Executive Summary:

The main purpose of the EVINCI-STUDY was to test the impact of combined anatomo-functional non invasive cardiac imaging for detection and characterization of Ischemic Heart Disease (IHD). The EVINCI-STUDY was a prospective clinical European multicenter trial performed in a cohort of 697 patients with suspected IHD. Patients with intermediate pre-test probability underwent clinical and biohumoral characterization, including novel circulating markers of cardiovascular risk.

They were admitted to a non-invasive cardiac evaluation, consisting of anatomic imaging, by multislice computerized tomography, combined with functional tests among radionuclide, magnetic resonance and ultrasound imaging. Heart catheterization was performed to validate non-invasive diagnosis and follow-up to assess outcome. The diagnostic accuracy of combined non-invasive anatomo-functional imaging was tested against reference methods for diagnosing epicardial coronary lesions (coronary angiography), vessel wall atherosclerosis (computerized tomography) and impaired coronary flow reserve (pressure wire). The individual profiles from anatomo-functional cardiac imaging and clinical-biohumoral data were combined and tested against outcome. A cost-benefit analysis (including an estimate of procedural/radiological risks) of the new diagnostic work-up was also be performed.

A relevant part of the EVINCI-STUDY was dedicated to the development of an advanced informatics platform able to synthetically present to the end-user (patients, physicians, etc.) the integrated diagnostic profile of the individual patient as resulting from clinical-biohumoral and multi-imaging assessment. Overall results were disseminated in cooperation with the European Society of Cardiology (ESC) and will guide the work of a dedicated ESC Commission which will release specific European Recommendations.

Project Context and Objectives:

In Europe the mortality due to cardiovascular diseases has progressively increased up to the last 20 years, when mortality flattened and then tended to decline. It has been estimated that 42% of the decrease in cardiovascular mortality can be ascribed to new medical and interventional treatments (including secondary prevention, treatment of heart failure and acute myocardial infarction), while 58% can be ascribed to a reduction in some cardiovascular risk factors (as smoking cessation, improved blood pressure control and cholesterol reduction). While cardiovascular mortality rates, adjusted for age, continue to decline, the crude mortality rates remain approximately stable in most western European countries and even increase in most eastern countries. Hence, due to the ageing of the population, cardiovascular disease is still the major cause of death across Europe and a major cause of morbidity and loss of quality of life. In particular, with the diffusion of new risk factors (physical inactivity, diabetes mellitus and obesity), the prevalence of ischemic heart disease (IHD), the most frequent among cardiovascular diseases, is actually increasing. Accordingly, better prevention and management of IHD is needed to further reduce early cardiovascular mortality and morbidity and to improve life expectancy and quality of life.

Further achievements in the fight against cardiovascular diseases could be obtained by developing and testing new strategies for the early detection and better characterization of IHD. These strategies should be based on non-invasive methods, should be cost-effective and ready for large scale clinical utilization in the next few years and should allow to identify new reliable end-points for prevention and treatment.

At present, invasive coronary arteriography (ICA) is widely considered the gold standard for the detection and characterization of IHD. However, ICA is not faultless. First of all it focuses on one specific anatomical feature of the disease, i.e. on the changes in coronary lumen caused by abnormalities in the wall of epicardial coronary arteries, but not on its functional correlates, namely the effect on myocardial perfusion and contraction. In addition, ICA has a limited sensitivity when compared to necropsy studies, where a significant gap was documented between the small number of angiographically visible lesions and the large number of occult plaques. Furthermore, ICA does not allow to detect the early stages of coronary atherosclerosis and to study coronary microcirculation, increasingly recognized as independent determinants of impaired blood flow, disease progression and adverse prognosis and hence potential targets of early treatment. Further limitations of ICA are related to its cost and to procedural risks that prevent its utilization on a large scale in patients with intermediate-low pre-test probability of the disease.

The structure of the coronary arterial wall can be accurately studied by intra-vascular ultrasound (IVUS). This method is more sensitive than ICA in detecting early coronary atherosclerosis that can be found also at angiographically normal sites; furthermore IVUS provides information on coronary remodeling and extraluminal plaques. The functional significance of coronary lesions can be assessed by intra-coronary Doppler flow and pressure wires. When angiographic data were compared with the methods for functional assessment, only 36% of patients with angiographically normal coronary arteries were completely normal. However, both IVUS and intra-coronary Doppler flow and pressure wires are again invasive, expensive and not routinely utilized.

Some of the limitations of ICA could be overcome by angiographic computed tomography of the coronary arteries (CTA), as it is non-invasive and enables the evaluation of both epicardial coronary lumen and arterial wall. The advantages of non-invasive coronary arteriography also carry some risks, mainly related to radiation exposure and to the contrast medium itself. Additionally, an intrinsic risk exists that a wide utilization of CTA, not supported by information on the functional significance of coronary lesions, could lead to an increase in the number of inappropriate invasive imaging procedures and even of unnecessary coronary interventions.

Several non-invasive functional tests, based on radionuclide (SPECT and PET), ultrasound (ECHO) or magnetic resonance imaging (MRI) methods, allow studying the functional correlates of coronary lesions. These techniques focus either on hemodynamic relevance (perfusion) or mechanical relevance (wall motion and contractility) of coronary stenoses. At present these functional tests and CTA can be utilized as gate-keepers to ICA. Recent surveys of the European Society of Cardiology have shown that non-invasive functional tests are under-utilized, with wide variability between different countries, so that several patients without significant IHD directly undergo ICA, as indirectly demonstrated by the large proportion of patients who do not receive any revascularization after ICA. On the other hand coronary lesions detected by ICA are often revascularized even if no demonstration that they affect either myocardial blood supply or mechanical function is provided.

We hypothesized that combining the anatomical information provided by CTA with the functional information provided by non-invasive tests could allow to early detect and better characterize the patients with suspected IHD. Since different non-invasive modalities provide different information, an integrated approach could improve our understanding of IHD, and could optimize patient management and utilization of health resources. Specifically, the number of invasive imaging procedures, the number of inappropriate revascularizations, and health costs due to inappropriate management could be reduced. Moreover, the recognition of patients with early disease could promote new prevention and early treatment programs. A possible risk of this approach could be an over-utilization and duplication of costly technologies. Accordingly, there is an urgent need to perform an intermodality comparison and to evaluate new integrated non-invasive diagnostic strategies for accuracy and cost-effectiveness against reference methods and patient outcome.

For the above reasons the European Society of Cardiology and its Working Group of Nuclear Cardiology and Cardiac CT endorsed the application of the EVINCI-study. The EVINCI-STUDY was a prospective, clinical, multi-centre, European trial in patients with suspected IHD. Patients with intermediate pre-test probability of the disease, defined after routine clinical screening including stress ECG, and fulfilling inclusion and exclusion criteria, were enrolled. They underwent laboratory characterization and non-invasive cardiac evaluation, consisting of anatomic coronary imaging by CTA, combined with functional imaging by radionuclide, ultrasound or magnetic resonance modalities. Subsequently, coronary arteriography, including invasive functional measurements, were performed to validate non-invasive diagnosis. Follow-up data were collected in each patient. A cost-benefit analysis of the new diagnostic work-up (including an estimate of procedural/radiological risks) was also performed. Furthermore, an advanced informatics platform, able to synthetically present to the end-user the integrated information, was developed. The study results were disseminated in cooperation with the European Society of Cardiology.

Main purpose of the study was to test the impact of a combined non invasive, anatomo-functional cardiac imaging strategy on the detection and management of IHD. Specific objectives were, in details:

Objective 1: To test the accuracy of anatomo-functional non-invasive cardiac imaging in the diagnosis of IHD. To this purpose the anatomic information provided by CTA was combined in every patient with the functional information provided by radionuclide cardiac imaging (SPECT or PET) to assess the relevance of coronary disease by its effects on myocardial perfusion. Additionally, MRI or ECHO imaging was performed to assess the relevance of coronary disease by its effects on myocardial contraction.

Non-invasive results were tested against invasive reference standards. The latter consisted of ICA integrated by intra-coronary pressure wire (to assess the hemodynamic relevance of coronary stenoses), by IVUS (to detect early coronary artherosclerosis) and by Doppler flow wire (to recognize microvascular dysfunction) whenever appropriate.

Objective 2 To evaluate the association of risk profiles assessed from clinical data and biomarkers with anatomo-functional patient characterization and outcome. To reach this goal the clinical characterization of patients (collected before non-invasive imaging) and the laboratory characterization (that included novel biomarkers of cardiovascular risk) were compared with patient characterization derived from anatomo-functional imaging and with patient outcome during the follow-up.

