Utilization, Outcomes and Costs of Implantable Cardioverter Defibrillators in Italy: A Population-Based Analysis Using Healthcare Administrative Databases

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Abstract: *Introduction*: The high cost of treatment with an implantable cardioverter defibrillator (ICD) requires continuous monitoring of its real effectiveness and appropriateness. The aim of this study was to evaluate epidemiological and economic impacts of ICD therapy in Lombardy, the most populated Italian region. *Materials and Methods*: We extracted data from DENALI, a data warehouse that organizes healthcare administrative databases concerning about ten million people covered by the Lombardy Health System (LHS). We estimated annual rates of first implant and of first replacement from 2000 to 2008. The cohort of patients who underwent a first ICD implantation between 2005 and 2007 was followed from discharge to December 31, 2008 in order to evaluate mean annual total healthcare cost per-capita, mortality and device replacement. *Results*: We identified 12,732 first implants and 4,833 replacements performed from 2000 to 2008 and we estimated the annual rates: first ICD implants increased from 55 to 236 (per million person-years), and the first replacement rates increased with a peak in 2005. A first ICD implantation cost €23,934 (standard deviation 4,986) on average and the LHS bore a further mean annual cost of €5,760 (95% confidence interval 5,592-5,931) per-capita during follow-up: 17% due to drugs, 12% to outpatient visits and 71% to hospitalizations. *Conclusions*: The results confirm the increase in ICD utilization in Italy, especially in the Lombardy region, and its high economic burden. Age and comorbidities of ICD recipients should be considered in assessing care since they influence survival outcome. Moreover, this study shows how healthcare administrative databases could be useful to understand the impact of a health intervention in large unselected populations.

Keywords: Cardiovascular disease, defibrillation, epidemiology, health care cost, health care utilization, retrospective studies.

INTRODUCTION

The implantable cardioverter defibrillator (ICD) was developed to prevent sudden cardiac death (SCD) in subjects with left ventricular systolic dysfunctions or heart failure. The extension of treatment indications (use of prophylactic ICDs in patients affected by non ischemic cardiomyopathy), clinical experience and improvements in the technical abilities of the device (implementation of cardiac resynchronization therapy through triple chamber biventricular ICD) have contributed to the exponential increase in the number of ICDs implanted in the last decades, both in the US and Europe [1-4]. In 2006, the number of first ICD implants was 577 per million person-years in the US, about five times higher than in Europe, and the difference could be attributable to several reasons [1, 5]. First of all, the first European guideline on ICD therapy was written only in 2001 and until then indications were provided at national level. Moreover, differences could be attributed to a shortage of specialized centres of electro-physiologists in some European countries, poorly developed local referral strategies and care pathways, different risk factors among populations and the economic impact of ICD implantation on public health expenditure or on health insurance programs [1, 5]. These aspects can also be the explanation for the variations in ICD utilization observed among European countries and in different areas within a same nation, as recently highlighted by the European White Book [1, 6, 7].

ICD treatment is expensive, both as regards the initial cost, connected with the implant procedure and the device, and as regards the subsequent costs for check-up, device replacement and possible complications (e.g. infections, lead and device failure) [8]. Given the substantial costs of the ICD, it is fundamental to evaluate the cost as well as the effectiveness of this treatment compared to conventional therapy in patients at high-risk of SCD. Many studies evaluated the cost-effectiveness of this treatment in primary and secondary prevention [9-12], but few evaluations were carried out in settings outside randomized clinical trials

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[13] and, given the careful selection of trial participants, there is a need to ascertain some aspects of ICD therapy in real practice.

However, to obtain clinical, epidemiological and economic information about ICD implantation activity in a population is very expensive, since it requires data collection on a large number of people for enough time to capture a long-term outcome (e.g. mortality, device replacement). Through administrative healthcare databases, this study evaluates the epidemiological and economic impact of ICD therapy in Lombardy, the most populated and one of the richest Italian regions.

