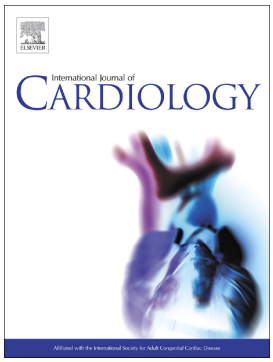

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Rationale and Design of a Multicenter, Randomized, Patients-blinded Two-Stage Clinical Trial on Effects of Endothelial Function Test in Patients with Non-obstructive Coronary Artery Disease (ENDOFIND)

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Abbreviations:

NOCAD: No obstructive coronary artery disease

Endo PAT: Endothelial peripheral arterial tonometry

MACE: Major adverse cardiovascular events

RHI: Reactive hyperemia index

Keywords: Peripheral Endothelial Function, Randomized Clinical Trial, Endothelial Function-guided Medical Therapy, Major Adverse Cardiovascular Events

Abstract

Abnormal peripheral and coronary endothelial function has been associated with increased risk of major adverse cardiovascular events (MACE) in cross-sectional retrospective and observational studies. However, prognostic value of routine clinical evaluation, diagnosis and treatment of endothelial dysfunction on incident MACE in patients with non-obstructive coronary artery disease (NOCAD) remains unknown. Endothelial Function Guided Management in Patients with NOCAD (ENDOFIND) is a multicenter, randomized, patients-blinded, parallel-controlled, two-stage clinical trial evaluating the impact of routine clinical peripheral endothelial function testing on initiation and/or intensification of cardiovascular preventive therapies in Stage I, and on the risk of MACE in Stage II in patients with NOCAD. One thousand participants with NOCAD on clinically indicated coronary computed tomography or invasive angiography will be enrolled and randomized 1:1, after baseline peripheral endothelial function evaluation to either endothelial function guided treatment group or standard of care control group. In Stage I, patients will be followed for 12 months and primary outcome will be the proportion of patients receiving prescriptions for cardiovascular evidence-based lipid, blood pressure and glucose lowering medications at the clinic visit immediately after endothelial function evaluation. Secondary outcomes are change in endothelial function measured as reactive hyperemia index and patients' adherence to evidence-based medications in 12 months. Study will be extended into Stage II where sample size and follow up duration will be reevaluated to ensure statistical power, and primary outcome will be incident MACE. ENDOFIND is proof-of-concept clinical trial of a disruptive endothelial function guided clinical intervention with potential benefits to NOCAD patients.

Condensed Abstract

ENDOFIND is a proof-of-concept clinical trial of a disruptive endothelial function guided clinical intervention with potential benefits to patients with no obstructive coronary artery disease (NOCAD). It is a multicenter, randomized, patients-blinded, parallel controlled two-stage clinical trial to evaluate the impact of routine clinical peripheral endothelial function testing on initiation and/or intensification of cardiovascular disease preventive therapies in Stage I, and on the risk of MACE in Stage II.

Background

Non-obstructive coronary artery disease (NOCAD), is used to describe patients with microvascular angina with no obstructive coronary artery disease (<50% stenosis) on coronary angiography[1]. Up to half of patients with signs and/or symptoms of stable ischemic heart disease have NOCAD[1-5]. Importantly, 10%-20% of the patients with NOCAD, who are a relatively young patient population, develop major adverse cardiovascular events (MACE) in five years [6] and 10%-17% of them would die in ten years[7]. Secondary prevention is helpful to improve the prognosis of NOCAD [8]. However, patients with NOCAD are significantly less likely to receive secondary prevention treatments compared to patients with obstructive coronary artery disease [9]. One-year lipid lowering medications use was 8-9% in patients with NOCAD and 34-39% in those with obstructive coronary artery disease, and one-year antihypertension medications use was 13- 15% and 30- 40%, respectively[6]. Whether initiation and/or intensification of secondary prevention by treating physicians is triggered by a diagnosis of endothelial dysfunction in patients NOCAD remains unknown.