Objective 3 To develop an advanced clinical and imaging reporting and integrated decision making tool in cardiology. An informatics platform was developed to synthetically and clearly present the integrated clinical and imaging diagnostic profile of individual patients. Specialized clinical decision making tools were part of the platforms based on image fusion of different imaging modalities (CT, SPECT, PET, MRI) and their integrated analysis with other clinical data. The tools targeted both researchers and physicians and would speed-up the deployment of the novel results obtained within EVINCI-study, and similar future studies, to clinicians at the point of care.

Objective 4: To define the most cost-effective work-up for the diagnosis and characterization of IHD. To this purpose the costs and the procedural risks (including radiation exposure) of non-invasive and invasive diagnostic procedures were prospectively collected. Cost-benefit and cost-effectiveness analyses were conducted alongside the EVINCI-study clinical trial.

Project Results:

The EVINCI-STUDY enrolled 697 patients with chronic chest pain and intermediate probability of having CAD based on Diamond & Forrester scale modified after exercise ECG. Data collection was concluded on 15 June 2012. This kind of patients, selected from 17 clinical centers in Europe, are currently referred directly to invasive coronary angiography. In the EVINCI protocol, by contrast, they were submitted to integrated non-invasive diagnostic testing largely based on cardiac imaging. After non-invasive screening, only patients with positive tests underwent heart catheterization (coronary angiography and invasive functional measurements when appropriate) as a reference method to define the presence and extent of functionally significant obstructive CAD (i.e. coronary disease potentially causing ischemia and usually treated by myocardial revascularization). Specifically the primary end-point was defined by the evidence of > 70% stenosis in at least one major coronary vessel at invasive coronary angiography or < 70% stenosis with impaired fractional flow reserve measured by intracoronary pressure wire. The different non-invasive strategies were compared for their diagnostic accuracy, and the costs and potential risks were monitored. This study design is in line with the push to perform comparative effectiveness research in Europe.

To assess the ability of non-invasive multimodality imaging to diagnose the presence of functionally significant obstructive CAD in the single patient, in order to properly address invasive coronary study and revascularization (when appropriate) to improve prognosis and quality of life, non-invasive imaging tests were chosen which would assess both coronary anatomic abnormalities and their functional effects. In each patient, coronary anatomy was assessed using multi-slice CT. Radionuclide imaging (either SPECT or PET) was used to measure myocardial perfusion at rest and during stress. The effects of myocardial ischaemia on ventricular function were assessed by either magnetic resonance imaging or echocardiography during stress.

The analysis performed so far in the 478 (over 697) patients (61% males, 60 ± 9 yrs) who completed the whole protocol, shows that the probability of significant CAD, based on clinical and stress electrocardiogram (ECG) evaluation, was largely overestimated. In fact, the average estimated probability of disease in the EVINCI population prior to non-invasive imaging testing was 59.2% while the actual prevalence of significant obstructive coronary disease, confirmed at heart catheterization (primary end-point) was 26.2%. According to these results, the EVINCI study suggests that the true prevalence of significant CAD in patients with stable angina is not adequately predicted by current models based on clinical and stress ECG data. In these patients, an adequate redefinition of probability based on new predictive models including biohumoral markers and non-invasive imaging screening could be able to avoid invasive procedures in up to 75 out of 100 patients. This approach could reduce costs, risks, and enable patients who are truly at risk to be effectively treated.

The EVINCI-STUDY was designed to first assess whether adding biohumoral markers to common clinical and ECG data would improve the estimate of the probability of significant CAD. Thus, as much as 35 different biomarkers were evaluated and added to available scores such as the Duke score including clinical risk factors ad stress ECG results. These models were tested for their accuracy to predict the presence of functionally significant obstructive CAD at ICA (Primary end-point). The results of this analysis show that five biomarkers are independent predictors of primary end-point. They express either metabolic profile (HDL cholesterol, HOMA index or aspartate transaminase) or inflammatory status (Interleukine-6 or

Osteopontin). Models adding all or some of these biomarkers to the Duke Score showed an improvement of diagnostic accuracy from 66% to 72-74% (P<0.001).

Indeed, the EVINCI study was centered on anatomo-functional cardiovascular imaging. The study turned out to be successful in the difficult task to get a sufficient number of patients to adequately compare different anatomo-functional non-invasive imaging strategies for their accuracy to diagnose the presence of functionally significant obstructive CAD as confirmed at ICA (Primary end-point).

There was sufficient power to compare either CTA vs SPECT or ECHO, and CTA vs nuclear modalities (SPECT or PET) or non nuclear modalities (Echo or MR). The number of patients submitted to PET or MR were not enough to assess the accuracy of these modalities alone. As expected, there were obvious differences among different stress modalities being perfusion nuclear imaging more sensitive but less specific than non nuclear imaging which is based on ischemia-induced wall motion abnormalities. Nevertheless, the final accuracy was very similar for all stress imaging. The novel result of the EVINCI study is the clear demonstration of the superiority of CTA for diagnosing the presence of obstructive CAD in this specific population of patients with intermediate-low prevalence of disease.

The EVINCI-STUDY however, was specifically designed to assess the value of anatomo-functional combinations over single stress modalities and against Primary End-Point. Not all comparisons turned out to have enough statistical power. There was sufficient power to compare CTA+SPECT, CTA+ECHO, CTA+SPECT/PET and CTA+ECHO/MR vs respective stress modalities without CTA. Anatomo-functional combinations with nuclear perfusion imaging were significantly more accurate than stress perfusion modalities alone. On the other hand, combining CTA with ECHO did not show significant improvements in accuracy as compared with ECHO alone. Moreover, while a significant difference was demonstrated for CTA+ECHO/MR vs ECHO/MR alone, the power for this comparison was lower than 80%. Moreover, when combinations including nuclear stress imaging were compared with combinations including non-nuclear stress imaging, the former were always more accurate.

In conclusion, the results of the EVINCI Study demonstrated that, in patients with suspected CAD and intermediate-low probability of disease,

1. CTA is the most accurate imaging modality for diagnosing the Primary End-Point.
2. There is no significant difference among different stress modalities (which preserve their know characteristics in opposite sensitivity and specificity).
3. Combination of CTA with perfusion nuclear imaging improves diagnostic accuracy of the non-invasive stress perfusion imaging alone.
4. Combinations of CTA with nuclear stress imaging were more accurate than combinations of CTA with non-nuclear stress imaging.

A second objective (Secondary End-point) of the study was to assess whether multimodal non-invasive cardiac imaging is able to characterize the coronary disease in the single patient as defined by four different clinical categories: 1) functionally significant obstructive CAD deserving revascularization; 2) non functionally significant CAD; 3) microvascular CAD; 4) No disease. Available data in the literature suggested that only patients with a functionally significant obstructive coronary disease (Category 1) should be revascularized. Accordingly, only these patients, whether identified before heart catheterization, should be addressed to

invasive procedures to confirm the indication. Nevertheless, both patients with atherosclerotic coronary disease without functional abnormalities (Category 2) or functional abnormalities of the coronary circulation without significant atherosclerosis (Category 3) are at prognostic risk and should be treated aggressively with drugs able to reduce atherosclerosis progression or improve coronary microcirculatory function, respectively. Patients with neither abnormalities (Category 4) should be reassured and should avoid any further testing.

The analysis performed so far in the 478 patients who completed the whole protocol, shows that 47.9% of the whole population had no disease (Category 4). Non-invasive evidence of functionally significant obstructive CAD was present in 26.1% (Category 1) and confirmed at ICA in the majority of these cases (19%). In the remaining 26% of patients (Category 2 or 3) only 6.5% had significant obstructive CAD at ICA and in only 1.3% there was also evidence of ischemia. These figures differed somewhat according to the modalities used.

Taken together these results suggest that a non-invasive multimodal anatomo-functional imaging approach is able to reliably characterize patients with stable angina and intermediate pre-test probability of CAD, indicating invasive testing in only 26.1%. These patients will show significant obstructive coronary disease at ICA that was revascularized in the majority of cases (19%) in the EVINCI study. On the other end, among the 73.9% of patients without indication to invasive study after non-invasive anatomo-functional screening only 7.1% would have shown an obstructive disease at ICA.

In summary among 100 patients commonly referred to coronary angiography we would spare 66.8 unuseful invasive studies, indicating 19% of appropriate revascularizations. We would perform only 7.1% of unuseful catheterizations and we would lose 7.1% of possible revascularizations. These general figures are substantially different according to the stress modalities combined with CTA or for CTA alone.

Among the 478 patients who completed the whole EVINCI protocol, 445 completed follow-up visits and were included in the Outcome study analysis. The EVINCI study was not designed to evaluate the impact of different biohumoral and imaging strategies on long-term prognosis. Only cardiovascular events occurring in a short term follow-up (from 30 to 400 days) were recorded. Cardiac death, non-fatal myocardial infarction, hospitalization for unstable angina or heart failure, and recurrent angina were considered major events (MACE). Myocardial revascularization was considered only if occurring after > 30 days from invasive coronary angiography and completion of the EVINCI protocol.