MATERIALS AND METHODS

Data Sources

We obtained data for the current analysis from the DENALI [14] data warehouse, which collects and organizes the administrative datasets of the publicly funded national healthcare system (HS) in Lombardy, a region in Northern Italy with universal healthcare coverage for about ten million inhabitants. DENALI contains the following information for each person covered by the Lombardy HS since 2000: demographic characteristics (e.g. gender, place and date of birth, date of death, place of residence and domicile), hospital discharges (with discharge diagnosis and procedures coded according to the International Classification of Diseases, 9th Revision (ICD-9-CM)), pharmaceutical prescriptions, outpatient claims (laboratory and diagnostic examinations, specialist medical visits) and related costs borne by the HS. A probabilistic record linkage [15, 16] was adopted in DENALI to match the anonymized data of the different datasets belonging to the same individual. This method provides the most accurate technique of matching files when they do not share a single common identifier or when there are errors or omissions in the identifiers [17, 18].

Time Trends in ICD Implantation and Replacement

We identified ICD implantations between 2000 and 2008 according to ICD-9-CM diagnosis and procedure codes reported on hospital discharges and we classified them into first implant or replacement. The first ICD implant for a patient was defined as a hospitalization with ICD-9-CM codes 37.94 or 37.95 joined to 37.96 in the performed surgical interventions and without codes V53.32, 996.04 in the principal diagnosis or V45.02 in any diagnosis. In addition, we required the absence of previous hospitalizations with code V45.02 in any diagnosis or codes 37.94-37.98 in the performed surgical interventions. A replacement was identified as a hospitalization reporting codes 37.94-37.98 in the performed procedures and not classified as a first ICD implant. For the description of codes used to classify ICDs, please see supplemental methods (Supplement **1**).

In the same period, we estimated the annual first ICD implant rates (per million person-years) using the average Lombardy population in each year as denominators [19]. Estimates were also stratified by gender and age classes (computed at the moment of the first implant): subjects aged under 65 years, 65-74 years, 75 years and over. To evaluate temporal trends, we standardized annual rates by age and sex using the 2001 Italian population as reference [19].

We also evaluated the annual first ICD replacement rates (per hundred implant-years) calculating the time at risk of each subject with a first ICD implanted (time from the date of first ICD until the date of first replacement, death, emigration, if occurred, or the end of the year). As before, the estimates were stratified by gender and age classes (computed at the moment of the first replacement).

Cohort Study

To analyze patient profiles and the healthcare economic impact of ICD treatment, we identified all subjects who received a first ICD between 2000 and 2008 and selected among them a cohort of patients satisfying the following criteria: I) covered by the Lombardy HS for at least 5 years between 1st January 2000 and the date of hospitalization for the first ICD implant (index hospitalization); II) first ICD occurred before 1st January 2008, in order to guarantee at least one year of observational time. Since replacement usually occurs on average 4-5 years after implantation (in relation to ICD manufacturers) [20-22], applying the first inclusion criteria we aimed at excluding some events that might actually be replacements of ICD implants occurred outside Lombardy. It should be noted that these criteria ultimately led to analyze patients who underwent a first ICD between 2005 and 2007.

Patients were followed from the date for admission of index hospitalization (baseline) until the 31st December 2008, recording vital status (death or emigration) and healthcare resources consumed: hospitalizations, pharmaceutical prescriptions and outpatient claims.

At baseline, we evaluated demographic characteristics (age, gender) and coexisting chronic conditions using diagnosis codes reported in the index hospitalization and in hospital admissions occurring before the ICD implantation [23]. Moreover, the pathologies were aggregated into a comorbidity score, known as the Charlson comorbidity index (CCI) [24]. The main features of the index hospitalization were also analyzed: cost, length of stay, presence of complications and concomitant cardiac procedures [25, 26].

