The T.A.R.Ge.T. project: a regional program to reduce hip fracture in elderly patients. Main results of retrospective phase

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Summary

The Tuscany Region was the first Italian Region to initiate a program for the prevention of hip fractures in over 65 year old. The T.A.R.Ge.T. project “Appropriate treatment of geriatric re-fractures in Tuscany” (Trattamento Appropriato delle Rifratture Geriatriche in Toscana), which is still on-going, includes a preliminary phase (2009-2010) for baseline analysis and education of the participating centers and a 4-year prospective phase (2011-2014). The monitoring system is performed horizontally analyzing 5 different flows: SDO (Performance Hospitalization), SPF (Pharmaceutical Distribution Dataset), FED (Direct Distribution Dataset), SAA (Registry of Patients), SPA (Specialized Outpatient) flows. In this review will be shown some of the most important results of analyzes of the retrospective phase. Between 2006 and 2011 only 26% of hip fractured patients has being treated with anti-osteoporotic drugs. The percentage of treatment increases 10% after the second fracture. Until 2011 there wasn’t in Tuscany a prevention program of bone fragility; patients treated with specific treatment only in severe cases: this phenomenon implies that mortality and re-fracture are higher on treated patients than in patients who did not have any kind of treatment.

The treated patients are the most severe and therefore they have a higher risk of death and re-fracture.

KEY WORDS: fractures; hip; anti-fracture drugs; re-fractures; persistence; institutional database.

Introduction

The Tuscany Region, through the T.A.R.Ge.T. project (Appropriate Treatment of Geriatric re-fracture in Tuscany) was the first region in Italy to enable a project to reduce hip fractures in elderly patients. The main objectives of the project can be summarized in the following three points:
1) activating a diagnostic therapeutic way aimed at the prevention of hip re-fracture;
2) building a comprehensive picture of the problems related to bone fragility of elderly hip fractured patients;
3) reducing waste of resources due to poor adherence to therapy.

The project involves a complex monitoring system based on the analysis of administrative public data set of the Tuscany Region, in particular the project is based on an horizontal analysis of different data set. This different type of analysis allows us to relate and study the sanitary type, pharmacological and economic effects of the project in the various areas.

The project started on 1 January 2011 and has developed on two different levels: the first retrospective level analysis regarding the 4 years prior to 2011 has allowed us to obtain a complete picture of the main indicators, the size and dynamics relating to geriatric fractures and their drug treatment in Tuscany. The second, prospective, level of analysis, instead, allows to evaluate the effects of the project and the changes of the epidemiological indicators respect to the previous four years.

Methods

We have analyzed five regional administrative database: SDO (Performance Hospitalization), SPF (Pharmaceutical Distribution Dataset), FED (Direct Distribution Dataset), SAA (Registry of Patients), SPA (Specialized Outpatient). The six administrative flows were analyzed in horizontal way, the first of hip fractured patients living in Tuscany from the year 2006 has been correlated with the information extracted from the other flows regarding drug treatment and other medical and personal information.

Hip fractured patients from 2006 to 2013

Each year there are about 6,000 over sixty patients hip fractured, of these about 5% re-fractured a second time within a year of the first fracture; the number of fractures per year in fact, is greater than the number of fractured (Figure 1).
The number of fractured and fractures fluctuate with the years; the differences found between the years are not significant from a statistical standpoint, obviously the oscillatory behavior is a typical factor of the phenomenon detected. The monitoring system allows to analyze data at the level of each business unit; the Table 1 shows the number of fractured patients from 2006 to 2013 in Tuscany hospitals (only hospitals with more than 200 hospitalizations in 2013 are shown).

### Hip fractured patients, age class analysis

The average age of hip fractured patients in Tuscany is about 80 years for women and 81 years for men. Table 2 and Figure 2 show the data of hip fractured patients over 65 in Tuscany from 2006 to 2013 by age clusters 5 years.

Within the relevant time we observed a shift in the number of fractured towards higher age classes. We observed a slight (but not yet significant) trend in lower incidence of younger age groups. This trend is more pronounced than the values of the general aging of the population. This phenomenon suggests a first effect of policies to raise awareness for the prevention of bone fragility that seem to be transposed by the younger patients.

### Gender analysis

Women represent the majority of hip fractured patients and that the composition does not vary within the relevant time (Table 3).
Analysis on hip fractured patients treated with antiosteo-
porotic medications

From 2006 to 2011 about 26% of patients being treated with
anti-osteoporotic drugs (AIFA Note 79). 92% of patients are
women.

Regarding gender analysis it is observed that on average on-
ly 10% of hip fractured patients males are started to drug
management while for women this percentage rises to around
31% (Table 4) (1).

Analysis on hip fractured patients treated with vitamin D

From 2006 to 2011 the percentage of hip fractured patients
treated with vitamin D has increased from 19 to 31%.

