BANDO GIOVANI RICERCATORI 2009

Ministero della Salute – Direzione Generale della Ricerca Scientifica e Tecnologica

Application resume

Title: TAVI versus traditional approaches in treating severe symptomatic aortic stenosis

Code	GR-2009-1605075
Institution accepting the project:	
Type of research:	Clinical
Length (months)	36
Total budget of the project	€ 503.000,00
Funding required to Ministry of Health	€ 380.000,00
Total amount of co-financings	€ 0,00
Institutional resources	€ 123.000,00

NIH primary classification

IRG: Healthcare Delivery and Methodologies

Study section: Health Services Organization and Delivery - HSOD

Keyword: HDM-HSOD-0675 - Healthcare quality, effectiveness, and outcomes; clinical practice guidelines; treatment and prevention outcomes; patient and provider satisfaction; health status and outcomes assessment; evidence-based practice; health-related quality of life; medical decision-making.

NIH secondary classification

IRG (2): Cardiovascular and Respiratory Sciences

Study section (2): Clinical and Integrative Cardiovascular Sciences - CICS

Keyword (2): CVRS-CICS-0363 - Clinical, population, or translational studies of the responses of the cardiovascular system to trauma or surgery: arrhythmias associated with cardiac surgery or cardiopulmonary bypass, cardiac sudden death, resuscitation, stenting, pacemakers;,cardiovascular injury and repair, and myocardial ischemia/reperfusion injury.

IRG (3): N/A

Study section (3): N/A

Keyword (3): N/A

Principal Investigator

Name: Rosato Stefano

Role: Researcher

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Current employment and institution: Researcher. Department of Cerebro and Cardiovascular Disease; National Centre for Epidemiology, Surveillance and Health Promotion; Istituto Superiore di Sanità; Rome ; Italy.

Profile of the principal investigator

EDUCATION

1. Lyceum "Guido Castelnuovo", Rome, Italy; Graduated at Scientific High School, July, 1992

2. University of Rome "La Sapienza", Rome, Italy; Graduated in Statistical Sciences, May 27, 2003.

POSITION HELD

Member of Research Group.

- Short term outcome study of Coronary Artery By-pass Graft (CABG) interventions in the Italian Cardiac Surgery Centers (Ministry of Health - ISS)(2002-2004)

- "Valutazione di Esito" nell'ambito della "Ricerca Finalizzata 2003" del Progetto strategico "Il Progetto Cuore II: risk assessment individuale, di struttura e dei percorsi prognostico terapeutici per le malattie cardiovascolari". Operative Unit 2. (2003-2006)

- EUPHORIC - European Public Health Outcome Research and Indicators Collection (EU Commission - SANCO) (2004-2007)

- Progetto Mattoni del Ministero della Salute - Mattone "Misura dell'Outcome" (Ministero della Salute - ISS)(2004-2008)

- Sperimentazioni Mattoni (Stenting - Angioplastica)

- Valutazione degli esiti per promuovere il miglioramento dell'efficacia nell'erogazione delle prestazioni ricomprese nei LEA (Convenzione Ministero della Salute/Dip. Qualità - ISS)(2008-2009)

- Sviluppo e produzione degli indicatori di esito per SIVeAS (Convenzione Ministero della Salute/Dip. Qualità - ISS) (2008-2009)

- Valutazione della performance: programma di valutazione delle decisioni e delle attività delle strutture sanitarie - Operative Unit 2. (convenzione CCM del Ministero della Salute - ISS) (2010-2011)

- Studio osservazionale per la valutazione di appropriatezza, efficienza ed efficacia delle procedure AVR-TAVI per il trattamento della Stenosi Aortica (Convenzione Ministero della Salute/Dip. Innovazione - ISS) (2010-2012)

Member of the Steering Committe and Responsible for the Istituto Superiore di Sanità

- Registro Italiano Stenting Carotideo - RISC2 ISS - Università degli Studi di Milano-Bicocca (2006-2008)

- Progetto "OSCAR per la Qualità" - Outcome Survey sui Centri che eseguono Angioplastiche coronariche: Risultati a 6 mesi per valutare la Qualità. ISS - Società Italiana di Cardiologia Invasiva (GISE) (2005-2007)

- Italian Network on Acute Coronary Syndromes (IN-ACS) Outcome. ISS - ANMCO - Heart Care Foundation (2006-2008)

- Progetto "Mattone Outcome - BYPASS" ISS - Dipartimento di Epidemiologia, ASL RME (2006-2008)

EXPERIENCE

From 2003 to date: Study design, data analysis and predictive models on the topic of the outcome research at the National Centre for Epidemiology, Italian National Institute of Health.

TEACHING ACTIVITIES

From 2005 to 2008: Teacher in several institutional courses concerning statistical methods in epidemiology.

From 2006 to date: Teacher in annually institutional courses concerning outcome research.