We analyzed data for the whole cohort and stratifying by age (patients aged under 65 years, 65-74 years, 75 years and over) and the differences among groups were evaluated with Pearson χ^2 test for nominal and discrete variables and Student's t-test with Bonferroni correction for continuous variables.

The survival analysis was carried out using the Kaplan-Meier approach for non-parametric estimate for replacement-free survival after the first ICD implant; the log-rank test was used for comparison among groups. Cox proportional hazards regression was performed to examine the effects of baseline covariates on the first ICD replacement during follow-up.

Direct healthcare cost was analyzed from the perspective of the HS and it was quantified using the amount of money that Lombardy HS reimbursed to providers of care. We estimated the mean annual per-capita cost after a first ICD implanted by means of the Bang and Tsiatis method [27]. We evaluated the total expenditure and the cost of specific health services related to the cardiovascular complexity level of patients with ICDs implanted (health services of interest), stratifying by three components: hospitalizations, drug prescriptions and outpatient visits supplied after the index hospitalization. Health services of interest were identified using ICD-9-CM codes reported in hospital discharges, ATC codes for pharmaceutical prescriptions and the description of outpatient claims (Supplement **2**).

RESULTS

ICD Utilization

A total of 12,732 first ICD implantations were performed in the population of Lombardy between 2000 and 2008, and the annual number increased rapidly from 55.3 (per million person-years) in 2000 to 236.2 in 2008 (Figure **1A**). Moreover, the highest annual relative growth with respect to the previous year was observed in 2005 (+34.9%). The same growth trend was detected in the analyses stratified by age and the annual number of implants was highest in subjects aged between 65 and 74.

During the study period, the annual first ICD replacement rate showed a growing trend: from 3.92 (95%CI: 1.69-7.73) in 2000 to 9.69 (95%CI: 8.99-10.42) in 2008, with a peak in the 2005 (15.26, 95%CI: 14.05-16.53) (Figure **1B**). No relevant differences among age classes were detected.

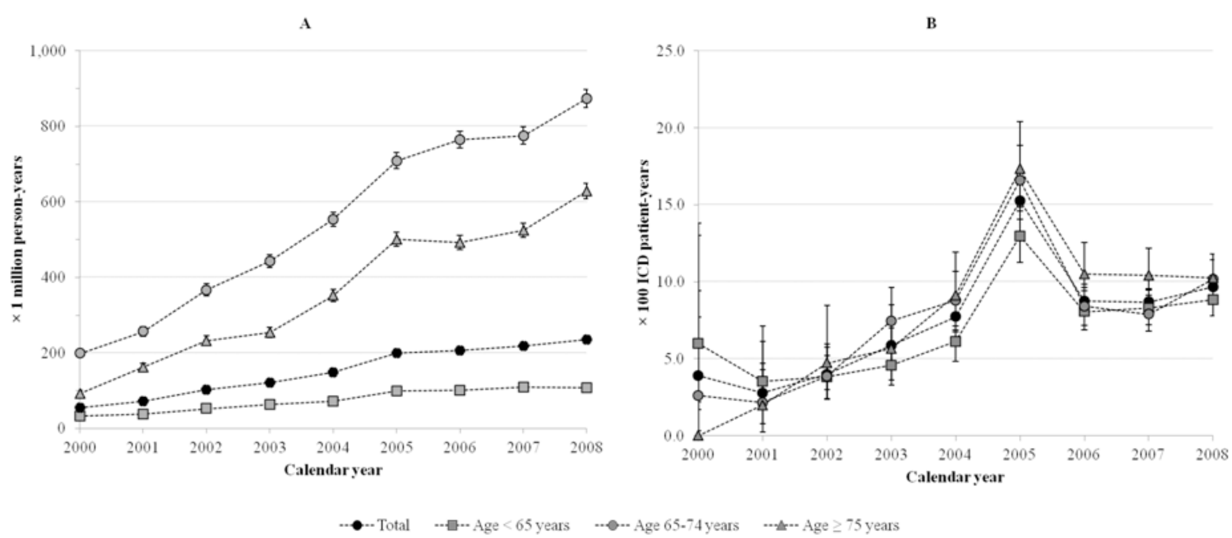

Figure 1: Trend in the ICD utilization from 2000 to 2008 in Lombardy (Italy).
Panel A=Annual number of first ICDs implanted (per million person-years) in the whole population and in subject aged under 65, between 65 and 74, 75 and over. Panel B= Annual first ICD replacement rate (per hundred patient-years) in the whole population and in subject aged under 65, between 65 and 74, 75 and over.

