1 Infection of Cardiac Implantable Electrical Devices: An Emerging Epidemiological Issue

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1.1 Cardiac Implantable Electronic Devices: Trends in Implantation Rates

In the last five decades, the use of cardiac implantable electronic devices (CIEDs), which include permanent pacemakers (PMs), implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices, has dramatically increased [1]. It is difficult to have a complete assessment of the number of CIEDs currently implanted all over the world, but a worldwide survey undertaken for calendar year 2009 showed in all countries an increase in implant numbers compared to a similar assessment performed 4 years before [2]. In this survey performed among 61 countries (25 from Europe, 20 from the Asia Pacific region, 7 from the Middle East and Africa, and 9 from the Americas), an overall number of 1,002,664 PM implants, (737,840 new implants and 264,824 replacements) and 328,027 ICDs (222,407 new implants and 105,620 replacements) was collected [2]. The USA had the largest number of cardiac pacemaker implants (225,567) and Germany the highest number of new PM implants per million population (927) [2]. Also for ICDs and devices for cardiac resynchronization therapy, the largest amount of implants was reported for the USA (133,262) with 434 new implants per million population. Also for biventricular ICDs, which showed an important increase in implants as compared to the previous survey, the largest number of implants was found in the USA (49,255 devices in 2009). A systematic review that analyzed CIED implant rates in Europe taking into account 58 studies published in the years 2004–2014 found an important rise over time in CIED implants with large geographic differences [3]. The ratio between the regions with the highest and lowest implant rates within the same

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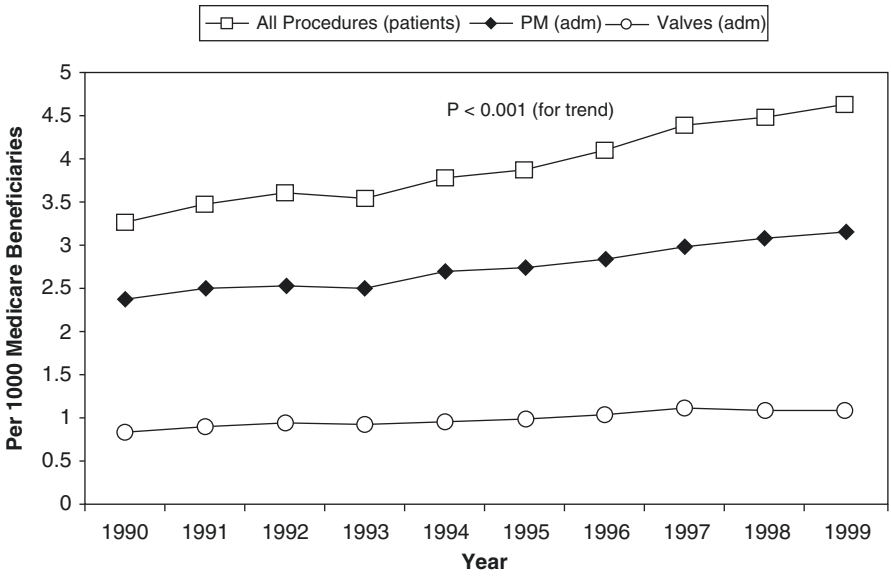

Fig. 1.1 Rates of prosthetic valve/cardiac device implantation and infection: 1990–1999 (Cabell CH et al., Am Heart J 2004;147(4):582–6)

country ranged between 1.3 and 3.4 for pacemakers and between 1.7 and 44.0 for defibrillators. The ratio between the countries with the highest and lowest implant rates ranged between 2.3 and 87.5 for pacemakers, between 3.1 and 1548.0 for defibrillators, and between 4.1 and 221.0 for resynchronization therapy devices. Implant rate variability appeared to be influenced by healthcare, economic, demographic, and cultural factors [3]. Nevertheless, the majority of the data available so far on device implantation rates come from retrospective studies or hospital discharge registries, and for this reason they may have some limitations. In the last 15–20 years, guidelines have expanded the indications for CIED implantation leading to a significant increase in their use [4, 5]. Furthermore, the improvement in survival among patients with heart disease who can develop the indication for an implanted cardiac device contributed to the increase in the number of CIED implants [6, 7]. An analysis of claims files from the Health Care Finance Administration for Medicare beneficiaries between 1990 and 1999 found an increase of cardiac device implantation rate of 42%, from 3.26 procedures per 1000 to 4.64 procedures per 1000 Medicare beneficiaries (Fig. 1.1) [8]. The implantation rate for PPMs and ICDs has increased by 19% and 60%, respectively, in the USA based on recent data report [9]. Additional data that support the increase of CIED implantations come from the National Hospital Discharge Survey (NHDS) that records data on approximately 1% of all discharges from nonfederal hospitals in the USA. Between 1999 and 2003, NHDS reported a 49% increase in the number of new CIED implantations, and, after 2003, a 12% increment of implantation rates (from 199,516 in 2004 to 222,940 in 2006) was also found [10]. An additional analysis based on administrative data at discharge from