Summary and collaborations

Transcatheter aortic valve implantation (TAVI) is a new interventional procedure for the treatment of severe symptomatic aortic stenosis (SSAS) that is less invasive than the conventional approach (aortic valve replacement - AVR) and is designed to treat high-risk patients. The TAVI procedure has been introduced into clinical practice prior to receiving evidence from randomized clinical trials (RCT), but on the bases of clinical experience and common sense considerations.

In spite of the relative newness of the approach (first performed in humans in 2002), it very quickly became of interest for patients who had previously attempted medical treatment (MT), palliative valvo-plastic (VP) and for patients eligible for AVR. For this latter subpopulation, the effectiveness of TAVI vs. AVR in terms of medium- and long-term outcomes has not been demonstrated. Since 2007, TAVI procedures have regularly been performed in Italy.

The first observational outcome study on the comparative effectiveness of TAVI, AVR, VP and MT for the treatment of SSAS in the subgroup of Italian SSAS population at high pre-operative risk is being proposed, involving all Italian hospitals where TAVI are provided.

Clinical and procedural information will be collected prospectively for each enrolled patient undergoing TAVI procedure.

Clinical and procedural information will be collected retrospectively analyzing clinical and administrative database (and registry) for each enrolled patient undergoing AVR, VP procedure or MT.

This study aims to

- to evaluate the short, medium, and long-term effectiveness of TAVI versus AVR, VP, or MT in a high pre-operative risk subgroup of the Italian SSAS population;

-build guidelines on TAVI procedure coding be proposed to the regional health systems;

-verify the use, appropriateness, and economic and organizational impact of TAVI and AVR procedures.

The study outputs will provide concrete support to professionals for properly identifying the target population for TAVI, making appropriate management choices, controlling direct costs, and enhancing patient quality of life and life expectancy. This study will also supply the National and Regional Health Systems with appropriate tools and methodologies to monitor economic and organizational aspects linked to the introduction of TAVI into the health system.

COLLABORATIONS

RECRUITED HOSPITALS. Clinical and follow-up data collection; support of clinical monitoring procedures.

REGIONAL HEALTH AUTORITIES (RHAs) - LOMBARDIA, FRIULI, VENETO, EMILIA ROMAGNA, TOSCANA,

CAMPANIA, CALABRIA, SICILIA. Check for completeness of perspective study cohort enrollment; provision of Hospital Discharge Records for retrospective data-gathering; follow-up data collection within the Regional Administrative Health Informative System and Regional Mortality Registry.

OPERATIVE UNIT (OU) 1 - DEPARTMENT OF EPIDEMIOLOGY OF THE REGIONAL HEALTH SYSTEM, LAZIO.

Participation in study protocol writing and minimal dataset definition; contribution to data management and analysis; cooperation in drafting the intermediate and final reports.

OU2 - CLINICAL MONITORING UNIT. Setting up of standardized operating procedures (SOPs) for clinical monitoring; periodical revision of hospital discharge diagnoses and identification of SSAS suspected ICD-9-CM codes; original clinical chart revision; drafting of clinical monitoring reports.

OU3 - SOFTWARE PROVIDER. Implementation of a dedicated web site; building database structure for data recording; creation of a document-sharing section for information exchange.

OTHER COLLABORATIONS

Italian Ministry of Health

AGENAS (National Agency of Regional Health Services)

FIC - Italian Federation of Cardiology

SICI -GISE - Italian Society of Interventional Cardiology

SICCH - Italian Society of Cardiac Surgery

ITACTA - Italian Association of Cardiothoracic Anaesthesiologists

Teaching hospitals, scientific institutes for research, hospitalization, and health care

Rational purposes and specific impacts on the subject

Aortic stenosis is the most common acquired valvular heart disease in the Western world, and its prevalence is strongly linked to the phenomenon of population aging. Due to its unfavorable prognosis, aortic stenosis represents, without doubt, an important public health issue.

The prevalence of aortic stenosis clearly increases with age. Prevalence is 1.3% in patients 65-75 years old, 2.4% in those 75-85 years old, and 4% in those over 85 years old.

Symptomatic severe aortic stenosis (SSAS) affects about 40% of all patients with aortic valve disease. After symptom onset, patients with SSAS, when untreated, show very poor prognoses, reach complete disability status, and exhibit significantly low survival rates.

The mean survival rates at 2 and 5 years are 40-50% and 20%, respectively. Aortic valve replacement (AVR) is the elective procedure of choice for these patients to achieve significant reductions in mortality and disability. Nevertheless, 33% of older patients with SSAS were denied surgery for various reasons.

Typically, advanced age alone is not considered a contraindication for AVR, despite the fact that patients aged 80 or more have twice the probability of operative complications compared with younger patients. Older people with SSAS often have si-

gnificant associated comorbidities, including reduced left ventricular function, impaired renal function, pulmonary hypertension, liver cirrhosis, or coronary artery disease. Each of these comorbidities significantly increases the risk of open heart surgery. Until the end of 2006, three alternatives were available for the most severe cases; one high risk, and two simply palliative: 1) performing an AVR despite contraindications, 2) performing a lifesaving plastic valve procedure (VP), or c) implementing a simple medical therapy (MT).