Recent evidence demonstrated that two-thirds of patients with NOCAD had demonstrable coronary microvascular and endothelial dysfunction[1]. In patients with NOCAD, patients with endothelial dysfunction display increased risk of aggregate cardiovascular events [1,10]. Thus, endothelial function testing may be valuable for identification of NOCAD patients at higher risk of MACE [1,11-14]. Currently, many mature, regulatory approved and reliable measurement methods of peripheral endothelial function exist, one of which is Endo PAT 2000 (Endo PAT 2000, Itamar Medical) [15]. Compared with endothelial function test on coronary artery directly, endothelial function test by Endo PAT 2000 on peripheral vascular is less expensive, convenient, requires less expertise to perform and non-invasive, and thus had been used by more clinics and hospitals. Reactive hyperemia index (RHI) is calculated as a ratio of pulse wave amplitude after cuff release compared with that at the baseline by Endo PAT 2000. A main advantage of the RHI is that the contralateral arm serves as its internal control and this index is a validated marker for endothelial function[16-18]. In theory, an endothelial-function personalized guided change in doctors' cardiovascular preventive medications prescription can potentially improve the management of high-risk patients with NOCAD and reduce MACE. However, whether these early aggressive interventions,

compared to standard of care, result in MACE reduction in patients with NOCAD has never been studied before.

Overall Objective

The Endothelial Function Guided Management in Patients with Non-obstructive Coronary Artery Disease (ENDOFIND) trial is designed to answer two important unmet clinical questions; 1) Does addition of routine clinical endothelial function testing to standard of care, result in initiation and/or intensification of preventive lipid, blood pressure and glucose lowering medications by treating physicians?; and 2) Does an endothelial function-guided management of patients with NOCAD result in long term MACE reduction?

Hypotheses

Our hypothesis is that routine clinical adjunctive testing of peripheral endothelial function will result in initiation and/or intensification of secondary preventive medications by treating physicians, and that these early aggressive endothelial function-guided pharmacologic interventions will result in reduction of MACE in NOCAD patients.

Methods

Study design

ENDOFIND is a multicenter, randomized, patients-blinded, parallel controlled two-stage clinical trial. Stage I aims to evaluate the effects of introducing routine clinical endothelial function testing on the change in addressing risk factor modification by the prescription of secondary prevention medications among patients with NOCAD. If the results of Stage I are positive, the sample size and observation time will be further expanded in Stage II to evaluate the effect and the cost-effectiveness of the endothelial function-guided management strategy in reducing long term MACE in this patient population.

Patient population, Inclusion and Exclusion Criteria

Patients with NOCAD from inpatient or outpatient departments in 22 participating hospitals across China will be recruited by their site-specific responsible physicians. Inclusion criteria include: Inclusion criteria include: 18 years of age or older, able to sign informed consent, have chest pain or chest tightness, and <50% coronary artery stenosis on computed tomography angiography（CTA）or coronary angiography (CAG). Exclusion criteria include: Current participation in other interventional clinical trials in the past 6 months, left ventricular ejection fraction<50%, previous myocardial infarction or percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), known cerebral disease (including stroke, transient ischemic attack, prior cervical or cerebral artery revascularization surgery or percutaneous intervention), diagnosed with hyperthyroidism (TSH< 0.1 mU/L) or hypothyroidism(TSH> 10 mU/L), liver disease (hepatic jaundice, cirrhosis or liver failure), chronic kidney disease (eGFR<60 mL/min per 1.73 m2), diagnosed with serious infectious diseases, autoimmune diseases, malignant tumor; psychiatric or cognitive impairment that affects the collection of accurate information, or factors based on which the responsible physician deem the patient to be unsuitable for inclusion in this research such as non-local residents or life expectancy less than one year.