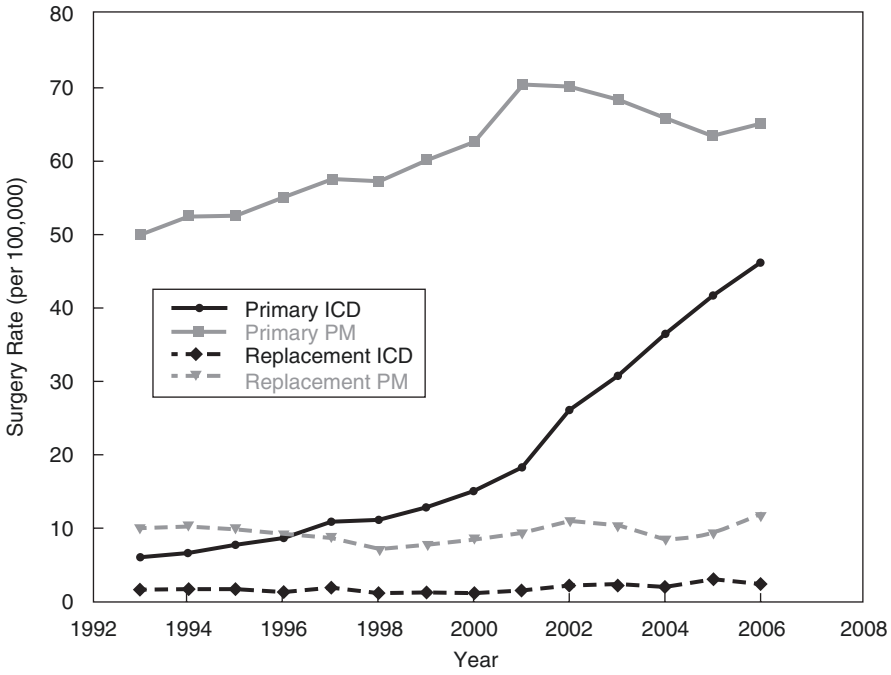

Fig. 1.2 The rate of operations per 100,000 persons of population for pacemakers and implantable cardioverter-defibrillators in primary procedures and replacements (From Kurtz SM et al., Pacing Clin Electrophysiol 2010;33(6):705–11)

1993 to 2006 showed that in the USA 2.4 million patients received a primary PM and 0.8 million received an ICD, while there were 369,000 PM replacements and 74,000 ICD replacements [11]. The rate of operations per 100,000 persons of population for pacemakers and implantable cardioverter-defibrillators in primary procedures and replacements. The marked increase in the rate of implants per 100,000 persons of population for ICDs is shown in Fig. 1.2 [11].

Greenspon et al. reported between 1993 and 2008, in the USA, an overall CIED implantation increase of 96% (average of 4.7% per year), and it was mainly due to ICD implantation resulting in an increase in implantation rates of 504% (Fig. 1.3) [12].

1.2 Epidemiology of CIEDs-Related Infections

Despite of the use of antibiotic prophylaxis at the time of device implantation, rates of device-related infection increased in recent years, and cardiac implantable electronic device infection is a more and more serious problem with high morbidity and mortality. It is important to underline that the rate of CIED infections increased faster and disproportionate as compared to the rate of CIED implantations. Possible

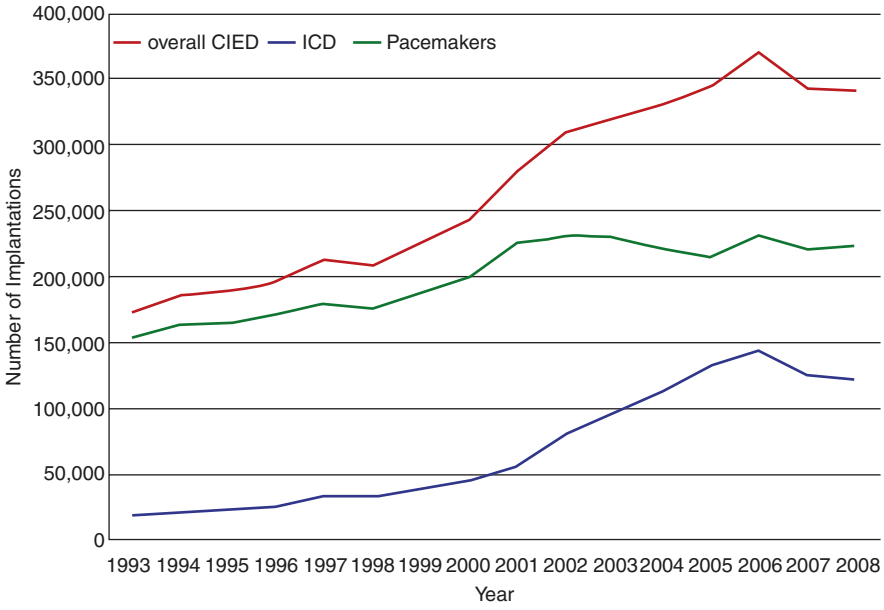

Fig. 1.3 Number of PM and ICD Implantations from 1993 to 2008 (From Greenspon AJ et al., J Am Coll Cardiol 2011;58(10):1001–6)