In recent years, a new therapeutic approach has become available for a large proportion of patients with very high or prohibitive operative risk. This transcatheter aortic-valve implantation (TAVI) is less-invasive than the surgical approach (AVR), and it is feasible for interventional cardiologists in hemodynamic laboratories. Seven years after the first-in-man clinical trial, over 6000 patients have been treated worldwide with TAVI.

Two manufacturers have led the development of transcatheter aortic bioprosthesis valve implantation technology: Edwards Life Sciences (Edwards SAPIEN Transcatheter Heart Valve; second generation) and CoreValve Corporation (CoreValve Percutaneous Revalving System; second generation). Although lacking official approval from the US Food and Drug Administration (FDA), both systems have been approved for use in Europe (CE-marked), where they are currently used. Other commercial manufacturers and improvements in valve technology are expected to appear in the near future.

Currently, there are two routes for transcatheter valve replacement in treating aortic stenosis: the retrograde route, which accesses the heart through the femoral artery, or the transapical access route, which accesses the heart by piercing directly through the left ventricle wall. The choice of technique is influenced by calcification and tortuosity of the femoro-iliac access route.

TAVI technology has been applied primarily in quite aged patients with a high number of comorbidities. Operative risk score calculators (i.e., logistic EuroSCORE, Parsonett score, Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM] score), which take into consideration the most important patient comorbidities, have been used to identify patients that are at very high or prohibitive surgical risk.

In Italy, since the introduction of this procedure three years ago, TAVI spread dramatically, increasing from 30 procedures performed in 2007, to about 700 in 2009. Moreover, it has been possible to observe how this procedure, originally limited to a specific high-risk patient subgroup, has exponentially broadened to include younger patients with no relevant contraindications to traditional surgical procedures.

The introduction of this new technology into clinical practice has had strong structural, organizational, and economic effects on the health system. In Italy, due to current device costs, an unplanned use of TAVI leads to unavoidable direct cost increases (2000 # for each device employed in the AVR procedure vs. 28000 # for each bio-prosthesis used in the TAVI procedure). Thus, according to the current trend, by 2010 we can expect an outlay of approximately 28 million # for 1000 TAVI, compared to 20 million # for the estimated 10000 AVR procedures. Moreover, the health providers' balance sheet is expected to include further expenditure increases for capital equipment investment (i.e., hybrid theaters), facilities, and personnel training. Finally, as reported in national and international consensus documents, because TAVI procedures must be performed by multidisciplinary teams in surgical or hybrid theaters, we can expect significant hospital internal reorganizations. Although the AVR vs. TAVI issue arouses lively interest at the international level, the current data are from only a few trials conducted by the companies that developed the devices, and few post-market studies are currently available.

Despite this rapid spread and the required economic effort, to date, the safety and efficacy of TAVI procedures have been measured by comparing the procedural and 30-day results to the predicted operative mortality calculated by questionable and outdated surgical risk calculators. Currently, no random controlled trials (RCTs) have been conducted to compare the efficacy of TAVI (transfemoral/percutaneous and transapical routes) to that of either routine palliative care (i.e. VP or MT) or AVR.

The new phenomenon of systematic reviews based on current administrative data, i.e., hospital discharge records (HDRs), is not currently feasible, because we lack consensus guidelines on coding TAVI procedures. Furthermore, regional systems may suggest different options; thus, the use of an ICD-9-CM code for a TAVI procedure in one hospital may not be the same as that used in other institutes or hospitals in the same region.

Non-pharmacological treatments often do not undergo experimental evaluation of efficacy in accordance with the rigorous scientific protocol of RCTs, due to the organizational conditions of health treatment supplies and the rapid development of health technologies. In these cases, observational outcome studies (OOSs) represent a valid scientific alternative to the experimental approach (i.e., RCT).

Therefore, in advance of results from dedicated randomized trials that will clarify the role of TAVI, a nation-wide observational study was recently launched in Italy, endorsed by the Superior Institute of Health (ISS, Istituto Superiore di Sanità). This OOS will evaluate the appropriateness and effectiveness of AVR and TAVI procedures. The study design was based on the national health survey, and it aimed to assess the comparative effectiveness of TAVI vs. AVR, VP, or MT. The study will be conducted in a high pre-operative risk subgroup of the Italian SSAS population admitted to Italian hospitals where TAVI and/or AVR are provided. The main objective of the study is to evaluate the actual advantages in the short, medium, and long-term prognoses (survival, occurrence of re-interventions, and major adverse cardiac and cerebrovascular events - MACCE) for patients treated with the new TAVI procedure compared to those treated with AVR, VP, or MT. The study will also account for potential differences in patient severity among the treatment groups. Moreover, given the strong economic impact of this new methodology on the health system, this study will assess whether the gain in patient prognoses can justify the expected direct cost increases.

In February 2010, a preliminary plenary assembly was held in cooperation with the Italian Ministry of Health, National Health Institute, National Agency for Regional Health Services, Italian Regions, and various Italian scientific societies and federations that represent professionals involved in this topic, including hospital-related professionals, individual cardiologists, and cardiac surgeons. This meeting ratified an alliance among all the constituents and a general consensus to participate in the national survey on the AVR vs. TAVI issue and in all related studies.