In a mean Follow-up time of 183 days, 16 MACE and 47 Revascularizations occurred (23 CABG and 24 PCI).

The presence of functionally significant obstructive CAD at ICA (Primary End-Point, CAD) significantly predicted survival free of both MACE (P = 0.016) and survival free of the combination of MACE and revascularization during follow-up.

We tested the hypothesis that also the 4 non-invasive anatomo-functional diagnostic categories could discriminate the risk of cardiovascular events. Patients showing positive CTA and positivity of one stress imaging test (Category IV) had a significantly higher risk of MACE than all the other patients taken together (P=0.035).

Including revascularizations as events, the four categories could be analysed separately. The first analysis was performed combining CTA with stress imaging (irrespective of modalities). Patients in category IV had the worst event-free survival, patients in Category III-II had an intermediate survival while patients in Category I had the best event-free survival.

When the analysis was repeated combining CTA either with Echo/MR or with SPECT/PET again patients in Category IV had the highest risk.

Accordingly, the discriminatory power of CTA alone for predicting cardiovascular events was significantly improved by adding stress imaging results (Harrel's C from 63% to 66%, P< 0.02), being not significantly different from the discriminatory power of ICA (Harrel's C 69%, ns).

Taken together the results of the outcome analysis of the EVINCI data demonstrate that a combined anatomo-functional non-invasive screening of patients with stable chest pain and intermediate probability of CAD, has not only the capability of avoiding unnecessary invasive procedures and selecting patients with high probability who need revascularization, but also provides information on the risk of cardiovascular events. MACE is more frequent in patients with positivity of both CTA and stress tests. Similarly the risk of MACE and successive revascularizations is best predicted by a combined positivity of anatomo-functional imaging, irrespective of the modality of stress test used. These results will probably have a high impact on future clinical use of cardiovascular imaging in patients with suspected IHD.

A huge European digital bank for multimodal cardiovascular imaging and a biological bank for blood samples were created throughout the study and will be relevant repositories of raw imaging data and biological samples to be considered for future studies and educational purposes.

One major output of the EVINCI-STUDY was the definition of a panel of simple biomarkers which could be combined in new diagnostic integrated device to be exploited by the industry as a new widely available tool for the screening of patients with suspected CAD prior to or together with cardiovascular imaging assessment.

A second major output of the EVINCI-STUDY was the implementation of a Multimodal Report (MMR) able to present to the final user (patients, physicians, imaging experts, etc.) the single and integrated information coming from clinical, biohumoral and multi-modal imaging data acquired in the single patient. MMR has the potential to be exploited by the industry as a novel aid to clinical diagnosis mainly based on imaging.

Based on the previous result, the EVINCI-STUDY generated a new web based tool for disseminating the design and approach of the EVINCI study and for training young cardiologists in the appropriate and more effective use of imaging tests for diagnosing ischaemic heart disease. This tool (EduCAD) is based on validated clinical cases selected from the EVINCI study. It is available at http://www.escardio.org/.

A detailed description of the S&T results for each WP is given below.

WP 0 Diagnostic Work-up and Follow-up

Start month: 3

End Month: 42

WP leader: P1 CNR

Task 0.1 Implementation of standardized procedures

Standardized procedures for patients enrolment, diagnostic work-up, follow-up and for transmission of data and materials have been implemented throughout the Consortium. Standard Operative Procedure (SOPs) have been produced and delivered to the European Commission. SOPs have been completed with 9 different Case Report Forms (CRFs) which allow to collect all relevant data gathered from clinical evaluation, blood sampling, health economics questionnaires, non-invasive and invasive imaging studies and follow-up.

Frameworks to allow generation of all clinical, biological and imaging raw data needed for the study have been established in the clinical centers participating to the Consortium.

Task 0.2 Enrolment, diagnostic work up and treatment

The enrolment of 697 patients eligible has been completed for the study and their clinical data and blood samples for centralized analysis of biomarkers were collected. According to the design of the study an adequate statistic power for each of the hypothesis to be tested has been achieved.

We performed non-invasive multimodality imaging by CTA combined with perfusion (SPECT or PET) and/or contraction (ECHO or MRI) stress imaging in an adequate number of patients.

Complete data of the patients who underwent analyses are available in the EVINCI Data-Base allowing analysis of the major end-points of the study. One of the main results of the EVINCI-STUDY is that current predictive models of CAD largely overestimate (almost double) the actual prevalence of significant disease in a large European population of patients with stable angina.

Invasive anatomic imaging by ICA in patients has been completed with at least one non-invasive test positive, and has been performed intracoronary measurements of FFR by pressure wire wherever appropriate.

Task 0.3 Follow-up

We obtained a complete follow-up of patients at 1 month from enrolment and every 6 months in an adequate number of subjects.

Among the 478 pts who completed the whole EVINCI protocol, 445 were submitted to follow-up visits and were included in the Outcome study analysis. They constitute 63.8% of the whole population of enrolled patients again very close to the predicted 70% (M 0.3).

WP 1 Clinical Profiles, Biomarkers and IHD prediction model

Start month: 1

End Month: 36

WP leader: P1 CNR

Task 1.1 Standardization of clinical data, blood samples and parameters to be analyse

Standardization of the procedures for collection of relevant clinical data and definition of Clinical CRFs has been obtained.

In order to standardize the procedure for collection of clinical data, a Clinical CRF has been defined which allows to collect patients clinical data needed at the Selection Visit and at Follow-up Visits.

To standardize the procedure for collection of biological samples, a Blood CRF has been defined, containing the detailed procedure for blood sample withdrawn, pre-analytical treatment, storage and shipment to P1-CNR.

Task 1.2 Biological bank

Collection, cataloguing, and definitive cryoconservation of biological samples at the Biological Bank of P1-CNR was performed in 89% of enrolled patients. The Biological Bank of P1-CNR is an operational facility for the collection, conservation, and management of biological samples, with sampling procedures that are standardized. The ID number associated to the single patient by the Central Server also labels the biological samples.

Task 1.3 Central biohumoral analysis

The biological variables chosen in the EVINCI-STUDY include the main indicators of the metabolic and inflammatory individual profiles, as well as specific markers of cardiovascular damage.

A complete analysis has been performed in all available samples, thus the 82% of the overall EVINCI patient population had a completed biohumoral profile obtained by the centralized analysis of laboratory data.

Collection, cataloguing, and definitive cryoconservation of biological samples at the Biological Bank of P1-CNR was performed in 89% of enrolled patients.

Task 1.4 Diagnostic predictive model based on clinical profiles and biomarkers.

Three functional end point have been defined:

The primary endpoint has been defined as presence of stenosis >70% at invasive coronary angiography or 30-70% and FFR<0.8 in a main vessel. A predictive model of primary endpoint has been set-up using clinical variables including patients' characteristics, symptoms, cardiovascular risk factors, disease probability and medical therapy.

Second predictive model has been developed using an Anatomic End-Point based on the results from non-invasive imaging, defined as presence of stenosis >50% at CTA.

A third Functional End-Point has been developed and is based on the presence of ischemia, as detected by at least one non-invasive imaging stress test.

Integrated predictive models of disease, based on clinical and biohumoral characterization of EVINCI patients, were demonstrated to be superior to current models.

The standardized procedures allowed to create reliable and useful methods to save and store biological sample and clinical as well biohumoral data that could be useful for further and additional sub-studies. After its further validation, the novel diagnostic model based on combined clinical, biomarkers and imaging data could be useful in clinical setting and industrially exploited.

WP 2 Non-Invasive Anatomical Assessment of CAD by CT Imaging

Start month: 1

End Month: 36

WP Leader: P4 LUMC

Task 2.1 Standardization of exams procedures and parameters to be analysed

SOPs for CT acquisitions and for CT analysis have been developed. The relevant parameters have been defined and entered by both the participating centers and the core lab into the Central Database. More specifically, CT examinations were quantitatively analyzed during post-processing and analysis. A 17-segment model was used to evaluate the extent of anatomic disease. First the presence of atherosclerosis was determined in each segment. Then, a 5-point scoring system was used for each segment to express stenosis severity. This extensive quantitative scoring method was evaluated against the invasive reference methods.

Task 2.2 Central CT imaging analysis

Quality control of CTA studies in active centers has been performed in the Core Lab. The CT-core-lab analyzed 571 CT examinations.