explanations for such a disproportionate rise in CDI rate are broader indications for CIED implantation, the growth in the number of complex procedures such as ICD and CRT implantations, and the increase in the prevalence of coexistent comorbidities among CIED recipients [13]. The rates of cardiac pacemaker implantations as well as the age distribution of populations have shown a series of changes in the populations. We are experiencing nowadays the so-called demographic transition in which the decline in death rate and birth rate may change the age structure. The imbalance between fertility rates and life expectancy leads to an increase in median age in the population especially in developed countries. Geriatric population, and more generally people aged 65 and over, is rapidly growing counting today 8.5% of people worldwide (617 million). Future predictions estimate that this percentage will rise up to 17% of the world's population in 2050 (1.6 billion) (Table 1.1) [14].

In this scenario, noncommunicable diseases, also known as chronic diseases, are becoming the major causes of death and contributors to the burden of disease and disability. The rise in morbidity of device implantations could be related to a higher prevalence of concurrent diseases including CKD and diabetes mellitus in CIED recipients; these comorbidities may facilitate device-related infections because of a weakened immune system as commonly reported in patients with diabetes mellitus and renal insufficiency. It is known that hyperglycemia favors the colonization and growth of a variety of organisms (i.e., *Candida albicans*), and many common infections are more frequent and severe in diabetic patients. Furthermore, some rare infections are observed almost exclusively among the diabetic population. This is

Table 1.1 Population aging: number and distribution of persons aged 60 years or over by region, in 2017 and 2050

	Population age +60 (millions)		Percentage change between 2017 and 2050
	2017	2050	
World	962.3	2080.5	116.2
Africa	68.7	225.8	228.5
Asia	549.2	1273.2	131.8
Europe	183	247.2	35.1
Northern America	78.4	122.8	56.7
Latin America and the Caribbean	76	198.2	160.7
Oceania	6.9	13.3	92.6

Modified from United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Ageing 2017—Highlights (ST/ESA/SER.A/397)

even more relevant if we consider that worldwide rates of type 2 diabetes are dramatically increasing. The WHO estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980, and over 60 million of these are currently living in Europe. Today, the global prevalence (age-standardized) of diabetes is around 8.5% in the adult population [15]. Since the year 2000, the International Diabetes Federation (IDF) has collected data on diabetes prevalence. According to recent data in 2011, about 285 million people worldwide were affected by diabetes, but this number is expected to rise to 439 million by 2030 (Fig. 1.4) [16]. A similar trend was found by the Institute for Alternative Futures that made a prediction for the prevalence of diabetes among Americans forecasting a 54% increase in 2030 (people with type 2 and type 1 diabetes will increase by 19,629,000–54,913,000 between 2015 and 2030). In addition to this, the annual number of people with diabetes with new end-stage renal disease will increase by 27,370 and the annual number of diabetes-related deaths will rise by 106,630 [17]. Similar to diabetes, also chronic kidney disease (CKD) is a common risk factor for infection in patients with a CIED and is an independent predictor of all-cause mortality in different conditions. As shown in Fig. 1.5, heart disease, arrhythmias, and CKD exert a series of negative influences on outcomes with harmful clinical implications [18]. Prevalence of CKD in the USA, recognized as a major noncommunicable disease, has recently been estimated as 11.6% of the adult population (23 million), compared with 10.6% (23.4 million) for diabetes, 33.3% (73.6 million) for hypertension, and 36.3% (80.0 million) for CVD [19]. According to the CKD Health Policy Model, the prevalence of CKD in adults aged 65 years or older in the USA is expected to be 36.4% in 2020 and 37.8% in 2030 (all CKD-stage combined), while stage 3a is expected to remain the most prevalent stage until at least 2030 [20]. The global incidence of CKD was around 11 million in 1990 and increased to more than 21 million people in 2016, thus with a 89% increase in incidence over the last 27 years [20] (Fig. 1.6).