Up to 5 of the best scientific work of the applicant, indicating the impact factor in the year of publication, the number of citations since the publication until request

for financing and the h-index.

Seccareccia, F; Perucci, CA; D'Errigo, P; Arcà, M; Fusco, D; Rosato, S; Greco, D. The Italian CABG Outcome Study: short-term outcomes in patients with coronary artery bypass graft surgery. EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY, 29 (1): 56-62 JAN 2006

IF = 2.1; N.Cit. =15

D'Errigo, P; Seccareccia, F; Rosato, S; et al. Comparison between an empirically derived model and the EuroSCORE system in the evaluation of hospital performance: the example of the Italian CABG outcome project. EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY, 33 (3): 325-333 MAR 2008

IF = 2.2; N. Cit. = 9

Scardovi, AB; De Maria, R; Coletta, C; Aspromonte, N; Perna, S; Infusino, T; D'Errigo, P; Rosato, S; et al. Brain natriuretic peptide is a reliable indicator of ventilatory abnormalities during cardiopulmonary exercise test in heart failure patients. MEDICAL SCIENCE MONITOR : INTERNATIONAL MEDICAL JOURNAL OF EXPERIMENTAL AND CLINICAL RESEARCH. 2006 May;12(5):CR191-5.

IF = 1.59; N. Cit. = 8

Coletta, C; De Marchis, E; Lenoli, M; Rosato, S; et al. Reliability of cardiac dimensions and valvular regurgitation assesment by sonographers using hand-carried ultrasounds devices. EUROPEAN JOURNAL OF ECHOCARDIOGRAPHY. 2006; 7, 275-283

IF= 1.92; N. Cit = 4

Rosato, S; Seccareccia, F; D'Errigo,;P; Fusco, D; et al. Thirty-day mortality after AMI: effect modification by gender in outcome studies. EUROPEAN JOURNAL OF PUBLIC HEALTH. 2009 Nov 27. [Epub ahead of print]

IF = 2.18; N. Cit. = 0

H-INDEX = 4

Up to 5 of the scientific work of the applicant on the subject of the request, indicating the impact factor in the year of publication, the number of citations since the publication until request for financing and the h-index

Seccareccia, F; Perucci, CA; D'Errigo, P; Arcà, M; Fusco, D; Rosato, S; Greco, D. The Italian CABG Outcome Study: short-term outcomes in patients with coronary artery bypass graft surgery. EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY, 29 (1): 56-62 JAN 2006

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Rosato S, D'Errigo P, Badoni G, Fusco D, Perucci CA, Seccareccia F. Comparison between administrative and clinical databases in the evaluation of cardiac surgery performance. G Ital Cardiol (Rome). 2008 Aug;9(8):569-78. (Italian).

N cit = 1

H-INDEX = 2

Up to 5 of the recent scientific work of the applicant, indicating the impact factor in the year of publication, the number of citations since the publication until request for financing and the h-index

Rosato, S; Seccareccia, F; D'Errigo,;P; Fusco, D; et al. Thirty-day mortality after AMI: effect modification by gender in outcome studies. EUROPEAN JOURNAL OF PUBLIC HEALTH. 2009 Nov 27. [Epub ahead of print]

IF = 2.18; N. Cit. = 0

Rosato S, D'Errigo P, Badoni G, Fusco D, Perucci CA, Seccareccia F. Comparison between administrative and clinical databases in the evaluation of cardiac surgery performance. G Ital Cardiol (Rome). 2008 Aug;9(8):569-78. (Italian).

N cit = 1

D'Errigo, P; Seccareccia, F; Rosato, S; et al. Comparison between an empirically derived model and the EuroSCORE system

in the evaluation of hospital performance: the example of the Italian CABG outcome project. EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY, 33 (3): 325-333 MAR 2008

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Scardovi, AB; De Maria, R; Coletta, C; Aspromonte, N; Perna, S; Infusino, T; D'Errigo, P; Rosato, S; et al. Brain natriuretic peptide is a reliable indicator of ventilatory abnormalities during cardiopulmonary exercise test in heart failure patients. MEDICAL SCIENCE MONITOR : INTERNATIONAL MEDICAL JOURNAL OF EXPERIMENTAL AND CLINICAL RESEARCH. 2006 May;12(5):CR191-5.

IF = 1.59; N. Cit. = 8

Coletta, C; De Marchis, E; Lenoli, M; Rosato, S; et al. Reliability of cardiac dimensions and valvular regurgitation assesment by sonographers using hand-carried ultrasounds devices. EUROPEAN JOURNAL OF ECHOCARDIOGRAPHY. 2006; 7, 275-283

IF= 1.92; N. Cit = 4

H-INDEX = 3

Originality of the project

This proposal describes the first observational multicenter study on the comparative effectiveness of TAVI vs. AVR, VP, or MT in a high pre-operative risk subgroup of the Italian SSAS population. The study design is based on a national survey, endorsed by the Superior Institute of Health (ISS, Istituto Superiore di Sanità), and has been recently launched in order to evaluate the appropriateness and effectiveness of AVR and TAVI procedures.