Baseline Demographics, Physical Examinations and Data Collection

Mobile phone application with electronic case report form will be developed, validated and used for data collection. Data collected at the baseline will include patients' demographics including date of birth, gender, education, occupation, and health insurance, lifestyles including tobacco smoking, alcohol drinking, diet pattern (food frequency), and time on sedentary life, medical history of hypertension, diabetes mellitus and hyperlipidemia, and current use of medications. Hypertension is defined as SBP≥140 mmHg or DBP≥90mmHg or current use of anti-hypertension medications. Diabetes mellitus is defined as either glycosylated hemoglobin (HbA1c) ≥6.5% or fasting plasma glucose (FPG) ≥126 mg/ dL (7.0 mmol/L) or 2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test; or currently taking blood glucose lowering medications or insulin. Hyperlipidemia includes the following: total cholesterol (TC) >200 mg/dL/(5.18 mmol/L); or low density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL (3.37 mmol/L); or high density lipoprotein cholesterol (HDL-C) <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.30

mmol/L) in women; or lipoprotein a >50 mg/dL (125 nmol/L), or persistent elevations of triglycerides (TG) ≥ 175 mg/dL (≥ 1.97 mmol/L); or currently receiving antilipidemic medications. The current medications use refers to statins, aspirin/clopidogrel, angiotensin converting enzyme inhibitors/angiotensin receptor blocker, β-receptor blocker, calcium channel blockers, insulin, hypoglycemic medicine, and nitrates. Baseline physical examinations will include measurements of blood pressure, heart rate, height, and weight. Baseline laboratory parameters to be collected include TC, LDL-C, TG, HDL-C, FPG, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood uric acid (BUA) and creatinine. Finally, baseline clinically indicated electrocardiograms, CTAs and/or CAGs will be reviewed and documented.

Following above routine clinical investigations, the responsible physician will determine eligibility of patients for participating in the study. Eligible patients willing to participate in the study will sign a written informed consent and will be referred for the non-invasive endothelial function testing prior to any medications changes. Non-invasive peripheral endothelial function will be assessed by reactive hyperemia index (RHI) using Endo PAT 2000 Machine (Itamar Medical Ltd, Caesarea, Israel) [15]. Endothelial function test will be administrated by an independent trained staff in a separate room (lab). The results will be entered immediately into the data management system. Patients will be kept blinded to the results and sent back to the referring physician for considerations of further prescription of medical treatments according to the RHI results that will be automatically fed back to the physician through the mobile phone application.

Randomization

Randomization will be done centrally and automatically by the computerized system which is built in the data management system. After the patient receives the endothelial function test, the Endo PAT report for patients who are allocated to the intervention group will be sent directly to the responsible physician via the mobile application. For patients who are allocated to the control group, no Endo PAT report will be received by the responsible physician. We will use permuted-block randomization, stratified by hospital, with a random size of blocks of 4, 6, and 8. Patients will be randomized in a 1:1 ratio into intervention group

and control group. Figure 1 depicts the study design.

Interventions

Prior to study's initiation, all participating physicians will receive a standard training on the management of patients with NOCAD and the interpretation of EndoPAT endothelial function test results, which is developed by the study steering committee and illustrated in Figures 2 and 3. Briefly, when reactive hyperemia index is <1.67 the following measures are recommended.

1) Start or reinforce lifestyle management including smoking cessation, physical exercise, dietary changes and sleep disorder treatment;

2) If the patient is not taking a statin, start a low dose statin. Otherwise increase the dose of the statin from low to moderate or moderate to high intensity;

4) Optimize blood pressure management (SBP <140 mmHg and DBP<90 mmHg) including use of an angiotensin converting enzyme inhibitor or angiotensin receptor blocker;

5) If the subject still has symptoms after 1 to 3 months, start calcium channel blocker;

6) Any other acceptable interventions that the physician considers to be suitable for potentially improving endothelial dysfunction including l-arginine, long-acting nitrates and/or enhanced external counterpulsation (EECP).

7) Regular glucose lowering treatment plus low-intensity statin will be used for patients with diabetes mellitus and aged 29-39 years; Regular glucose lowering treatment plus moderate-intensity statin will be used for patients with diabetes mellitus and aged 40-75 years but without other CVD risk factors; Regular glucose lowering treatment plus high-intensity statin will be used for patients with diabetes mellitus plus other CVD risk factors and aged 40-75 years.

The above recommendations were developed based on the current evidences on the management of patients with NOCAD[13,19-30], with the purpose to assist the participating

physicians to improve their management of patients with NOCAD with impaired endothelial function test results.