Cohort Study

We identified 5,814 subjects who underwent a first ICD implantation between 2005 and 2007. The baseline characteristics of patients, according to age classes, are shown in Table **1**. Subjects were principally male and the mean age was 65.0 years with standard deviation (SD) 12.0. Patients younger than 65 years accounted for 39.7% of the cohort and these subjects suffered from a lower number of chronic diseases. The prevalent chronic conditions at the time of the first ICD implanted were: heart failure (82.8%), acute myocardial infarction (39.8%) and diabetes mellitus (21.3%).

The mean cost for the index hospitalization was €23,934 (SD 4,986) and differences in cost among age groups were not observed. The mean length of stay was 10.6 days and older age was associated with a longer stay. Most patients did not undergo any cardiac procedure other than ICD implantation (66.9%) during the index hospitalization and the highest number of subjects who underwent additional cardiac procedures (35.7%) was in the "65-74 years" age class. Overall,

Table 1: Characteristics of the Study Population at Baseline and Main Features of the Hospitalization for a First ICD Implanted (Index Hospitalization), Stratified by Age Class

	<65 years	**65-74 years**	**≥75 years**	**All**
	(n=2,308)	**(n=2,289)**	**(n=1,217)**	**(n=5,814)**
Baseline characteristics				
Male, n (%)	1,917 (83.1)	1,902 (83.1)	985 (80.9)	4,804 (82.6)
Age, mean ± SD	53.4 ± 10.0	69.6 ± 2.9	78.2 ± 2.8	65.0 ± 12.0
CCI*, n (%)				
0-1	1,128 (48.9)	712 (31.1)†	307 (25.2)†,‡	2,147 (36.9)
2-3	811 (35.1)	913 (39.9)†	461 (37.9)	2,185 (37.6)
≥4	369 (16.0)	664 (29.0)†	449 (36.9)†,‡	1,482 (25.5)
Comorbidities, n (%)				
Myocardial infarction	774 (33.5)	979 (42.8)†	561 (46.1)†	2,314 (39.8)
Congestive heart failure	1,795 (77.8)	1,985 (86.7)†	1,035 (85.0)†	4,815 (82.8)
Diabetes mellitus	409 (17.7)	547 (23.9)†	281 (23.1)†	1,237 (21.3)
Renal diseases	156 (6.8)	351 (15.3)†	289 (23.7)†,‡	796 (13.7)
Chronic pulmonary disease	245 (10.6)	472 (20.6)†	270 (22.2)†	987 (17.0)
Cerebrovascular diseases	206 (8.9)	370 (16.2)†	256 (21.0)†,‡	832 (14.3)
Cancer	127 (5.5)	203 (8.9)†	143 (11.8)†,‡	473 (8.1)
Liver diseases	123 (5.3)	110 (4.8)	59 (4.8)	292 (5.0)
Index hospitalization				
Cost (€), mean ± SD	24,109 ± 5,129	23,897 ± 4,559	23,670 ± 5,452	23,934 ± 4,986
Length of stay (days), mean ± SD	9.6 ± 9.0	10.7 ± 8.8†	12.0 ± 10.1†,‡	10.6 ± 9.2
Concomitant cardiac procedures§, n (%)				
None	1,586 (68.7)	1,472 (64.3)†	831 (68.3)‡	3,889 (66.9)
At least 1	722 (31.3)	817 (35.7)†	386 (31.7)‡	1,925 (33.1)
Complications‖, n (%)				
None	2,275 (98.6)	2,239 (97.8)	1,183 (97.2)†	5,697 (98.0)
At least 1	33 (1.4)	50 (2.2)	34 (2.8)†	117 (2.0)

