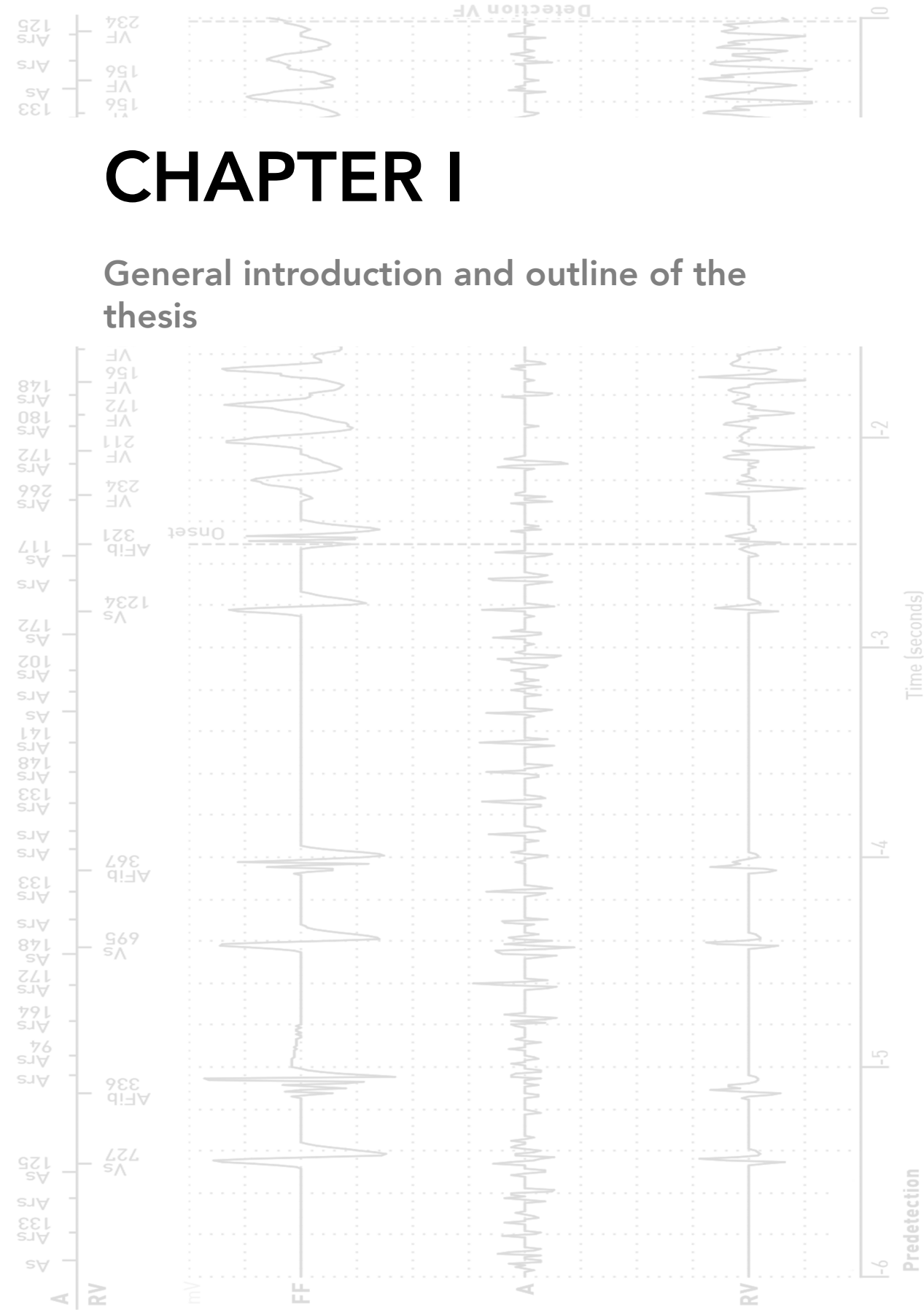
CHAPTER I

General introduction and outline of the thesis



General introduction and outline of the thesis

Chronic Kidney Disease (CKD) is highly common in the western civilization and the incidence of CKD is expected only to rise the upcoming decades. As the kidneys play an important role in various vital processes in the human body, CKD is associated with a broad spectrum of complications and thereby with an impaired survival. The treatment of patients with CKD focuses on the prevention of further progression of the kidney damage and furthermore it focuses, especially in patients with more severe CKD, also on the complications resulting from the disease. End Stage Renal Disease (ESRD), the final stage in the spectrum of patients with Chronic Kidney Disease (CKD Stage V), requires renal replacement therapy (dialysis treatment or kidney transplantation). This stage of the disease is particularly associated with an abysmal outcome with estimated annual mortality rates around 20%. Cardiovascular diseases, especially Sudden Cardiac Arrhythmias (SCA), substantially contribute to the poor survival of these patients and could therefore form an important therapeutic target in order to improve the outcome of ESRD patients.[1]

Sudden Cardiac Death in ESRD patients

Results of large observational registries indicate that cardiovascular mortality accounts for about 40% of total mortality in dialysis patients. Of the patients that die due to cardiovascular mortality it is reported that around 65% of the patients dies suddenly, which then is defined as Sudden Cardiac Death (SCD). SCD thus accounts for almost 25% of the total mortality of dialysis patients.[1] Although registry data, given its observational nature, may be subject to certain bias, the numbers reported can be considered accurate since they were confirmed in multiple randomized controlled trials that used objectively adjudicated end points.[2, 3]

The mechanisms that underlie the development of SCA that eventually result in SCD are complex and include, next to traditional mechanisms, such as ischemic heart disease, also many disease specific mechanisms.[4, 5] These disease specific mechanisms are in part caused by the disease, such as the development of left ventricular hypertrophy and myocardial fibrosis,[6-8] vascular calcification,[9] or sympathic overactivity,[10] but also in part by the treatment such as for instance the occurrence of large volume and electrolyte shifts during dialysis therapy. [1, 11]

Interventions aiming at reducing Sudden Cardiac Death in patients with ESRD