As reported by Greenspon et al., the incidence of four major comorbidities (renal failure, respiratory failure, heart failure, and diabetes) in patients with CIED

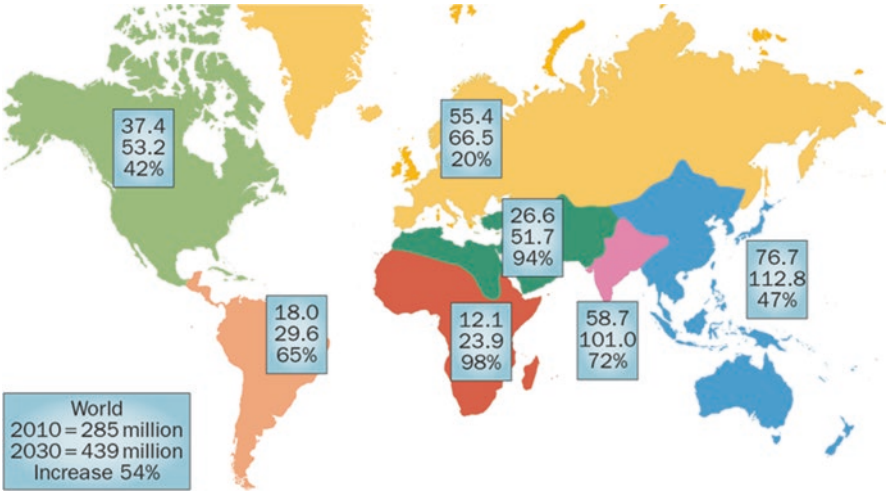

Fig. 1.4 Diabetes worldwide prevalence in 2010 and projections for 2030. The first two values for each box represent the number of people affected by diabetes mellitus (in millions) for each of these seven world regions (identified by colors) for 2010 and the projection for 2030, respectively. The last number shows the relative increase from 2010 to 2030 (From Chen et al. [16], reproduced with permission)

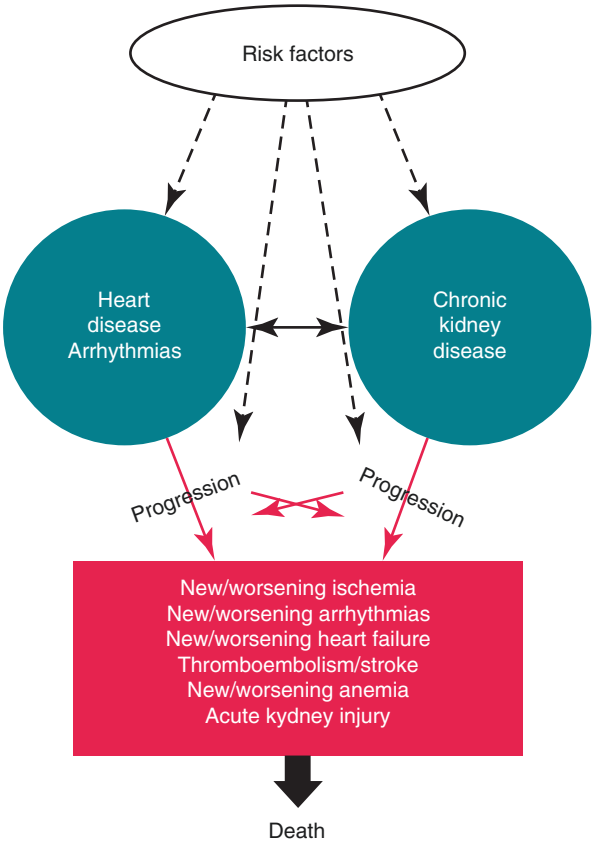

Fig. 1.5 The complex interplays between heart disease, arrhythmias, and chronic kidney disease, in relationship with risk factors, progression of the diseases, complications, and death (From Boriani G et al., Europace 2015;17(8):1169–96)

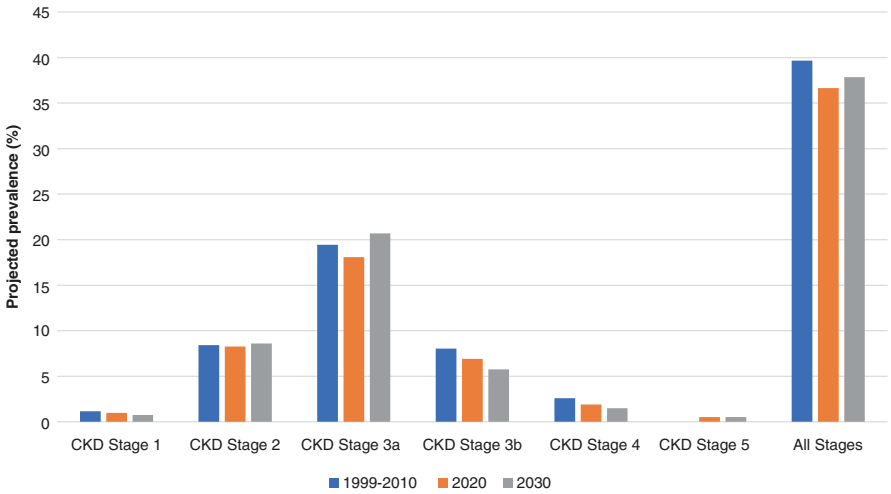

Fig. 1.6 Projected prevalence of chronic kidney disease (CKD) in 2020 and 2030 in individuals with 65 years or more [20]

infection remained relatively constant from 1993 through 2004 when a noticeable increase was seen, and in parallel, the similar trend was observed in the infection rate during the same period [12] (Fig. 1.7).