Male patients increased from 11 to 20% while the female pa-
tients increased from 21 to 34%.

We also observed a significant increase in the use of vitamin D
from 2010. This increase occurred for both sexes (Table 5).

First year mortality of the hip fractured patients

Analyses on mortality appeared immediately difficult to as-
se ss because of the advanced age of the hip fractured pa-
tients. Moreover the consequent high comorbidity greatly
complicates any attempt to correlate the event of death with
hip fracture and with its drug treatment.
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Figure 3 - Hip fractured elderly patients trend for each age classes.

Table 3 - Hip fractured patients, gender analysis from 2006 to 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Male</th>
<th>%</th>
<th>Female</th>
<th>%</th>
<th>Tot.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>1275</td>
<td>22%</td>
<td>4431</td>
<td>78%</td>
<td>5706</td>
<td>100%</td>
</tr>
<tr>
<td>2007</td>
<td>1192</td>
<td>22%</td>
<td>4238</td>
<td>78%</td>
<td>5430</td>
<td>100%</td>
</tr>
<tr>
<td>2008</td>
<td>1196</td>
<td>21%</td>
<td>4367</td>
<td>79%</td>
<td>5563</td>
<td>100%</td>
</tr>
<tr>
<td>2009</td>
<td>1245</td>
<td>22%</td>
<td>4314</td>
<td>78%</td>
<td>5559</td>
<td>100%</td>
</tr>
<tr>
<td>2010</td>
<td>1371</td>
<td>23%</td>
<td>4465</td>
<td>77%</td>
<td>5836</td>
<td>100%</td>
</tr>
<tr>
<td>2011</td>
<td>1316</td>
<td>24%</td>
<td>4116</td>
<td>76%</td>
<td>5432</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 4 - Hip fractured patients treated with anti-osteoporotic medications, gender analysis from 2006 to 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Male Fractured</th>
<th>Treated</th>
<th>%</th>
<th>Female Fractured</th>
<th>Treated</th>
<th>%</th>
<th>All patients Fractured</th>
<th>Treated</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>1275</td>
<td>141</td>
<td>11%</td>
<td>4431</td>
<td>943</td>
<td>21%</td>
<td>5706</td>
<td>1084</td>
<td>19%</td>
</tr>
<tr>
<td>2007</td>
<td>1192</td>
<td>127</td>
<td>11%</td>
<td>4238</td>
<td>1026</td>
<td>24%</td>
<td>5430</td>
<td>1153</td>
<td>21%</td>
</tr>
<tr>
<td>2008</td>
<td>1196</td>
<td>155</td>
<td>13%</td>
<td>4367</td>
<td>1043</td>
<td>24%</td>
<td>5563</td>
<td>1198</td>
<td>22%</td>
</tr>
<tr>
<td>2009</td>
<td>1245</td>
<td>151</td>
<td>12%</td>
<td>4314</td>
<td>1125</td>
<td>28%</td>
<td>5559</td>
<td>1276</td>
<td>23%</td>
</tr>
<tr>
<td>2010</td>
<td>1371</td>
<td>256</td>
<td>19%</td>
<td>4465</td>
<td>1411</td>
<td>32%</td>
<td>5836</td>
<td>1667</td>
<td>29%</td>
</tr>
<tr>
<td>2011</td>
<td>1316</td>
<td>259</td>
<td>20%</td>
<td>4116</td>
<td>1408</td>
<td>34%</td>
<td>5432</td>
<td>1667</td>
<td>31%</td>
</tr>
</tbody>
</table>

Table 5 - Hip fractured patients treated with vitamin D and calcium, gender analysis from 2006 to 2011.

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Table 6 - Patients died within one year after hip fracture from 2006 to 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Male</th>
<th>Female</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fractured</td>
<td>Treated</td>
<td>%</td>
</tr>
<tr>
<td>2006</td>
<td>1275</td>
<td>405</td>
<td>32%</td>
</tr>
<tr>
<td>2007</td>
<td>1192</td>
<td>392</td>
<td>33%</td>
</tr>
<tr>
<td>2008</td>
<td>1196</td>
<td>410</td>
<td>34%</td>
</tr>
<tr>
<td>2009</td>
<td>1245</td>
<td>411</td>
<td>33%</td>
</tr>
<tr>
<td>2010</td>
<td>1371</td>
<td>423</td>
<td>31%</td>
</tr>
<tr>
<td>2011</td>
<td>1316</td>
<td>384</td>
<td>29%</td>
</tr>
</tbody>
</table>

Another important element to consider is the fact that with a few exceptions does not exist in the Tuscan Region an institutional prevention program for bone fragility. Patients are treated with specific treatment only in severe cases. This phenomenon implies that mortality is higher on treated patients than in patients who did not have any kind of treatment. The treated patients are the most severe and therefore they have a higher risk of death. The trend in mortality decrease on men, while remaining virtually unchanged for women (2) (Table 6, Figure 4).