Intervention group: The Endo PAT test results will be sent to the responsible physician automatically by the computer system, after the randomization is made. Accordingly, the responsible physician will initiate and/or intensify preventive medical treatments.

Control group: The responsible physician will prescribe guidelines based standard of care medical treatments to patients without any adjunctive endothelial function test results sent from the data management system.

In both group, information on new or modified medical prescriptions and risk factors modifications should be entered in to the mobile application by the responsible physician.

Blinding

In both intervention and control groups, responsible physicians are not share with the patients the results of the endothelial function test nor if he/she have received the results report. Patients will be kept blinded to the randomization grouping and results of Endo PAT testing.

Follow-up

Patients will be followed up at 3, 6, and 12 months in stageIand annually in stage II. Data on current usage and prescription of medical treatments will be collected. Endothelial function will be re-tested at 12 months. Quality of life will be measured using EQ-5D at 12 months, and annually afterwards. Body weight, height, blood pressure, heart rate, fasting blood lipid, and glucose will be followed up at 12 and 36 months.

MACEs will be followed up at each visit, including all-cause mortality, cardiovascular death and non-fatal adverse cardiovascular events (defined as myocardial infarction, stroke or cardiovascular revascularization including PCI or CABG). An adjudication committee will review all events and confirm final diagnoses.

Cardiovascular events are defined, and will be evaluated, according to the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials report [31]. Cardiovascular death includes sudden death, fatal myocardial infarction, fatal stroke, death from heart failure or cardiogenic shock, and death from other cardiovascular causes (e.g. pulmonary embolism, aortic dissection, pericardial tamponade or cardiovascular operation-related reasons). Stroke includes both hemorrhagic and ischemic stroke but not TIA. Myocardial infarction is defined according to Third Universal Definition of Myocardial Infarction and based on 99th percentile values for biomarkers detection thresholds supported by aforementioned report.

Outcomes

The primary outcome for Stage I will be the proportion of patients whose medication treatment are intensified in comparison with the treatment before the intervention. The intensification include any addition in class or dosage in physician's prescription of statins, anti-hypertension medication, and glucose lowering medications or insulin except among patients with contraindications.

Secondary outcomes include the following: (1) The improvement in endothelial function (RHI) from the baseline to 12 months follow-up. (2) Improvement in cardiovascular risk factors (LDL-C) from the baseline to 12 months; (3) Percentage of patients using medication for lowering lipid, blood pressure, and glucose at 3, 6 and 12 months except among patients with contraindications; (4) Percentage of patients with healthy lifestyle (defined as non-smoking, time of sedentary activity decreasing at least 30 minutes or more , and a body mass index of < 25 kg/m2) at 3, 6 and 12 months;

The primary outcome for Stage II will be the incidence of MACE.

Sample size estimation

Stage 1 will recruit 1,000 participants, which will allow us to detect a moderate effect size of 10% in the primary outcome, with a statistical power of 89% and type one error at 5%. We assumed the proportion of patients with appropriately prescriptions in control group is 50%

according to the previous reports[32].

The sample size for Stage II will be reevaluated according to the results of Stage I.

Statistical analysis methods

Our primary analysis will follow the intention-to-treat principle. Patient characteristics will be described by treatment allocation. For dichotomous outcomes, logistic regression model will be used to estimate the overall intervention effect, adjusting for hospital clustering effect and possible imbalanced variables at baseline. We will also test if the intervention effect is modified by age, gender, cardiovascular risk factors and number of medications. For continuous outcomes, a mixed linear model with random slopes and random intercepts will be used. Random effects for hospitals will be incorporated. The treatment effect will be represented by an interaction between time and treatment group. Patient- and system-level factors that are thought of as clinically significant will be further adjusted for secondary analysis. Correlations between endothelial function and sleep disorders will be analyzed by multiple linear regression to adjust for age, gender and other confounding factors.

For MACE incidence during follow-up, we will use multivariate Cox regression models to test the difference between intervention groups, adjusting for hospital clustering effect and possible imbalanced variables at the baseline. We will also test if the intervention effect is modified by age, gender, cardiovascular risk factors and number of medications. In addition, the Kaplan-Meier curves will be plotted by treatment allocation, and log-rank test will be employed.

