Giovani ricercatori

Preliminar Project

Title: TAVI versus traditional approaches in treatment of severe and symptomatic aortic stenosis patients

Letter of intent

This is an observational outcome study (OOS) that aims to assess the actual gain in patients prognosis of a new interventional procedure (transcatheter aortic valve implantation, TAVI) versus the traditional approaches (aortic valve replacement, AVR; valve-plastic, VP; medical therapy, MT) for the treatment of severe and symptomatic aortic stenosis (SSAS) in a high pre-operative risk subgroup of the Italian population .

Valvular aortic disease, because of his ill-omened prognosis and his growing prevalence in western countries, especially among elderly, represents an important public health issue.

Aortic stenosis is a common condition in all western countries with a clear increase in prevalence with age: 1.3% in patients aged 65-75 years, 2.4% in those aged 75-85 years, and 4% in patients older than 85 years.

Symptomatic severe disease affects about 40% of all aortic valvular patients and, if untreated, shows a very poor prognosis progressively evolving towards a complete disability. The mean survival rate is 40-50% and 20% at 2 and 5 years respectively. AVR is the elective procedure for SSAS patients. With proper selection, operative mortality is quite low, even in elderly patients, and long-term results have proved satisfactory. Nevertheless, as reported in the Euro Heart Survey (2003), 33% of elderly patients with SSAS were denied surgery because of their health condition and associated comorbidities. Therefore, till some years ago, three different alternatives, either very hazardous or palliative, were available for very high risk SSAS patients: a) performing a lifesaving VP procedure, b) executing an AVR despite contraindications or c) implementing a simple medical therapy.

In recent years a new therapeutic approach (TAVI) is available for this kind of patients, feasible in hemodynamic laboratories by interventional cardiologists. Seven years after the first-in-man, over 6000 patients worldwide have been treated by TAVI.

In Italy, since its introduction, TAVI spread dramatically, moving from 30 procedures performed in 2007 to about 700 in 2009; moreover it has been possible to observe how this practice, originally addressed to a specific high-risk patient subgroup, is broadening exponentially to younger patients and without relevant contraindications versus traditional surgery procedure.

Because of current device costs, the employment of TAVI will lead to unavoidable direct costs increase for the National Health System (2000 euro for each device employed in the AVR procedure vs. 28,000 euro for each bio-prosthesis used in the TAVI procedure). Thus, taking into account the current trend, an outlay of 28 million euro for about 1000 TAVI against 20 million euro for the estimated 10,000 AVR is expected in Italy in 2010.

To date, in spite of its quick spread, TAVI safety and efficacy have been evaluated only by comparing the procedural and 30-day outcomes with predicted operative mortality as calculated by questionable surgical risk calculators (i.e. EuroSCORE, ES), but no RCTs have determined results comparing TAVI against routine palliative care (i.e. VP or MT) or TAVI against AVR. Moreover, no studies have yielded reliable information on medium- and long-term TAVI effectiveness or cost-effectiveness profiles.

To address comparative effectiveness evaluations, OOSs are increasingly used. They represent a valid approach to evaluating comparative treatment effectiveness in real populations mainly when, as in this case, experimental studies are difficult to set up. OOSs can be easily described as an alternative / complement to experimental studies, making the most of tools and methodologies suitable to achieving the same aims of RCTs, but avoiding some known problems related to trial organization.

This proposal describes the first observational multicenter study on the comparative effectiveness of TAVI versus AVR, VP or MT 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 find out the actual gain in the short, medium and long-term prognosis (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 collect clinical and procedural information two different strategies will be pursued:

- perspective 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.

Concerning the perspective strategy, as national TAVI coding guidelines are not yet available and an administrative data collection is not feasible, an "ad-hoc" data collection system will be set up.

For the retrospective strategy, to proper identify VP patients, data from the register of the hemodynamic laboratories activity, kept by the Italian Society of Interventional Cardiology (GISE) will be exploited. 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. 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.

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.

The main originality of the project is that it represents the first attempt to assess TAVI effectiveness at short, medium and long-term, in comparison with all treatments available before TAVI introduction in clinical practice, accounting for possible differences in patient severity among the treatment groups. Moreover, given that the spread of a new methodology in clinical practice has a strong economic impact on the health system, this study will allow monitoring if the expected direct costs increase is balanced by an actual gain in patients prognosis.

The study outcomes detection (survival, occurrence of re-interventions and MACCE) will be implemented using the administrative database by linking each enrolled TAVI from the perspective database with its related HDR. This circumstance will allow defining objective and region-specific criteria to identify TAVI procedures coding from administrative database and to work out a shared proposal of a TAVI coding standardized guideline.

Some possible weaknesses may however affect the achievement of the objectives. In particular, as the recruitment of hospitals performing TAVI is voluntary based, the number of participating hospitals may be one of the possible issues as the absolute number of recorded TAVI procedures could be insufficient to detect the possible differences among treatments under study (low power). Moreover, as the homogenous distribution of participant hospitals across national territory is not assured, the enrolled hospitals could not be representative of the Italian setting.

Another criticism, typical of long term follow-up cohort studies, is linked to the outcome detection. Being this study designed to evaluate long term comparative effectiveness, of TAVI versus the traditional approaches, a follow-up of at least 24 months to detect MACCE in the studied population will be necessary. To overcome this problem, follow-up data collection within the Regional Health Informative System (retrieval of subsequent in-hospital MACCE for each enrolled patient) and the Regional Mortality Registry (patients life status) will be implemented.

Still, the main criticism will be to pick out, retrospectively, the SSAS diagnosis from the selected clinical charts; the main problem is linked to the lack in specificity of the ICD 9CM code 424.1 (valvular aortic disturbs); even so, it is the sole diagnostic code that can be used to identify SSAS. To overcome this problem, the outlining of certain diagnostic criteria to be met by clinical charts anamnestic information is necessary in order to get the most accurate and rigorous definition of SSAS diagnosis.

Moreover, the AVR procedures are definitely recorded in HDR and easily recognizable due to the high specificity of their ICD 9 CM codes. For these procedures loss or misclassification problems represent very rare events. This is not the case of MT where the risk that not all SSAS patients treated only by MT is properly recognized remains an actual study weakness.

Finally some SSAS patients could not be admitted in hospital, thus resulting completely missing.

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