These observations support the hypothesis that the pacemaker population, suffering from a large variety of chronic diseases, such as diabetes or chronic kidney dysfunction, is more susceptible to infection. In 2015 Polyzos et al. performed a systematic review and meta-analysis founding significant host-, procedure-, and device-related risk factors for infection after CIED implantation: variables associated with a significant increase in the risk of CIED-associated infection at multivariable analysis are summarized in the Table 1.2 [21].

However, the real etiology of the rate increase in CIED infection and particularly the discrepancy between the rise in CIED infections and implantation rates are not completely clear, although the older population and the increasing burden of comorbidities appear to play a major role. Despite of the conduction of many studies so far, the real incidence of CIED's infection is unknown, with a reported prevalence among CIED patients ranging from 0.13 to 19.9% [22]. This reported variety in the occurrence of CIED-related infection is probably due to the poor quality of the data that come from retrospective studies or single-center registries and nonuniform definitions of CIED infections. Indeed, there are no standardized definitions for CIED infections, and in the literature the occurrence was measured in different ways [23]. Moreover, the absence of accurate denominators and different follow-up periods also prevents the exact knowledge of CIED incidence rate [24]. In addition to this, in the majority of the studies, CIED infections are identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for cardiac or vascular device infection, endocarditis, and in general any infection in the setting of CIED implantation regardless if they have been clearly related to the CIED itself or not. For this reason, some authors incorporated multiple distinct

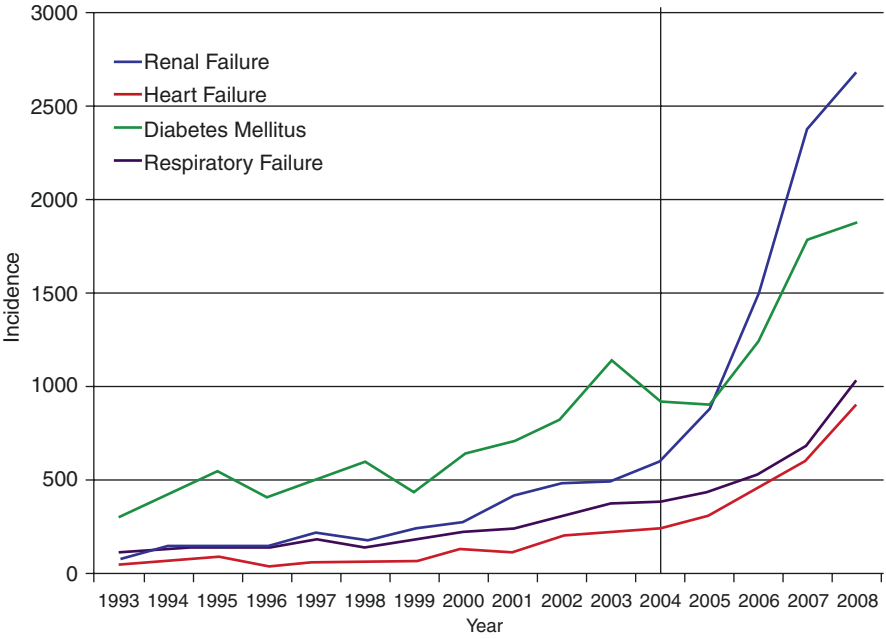

Fig. 1.7 Incidence of comorbidities in patients with CIED infection (From Greenspon AJ et al., J Am Coll Cardiol 2011;58(10):1001–6)