*Charlson Comorbidity Index. † p-value<0.05 vs. "Age < 65 years" group. ‡ p-value<0.05 vs. "Age 65-74 years" group. § diagnostic cardiac catheterization, pacemaker, percutaneous coronary intervention, coronary artery bypass grafting surgery, catheter ablation, heart valve surgery. || pneumothorax, tamponade, mechanical complication, infection associated with implant, other cardiac complication, hematoma/hemorrhage, acute renal failure requiring new hemodialysis, death.

Table 2: Mean Annual Healthcare Costs in Euros (and Confidence Interval 95%) Per-Capita During the Follow-Up in Study Population and Stratifying by Age Class

	Age<65 years	Age 65-74 years	Age≥75 years	All
Total costs	5,675 (5,316-5,997)	5,894 (5,637-6,161)	5,675 (5,338-6,049)	5,760 (5,592-5,931)
Hospital admissions	4,074 (3,731-4,351)	4,141 (3,903-4,381)	3,882 (3,623-4,161)	4,062 (3,920-4,193)
Drug prescriptions	924 (879-969)	1,028 (992-1,071)	1,036 (986-1,095)	987 (962-1,017)
Outpatient visits	677 (564-802)	725 (637-814)	756 (632-882)	711 (661-761)
Costs of interest*	4,209 (3,910-4,452)	4,314 (4,038-4,527)	3,973 (3,743-4,259)	4,203 (4,074-4,323)
Hospitalizations*	3,605 (3,323-3,832)	3,609 (3,334-3,831)	3,305 (3,064-3,580)	3,547 (3,418-3,667)
Drug prescriptions*	288 (274-302)	329 (314-342)	304 (288-319)	307 (299-316)
Outpatient visits*	316 (302-330)	377 (361-392)	364 (341-379)	349 (341-358)

*Typical costs and consumptions concerning the cardiovascular complexity level of a patient with ICD implanted (Supplement **2**).

2.0% of patients suffered one or more complications during the hospital stay and the proportion of patients with complications increased with age.

During a mean follow-up of two years, 893 patients died (15.4%) and death occurred at index hospital discharge in 0.3% of cases.

The survival analysis for replacement-free survival of first ICD implanted patients showed that at 1 year the probability of replacement was 3% and increased to 6% 2 years after index hospitalization, to 12% 3 years after and to 27% 4 years after (Figure **2**). No statistically significant differences were found among age groups (log-rank test, p-value = 0.2520). Moreover, none of the demographic and clinical baseline characteristics were found to be predictors of first device replacement (Table **3**).

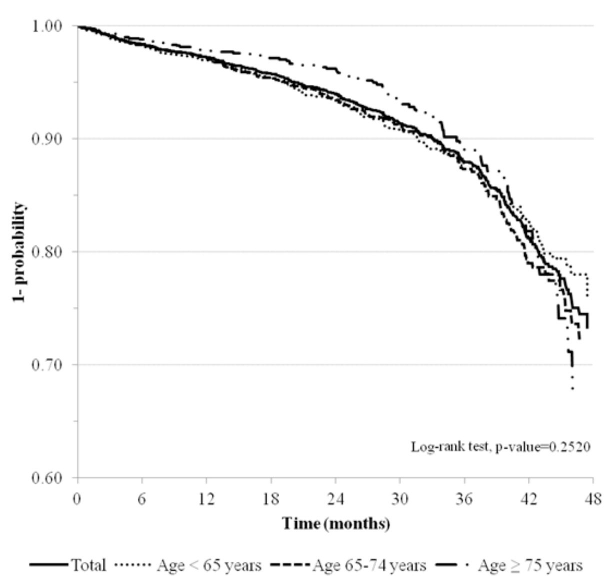

Figure 2: Replacement-free survival of first ICD during follow-up in the whole population and stratifying by age class (Kaplan-Meier curves).