This study represents the first attempt to assess the short, medium, and long-term effectiveness of TAVI compared to other treatments currently available in clinical practice. The study will also account for potential differences in patient severity among the different treatment groups.

Our primary point of originality is that we combine two traditionally different approaches, prospective and retrospective, into a single study. Due to the recent introduction of the TAVI procedure into the health system, it is not feasible to review it from the administrative database. There are no shared or standardized coding guidelines to identify data related to the TAVI procedure. Therefore, it is necessary to use an ad hoc, prospective, data-gathering approach for TAVI procedures. In contrast, a prospective approach is inappropriate for gathering AVR, VP, or MT data, because, currently, patients considered a high operative risk are most likely recommended for a TAVI procedure rather than the traditional, more hazardous or palliative treatments. Thus, it is reasonable to use a retrospective data-gathering approach for collecting data on AVR, VP, or MT procedures performed in patients considered a high operative risk.

Moreover, another point of originality will be the method of recording data and patient follow up. Due to the high interest and assured collaboration of many Regions in the project, we will set up an administrative internal linkage to the HDR System or use the Regional Mortality Registry (RMR) for follow up; this strategy will minimize the proportion of patients lost to follow up and achieve more accurate results.

For the achievement of the proposed results, it will be necessary to consider different databases. Therefore, we propose to ensure linkage among the following databases: the clinical ad hoc database for TAVI, the Italian Society of Interventional Cardiology (GISE) Registry of hemodynamic laboratories for VP, and the HDR for AVR and MT. In addition, to properly outline the risk profile of AVR, VP, and MT patients, HDRs and records from the GISE Registry should be linked to individual clinical charts. Finally, all the selected records should be linked to the RENCAM to facilitate the follow up.

TAVI patient outcome (survival, occurrence of re-interventions, and MACCE) recording will be implemented in the administrative database by linking each enrolled TAVI procedure in the prospective database to its corresponding HDR. Thus, from the administrative database, we can define objective, region-specific criteria for identifying distinct TAVI procedures. Then, we can work out a shared proposal of standardized guidelines for TAVI coding.

Moreover, the measure of the unaddressed need that the proposed study will address is reflected in the undisputed will of national and regional institutions, scientific societies, hospitals, and individual specialists, to cooperate in this study with the common aim of obtaining evidence-based information on the use of TAVI vs. other available treatments.

Finally, a primary strength of this study is the establishment of a clinical monitoring system aimed at controlling the quality of recorded data. To this aim, independent observers, according to specific standardized operating procedures, will visit each participating hospital and compare data from the transmitted records to those reported in the original clinical charts. These procedures will allow assessments of the reliability and completeness of the database and help maintain consistent quality control. Moreover, the analyses of "suspected ICD-9-CM codes" from the HDR and their corresponding original clinical charts will guarantee the completeness of TAVI cohort enrollment.

Development strategy of the project, methodology, preliminary data and bibliographic references

The rapid growth of health technology and medical devices can often make it difficult to conduct the rigorously scientific protocols of RCTs. Observational outcome studies can provide prompt results and scientific evidence to support medical decisions. Implementing this type of study is easier than implementing RCTs to yield answers from real clinical practice while avoiding some experimental constraints such as "eligibility and/or exclusion criteria". This feature is particularly appropriate to monitor a current situation in its ongoing evolution.

OOSs, while non-experimental, are being increasingly used to assess and compare treatments. Their main peculiarity is the implicit lack of randomization. Methods of study design and analysis implemented to balance this characteristic are generally called "risk adjustment". These methods compensate the lack of randomization, controlling all known factors associated with

the outcome and heterogeneously distributed among the categories of exposure under study.

TAVI has been introduced in clinical practice without experimental evidence; only few studies, mostly at short term end-point and conducted by the providers themselves, have been implemented; on the other hand, an experimental randomized study on TAVI could be very difficult to set up, both for the slowness to get results and for ethical problem due to the randomization of patients between the two different alternatives.

Considering also that the TAVI procedure is yet into clinical practice, it represents the ideal situation to implement an OOS.

The main objective of the study is to find out the actual gain in the short, medium and long-term prognosis terms (survival, occurrence of re-interventions and major adverse cardiac and cerebrovascular events - MACCE) of the new TAVI procedure, in comparison with AVR, VP and MT in a high pre-operative risk subgroup of the Italian SSAS population.

To reach this purpose two different strategies will be pursued:

- prospective data collection for SSAS patients undergoing a TAVI procedure in the participating Italian hospitals;

- retrospective data collection for high pre-operative risk SSAS patients undergoing the traditional approaches (AVR, VP and MT) in the year preceding the TAVI introduction in the National Health System.

The present study is designed as a spin-off of a nation-wide observational study endorsed by the Superior Institute of Health (ISS, Istituto Superiore di Sanità), in order to evaluate appropriateness and effectiveness of AVR and TAVI procedures. The prospective data collection for SSAS patients undergoing TAVI procedure will be carried out according to the strategy suggested by the main study.

