicated in addition to TTE. We hypothesize that TEE will provide significantly more treatment relevant diagnostic findings than TTE.

Study design and power calculation

Study design, study population, inclusion / exclusion criteria

CONTEST will be a prospective multicenter diagnostic comparative effectiveness study. Patients with acute stroke in whom echocardiography is indicated will be studied by TTE and TEE.

Main inclusion criteria are: (1) acute ischemic stroke or TIA, (2) age ≥18 years, (3) informed consent. Patients with already defined stroke etiology and determined secondary prevention treatment strategy prior to echocardiography (e.g. atrial fibrillation, carotid artery stenosis, cervical artery dissection) will be excluded.

Sample size calculation

We hypothesize that TEE will provide 5% treatment relevant diagnostic findings as compared to 3% for TTE, resulting in an absolute difference of 2% (with assumed 3% findings by TEE only, 1% findings by TTE only, and 2% findings by both TEE and TTE). In order to achieve 80% power to demonstrate this hypothesized effect using a two-sided McNemar test with alpha = 0.05, a sample of n=840 patients is needed. Accounting for ~5% possible drop-outs or incomplete data, we plan to enroll 880 stroke patients.

Methods

Study organization, participating sites

The study will be organized and coordinated by the Department of Neurology, University Medical Center Hamburg-Eppendorf (UKE) together with the General and Interventional Cardiology, University Heart Center Hamburg (UHZ). Patients will be enrolled in six German stroke centers. TTE and TEE will be performed according to a standardized protocol across all centers. Consecutive patients referred to the Stroke Unit of each center will be screened for enrollment during the course of the study.

Study coordination:

- PD Dr. Götz Thomalla, Dept. of Neurology, University Medical Center Hamburg-Eppendorf
- PD Dr. Renate Schnabel, General and Interventional Cardiology, University Heart Center Hamburg

Responsible biostatistician:

- Eik Vettorazzi, Department of Medical Biometry and Epidemiology (Chair: Prof. Dr. K. Wegscheider), University Medical Center Hamburg-Eppendorf

List of participating sites (Local Principal Investigator):

- University Medical Center Hamburg Eppendorf and University Heart Center (PD Dr. Götz Thomalla and PD Dr. Renate Schnabel)
- Albertinenkrankenhaus Hamburg (PD Dr. Michael Rosenkranz)
- Klinikum Pinneberg, Pinneberg (Prof. Dr. Max Nedelmann)
- Helios Klinikum Wuppertal (Prof. Dr. Stefan Isenmann)
- Kreiskliniken Reutlingen (Dr. med. Frank Andres)
- SRH Klinikum Karlsbad- Langensteinbach (Prof. Dr. med. Michael Fetter)

Endpoints and endpoint adjudication

Primary endpoint is the frequency of diagnostic findings that lead to a change in acute treatment or treatment for secondary prevention (e.g. surgery in case of myxoma, or oral anticoagulation in case of atrial thrombus). Treatment relevant diagnostic findings will be identified by a central endpoint adjudication committee comprising both cardiologists and neurologists. Secondary endpoints comprise the frequency of other major or minor risk factors for cardiac embolism detected by TTE or TEE.

Statistical analysis

Proportion of treatment relevant diagnostic findings will be compared between TTE and TEE using two-sided McNemar test with a significance level of 0.05.

Milestones / Timeline

Months	Major Actions	Milestones to be reached
M01-03	• Finalize study protocol • Ethics Committee submission • Set-up trial infrastructure	• Final study protocol • Ethics approval
M04-06	• Initiate participating centers • Enroll first patient • Start endpoint adjudication	• All centers initiated • First patient enrolled • 6-month progress report
M07-09	• Continue patient enrollment • Continue endpoint adjudication	• First 440 patients enrolled
M10-12	• Continue patient enrollment • Continue endpoint adjudication	• Endpoint adjudication completed for first 440 patients • 12-month progress report
M13-15	• Complete patient enrollment • Continue endpoint adjudication	• 880 patients enrolled
M16-18	• Complete endpoint adjudication • Statistical analysis • Preparation of publication of results	• Endpoint adjudication completed for all patients • Statistical analysis completed • Draft of publication of study results

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