The analysis of the hip re-fracture

The analysis of the hip re-fracture is the most important aspect of the whole project. In fact the first objective of the project is the "reduction of hip re-fractures on the elderly osteoporotic". For all hip fractured patients for each year we calculate the incidence of hip re-fracture in the following years. The analysis of the aggregate values of the eight years showed that in the year after the fracture approximately 1% of patients re-fracture. The second year shows a percentage double while the third year (following the first fracture) the percentage of re-fracture decreases progressively. In particular: in the first year (the same of the major fracture) the average percentage is equal to 0.96%, the second year 1.96%, the third year 1.48, the fourth 1.17%, the fifth 0.99%, the sixth 0.75%, the seventh 0.63% and the eighth 0.53%. The cumulative values are the following: first year 0.96%, second year 2.96%, third year 4.41%, fourth year 5.57%, fifth year 6.56%, sixth year 7.32%, seventh year 7.95%, eighth year 8.47%.

These values have been processed without taking account of the mortality which in elderly fractured patients appears very high. There is not significant differences in the incidence of re-fracture between 2006 and 2013 for each interval (3-6) (Table 7).

Correlation between hip-re-fractures. Drug treatment and persistence in therapy. A preliminary analysis

Based on these data it was decided to carry out a comparative analysis of the values and trends detected on re-fracture with the values and trends identified by the percentages of
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Table 7 - Incidence of re-fractures from 2006 to 2013.

<table>
<thead>
<tr>
<th>Year</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-fractures in 1st Year</td>
<td>0.88%</td>
<td>0.98%</td>
<td>0.88%</td>
<td>0.82%</td>
<td>1.24%</td>
<td>0.93%</td>
<td>0.82%</td>
<td>0.98%</td>
</tr>
<tr>
<td>Re-fractures in 2nd Year</td>
<td>2.03%</td>
<td>1.86%</td>
<td>2.23%</td>
<td>1.96%</td>
<td>2.00%</td>
<td>1.54%</td>
<td>1.86%</td>
<td></td>
</tr>
<tr>
<td>Re-fractures in 3rd Year</td>
<td>1.47%</td>
<td>1.52%</td>
<td>1.38%</td>
<td>1.37%</td>
<td>1.42%</td>
<td>1.54%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-fractures in 4th Year</td>
<td>1.12%</td>
<td>1.09%</td>
<td>1.30%</td>
<td>0.84%</td>
<td>1.40%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-fractures in 5th Year</td>
<td>0.93%</td>
<td>0.98%</td>
<td>1.02%</td>
<td>0.93%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-fractures in 6th Year</td>
<td>0.81%</td>
<td>0.75%</td>
<td>0.65%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-fractures in 7th Year</td>
<td>0.56%</td>
<td>0.67%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-fractures in 8th Year</td>
<td>0.53%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The data in Table 8 show that the percentage trend of treated patients and the related adherence value do not seem to affect particularly the trend of re-fracture.

In the last two periods we can also observe an increase of re-fractures in the presence of an increase of treated patients.

The persistence on therapy value appears constant.

These results however should not lead to hasty conclusions about a not reverse relationship between treatment and re-fracture. In fact in a further analysis we noticed that there is significant differences in the percentage of treated people in case of fracture or re-fracture.

From 2006 to 2010 we calculated the percentage of patients treated after the first fracture. Then we calculated the same percentage of patients treated after re-fracture who had not been treated before.

The result is significant, the first fractures are treated on average for 34% of cases, while the re-fracture are treated for 43% of total re-fracture, the difference is 9%.

The results of this analysis explains the trend first observed: in absence of a prevention policy operators are more likely to treatment in cases of re-fracture rather than in cases of the first fracture is not therefore treatment which affects the trend of re-fracture but is the increase in re-fracture that influences operators to treat patients.

Adherence in therapy in T.A.R.Ge.T. project

Among the objectives of the project is placed particular emphasis on “reducing waste of resources due to poor adherence in therapy”; it is evident that a good adherence can allow a higher efficacy of the drugs with the consequent reduction of re-fracture.

The analyzes performed on the Administrative Database may allow the analysis of adherence in therapy.

Table 9 shows some of the results obtained with the analysis of persistence in therapy over the entire population of patients treated with anti osteoporosis drugs (AIFA note 79) in 2010.

The data shown are calculated on the basis of days of therapy for each patient. All data were adjusted by the bias identified and finally were made comparable one another standardizing on a monthly basis (some drugs in the database show the monthly value as 28 days or 37.5 and their multiples, etc.).

As regards the hip fractured patients, the current methodologies of analysis used to determine adherence in therapy are limited by the reduced number of hip fractured patients treated. These issues have been resolved using methodologies based on “longitudinal analysis” and the results are being published.