The project consist in the following four phases:

The FIRST PHASE will last 6 months (0-6): A further peer review of the scientific literature of SSAS treatments will be performed. The prospective operative protocol will be developed. The algorithm that will allow to identify the patients who underwent traditional approaches (AVR, VP and MT) using the administrative databases will be built.

The SECOND PHASE will last 6 months (6-12): Prospective data collection will be started. The Algorithm that allows to identify the patients who underwent traditional approaches (AVR, VP and MT) will be implemented on the administrative databases. Clinical monitoring activities will be set up to completeness assessment.

The THIRD PHASE will last 18 months (12-30): Data collection will continue. Follow up data within Regional HDR and Regional Mortality Registry will be collected. Clinical monitoring activities will become operative. Interim epidemiological and statistical analysis will be performed.

The FOURTH PHASE will last 6 months (30-36): Epidemiological and statistical analysis on collected data will be implemented. All scientific founding concerning the declared objectives will be published in a scientific report and presented in a final workshop.

To compare traditional treatments with TAVI, according to the recently published Italian TAVI guidelines, only patients aged >= 75 with an ES >= 20, or aged >= 85 with an ES >= 10 will be considered. Moreover, patients characteristics will be used to obtain severity adjusted outcome estimates for valid comparison between treatments.

Hospitals of the National territory where TAVI procedure are performed will be identified analyzing the Register of the hemodynamic laboratories activity, kept by the Italian Society of Interventional Cardiology (GISE Register); Hospitals will be subsequently invited to participate to the study. In the second phase data collection will be started for hospitals that will accept to participate to the study. For the retrospective strategy, to proper identify VP patients, data from the GISE Register will be exploited again. On the contrary, AVR and MT population will be settled analyzing regional (Lombardia, Emilia Romagna, Toscana, Lazio, Campania, Sicilia) hospital discharge record (HDR) database from July 01th 2006 to June 30th 2007 (one previous year of the introduction of TAVI procedure in the NHS).

In particular for

- VP population: Comorbidities and characteristics needed to define the surgical risk (ES) of selected patients from the GISE register will be drawn from clinical charts linked to the selected records.

- AVR and MT population: To narrow the high-risk SSAS population, only HDRs of patients aged >= 75 with ICD 9 CM code of aortic stenosis disturbs (424.1) will be considered. Then, to identify AVR procedures ICD 9 CM code 35.20, 35.21 or 35.22 will be used. Finally, the absence of any valvular procedure within the study period will be used to identify patients undergoing MT. Comorbidities and characteristics needed to define the surgical risk (ES) of selected patients will be drawn from clinical charts linked to the selected HDRs or to records from the GISE register.

The considered outcomes to compare the different treatments are: mortality at 30 days, one year and two years; major adverse cardiac and cerebrovascular events (MACCE) at one and two years; occurrence of cardiovascular re-intervention at 30 days, one year and two years.

The definition of patients' outcome will be implemented in a first phase linking the selected records with HDRs; in particular:

- for life status definition: analyzing the discharge modality of the admission itself, and all the following ones of the same patient;

- for MACCE and re-intervention: analyzing the diagnosis and procedural fields of the admission itself, and all the following ones of the same patient.

In a second phase, all the patients without any following admission and discharged alive before the specific end point, will be linked with the Regional Mortality Register.

Once the risk profile of patients will be drawn and the outcome defined, statistical analysis will be implemented using the propensitive score with the match methodology to equalize the pre-operative risk of patients.

INTERNATIONAL PRELIMINARY DATA

In Europe take place approximately 50,000 AVRs annually and about as many are performed in the USA. AVR has a significant survival benefit with 1, 2, and 5-year survival rates of 87%, 78%, and 68%, respectively, vs. 52%, 40%, and 22% in those without AVR ($p < 0.001$). Over time, even the early outcome improves: currently, operative mortality of isolated AVR is 2-5% in patients <70 years and 5-15% in older adults.

A recent study shows TAVI procedural success rate of 93.3% and 30-day mortality rate of 10.4%. Moreover, survival rates at 1 and 2-year follow-up were 76% and 64%. Patients free of MACCE at 1- and 2-year follow-up were 72% and 60%, respectively.

ITALIAN PRELIMINARY RESULTS

A national preliminary analysis has been performed on national hospital discharge records (HDR 2007) and on data from the Interventional Cardiology Register (GISE 2008). In 2007, a total of 44,633 hospital admissions for patients aged 70 years and older with a 424.1 ICD-9-CM code (Aortic Stenosis Disorders, ASDs) were recorded. The 30-day in-hospital mortality rate (HMR) was 4.27% (22,558 >=80 years, HMR 6.18%).

In 2007, 9582 AVR procedures associated with the 424.1 ICD-9-CM code were recorded (HMR: 3.24%). Considering patients >=70 years, the number of admissions was 5458 with an HMR of 4.29% (1302 >=80 years, HMR 5.38%).