code-based criteria to increase the sensitivity of the search [25]. A wide range of values of CIED infection's incidence has been reported in the literature. In the Danish PM register, more than 460,000 patients who underwent pacemaker implantation between 1982 and 2007 were analyzed, and incidence of infection was 1.8 per 1000 pacemaker-years after the first implantation and 5.3 per 1000 pacemaker-years after pacemaker replacement [26]. The analysis of the Nationwide Inpatient Sample discharge record (NIS) showed that between 1993 and 2008, the overall infection rate was 1.6%, and within the study period, approximately 690,000 patients were treated for CIED infections. More in detail, the incidence of infections increased by 210%, from 2660 cases in 1993 to 8230 cases in 2008, and the rate of infections increased significantly, from 1.53% in 2004 to 2.41% in 2008. Nevertheless, the annual rate of infections did not change until 2004 (Fig. 1.8) [12]. Voigt et al., using the National Hospital Discharge Survey database from 1996 through 2003, reported a 49% rise in the number of new CIED implantations and an increase of 3.1-fold of a total number of hospitalizations with CIED infection (2.8-fold for PMs and six-fold for ICD). As mentioned above, they also found an excessive increase of infection rates compared to the number of implantations according to previous studies [1]. Carrasco F et al. conducted one of the largest series of infective endocarditis diagnosed with vegetation on cardiac devices. More than 7000 patients which undergone a PM or ICD implantation with a follow-up period >25 years (from 1987 to 2013) were evaluated. A significant increase of infective endocarditis incidence

Table 1.2 Variables associated with a significant increase in the risk of CIED-associated infection at multivariable analysis

Number and type of studies	
Host-related factors	
Age	3 retrospective studies
Male sex	1 case-control study, 1 retrospective study
Diabetes mellitus	1 case-control study, 1 retrospective study
Chronic kidney disease/dialysis	1 prospective study, 2 case-control studies
COPD	1 prospective study, 1 case-control study
Anticoagulants	2 case-control studies
Corticosteroids	1 case-control study
CVC	1 retrospective study
History of device infection	Opinion of experts
Implant site trauma	Opinion of experts
Procedures-related factors	
Lack of antibiotic prophylaxis	2 prospective studies, 1 case-control study, 2 retrospective studies
Device replacement/revision	2 prospective studies, 3 case-control studies, 2 retrospective studies
Reintervention	2 prospective studies
No. of prior device-related procedures	1 retrospective study
Temporary pacing	1 prospective study
Procedure duration	1 prospective study
Operator experience	1 retrospective study
Lead dislodgement	Opinion of experts
Post-operative hematoma	1 prospective study
Device-related factors	
ICD device	1 prospective study
CRT	2 retrospective studies
Dual-chamber system	1 case-control study
Number of leads	1 case-control study
Abdominal pocket	Opinion of experts
Epicardial leads	1 case-control study

Based on Polyzos KA et al., Europace 2015;17(5):767–77
COPD chronic obstructive pulmonary disease, *CVC* central venous catheter, *ICD* implantable cardioverter-defibrillator, *CRT* cardiac resynchronization therapy

was found during the follow-up, and more interesting they observed an increasing trend in incidence: from 1.4/1000 of all implanted pacemaker in the period of 1987–1993 to 2.5/1000 in 1994–2000, 3.3/1000 in 2001–2007, and 4.5/1000 in the period of 2008–2013 [27]. Similar results were found in a retrospective cohort study of residents of Olmsted County in Minnesota, between 1975 and 2004; the incidence of definite device infections was 1.9 per 1000 device-years over a total person-time of follow-up of 7578 years [28]. In a multicenter and prospective survey of the incidence and risk factors of CIED infections after PPM or ICD implantations (The PEOPLE study), a total of 6319 patients were enrolled and followed for

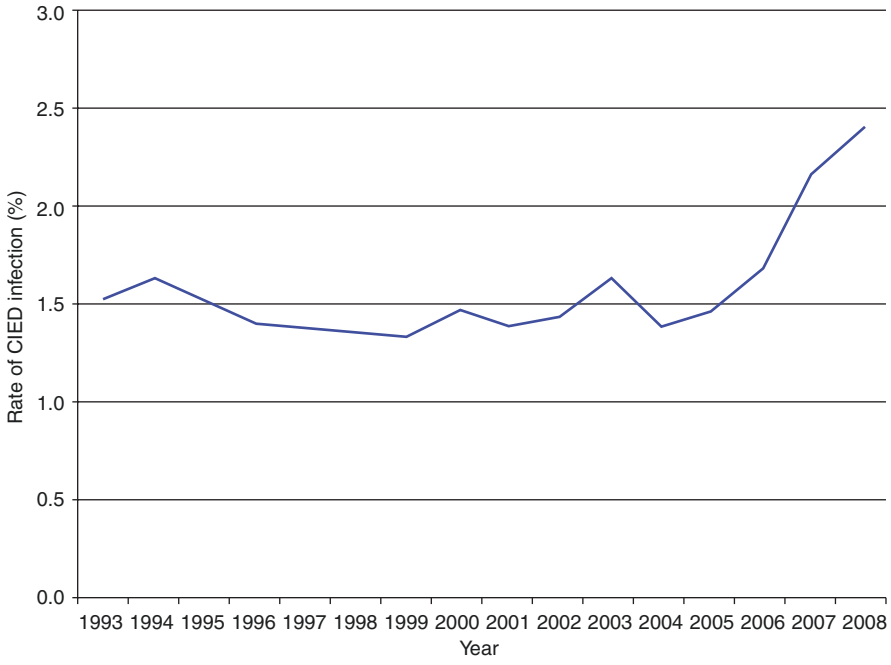

Fig. 1.8 Rate of CIED infection (From Greenspon AJ et al., J Am Coll Cardiol 2011;58(10):1001–6)