After a first ICD implant, the Lombardy HS spent on average €5,760 (95%CI: 5,592-5,931) annually for the treatment of each subject implanted: the main source of expenditure was in-hospital care (€4,062), followed by pharmaceutical treatments (€987) and outpatient visits (€711) (Table **2**). No differences were found in mean annual costs among age classes, with the exception of expenditure for drug therapies which was lower in people younger than 65 years (€924, 95%CI: 879-969). Regarding the cost of healthcare services of interest related to the cardiovascular complexity of a patient after an ICD implant, the annual total cost per-capita was €4,203, which is about 72.9% of total HS expenditure. Age did not impact the total cost for services of interest, but differences among age classes were detected in outpatient visits, for which the cost was lower in younger subjects (€316, 95%CI: 302-330), whereas the expenditure attributable to drug prescriptions was higher in subjects aged between 65 and 74 (€329, 95%CI: 314-342).

DISCUSSION

Italy is one of the European countries with the highest rate of ICDs implanted [1, 5]. The National ICD Registry of the Italian Society of Arrhythmology and Cardiac Pacing estimated that the implantation rate (per million inhabitants) reached 181 in 2005, 193 in 2006 and 221 in 2007 [28]. Our paper confirms the striking growth in the use of ICDs in Italy in recent years and the highest annual relative growth with respect to the previous year was observed in 2005 (+35%). This peak may be due to the positive results achieved in randomized clinical trials [3, 4, 29, 30] and published in the first half of the decade 2000-2010, which enlarged the inclusion criteria for ICD implantation.

Table 3: Effect of Baseline Demographic and Clinical Characteristics on first ICD Replacement, Using Cox Proportional Hazard Model

	Group	Hazard ratio	Confidence Interval 95%	p-value
Gender	Female	1	-	
	Male	0.893	0.716-1.114	0.3168
Age class	<65 years	1	-	
	65-74 years	1.050	0.869-1.268	0.6127
	≥75 years	0.848	0.658-1.091	0.1993
CCI*	0-1	1	-	
	2-3	0.986	0.810-1.200	0.8876
	≥4	1.071	0.850-1.350	0.5627
Concomitant cardiac procedures†	none	1	-	
	al last 1	1.100	0.920-1.314	0.2950
Complications‡	none	1	-	
	al last 1	1.157	0.598-2.238	0.6652

*Charlson Comorbidity Index. † diagnostic cardiac catheterization, pacemaker, percutaneous coronary intervention, coronary artery bypass grafting surgery, catheter ablation, heart valve surgery. ‡ pneumothorax, tamponade, mechanical complication, infection associated with implant, other cardiac complication, hematoma/hemorrhage, acute renal failure requiring new hemodialysis.

In addition, our results show that Lombardy is a region with a higher ICD implantation rate than the Italian and European ones [6, 7]. Indeed, comparing our result, conveniently standardized, with the data reported by the Italian registry in the same period, we observed that Lombardy has an average implantation rate 7.3% higher than the Italian rate [28]. Moreover, comparing it with the European trend [1, 31], the number of first ICDs implanted in Lombardy is more than twice that observed in Europe for the aforementioned reasons. An additional explanation may be related to the appropriateness of the treatment, but the evaluation of this matter in a general population and using only healthcare administrative databases is very difficult.