Ethical considerations

The intervention in this study included non-invasive tests and prescription of existing, commonly used, and evidence-based medications for prevention of cardiovascular disease. The risk for the participants should not be more than that in routine clinical practices and thus considered minimum. The data collected in the study will be entered and stored in a central computerized system with user name assigned centrally and passwords protected. Only de-identified data will be used for data analysis.

The study was approved by the Peking University Institutional Review Board (IRB00001052-19057), and a written informed consent will be obtained from all participants. The trial is registered on clinical trial.gov (NCT04013204).

Study management and quality control

The study was designed and will be managed under the leadership of the study steering committee, which reviewed and approved the research protocol, case record forms, and research reports. An independent clinical endpoint committee was established to objectively and independently review MACE. An independent central laboratory was set up in Beijing to measure endothelial function for the study evaluation. Before the study was initiated, all research personnel completed a half day research project training on the study protocol, the use of the mobile application, endothelial function test results interpretation as well as the recommended interventions.

We have taken several measures to mask the assessors from participants' group assignment. First, all baseline assessments will be performed prior to randomization. Second, the assessors of endothelial function will be an independent staff from the responsible physicians and will have no access to the randomization allocation.

Peking University Clinical Research Institute is responsible for the data management and project management of this trial. A web-based electronic data capture system was developed to assist data collection, randomization and participants allocation, data query and validation, follow up and remote data monitoring. Besides, site visits to each study center by a professional project management team will be done to monitor the protocol violations, data authenticity and research subject’s protection.

Study Status

The first participant was enrolled on 23 July 2019. Intervention and follow-ups are planned to be completed before the end of December 2022.

Discussion

To our knowledge, ENDOFIND is first randomized controlled trial worldwide to evaluate the effects of introducing non-invasive endothelial function testing into routine clinical practice on the prescription of evidence-based secondary prevention medications and the long-term risk of MACE among patients with NOCAD. The study supports and advances the concept of the need for disease base personalized medicine for the reduction of cardiovascular diseases.

The study has the following strengths. First, the central randomization is used to maximally reduce arbitrary recruitment allocation of study patients, and hence ensure the comparability between the study groups. Second, study subjects are blinded to the endothelial function test results. This will reduce the possibility of patients' self-treatments, including life style changes in the event of an abnormal endothelial function test, which may ultimately influence clinical outcomes. Third, endothelial function test results for patients in the control group will be not accessible to the responsible physicians. This will ensure that his/her medications prescriptions and management of control patients will not be influenced by his/her knowledge of endothelial function. Fourth, the specially designed web-based multi-function data management system helps ensure the implementation of central randomization, concealment of the allocation, blinding of patients towards endothelial function test results. Using this system, the endothelial function test results will be automatically fed back to the responsible physicians at the same clinic visit, reducing the time burden on both the patients and the physicians and greatly enhancing the efficiency and adherence to the study protocol. Fifth, a professional clinical research management team will assist the implementation of the study protocol. Sixth, an independent adjudication committee will be established for the diagnosis of MACEs. Finally, the two-stage study design allows for minimization of study resources to gain enough knowledge of the intervention before the resource-consuming large-scale randomized trial on long term clinical outcomes is initiated.

The study also has some limitations. First, due to the nature of the intervention, we are not able to blind the responsible physicians with respect to patient allocation. Theoretically, we cannot rule out the possibility that responsible physicians may change their prescriptions and intervention based just on patient allocation but not the test results. However, we believe

that this possibility should be very small. Second, there is not a clinical guideline at present on how to manage and risk stratify patients with NOCAD based on endothelial function test results. The recommendations made in our study are based on the current knowledge and literature regarding interventions that are effective in improving endothelial function as well as reducing the risk of adverse cardiovascular events. The intervention is multifaceted and has multifaceted effects. The best outcome to reflect all the multifaceted effects should be MACE, which requires a large sample size and longer follow up period. Our two-stage study design increases the feasibility of this trial and offers an adaptive design for stage 2 based on stage 1 results.