After start of the inclusion patients by the participating centers, original anonymised DICOM data were collected in a Central Digital Bank. The data sets were then further analyzed and reconstructed. The axial data sets have been reviewed and the appropriate phases for the different coronary arteries have been selected. Coronary calcium scoring was performed with the application of dedicated software. Agatston calcium scores were obtained per coronary artery and per patient. For all CTA images, quality was scored using a 4 point scale (good, moderate, poor or uninterpretable). Subsequently, curved multiplanar reformatations in different angulations were obtained for all coronary arteries and side-branches. The processed data for the almost 600 CT angiography studies have been read.

In total 571 CTA studies were analyzed. CA-score scans were available in 410 patients. In total, 198 scans were scored good quality, 191 moderate and 117 poor quality. A right-dominant coronary artery system was observed in 439(86%) patients, 47(9%) had a left-dominant system and 22 (4%) patients a co-dominant system. 24 patients demonstrated an anomalous coronary ostium.

A total of 189 patients presented with a significant stenosis (>50%). In these patients, 336 vessels contained a significant stenosis. 16% of patients had 1-vessel disease, 9% of patients had 2-vessel disease and 6% of patients presented with 3-vessel disease.

The right coronary arteries contained a significant stenosis in 87 patients. In 20 patients the left main was significantly diseased. In 142 patients a significant stenosis was present in the left descending arteries. 87 patients had a circumflex lesion.

A comparison was made between CTA stenosis and invasive coronary angiography. From this diagnostic accuracy was calculated. The results of accuracy for the centers were: Sensitivity = 91%, Specificity = 82%,Positive Predictive Value = 67%, Negative Predictive Value = 96%.

Task 2.3 Comprehensive assessment of "anatomic" coronary disease by CT (P4-LUMC) (months 19 - 42)

CTA studies were analyzed to assess stenosis degree. A plaque was classified as <30%, 30-50%, 50-70%, 70-90% or >90%. A stenosis of >50% was considered significant. Coronary segments were labeled according the AHA 17 segment model. If a segment was deemed uninterpretable, this was mentioned in the comment section of the CRF. The coronary ostia were assessed to check for anomalies. Additional non-coronary findings (calcium in valves, abnormalities etc.) were reported in the CRF.

In summary per study the following parameters were analyzed and entered in the CRF:

- Ca-score (per vessels and per patient)
- Image quality
- Coronary ostia

- Stenosis degree per segment (AHA 17 segment model)
- Additional non-coronary findings

In addition to the diagnostic accuracy reading, the CTA studies were evaluated for plaque characterization, both visually and quantitatively.

WP3 Non-Invasive Functional Assessment of IHD by Stress Imaging

Start month: 1

End Month: 36

WP leader: P1 CNR

Task 3.1 Standardization of exams procedures and parameters to be analysed (months 1 -2)

Standardized procedures for imaging acquisition protocols including: scanning parameters, stress protocols, data acquisition and storage, minimization of radiation dose (when applicable) as well as transferring process to the respective core labs have been developed.

Standardized procedures for imaging analysis have been also developed to allow extraction of complete state of the art parameters from each modality to be entered into the Central Database. These activities resulted in SOPs and CRFs for each imaging modality which have been implemented by the participating centers.

Task 3.2 Central SPECT imaging analysis (P8-RBHT) (months 7 - 36)

MPS stress and image acquisition processing and analysis was agreed to be according to procedure guidelines published on behalf of the EANM and ESC.

Anonymised planar projection images were downloaded in DICOM from the database. Local site reconstructions were also downloaded but these were not used for core lab analysis. The planar raw data was reconstructed by the core lab using iterative techniques.

Core lab reconstructed tomograms were viewed in the software packages QPS and QGS (Cedars Sinai Medical Center) by a single experienced observer (SRU) using a dedicated workstation (Hermes Medical Systems). Information on patient age, gender, height and weight were available together with the nature of presenting symptoms (typical angina, atypical angina, non-anginal chest pain) and information on the stress procedure. No other clinical information was routinely available and so core lab reporting was mainly blind to usual clinical information. The following parameters were recorded.

For stress and rest studies individually:

- Overall image quality (Q score: 3 excellent, 2 good, 1 fair, 0 poor)

- Artifact scores for motion, low count, reconstruction and attenuation (M, C, R & A scores, 0 absent, 1 mild, 2 moderate, 3 severe)
- Segmental defect scores using a 17 segment model (0 normal, 1 mild, 2 moderate, 3 severe, 4 absent activity). From the segmental scores, summed stress, rest and difference scores were derived (SSS, SRS, SDS). A unique feature of this analysis compared with other published scores is that the defect scores were judged by the reporter and not by automated quantification. Thus, summed defect scores >0 were considered abnormal.
- Left ventricular end diastolic volume and ejection fraction (LVEDV & LVEF)

For the study as a whole:

- Overall study report (normal, reversible, fixed, mixed)
- Confidence score in this report (3 excellent, 2 good, 1 fair, 0 poor)

353 patients underwent MPS and 351 studies were received and processed by the core lab. 2 studies were corrupted in transfer and uncorrupted data were not received by the time of core lab closure. 70% of studies were normal and 30% abnormal, 72% had no inducible ischaemia and 28% had inducible ischaemia. 5 studies (1%) were labeled as indeterminate because no rest study was available either because of patient choice or site choice when the stress study was felt possibly to be abnormal. 11 studies (3%) were labeled as not evaluable because of inadequate image quality.

Mean SSS was 2.9 (out of possible 68) with maximum 39, mean SRS was 1.9, maximum 16 and mean SDS was 2.0, maximum 35. Stress LVEF was mean 64%, SD 9.6% and rest LVEF was mean 64%, SD 10.6.

Report confidence was excellent in 29%, good in 34%, fair in 24% and poor in 13%. Stress image quality was excellent in 23%, good in 34%, fair in 34% and poor in 9%. Rest image quality was excellent in 27%, good in 38%, fair in 28% and poor in 7%.

Accuracy of MPS for the detection of anatomical stenosis defined by invasive coronary angiography: when report confidence was high or image quality was excellent, sensitivity and specificity were high, but lower confidence and image quality led to reduced accuracy. In clinical practice when full patient information is available, it is anticipated that higher accuracy could be achieved with the lower quality images.

Compared with an invasive angiography standard of >50% stenosis, MPS sensitivity was reduced and specificity was increased. Again, there was reduced accuracy as image quality reduced.

Comparison between core lab and local clinical reports was only moderate with 63% agreement when image quality was excellent, 58% when good or better, and 49% when fair or better. In particular, many studies that were reported as normal by the core lab were reported as abnormal locally. This suggests lower specificity of reporting locally and the potential for valuable collaboration between the core lab and local experts to unify reporting style.

Conclusions:

- This is a preliminary analysis with much scope for more detailed analysis and comparison
- MPS accuracy against ICA is 85-90% with good quality images but falls with poorer images
- Reporting in the absence of clinical information is not advisable
- ICA accuracy for assessing coronary function is approximately 70%
- Wider dissemination of new camera technology needs greater experience.

Task 3.3 Central PET imaging analysis (P2-U. Turku, P18-KRITUM) (months 7 - 36)

3.3.1 Central PET imaging readings with regard to perfusion

131 patients underwent PET MPS and of these 89 studies were received and processed by the core lab. The reports of PET MPS from recruiting centres were available in 103 studies. The remaining studies were not received before the core lab closure. The overall image results are shown in 3.3. 64% of studies were normal and 30% abnormal,

3.3.2 Data entry of the centrally evaluated PET scans into the central database

During the period, all acquired PET studies have been received from central database, analyzed and the results have been submitted as CRFs into the central database. The quality of PET scans was mostly good with a few exceptions. In all cases, however, qualitative analysis was feasible.

The general analysis was based on clinical readings of images using criteria that have been used in earlier prospective studies. The 17 segments were scored according to predetermined scale. If abnormal findings were detected in stress images in more than one segment and that was normalized at rest, the finding was classified as positive for ischemia. The posteroseptal segments (the membraneous part of septum) were classified positive only if they were connected to abnormal findings in other segments.

With respect to the quantitative flow results, it is clear that absolute flow quantification provides valuable information compared with conventional myocardial scintigraphy. Although the static perfusion patterns are rather homogeneous (traditionally indicating rather normal flow), in 78% patients, the global flow reserve was less than 2.5, which is considered as reasonable a priori threshold. When calculating the number of patients with a flow reserve smaller than 2.25, 60% of all studies where positive indicating a clear prevalence for reduced myocardial perfusion in absolute terms. With a cutoff of 2.0 in global flow, still 45% abnormality was found.

Using the 17 segment AHA model for analysis, similar and consistent values were found for abnormal segments:

Mean SD Min Max 1 Quartile 3 Quartile

Cutoff: 2.50 76 8 59 94 71 82

Cutoff: 2.25 64 10 41 82 59 35

Cutoff: 2.00 46 10 18 64 71 53

These global and regional results point out that the study population was well selected and showed a good homogeneitiy. The EVINCI trial has the potential to allow the optimization of this cutoff.