12 months in 44 centers in France. Among this cohort, the incidence of CIED infections was 0.56% after de novo implantation and 0.99% for non-de novo procedures [29]. Although previous studies, according to several national databases, reported a rate of CIED infections between 2 and 4% with a 124% and 57% rise in infection rate from 1990 to 1999 and from 2004 to 2006, respectively, most recent data shows that the mean incidence of CIED is 0.1–0.7% for PPM infection and 0.7–1.2% for ICD [30]. Furthermore, a recent European survey has described a great variation in CIED infection rates across different centers reporting an infection incidence <0.5% in 27% of centers, while 22% of them presented an incidence of >2% [31]. In addition, recent data report that the risk of infection may increase up to tenfold if the patient is undergoing a lead replacement or a device upgrade [32]. In a cohort of more than 200,000 patients reported from the National Cardiovascular Data Registry in the USA, a higher infection rate in patients who underwent a generator replacement compared to those who underwent initial implantation (1.9% versus 1.6%) was shown [33]. Moreover, some studies suggest that infection rates vary across different types of CIEDs reporting a greater risk of infection in implantable cardioverter-defibrillators rather than in permanent pacemakers [34]. The more complex CIED system is implanted, the higher is the infection risk, so the infection risk is higher in patients that receive ICDs and even more relevant in CRT [35]. The longer implantation time that requires ICD or CRT-D/P devices may lead to a higher risk of infection due to longer exposure times and prolonged manipulation during

the procedure [36]. Mortality associated with CIED infections is significant and it is device-dependent. As reported by Sohail et al., the standardized adjusted total long-term mortality was 26.5–35.1%, and mortality continues to be high for many years even after successful treatment of the acute CIED infection [25]. Analysis of more than 200,000 admissions with a CIED procedure in 2007 showed that the mortality of the patients with CIED infection at the end of the first year was approximately twice compared to those without device infection. This mortality persisted for at least 3 years after the resolution of CIED infection, but the real cause of this persistent increased risk of death remains uncertain [37].

1.3 The Financial Burden of CIED-Related Infections

In view of the increased awareness of the clinical importance of CIED-related infections, in recent years an increasing interest emerged on their financial burden. CIED infections result in prolonged hospitalizations, prolonged antimicrobial therapy, need for device extraction, and frequently need for device reimplantation. In 2011 Sohail et al. reported on the risk-adjusted total and incremental admission mortality, long-term mortality, admission length of stay, and admission cost associated with infection in a retrospective cohort of more than 200,000 Medicare patients admitted for CIED generator implantation, replacement, or revision during year 2007. A total of 5817 admissions with infection were recorded, and in these cases, significant increases in length of hospital stay and in adjusted in-hospital and long-term mortality were found. Approximately half of the incremental long-term mortality occurred after discharge. The standardized adjusted incremental and total admission costs with infection were $14,360–16,498 and $28,676–53,349, according to device type, respectively. The largest incremental cost with infection was intensive care, which accounted for more than 40% of the difference. Adjusted long-term mortality rate and cost ratios with infection were significantly greater for pacemakers than for implantable cardioverter-defibrillators or cardiac resynchronization therapy/defibrillator devices [25]. More recently, Greenspon et al. conducted a retrospective cohort analysis of 5401 Medicare patients who developed a device-related infection in the year following implantation/upgraded CIED [38]. In the year following infection, 64% of patients underwent device extraction, of whom 39% had their device replaced and 25% had their device extracted without replacement, with around 62% of patients hospitalized and around 25% of patients who died. The cost for Medicare was on average $62,638 for patients who required device extraction and replacement and $22,856 for patients who required device system extraction, with no need for device reimplantation. These data clearly outline that management of CIED infection is associated with high healthcare expenditures in the year following infection as well as with very severe outcomes in a substantial proportion of patients. Hospitalizations were the largest cost driver among patients with infection in this current investigation and infection-related costs, including cost of extraction and replacement, which accounted for more than half of total costs [38]. Also some European analyses confirm that CIED infections are expensive and associated with