Concerning the first ICD replacement rate, there is a lack of scientific literature on this topic [32] and this study is the first to estimate the replacement rate, using the time at risk of patients with an ICD as the denominator. We observed a growing trend during 2000-2008 in Lombardy, with a peak in 2005 possibly explained by FDA recalls for some devices in that period [33]. There is a clinical need to extend ICD longevity, since any replacement implies either risks of complication, including severe ones such as device system infection, or increased costs (related to device and hospitalization) that could be minimized with evolving device technology [34]. We observed that the probability of the first device replacement was 6% two years after implantation and 27% four years after, and these estimates are similar to those reported in the latest publications [21, 22]. However, these probabilities might be underestimated since subjects who died before a device replacement might have a higher probability of ICD substitution. Finally, we detected that none of the demographic and clinical baseline characteristics are predictors of first device replacement but this result may be affected by the short follow-up time: in our cohort the maximum follow-up time was 4 years and, since replacement usually occurs on average 4-5 years after implantation [20-22], we might have observed mostly premature device failures that may be due to device technical problems.

Using healthcare administrative data, we were able to monitor ICD utilization in a general population to evaluate charac-teristics and survival of patients who underwent ICD implantation, to estimate ICD longevity and also to assess the economic healthcare impact of treatment of these patients. The Lombardy HS spent on average €23,934 for a first ICD implant in the period 2005-2008. This reimbursement cost varies among European countries: in 2009 the expenditure for ICD implantation (procedure, hospitalization and device) was €23,072 in Belgium [12], €17,152 in Germany [35] and between €12,000 and €17,000 in France according to the type of device [36]. In the US, the procedural cost was €22,935 [37], which is similar to the one we found in Italy, even though the length of stay was different: 11 days in Italy against the 5 days in the US during a similar time frame [26, 32]. It is noteworthy that marked differences still exist between European countries with regard to the type and extent of reimbursement for ICD implants, including lack of added reimbursement for the more sophisticated and costly devices such as biventricular ICDs [38]. We estimated that HS spends on average €5,760 annually for the care of a patient after the first device implant (of which 73% is directly attributable to the cardiovascular complexity level of the patient with ICD implanted), and the cost borne for the care of these people represents 0.3% of the total annual expenditure of the Lombardy HS. Direct cost estimates are very useful for healthcare resource allocation, as they also make it possible to perform cost-effectiveness analyses on ICD implantation using estimates coming from the general population framework.

The use of administrative healthcare databases in order to monitor a disease and to evaluate its direct economic impact is important but non exhaustive. Indeed, administrative databases lack information about indirect costs, quality of life, and clinical conditions of patients, making the examination of interesting aspects difficult or impossible. For example, in this study complications and comorbidity diseases at first ICD implant could be under-reported, the type of device implanted (single chamber, dual chamber or biventricular device for cardiac resynchronization therapy) is unknown, clinical data on left ventricular function are missing and information on diagnosis is insufficient to distinguish between primary and secondary prevention.

Another limitation to our study is related to the validity of the algorithm used to classify ICD in first implant and replacement: the algorithm relies on previous hospitalizations available in DENALI to identify a device replacement, therefore a replacement might be erroneously classified as a first implant if the patient underwent the first ICD outside Lombardy HS or before 2000 (first year of DENALI registration). As a consequence, the estimated rates might be affected by bias, but we expect such bias to be close to zero from 2005 on, due to the increase of observational time for each subject covered by Lombardy HS.

The joint use of information coming from National ICD registries and health administrative databases could overcome the limitation of both sources of data and it could improve the monitoring of ICD therapy. It appears appropriate to combine clinical data collected in registries with long-term outcomes and economic data. This approach should be strongly implemented, because the differences in costs and the frequency of device implantation underline the need for more in-depth evaluation of the appropriateness of the treatment. A recent study demonstrated that people receiving ICDs in clinical practice were significantly older and had more comorbidities than those enrolled in a randomized clinical trial [39], as well as being less monitored after the procedure by physicians with considerable experience [40]. It is demonstrated that in the “real world” the patient’s clinical profile may be characterized by important concurrent co-morbidities which may affect both outcome and costs and the current priority of clinicians and regulatory agencies is to evaluate the efficacy of ICD and cardiac resynchronization therapy in routine clinical practice.

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