Conclusions:

- The number of PET studies was reasonable low in this study as compared to SPECT studies and furthermore, not all studies were available for this preliminary analysis.
- The accuracy of PET was in the range what has been published earlier.
- The accuracy of corelab analysis and centre's own analysis were similar. The corelab tended to have somewhat lower PPV but higher NPV than centres own analysis
- This is a preliminary summary and further analysis will reveal valuable information how to clinically interpret and integrate absolute flow information
- Image acquisition and reconstruction could profit from higher standardization due to the increased complexity of dynamic PET especially with the use of listmode data.

Task 3.4 Central ECHO imaging analysis (P1-CNR, P11-SERMAS) (months 7 - 36)

323 patients underwent stress echocardiography and of them 205 were received and processed by the core lab. 94.6% of studies were normal and 1% abnormal at rest, 93.2% had no inducible ischaemia and 1.5% had inducible ischaemia.

Study quality was good in 40 (12.4%), fair in 237 (73.6%), and poor in 31 (9.6%), which could not be interpreted, with an overall feasibility of 86% considering other 14 examination for which image quality was not available. The average quality was mainly moderate both in the 196 patients studied with dobutamine, and the 106 patients studies with dipyridamole stress.

In the 85 dipyridamole stress echo studies, interpretable wall motion assessment was made in 82 patients (96%), whereas coronary flow reserve could be assessed only in 42 patients (49%). Of these, 20 (47) showed abnormal values (CFR<2.0).

Comparison between core lab and local clinical reports was fair with 80% agreement when image quality was good, 78.9% when fair, and 72.7 % when poor. In particular, many studies that were reported as normal by the core lab were reported as abnormal locally. This suggests a possible influence of clinical and ECG information blinded to the core labs, as well as more aggressive reading criteria in reporting locally, which might translate into significant inter-center variability, with higher sensitivities and lower specificity in centers adopting aggressive reading policy versus those with conservative reading policy, ignoring minor or questionable degrees of hypokinesis (Hoffmann et al, JACC 1997). This is an inherent

problem of the stress echo interpretation but these differences may have been overcome by a quality control check of the peripheral centers.

In summary :

1- pharmacological stress echo with either dobutamine or dipyridamole was highly feasible and interpretable, with images of unchanged quality during stress;

2- Abnormal wall motion results were less frequent than abnormal coronary flow reserve response;

3- In absence of predetermined reading criteria, previous experience in joint reading among different readers, and quality control of readers, the rate of positive results can vary substantially in different centers

Conclusions:

- Stress echocardiography can play an important role in a non-invasive multimodal anatomo-functional imaging strategy to characterize patients with stable angina and intermediate pre-test probability of CAD, improving the specificity and predictive value rates in combination with CTA.
- Non imaging parameters such as clinical and ECG findings, maximum heart rate, strict adherence to the protocol, image quality, together with the operator's experience can lead to a higher variability between the core-labs and the local centers, allowing the possibility to achieve better accuracy levels.

Task 3.5 Central MRI imaging analysis (P1-CNR) (months 7 - 36)

A total of stress MRI 144 cases were received by the core-lab. Forty-four4 were considered of too low quality in terms of SNR and CNR, and because of the presence of artifacts. The final analysis considered a population of 102 patients. Among them 17 showed a positive test for inducible ischemia. Considering an endpoint of coronary stenosis >70% an overall diagnostic accuracy of 90.2% with a specificity of 97.5% and a sensitivity of 65.2% were obtained. Considering an endpoint of coronary stenosis >50% an overall diagnostic accuracy of 90.2% with a specificity of 100% and a sensitivity of 63 % were obtained. The results of the present analysis are strongly limited by the low number of patients enrolled in the subgroup of stress MRI. However, the test confirmed a very high specificity (100%) and good diagnostic accuracy (90%). Furthermore the rather low sensitivity shown in the present study (range 65.2-63%) seems to be strongly dependent from the overall low prevalence of the disease in the enrolled population and influenced by to the variable quality of images. Finally, a very variable methodological approach was also encountered. This reflects also the different philosophy of each center. Some centers rely to functional abnormalities rather than to perfusion abnormalities. Due to the low number of positive test, which was also a function of a low prevalence of the disease in the enrolled patients as clearly shown by invasive coronary angiography, we were forced to merge the results obtained by the different pharmacological

stressors and so doing introducing a bias in the evaluation of diagnostic accuracy. In fact it is well known that tests based on perfusion abnormalities have a different accuracy with respect to tests based on inducible functional abnormalities. The variable methodological methodology adopted in the different peripheral centers might have further reduced the overall sensitivity.

Task 3.6 Comprehensive assessment of functional coronary disease by non-invasive stress imaging (P1-CNR and the other participants) (months 19 - 42)

The results of the central analysis of the different stress imaging modalities show the ability of each different modality to detect patients with severe coronary artery disease. The comparison of radionuclide imaging techniques (SPECT or PET) with those based on ischemia-induced ventricular wall motion abnormalities (Stress echo or stress MRI) show a good level of accuracy of both approaches. However, radionuclide imaging is characterized by a greater sensitivity, while stress echo is characterized by a greater specificity. In the clinical field, this information can facilitate the choice of the operator in selecting the most appropriate imaging modality for each individual patient.

As to stress MRI, the results of this study confirm the good sensitivity of this method in detecting patients with severe coronary stenoses. However, the analysis was limited to those images that were considered of adequate quality. Thus, despite the high image quality of standard cine images obtained at rest, the results of this study suggest that stress MRI protocols still need further refinements and homogenization between the different centers.

Considering all the imaging modalities together, the results of the stress imaging were anyway less accurate than the anatomic definition of coronary stenoses by CTA.

WP 4 Integrated Anatomo-Functional characterization of IHD

Start month: 1

End Month: 30

WP Leader: P2 U. Turku

Task 4.1 Standardization of exams procedures and parameters to be analysed

SOPs for ICA acquisitions protocols have been developed and distributed among the participating centers, SOPs for ICA analysis, resulting in ICA CRF have been developed and distributed among the participating centers. The relevant parameters have been defined and are entered by both the participating centers and the core lab into the Central Database.

Task 4.2 Central invasive exams analysis

The participating centres have submitted all ICA data to central database at CNR. The results of invasive coronary analysis include vessel branch based analysis of all lesions using quantitative coronary angiography (QCA). All analysis data in a form of CRF has been transferred to central database. This data has been merged with FFR data from recruiting sites and validation model for non-invasive imaging approaches was created. Core-lab has established its own database for additional and detailed analysis results not required by the protocol. An algorithm was created employing local ICA data, core-lab QCA and FFR was created used as a reference for noninvasive imaging approaches. In addition, core-lab has established its own database for additional and detailed analysis results not required by the protocol.

The combination of PET MPS and CT angiography has been preliminarily analysed. The number of patients could be included in this analysis was 93 (PET centres own analysis, CTA report and ICA report available).

Conclusions

- All enrolled ICA data has been sent to Core-lab and analysed successfully.
- The general quality of ICA was acceptable, only in small fraction of the high confidence QCA was not possible.
- The FFR results obtained from centres have been received to central database.
- The effect of combining CTA and PET data improved PPV but this effect was quite small and the effect to accuracy was minimal. However, this analysis required all 3 tests performed (PET, CTA, ICA) and currently the patients numbers remained lower.

Task 4.3 Validation model of non-invasive multimodality imaging

We assessed the accuracy of non-invasive anatomic imaging by CTA against ICA and the comparative intermodality accuracy of non-invasive 'functional' imaging against ICA.

The results of the EVINCI Study demonstrated, in patients with stable angina, suspected CAD and intermediate-low prevalence of significant obstructive disease, that:

1. Among single imaging modalities CTA is the most accurate for diagnosing Primary End-Point while there is no significant difference among different stress modalities (which preserve their know characteristics in opposite sensitivity and specificity).
2. Combination of CTA with perfusion nuclear imaging improves diagnostic accuracy of the non-invasive stress perfusion imaging alone.
3. Combinations of CTA with nuclear stress imaging were more accurate than combinations of CTA with non nuclear stress imaging.

We also evaluated the role of multimodality non-invasive approaches for characterization of IHD in anatomo- functional categories against ICA.

1. The results of the EVINCI Study demonstrate that a non-invasive multimodal anatomo-functional imaging approach is able to reliably characterize patients with stable angina and intermediate pre-test probability of CAD, indicating invasive

testing in only 26.1%. These patients will show significant obstructive coronary disease to be revascularized at ICA in the majority of cases (19%).