Assessment of the total cost of treatment and quantification of waste

Based on the data in Table 9 we made a brief reflection on the economic effects of appropriate therapy.
The T.A.R.Ge.T. database also contains the information on regional expenditure for each drugs (in Administrative Database these kind of data has a very high degree of reliability). Were considered: alendronate, risedronate, strontium ranelate, ibandronate. These four drugs in 2010 have covered more than 79% of total spending in osteoporosis therapy. For each drug was calculated the persistence average (for all classes of age) for one year. Considering the level of persistence on therapy in one year for all patients who started an anti-fracture therapy in 2010, it was calculated the share of expenditure for therapies not persistent and therefore will not have the expected effects on the health of the patient (Table 10). More than 5 million euro in 2010 were spent in Tuscany for not effective therapy. The increase of one percentage point shift over then 141.000 euros from the “good therapy area” to the area of “waste and ineffective therapy” (7, 8-14).

Conclusions and future prospects

The T.A.R.Ge.T. project is the first example of horizontal “analysis” of the data contained in the flows of the regional database. The statistical analysis of administrative databases were not difficult, but the absence of a methodological framework did not provide certainty about the actual capacity of monitoring system to support the information needs of the project. Moreover the “Administrative” nature of Databases initially posed some doubts about the real possibility of using the data for the purposes of medical-scientific of the project. These problems have led initially to a careful analysis of the results and a continuing search for evidence with objective data (scientific medical and statistical) in order to validate the results obtained. The work carried out has identified some specific paths of analysis and appropriate indicators in order to enable effective monitoring system. The data presented in the previous chapters provide a summary of the main analyzes performed; many other analyzes were developed that have identified several other indicators which are not shows in this work. The monitoring system of the T.A.R.Ge.T. project is based on many “frequency analyzes” through which we will be able to measure the results of the interventions on prevention system. The results obtained and the knowledge gained on the methodologies of “horizontal” Administrative Database analysis led us to pursue a different type of analysis. In fact, the data available if differently organized within the database and then processed with appropriate tools, can be
analyzed through typical methods of “Longitudinal” analysis. Longitudinal analysis as well as provide information on changes in volumes and trends shows information on the various relationships between variables that can occur in the system. The main advantage of these methods consists in the possibility of studying the “individual development” of all outcome. This development may be related with the development of one or more predictors present in the system (15-19). Since the autumn of 2014 it was decided to pull out all the data available in the T.A.R.Ge.T. database. All the data have been restated through a new software (data manager) and stored on a new Database internal to our structure. This new approach allowed us to organize all the data on the basis of the identification number of the patient but, unlike the previous system, the current methodology has allowed us to “spread” the information chronologically on individual timelines of each individual patient. In this way it is possible to proceed with inferential advanced analysis using various models (GEE: Generalized Estimating Equation; LMM Linear Mixed Models; GLMM Generalized Linear Mixed Models).

The new methods allowed to “correct” many database errors, allowed to integrate the missing data with the same information extracted from different flows, and finally made it possible to identify exactly the number and the nature of all the “missing data” and all the database errors. The new system of data management, and in particular the software used allows the extraction of data in different formats so as to be immediately processed by the different software used in various advanced statistical analysis. This new way of data integration, and in particular the use of external data management allows the integration of data extracted from T.A.R.Ge.T. databases with additional data extracted from the regional system (different from T.A.R.Ge.T. database). This way permits to extend and integrate the analysis with information about use of other drugs (multi-pharmacy analysis), other diseases (comorbidity analysis), etc. These additions may be required through special requests to the Regional Information Systems (after special authorization of the competent departments) without involving and modifying the method of updating and integrate of T.A.R.Ge.T. data, now consolidated and efficient. These new methodologies may provide many and different information about bone fragility, and in particular on the hip-fracture patients.

Table 10 - Economic effects of appropriate therapy for the major anti-fracturative drugs in 2010.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Alendronate</th>
<th>Risedronate</th>
<th>Strontium</th>
<th>Iblandronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate + Calcitriol</td>
<td>60.76%</td>
<td>66.29%</td>
<td>65.71%</td>
<td>64.03%</td>
</tr>
<tr>
<td>Risedronate</td>
<td>59.24%</td>
<td>33.77%</td>
<td>36.29%</td>
<td>55.57%</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>100.00%</td>
<td>100.00%</td>
<td>100.00%</td>
<td>165.89%</td>
</tr>
<tr>
<td>Iblandronate</td>
<td>100.00%</td>
<td>100.00%</td>
<td>100.00%</td>
<td>165.89%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total patients</th>
<th>5,024,409.20</th>
<th>4,208,901.78</th>
<th>2,910,783.88</th>
<th>2,010,158.99</th>
</tr>
</thead>
</table>

References