In summary, this study will address an unmet clinical need by providing high quality data on the value of introducing non-invasive endothelial function testing into routine clinical practice. In addition, the results of this trial will help us better understand the mechanism of the prognosis of patients with NOCAD and whether an endothelial function-based personalized management strategy can reduce MACE in this challenging patient population.

Disclosure

Dr. Lerman serves as an advisor for Itamar Medical. All other authors have no conflicts of interest to disclose and have approved the final article. The authors are solely responsible for the design and conduct of the study, data analysis, the drafting and editing of the manuscript, and its final contents.

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and technology plan project of Shijingshan district committee of science and technology (No Serial number).

Table 1. Time-line schedule of study

	Screening	Recruitment, randomization & intervention	Follow ups		
			Stage I		
	V1	V2	V3	V4	V5
	Day -14–0	Day 0[1]	3rd month ± 30 day	6th month ± 30 day	12th month ± 30 day
Informed consent & patients' recruitment		X			
Demographic data[2]		X			
Lifestyle (smoking, exercise, diet, etc.)		X	X	X	X
History of disease and medication use[3]	X		X	X	X
Blood pressure, weight & height	X				X
ECG, CTA & CAG[5]	X				
Bio chemistry[6]	X				X
Endo PAT		X			X
Randomization		X			
Intervention		X			
Follow on cardiovascular events[8]			X	X	X
Quality of life[9] (patients fill this in themselves)		X			X

*Notes:

1) Physical examination: blood pressure, heart rate, height, and body weight;
2) Blood biochemistry: TC, TG, HDL-C, LDL-C, FPG and HbA1c;
3) Cardiovascular and cerebrovascular events: all-cause mortality, cardiovascular death, nonfatal myocardial infarction, ischemia-driven revascularization, nonfatal stroke, and stent thrombosis.

4) Quality of life: using EQ-5D.

Figure 1 Title: Study design in Stage I

Figure 1 Legend: NOCAD: no obstructive coronary artery disease; CVD: Cardiovascular disease; MACE: major adverse cardiovascular events

Figure 2 Title: Statins Intensity

Figure 2 Legend: LDL-C, low density lipoprotein cholesterol

Figure 3 Title: Recommended clinical management based on peripheral endothelial function testing

Figure 3 Legend: RHI, reactive hyperemia index; ASCVD, atherosclerosis cardiovascular disease; LDL-C, low density lipoprotein cholesterol; Risk factors include: overweight (BMI ≥ 30kg / m2) or obesity (BMI ≥ 25kg / m2); type 2 diabetes; hyperlipidemia; hypertension; smoking; early family history of ASCVD (male < 55 years old; female < 65-year-old).

Reference

1. Shaw J, Anderson T. Coronary endothelial dysfunction in non-obstructive coronary artery disease: Risk, pathogenesis, diagnosis and therapy. Vascular medicine (London, England) 2016;21:146-55.

2. Lee BK, Lim HS, Fearon WF, et al. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. Circulation 2015;131:1054-60.

3. Humphries KH, Pu A, Gao M, Carere RG, Pilote L. Angina with "normal" coronary arteries: sex differences in outcomes. Am Heart J 2008;155:375-81.

4. Johnson LW, Krone R. Cardiac catheterization 1991: a report of the Registry of the Society for Cardiac Angiography and Interventions (SCA&I). Cathet Cardiovasc Diagn 1993;28:219-20.

5. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886-95.

6. Johnson BD, Shaw LJ, Pepine CJ, et al. Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: results from the NIH-NHLBI-sponsored Women's Ischaemia Syndrome Evaluation (WISE) study. European heart journal 2006;27:1408-15.

7. Kenkre TS, Malhotra P, Johnson BD, et al. Ten-Year Mortality in the WISE Study (Women's Ischemia Syndrome Evaluation). Circulation Cardiovascular quality and outcomes 2017;10.

8. Kissel CK, Nikolaou D. Cardiac Rehabilitation and Exercise Prescription in Symptomatic Patients with Non-Obstructive Coronary Artery Disease-a Systematic Review. Current treatment options in cardiovascular medicine 2018;20:78.