2. On the other hand, among the 73.9% of patients without indication to invasive study after non-invasive anatomo-functional screening only 7.1% would have shown an obstructive disease at ICA.

WP5 Central data bank, integrated analysis of EVINCI-study results

Task 5.1: Development of Central Server, Digital Bank and Database and

Task 5.2: Management of Central Server, Digital Bank and Database

Central to the EVINCI-study project was to establish a web site connected to a Central Server to allow centers to automatically enroll patients, receive an ID code for each center and enter anonymised relevant data obtained throughout the study. The designed and developed system allowed to store all information in a central database for further analysis. The same web site has been also intended to allow Core Labs to enter results of their analysis and to populate the same database in a specific dedicated session. Different account profiles (with dedicated username and password) have been created in order to set rules to access and manage data.

At the end of the study, the central Server and Data Base have been populated with data related to 695 patients enrolled within end of May 2012: 391 SPECT, 119 PET, 344 ECHO, 166 MRI, 592 CTA, 398 ICA.

Another activity central to the EVINCI-study was the creation of a Digital Bank which allows all imaging data collected in different centers by different modalities and technologies to be centrally stored (at the Coordinator Center) in an anonymised way and in a standard format accessible to each center and to the Core Labs. A communication network connecting all enrolling centers and Core Labs has been created.

Additionally, all DICOM images sent to the coordinating center were stored in the GE AW 2.0-5.0 Server in order to allow each center (both enrolment and core labs) to visualize the anonymized datasets. A VPN (Virtual Public Network) connection was used to guarantee the remote visualization of clinical cases stored in the server. Also in this case, the login and password and the instruction needed to establish the connection were received by each center.

At the end of the study the following exams have been received by the Coordinator Center (Pisa), stored in the Digital Bank and sent back to the Core Labs for analysis: 355 SPECT (shipped 355), 129 PET (shipped 129), 277 ECHO (shipped 277), 154 MRI (shipped 154), 579 CTA (shipped 579), 351 ICA (shipped 351).

Moreover, an analysis of the data has been completed by the Coordinator Center to control for quality of data entry related to all 695 enrolled patients. Some abnormalities in data entry have been identified and thanks to a continuing communication between web manager and centers all errors have been corrected.

Task 5.3: Outcome predictive model and association study

Among the 478 pts who completed the whole EVINCI protocol, 445 patients were submitted to follow-up visits and were included in the Outcome study analysis. The EVINCI study was not designed to evaluate the impact of different biohumoral and imaging strategies on long-term prognosis. Only cardiovascular events occurring in a short term follow-up (from 30 to 400 days) have been recorded. They included cardiac death, acute myocardial infarction, hospitalization for unstable angina or heart failure and recurrent angina as major events (MACE) and revascularizations. In particular events and revascularizations occurring within 30 days from invasive coronary angiography and completion of the EVINCI protocol were not considered as events in the follow-up but as complications or procedures of the clinical work-up.

In a mean Follow-up time of 183 days, 16 MACE and 47 Revascularizations occurred (23 CABG and 24 PCI).

No clinical variable resulted as independent predictor of outcome in the EVINCI population during the short period of follow up.

Based on biohumoral data, a predictive model of patients' outcome has been performed. Among biohumoral variables, MACE + Revascularization during follow-up were correlated with urea, uric acid, HDL cholesterol, CK-MB, Lp(a), ApoA1, Leptin, Osteopontin, and MMP9.

The multivariate model selected with stepwise method contained HDL cholesterol, and Lp(a) as independent predictors of primary endpoint. This model showed an accuracy to predict outcome of 64%, after Harrel's C analysis.

At Kaplan-Mayer analysis, as expected, the presence of functionally significant obstructive coronary disease at ICA (Primary End-Point, CAD) significantly predicted MACE at follow up ($P = 0.016$) or the combined end-point of MACE and revascularizations.

We tested the hypothesis that also the 4 non-invasive anatomo-functional diagnostic categories could discriminate the risk of cardiovascular events. Patients showing positive CTA and positivity of one stress imaging test (Category IV) had a significantly higher risk of MACE than all the other patients taken together ($P = 0.035$). Including also revascularizations as cardiovascular events the four categories could be analysed separately. The first analysis was performed combining CTA with stress imaging (irrespective of modalities). Actually, patients in Category IV (CTA positive, Stress Imaging positive) had the highest risk, patients in Category III-II had an intermediate risk while patients in Category I had the lowest risk.

When the analysis was repeated combining CTA either with Echo/MR or with SPECT/PET again patients in Category IV had the highest risk.

Accordingly, the discriminatory power of CTA alone for predicting cardiovascular events was significantly improved by adding stress imaging results (Harrel's C from 63% to 66%, $P< 0.02$), being not significantly different from the discriminatory power of ICA (Harrel's C 69%, ns).

Taken together the results of the outcome analysis of the EVINCI data demonstrate that a combined anatomo-functional non-invasive screening of patients with stable angina and

intermediate probability of CAD, has not only the capability of avoiding unnecessary invasive procedures and selecting patients with high probability to need revascularization, but also provides information on the risk of cardiovascular events. MACE are more frequent in patients with positivity of both CTA and stress tests. Similarly the risk of MACE and successive revascularizations is best predicted by a combined positivity of anatomo-functional imaging, irrespective of the modality of stress test used. These results will probably have a high impact on future clinical use of cardiovascular imaging in patients with suspected IHD.

To investigate the association between biomarkers and imaging, the indicators of coronary vascular disease from invasive as well as non-invasive imaging were used in combination with the biohumoral model to build up different models to be tested versus outcome. The addition of biohumoral variables determined a trend to improve the predictive power of any combination. This improvement was statistically significant only when biohumoral data were used in association with the presence of ischemia at Stress Imaging (P = 0,001).

Significant results

A secure exchange of raw data from enrolment centers to coordinator center and from coordinator center to Core-Labs was ensured using an informatics network.

Population of Data-Base connected to the Central Server with all relevant information and analysed data for all enrolled patients was completed. Population of Digital Bank with all raw imaging data received from enrolment centers was also completed.

Integrated models of clinical profiles, biomarkers and imaging profiles were demonstrated to better predict outcome.

The developed technological systems allowed to create reliable and useful methods to save and store data and raw images that could be useful for further and additional sub-studies.

WP 6 Cost-Benefit analysis and evaluation of Procedural Risks

Start month: 1

End Month: 36

WP Leader: P10 UniGe

Task 6.1 Standardization of questionnaires and parameters to be analysed

The identification and the measurement of the strategies considered were achieved by standardized questionnaires for data collection.

The questionnaires have been drafted as a Case Report Form (CRF), the CRF have been drawn up on a paper and electronic version in English language.

Two type of CRF have been provided:

- The General Health Economics CRF (patient level);
- The Specific health economics CRFs (Centre level)

The Specific Health Economics CRF is aimed at identifying and quantifying direct medical costs of the exams performed that include information about professional involved, consumer good, stocktaking good and drugs used and hospital inpatients as number of hospitalizations and days in hospital. The direct medical costs are computed by the micro-costing approach: each component of hospital resource used in the different diagnostic tests is identified. Once the quantities of resources are identified (e.g. working minutes of a radiologist), the prices, as unit costs, of those resources will be derived (e.g. radiologist's wage).

Standardized Health-Economics and Quality of Life questionnaire (HEALTH-ECON-CRF) to be filled at enrolment and at the last follow-up visit.

Task 6.2: Cost-benefit models

The diagnostic accuracy of combined non-invasive "anatomo-functional" imaging was tested versus the reference method: the invasive coronary angiography. A cost effectiveness analysis of the new diagnostic work up versus the gold standard was also performed. The objective of the Health Economics analysis was to define the most cost-effective work-up for the diagnosis and characterization of IHD. To this purpose the costs and the effects of non-invasive and invasive diagnostic procedures have been prospectively collected.

The Incremental Cost-Effectiveness Ratio (ICER) was derived as summary measure of economic assessment. The cost effectiveness model has been performed comparing the alternative combinations of non invasive exams against the invasive procedure in terms of both their costs and consequences in order to define the most cost effective procedure. Costs have been deflated and placed on a common base year (2012). As in calculating ICER we followed a country-specific approach, we estimated an overall ICER applying Purchase Power Parities (PPPs), that are rates of currency conversion eliminating differences in price levels between countries. Therefore, we used mean costs for countries and we adjusted between countries using PPPs.

The ICER estimates the incremental cost per unit of effect defined as accurate diagnoses of CAD (one point % of accuracy) resulting from invasive standard testing versus multimodality non invasive strategy.

The value of ICER estimates the cost or the cost saving achieved for each point percentage of accuracy in performing the combination of non invasive strategy versus the standard invasive coronary angiography strategy. The ICER is performed taking into account an institutional perspective (only direct medical costs).