significant health-economic burden. Data from the UK collected between 2013 and 2015 for 84 patients showed that the cost of infection ranged from £5139 (PPM) to £24,318 (CRT-D). Different treatment strategies were adopted, and 49% of the patients underwent CIED extraction and reimplantation during the same admission, while 51% underwent extraction but were then discharged home to be readmitted for day-case reimplantation [39]. Data on the costs associated with CIED infections were also collected in Germany for ICDs implanted over 2010–2013 through analysis of German health insurance claims data. The risk of CIED-associated infection was 3.4% overall, either 2.9% for de novo procedures or 4.4% for replacement procedures. Mean 3-year incremental expenditure per patient for patients with CDI compared with controls was €31,493 for de novo implant patients and €33,777 for replacement patients. Mean incremental expenditure was €59,419 per patient with a major infection. All these data highlight that CIED-associated infections are highly expensive for healthcare providers, thus stressing the need for strategies to minimize their occurrence [40]. A strategy for reducing the risk of CIED infection is the use of the TYRX antibacterial envelope and in a modelling study from the UK; the TYRX envelope was found less costly and more effective over a 12-month time horizon than conventional care when utilized in patients with an ICD or CRT-D [41].

Average costs of infection per patient and data from some European countries are reported in Fig. 1.9 [42–45].

Given the epidemiological burden of arrhythmic conditions requiring CIEDs, the importance and clinical implications of CIED infections, the complexity of managing CIED infections, as well as the important financial implications of infections, the ideal approach to this complex topic should be that of health technology assessment (HTA), in order to provide a multidimensional and multidisciplinary approach,

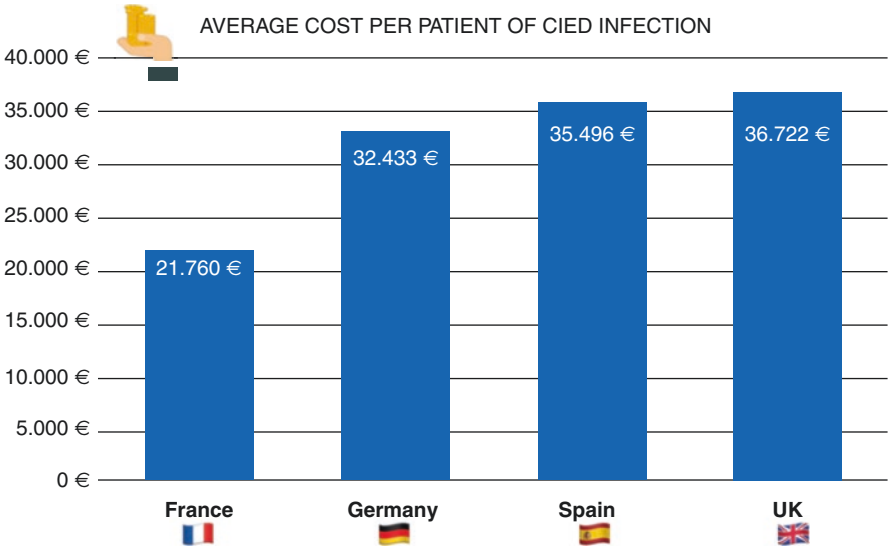

Fig. 1.9 Average costs of infection per patient from some European countries [42–45]

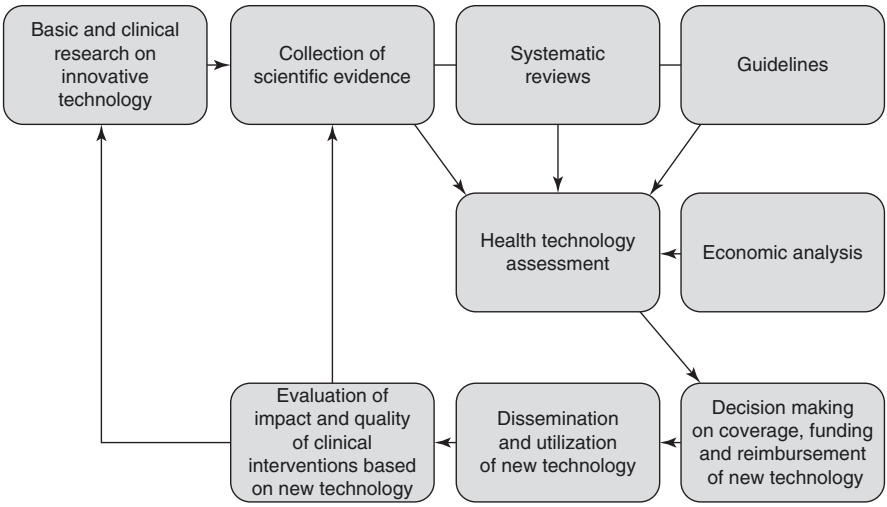

Fig. 1.10 The virtuous circle of health technology assessment (From Boriani G. et al., Eur Heart J 2013;34(25):1869–74)

putting together inputs from clinicians, clinical guideline groups, epidemiologists, biostatisticians, economists, commissioners, and health policy-makers (Fig. 1.10) [46].

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