9. Paolisso P, Bergamaschi L, Saturi G, et al. Secondary Prevention Medical Therapy and Outcomes in Patients With Myocardial Infarction With Non-Obstructive Coronary Artery Disease. Front Pharmacol 2019;10:1606.

10. Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. Circulation 2002;106:653-8.

11. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation 2007;115:1285-95.

12. Martin BJ, Anderson TJ. Risk prediction in cardiovascular disease: the prognostic significance of endothelial dysfunction. Can J Cardiol 2009;25 Suppl A:15A-20A.

13. Versari D, Daghini E, Virdis A, Ghiadoni L, Taddei S. Endothelial dysfunction as a target for prevention of cardiovascular disease. Diabetes Care 2009;32 Suppl 2:S314-21.

14. Xu Y, Arora RC, Hiebert BM, et al. Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis. Eur Heart J Cardiovasc Imaging 2014;15:736-46.

15. Axtell AL, Gomari FA, Cooke JP. Assessing endothelial vasodilator function with the Endo-PAT 2000. Journal of visualized experiments : JoVE 2010.

16. Flammer AJ, Anderson T, Celermajer DS, et al. The assessment of endothelial function: from research into clinical practice. Circulation 2012;126:753-67.

17. Kuvin JT, Patel AR, Sliney KA, et al. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. American heart journal 2003;146:168-74.

18. Lavie P, Schnall RP, Sheffy J, Shlitner A. Peripheral vasoconstriction during REM sleep detected by a new plethysmographic method. Nat Med 2000;6:606.

19. Verma S, Anderson TJ. Fundamentals of endothelial function for the clinical cardiologist. Circulation 2002;105:546-9.

20. Atkeson A, Yeh SY, Malhotra A, Jelic S. Endothelial function in obstructive sleep apnea. Prog Cardiovasc Dis 2009;51:351-62.

21. Sorrentino SA, Besler C, Rohrer L, et al. Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy. Circulation 2010;121:110-22.

22. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 2003;23:168-75.

23. Clarkson P, Adams MR, Powe AJ, et al. Oral L-arginine improves endothelium-dependent dilation in hypercholesterolemic young adults. J Clin Invest 1996;97:1989-94.

24. Sidhu JS, Kaposzta Z, Markus HS, Kaski JC. Effect of rosiglitazone on common carotid intima-media thickness progression in coronary artery disease patients without diabetes mellitus. Arterioscler Thromb Vasc Biol 2004;24:930-4.

25. Verhaar MC, Honing ML, van Dam T, et al. Nifedipine improves endothelial function in hypercholesterolemia, independently of an effect on blood pressure or plasma lipids. Cardiovasc Res 1999;42:752-60.

26. Blum A, Shamburek R. The pleiotropic effects of statins on endothelial function, vascular inflammation, immunomodulation and thrombogenesis. Atherosclerosis 2009;203:325-30.

27. De Keulenaer GW, Segers VFM, Zannad F, Brutsaert DL. The future of pleiotropic therapy in heart failure. Lessons from the benefits of exercise training on endothelial function. Eur J Heart Fail 2017;19:603-14.

28. Joint Task Force for Guideline on the A, Management of Cardiovascular Risk in C. [Guideline on the assessment and management of cardiovascular risk in China]. Zhonghua Yu Fang Yi Xue Za Zhi 2019;53:13-35.

29. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;74:e177-e232.

30. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e285-e350.

31. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). J Am Coll Cardiol 2015;66(4):403-69.

32. Naue VM, Camargo G, Sabioni LR, et al. Changes in Medical Management after Coronary CT Angiography. Arq Bras Cardiol 2015;105:410-7.

Highlights

- ENDOFIND is a proof-of-concept clinical trial of a disruptive peripheral endothelial function guided clinical intervention with potential benefits to patients with no obstructive coronary artery disease (NOCAD).
- ENDOFIND is a multicenter, randomized, patients-blinded, parallel controlled two-stage clinical trial.
- It evaluates the impact of routine clinical peripheral endothelial function testing on initiation and/or intensification of cardiovascular disease preventive therapies in Stage I, and on the risk of MACE in Stage II