TAVI is a relatively new procedure and any investigation of administrative data (available up to 2007) is not feasible. The Italian Society of Interventional Cardiology (GISE) maintains a register of activity of hemodynamic laboratories. Some results are published on their website (www.gise.it)(12). In 2008, 450 TAVIs were performed in Italy, 322 with Corevalve and 128 with the Edward's valve.

Finally, as Tamburino et al. report in an as-yet-unpublished paper, a total of 663 consecutive patients undergoing TAVI in one of the 14 enrolled centers from June 2007 to December 2009 were followed up. Procedural success and intraprocedural mortality were 98% and 0.9%, respectively. Mortality rates were 5.4% at 30 days, 10.5% at 6 months, 13.3% at 1 year, and 14.6% at 2 years. MACCE rates were 6.4% at 30 days, 12.9% at 6 months, 15.2% at 1 year, and 15.8% at 2 years.

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Structure and equipment available for research and collaborations

The coordinating center (Istituto Superiore di Sanità) will make use of the cooperation of all hospitals performing TAVI that agree to participate in the project. All regional health authorities (RHAs) where the hospitals performing the studied procedures are located will be asked to participate. Their main task will be to support some project activities, like the complete enrollment of the study cohort, easing contact and recruitment of the selected hospitals, and establishing administrative follow-up.

Finally, three operative units (OUs) will be directly involved in the study: one independent OU will cooperate with the coor-

dinating center to set up and realize all the clinical monitoring activities; one OU will cooperate with the coordinating center in all scientific activity and workshop organizations; and the third OU will be responsible for all informatics activities and software management.

A detailed description of the activities follows.

COORDINATING CENTER - ISTITUTO SUPERIORE DI SANITÀ

Study protocol writing and minimal data set definition. All activities related to the building and set up of a dedicated website for data collection and information diffusion. Periodical data collection control and drawing up of intermediate reports. Participation in periodic meetings for information sharing. Participation in the writing of all scientific papers representing official outputs of the project. The coordinating center will also perform all other activities not listed as OU activities.

For fulfillment of all listed activities, five PCs, three printers, a fax, and a share of consumables and supplies will be put at Project disposal. Moreover, a dedicated portion of a local server for the storage of data from the hospitals will be created. The SAS and STATA statistical packages will be used for data analysis.

RECRUITED HOSPITALS

Participation in the study protocol, drawing up and minimal data set definition; clinical data collection; participation in periodic meetings for information sharing. Regarding equipment, in each hospital a PC with an internet connection for data recording, a printer, and a fax will be put at Project disposal. At least one person (a cardiologist) will be employed in each hospital to support and interact with personnel involved in the clinical monitoring procedures.

REGIONAL HEALTH AUTHORITIES (RHAs) - Lombardia, Friuli, Veneto, Emilia Romagna, Toscana, Campania, Calabria, Sicilia.

Cooperation in activities related to the check of the complete enrollment of the study cohort; supply of Regional HDRs to find retrospectively the AVR and the MT performed in the previous year of TAVI introduction ; follow-up data collection within the Regional Administrative Health Informative System (retrieval of subsequent in-hospital major adverse cardiac and cerebrovascular events for each enrolled patient), and the RMRs (patient life status). Participation in periodic meetings for information sharing. Dissemination of a) clinical guide lines for appropriate patients' selection to AVR or TAVI and analysis of the related organizing problems; b) indication for TAVI procedures coding in administrative control (ASP LAZIO). In each RHA, a PC for data management, a printer, and a fax will be put at Project disposal.

OU 1 - DEPARTMENT OF EPIDEMIOLOGY OF THE REGIONAL HEALTH SYSTEM, LAZIO

Participation in study protocol writing and minimal data set definition; contribution to data management and analysis; participation in periodic meetings for results interpretation. Cooperation in the drafting of the intermediate and final reports. Sharing of all project scientific activities and workshop organizations. Two PCs, a printer, and a fax will be put at Project disposal.

The SAS statistical package will be used for data analysis.

OU2 - CLINICAL MONITORING UNIT

Setting up of standardized operating procedures (SOPs) to be followed in each participating hospital to compare information recorded in the project and that reported in the original clinical charts.. Cooperation in the drafting of the intermediate and final reports for the clinical monitoring section. Four dedicated specialists will be employed to fulfill activities provided for the clinical monitoring procedures. Four notebooks, a PC, a printer, and a fax will be put at Project disposal.

OU3 - SOFTWARE PROVIDER

Implementation of a dedicated password-protected web site accessible by each participating hospital. Building of a database structure for data recording. Creation of a document-sharing section on the web site aimed at implementing information exchange among all the parties involved in the Project (national and regional institutions, hospitals, professionals, etc.). Creation and management of a local server section dedicated for the storage of data from hospitals. Two PC, a storage block for data manteinance will be put at Project disposal.