In the MODEL A, the most cost-effective combination is CTA+SPECT in Switzerland, France and Spain, followed by CTA+PET in Italy, CTA+MRI in Finland and then CTA+ECHO. In Italy the CTA+PET is the most cost-effective combination, in Poland CTA+ECHO and in Finland CTA+MRI is the most cost-effective combination. A warning has to be raised with reference to the significance of data of CTA+PET in Switzerland and CTA+MRI in Spain, as there is only one observation.

In MODEL B, the most cost-effective combination is SPECT+CTA in Switzerland, France, Spain and Italy, and ECHO+CTA in Finland and Poland. A warning has to be raised with reference to the significance of data of PET+CTA in Switzerland and MRI+CTA in Spain, as there is only one observation.

Results present similarities among countries showing that the different combinations have almost the same ordinal position in respect to ICA, but the relative cost effectiveness of the different combinations expressed in ICER varies among countries. These differences are mainly explained by the relative differences in the costs among the different combinations in the different countries.

In MODEL A the overall ICER shows that CTA+SPECT is the most cost-effective combination in respect to ICA, followed by CTA+PET, CTA+MRI and CTA+ECHO.

In MODEL B the overall ICER shows that SPECT+CTA is the most cost-effective combination in respect to ICA, followed by ECHO+CTA, MRI+CTA and PET+CTA.

Task 6.3 Procedural Risks evaluation (P1-CNR, P10-UniGe) (months 4 - 36)

A specific informed consent for each diagnostic modality specifying radiation doses and risks has been developed and distributed to all patients. This information allowed to estimate the overall procedural risks for the patient associated with the different noninvasive and invasive diagnostic approaches.

WP7 Advanced clinical reporting of non-invasive multimodality cardiac imaging results

Task 7.1: Image fusion analysis

This task dealt with the development of a new tool allowing integrated representation of anatomo-functional information derived from noninvasive multimodality cardiac imaging. In particular, the quantitative integration of coronary artery anatomy from Computed Tomography Angiography (CTA) and regional functional information derived from Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI). To reach this purpose a new method called Hybrid Image Tool (HIT) has been developed.

The basic idea behind the HIT is to exploit image analysis tools yet available at the involved sites for clinical or pre-clinical research purposes and to develop interfaces, based on the standard eXtensible Markup Language (XML) protocol, for the communication of different modules.

In detail, the developed method can be described considering four main modules:

1) the volumetric registration tool, based on iterative closest point (ICP) and mutual information (MI) algorithms, for spatial matching of reference (anatomical) and floating (functional) datasets producing the XML transformation file containing the parameters of rigid transformation ;
2) the quantitative analysis of functional datasets based on validated software normally used in the clinical routine able to produce the XML MIST (Multimodal Image Storage and Transfer) file containing geometrical and quantitative information (task 7.1.3). The MunichHeart software developed in Munich and the HIPPO software developed in Pisa were considered.
3) the generator of the derived functional datasets;
4) the 3D visualization tool of integrated anatomical and quantitative functional information. The GE AW-Server 2.0-5.0 has been used.

The modules composing the described tool are managed using a dedicated graphical user interface.

The method developed in the present project has the important advantage of allowing a real 3D combination and visualization of complementary data such as the presence and severity of

the stenosis with the perfusion and mechanical function of the corresponding myocardial territory, thus challenging our ability to assign its functional meaning to anatomical lesions.

This method has also the advantage that it could be integrated in other software tools allowing image registration, quantitative image analysis and 3D visualization of complementary information. This process only requires the involvement of owners and developers modules. In prospective, it could be applied to combine additional complementary information such as metabolism by FDG-PET, myocardial contractility by tagging-MRI, myocardial perfusion and viability by MRI and also include other modalities such as SPECT imaging.

Task 7.2: Synthetic 4D dynamic heart model

The central purpose of this task was the development of a multimodal report (MMR) in order to organize, integrate and visualize all the available information (clinical, biological and cardiac imaging data) belonging to a single patient. The MMR has been designed in order to share information among different subjects (cardiologist, cardiac surgeon, family doctor and the patient himself), to be appreciated as support for decision making and follow-up and also to be suitable for educational purposes. All the available information has been organized in several sections.

The first one ('The Heart') provides the patient with the basic notions on circulation as well as with the explanation of the medical jargon used in the report. The following sections ('Description', 'ECG', 'LV Imaging', 'CA Imaging') contain all the clinical and instrumental data of the patient giving a detailed clinical evaluation of cardiac disease, and 'Integration' section is able to provide a combined visualization of all available information. This section is able to provide the high resolution integration described in Task 7.1, and also the low resolution integration that is a synthetic 'picture' of the patient's cardiac disease. Indeed it integrates all the instrumental data in a low resolution graphic model composed of 17 sectors according to the widely used AHA standard segmentation.

The last two sections ('Diagnosis' and 'Decision') explain the diagnosis in terms of evidence and causes and describes the treatment suggested to the patient respectively. The development of the described MMR had the aim to reduce the gap in communication between healthcare providers and users, by offering an all-in-one multimedia instrument for describing the patient disease, basic medical concepts, through graphics, animations, and a plain yet authoritative language. By providing patients with the basic notions and technological means to be aware of their health status, they can truly become part of the decision process. In addition, this approach may also contribute to improve the communication between all the health operators that also may have different knowledge and use different language about ischemic heart disease and about cardiac imaging modalities.

Starting from the described MMR and using all the information included in it and described above, we developed a web-based educational tool (EduCAD) directed to young cardiologists for training in the appropriate use of multimodal imaging technology for diagnosis and treatment of ischemic heart disease, thus promoting the culture of multimodal imaging for cardiac diseases assessment. The developed educational tool has been included in a dedicated web site (http://www.escardio.org/educad).

Potential Impact:

The number of patients with suspected or documented IHD is steadily increasing. This is caused by the ageing of the population and by an increase in other cardiovascular risk factors as physical inactivity, diabetes mellitus and obesity. Thus, IHD remains still the leading cause of death and the main determinant of health costs in Europe. The fight against this trend includes developing and testing new strategies for the early detection and better characterization of patients and, thus more accurate guidance of therapy.

Non invasive imaging plays a crucial role in the management of IHD, but the evidence-based and economically optimized use of imaging is challenging since there is limited data available to guide the usage of various advanced and often costly procedures. The rapid technical development has also produced new techniques that are often competitive or complementary to earlier methods. Therefore, an European-wide multi-centre clinical trial is the only possibility to provide comprehensive information in larger populations.

This trial has definitely provided answer to most of the current burning questions in use of imaging in IHD.

According to its results, the EVINCI-STUDY suggests that the true prevalence of significant CAD in patients with stable anginal-like chest pain is not adequately predicted by current models based on clinical and stress ECG data. In these patients, an adequate redefinition of probability based on new predictive models including biohumoral markers and non-invasive imaging screening could be able to avoid invasive procedures in up to 70 out of 100 patients.

The results of EVINCI-STUDY show that five biomarkers are independent predictors of primary end-point. They express either metabolic profile (HDL cholesterol, HOMA index or aspartate transaminase) or inflammatory status (Interleukine-6 or Osteopontin). Models adding all or some of these biomarkers to the Duke Score showed an improvement of diagnostic accuracy from 66% to 72-74% ($P < 0.001$).

The novel result of the EVINCI-STUDY is the clear demonstration of the superiority of CTA for diagnosing the presence of obstructive CAD in this specific population of patients with intermediate-low prevalence of disease.

In patients with suspected CAD and intermediate-low probability of disease, the results of the EVINCI-STUDY demonstrated that

- CTA is the most accurate imaging modality for diagnosing the Primary End-Point.
- There is no significant difference among different stress modalities (which preserve their know characteristics in opposite sensitivity and specificity).
- Combination of CTA with perfusion nuclear imaging improves diagnostic accuracy of the non-invasive stress perfusion imaging alone.
- Combinations of CTA with nuclear stress imaging were more accurate than combinations of CTA with non nuclear stress imaging.

EVINCI results suggest that a non-invasive multimodal anatomo-functional imaging approach is able to reliably characterize patients with ascertained or suspected stable angina and intermediate pre-test probability of CAD, indicating invasive testing in only 26.1%. These patients will show significant obstructive coronary disease at ICA, and will undergo coronary

revascularization in the majority of cases (19%). On the other end, among the 73.9% of patients without indication to invasive study after non-invasive anatomo-functional screening only 7.1% would have shown an obstructive disease at ICA.

In summary among 100 patients commonly referred to coronary angiography we would spare 66.8 unuseful invasive studies, indicating 19% of appropriate revascularizations. We would perform only 7.1% of unuseful catheterizations and we would lose 7.1% of possible revascularizations. These general figures are substantially different according to the stress modalities combined with CTA or for CTA alone.

Based on the above considerations, the approach derived from the EVINCI-STUDY could have a significant and positive impact on patients, health providers and health organizations. From the patient's perspective, a non invasive approach to the diagnosis of coronary artery disease could reduce the risks and discomfort related to unnecessary invasive diagnostic procedures. From the point of view of health providers, the results of the EVINCI-STUDY could guide future investments based on the information regarding accuracy, sensitivity and specificity of currently available non invasive imaging modalities. From the societal point of view, the reduction in the number of unnecessary diagnostic procedures could reduce the costs related to the diagnostic process, which are progressively growing. Finally, such an approach could enable patients who are truly at risk to be effectively treated, thus limiting the clogging of health facilities caused by the huge amount of inappropriate tests.

The results of the outcome analysis of the EVINCI data demonstrate that a combined anatomo-functional non-invasive screening of patients with stable chest pain and intermediate probability of CAD, has not only the capability of avoiding unnecessary invasive procedures and selecting patients with high probability who need revascularization, but also provides information on the risk of cardiovascular events. MACE are more frequent in patients with positivity of both CTA and stress tests. Similarly, the risk of MACE and successive revascularizations is best predicted by a combined positivity of anatomo-functional imaging, irrespective of the modality of stress test used. These results will probably have a high impact on future clinical use of cardiovascular imaging in patients with suspected IHD.

Those results are expected to make huge impact to the current clinical practices and consequently to the economical burden for Healthcare Policy Makers.

In general, however, changes in clinical practices takes time since these are often determined by local subjective opinions, earlier experience and logistical limitations. In this context the primary target group in dissemination of study results is clinicians that in primary patient care determine which tests are used. The EVINCI consortium has expertise and up-to-date technologies and includes most of the European top cardiovascular imaging centres which will ensure the take up of those results in the scientific community.

To achieve the abovementioned impacts, the dissemination of study results has been carefully planned and performed.

EVINCI-STUDY web site was designed to present the project objectives and methodologies. The European Society of Cardiology (P14-ESC) has established a specific WEB site

(http://www.escardio.org/communities/Working-Groups/EVINCI/) directly accessible through the ESC WEB site in the Working Groups (WGs) area

The scientific content, including the state of advancement of the project and the major results, was updated regularly. The website was set to facilitate the visibility of the project and to acknowledge the EU support.

The EVINCI-STUDY has been registered in the WEB Registry of US National Institutes of health (http://clinicaltrials.gov/) with the number NCT00979199.

The first international EVINCI-STUDY Meeting has been organized in December 2009 in Pisa with the title "Multi-Imaging in Cardiology" and under the support of two WGs of the ESC (Cardiovascular Magnetic Resonance WG, Nuclear Cardiology and Cardiac CT WG) and of the ESC Council on Cardiovascular Imaging. The Faculty included PIs of most of the EVINCI-STUDY centers together with distinguished scientists dedicated to cardiovascular imaging coming from Europe and US. It was an occasion to discuss the background of the EVINCI-STUDY also in comparison with other European programs financed under the FPVII initiative and similar programs currently on going in the US.

Workshops internal to the consortium (but opened to the health authorities and to the industry) were organized to present the results of central analysis. Communications on the progresses of the EVINCI-study to the scientific community were issued by presentations to the annual ESC and other scientific meetings and will be submitted to other medical society's annual meetings.

The background and the design of the EVINCI-STUDY, together with the advancements of the project, have been reported by P1-CNR in different talks presented at the ESC WG5 Meetings and in plenary sessions of the ESC Meetings of Barcelona 2009 and Stockholm 2010, at the ICNC Meeting of Barcelona 2009 and at the WG5 Fall 2009 Brainstorming Meeting of Capri. It has also been presented at different Italian National Meetings in 2009 and 2010.

The following major dissemination meetings have been organized to present the project results:

- EVINCI Final Meeting (Madrid, June 25-26 2012)
- EDUCAD Meeting (Brussels, April 11-12, 2012)

In order to encourage participation of young researchers to the EVINCI Final Meeting, thus contributing to dissemination and uptake of the project results, travel grants have been awarded by ESC to young researchers. The advertisement has been posted on the ESC and EVINCI web sites and disseminated through the network of partners. Grant awardees have been 10 young cardiologists who have been granted up to 1000 Euros to participate to the final EVINCI Meeting in Madrid. They would hopefully act as local ambassadors of the project in their local institutions / societies.

A dissemination plan was designed to optimize promotional objectives and goals. Target groups were identified in all member states and in the other European countries. For each target group, the route to establish contact was decided; to identify a strategy to reach the

target; to set rules for dissemination: what knowledge and to what level it is worth disseminating .

Several activities were identified in order to announce EVINCI final results & conclusions, promote eduCAD as unique innovative educational platform (derived from recorded EVINCI clinical cases) in the field of multi-modality imaging.

Targeted audience of the proposed dissemination has been composed by:

- All ESC members (64000 persons)
- Overall imaging communities (EAE, CMR, NUC&CT, e-cardiology) (4500-5000 members)
- eduCAD for the young cardiologists (<35) (8000 persons)

The following tools have been developed to disseminate information and promote EVINCI-STUDY results also post-project: EVINCI brochure & Educad flyer; EVINCI advert; ESC web site; Press release & Press Kit; ESC Newsletters & E-mailings

The EVINCI brochures aim to present and promote the study, disseminate the project results, and raise visibility about the project. It has been distributed at the Final EVINCI meeting in Madrid, at the European Society of Cardiology Congress 2012 at the ESC stand, and in other imaging meetings (ESC meetings such as EuroECHO, EuroCMR congress, or ICNC Partners' institutions).

The EDUCAD Flyer aims to present and promote eduCAD to imaging community (focusing on young cardiologists) as major training tool in cardiology imaging. It was largely distributed at the ESC meetings and EVINCI Final meeting and through the partners' network.

Electronic format of EVINCI and EDUCAD advert has been prepared for insertion into various ESC Journals (mainly: European Heart journal & EHJ-Cardiovascular imaging). ESC benefits from free slots into the whole ESC Journal family. EVINCI should capitalize on those opportunity to appear in peer reviewed journal with high impact factor. Posters were also produced.

A Press Conference has been organized in Madrid on 26/06/2012. Juhani Knuuti, Jose Luis Zamorano and Danilo Neglia were interviewed by 10 journalists coming both by local journals and by representatives of international press agencies. National TV also attended. A press kit has been made available.

The press release has been distributed to the ESC database of journalists (3000 contacts: BBC, Telegraph, Daily Mail, Nouvel Obs, Figaro, Monde, NY Times, AP (wire), Reuters (wire), WSJ, Heart.Org, MedPage, MedScape, etc.

Further dissemination will continue post project in August 2012 at successive ESC Congresses.

Live interviews (“ESC TV Talk”) will be held during ESC Congress (displayed on web and plasma screens).

Emailing campaign was carried out. ESC newsletters were used to reach distinct audiences and social media opportunities (facebook - twitter) were also explored.

Expected results to be commercially exploited include:

(i) predictive models of pre-test probability of IHD, post-test cardiovascular risk stratification and cost-benefits evaluation to be included in noninvasive imaging modalities users' manuals;
(ii) software for multimodality imaging analysis and display;
(iii) 4D heart dynamic model for clinical decision making in cardiology;
(iv) new end-points to be used in pharmacological trials in IHD.

EVINCI created a huge European digital bank for multimodal cardiovascular imaging and a biological bank for blood samples which will be relevant repositories of raw imaging data and biological samples to be considered for future studies and educational purposes.

One major output of the EVINCI-STUDY was the definition of a panel of simple biomarkers which could be combined in new diagnostic integrated device to be exploited by the industry as a new widely available tool for the screening of patients with suspected CAD prior to or together with cardiovascular imaging assessment.

A second major output of the EVINCI-STUDY was the implementation of a Multimodal Report (MMR) able to present to the final user (patients, physicians, imaging experts, etc.) the single and integrated information coming from clinical, biohumoral and multi-modal imaging data acquired in the single patient. MMR has the potential to be exploited by the industry as a novel aid to clinical diagnosis mainly based on imaging.

Based on the previous result, the EVINCI-STUDY generated eduCAD, a new web based tool for disseminating the design and approach of the EVINCI study and for training young cardiologists in the appropriate and more effective use of imaging tests for diagnosing ischaemic heart disease. EduCAD is based on validated clinical cases selected from the EVINCI-STUDY. It is available at www.escardio.org/educad.

List of Websites:

http://www.escardio.org/communities/Working-Groups/EVINCI

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