OTHER COLLABORATIONS

Italian Ministry of Health

AGENAS (National Agency of Regional Health Services)

FIC - Italian Federation of Cardiology

SICI -GISE - Italian Society of Interventional Cardiology

SICCH - Italian Society of Cardiac Surgery

ITACTA - Italian Association of Cardiothoracic Anaesthesiologists

Teaching hospitals, scientific institutes for research, hospitalization, and health care

Relevance of the project for the National Health Service (on basis of rapid trasferibility on assistance)

TAVI is a new interventional procedure for the treatment of SSAS that is less invasive than the conventional approach (AVR) and is designed to treat high-risk patients. The TAVI procedure has been introduced into clinical practice prior to receiving results from comparative efficacy studies. During the last 3 years, some scientific societies have aimed to identify a set of criteria for SSAS patient management, derived by consensus among cardiologists and cardiac surgeons. These documents have appeared in the international scientific literature, with the acknowledgement that the suggested criteria are not based on evidence from RCT results (which are not currently available), but on clinical experience and common sense.

This proposal describes the first observational multicenter study on the comparative short, medium, and long-term effectiveness of TAVI versus AVR, VP, or MT in a high pre-operative risk subgroup of the Italian SSAS population. The study design was based on a national survey, endorsed by the Superior Institute of Health (ISS, Istituto Superiore di Sanità), and has been recently launched in order to evaluate the appropriateness and effectiveness of AVR vs. TAVI procedures.

This study is relevant to the National Health System because it will establish the transferability of knowledge through the proposed linking of databases and codification of TAVI procedures. This knowledge will facilitate assessments of the relative performance of different TAVI procedures, and the comparative effectiveness of TAVI vs. AVR, VP, or MT in a high pre-operative risk subgroup of the Italian SSAS population.

In general, the dissemination of a new methodology in clinical practice has strong structural, organizational, and economic effects on the system. In Italy, due to the current cost of devices, the use of TAVI procedures is expected to substantially increase direct costs. Further expenditure increases are expected for capital equipment investment (i.e., hybrid theaters), facilities, and personnel training. Indeed, due to the requirement that TAVI procedures must be performed by multidisciplinary teams in surgical or hybrid theaters, it is expected to require considerable hospital internal reorganization.

From this point of view, this study will supply the national and regional health systems with appropriate tools and methodologies for monitoring direct cost increases due to the TAVI procedure implementation. The cost increases can then be related to the actual gains in SSAS patient prognoses. In particular, the study will allow assessments of the short, medium, and long-term prognoses (survival, occurrence of re-interventions, and MACCE) of high pre-operative risk SSAS patients undergoing the new TAVI procedure compared to those associated with traditional surgery (AVR) or palliative care (VP and MT); this will facilitate valuations of using the different procedures.

In this connection, findings from this study will provide concrete support to professionals for properly identifying the target population for TAVI, making appropriate management choices, controlling direct costs, and enhancing patient quality of life and life expectancy.

Moreover, the proposed study design and methodology will offer the potential of standardizing the coding system and establishing specific routines and methodologies to ensure quality control. In addition, the link between clinical and administrative databases will establish systematic administrative control.

In conclusion, this observational outcome study will: 1) assess the appropriateness, effectiveness, and efficiency of TAVI in comparison with other standard therapeutic approaches currently available for high-risk SSAS patients, and 2) facilitate the use of this knowledge for improving the management of TAVI procedures, with both clinical and economic considerations.

Compliance to call

YES

Co-financings

Co-funding institutions

Institution	Available from	Amount

Overall costs of the project

Costs items and brief description	Total	Part covered by MoH funds [a]
1. Permanent staff 1 senior researcher, 1 administrative assistant	€ 90.000,00	None
2. Project Staff (ad hoc contracts/consultants/fellowship) 1 researcher, 1 technical assistant	€ 100.000,00	€ 100.000,00
3. Travel Costs and Subsistence Allowances support to regional activities for data management, meetings	€ 40.000,00	€ 35.000,00
4. Equipment	€ 25.000,00	€ 15.000,00

Costs items and brief description		Total	Part covered by MoH funds [a]
4 PCs, 1 Notebook, 2 printers, 1 fax, a storage block for data manteinance.			
5. Consumables and Supplies directly linked to the Project Stationery articles, reams, folders, toner cartridges, 1 user license for SAS statistical package.		€ 30.000,00	€ 20.000,00
6. Dissemination of results (publications, meetings/ workshops etc.) Scientific publications, meetings and workshops organization		€ 40.000,00	€ 32.000,00
7. Data handling and analysis (specify) Clinical monitoring procedures, web site implementation. RHA's activities aimed selecting the study cohort and collecting follow-up data.		€ 140.000,00	€ 140.000,00
8. Overheads for all Institutions involved (specify) Coordinating Center (ISS)		€ 38.000,00	€ 38.000,00
Totale		€ 503.000,00	€ 380.000,00
TOTAL BUDGET OF THE PROJECT:	€ 503.000,00		
TOTAL AMOUNT OF CO-FINANCINGS:	€ 0,00		
FUNDING REQUIRED TO THE MINISTRY OF HEALTH:	€ 380.000,00		
INSTITUTIONAL RESOURCES:	€ 123.000,00		

a: MoH - Ministry of Health