Several interventional strategies aiming at reducing SCD in dialysis patients have been investigated. However, unfortunately most prospective randomized controlled trials did not show a beneficial effect on reducing SCD, or other outcome parameters so far. For instance two large trials investigating the effect of statins on outcome in dialysis patients failed to show positive results.[2, 12] Studies investigating other medical treatment strategies, including erythropoietin, angiotensin converting enzyme (ACE) inhibitors/ angiotensin receptor blockers (ARB) and β-blockers also did not show unequivocal positive results in the general dialysis population.[13-18] Although it must be mentioned that in a selective group of dialysis patients a beneficial effect for β-blockers has been demonstrated in a prospective setting.[17] Moreover, the ARB candesartan demonstrated a significant reduction in cardiovascular events in dialysis patients.[15] On the other hand another prospective trial evaluating ACE inhibitors failed to show positive results.[16]

Since dialysis therapy itself has been suggested as an important mechanism for the occurrence of SCD a beneficial effect from changing dialysis modality was anticipated.[3, 11] Nonetheless, multiple studies investigating low – dose versus high – dose dialysis therapy and/or low – flux vs. high – flux dialysis therapy did not show positive results.[3, 19] Recent trials investigating the beneficial effects of increasing dialysis frequency however, did show positive results on soft end points, as for instance reduction in left ventricular mass, or, on combined end points including survival.[20, 21] However, these trials should be confirmed in future trials and preferably with survival as the primary end point.
Because ischemic heart disease is considered one of the most important factors contributing to SCD in the general, as well in the dialysis population, it is hypothesized that revascularization of dialysis patients would reduce the incidence of SCD.[4, 22] Based on current data indeed it can be concluded that optimal revascularization would probably improve outcome in this patient group.[22, 23] Nonetheless, it should also be concluded that even despite optimal revascularization an important hazard for SCD remains.[24]
Since prophylactic ICD implantation has proven to improve outcome in various patient populations with an increased risk for SCD, such as for instance in survivors of an out of hospital cardiac arrest(OHCA), patients with severe heart failure and patients with congenital heart disease associated with arrhythmic events,[25] it can be hypothesized that prophylactic ICD implantation might be beneficial in patients with ESRD. Currently this hypothesis is supported by several observational studies.[26-28] For instance, it has been reported that the occurrence of appropriate ICD therapies in current ICD populations is related to the severity of renal failure and that in particular patients with ESRD show an increased incidence of appropriate ICD therapies.[27, 28] Moreover a retrospective analysis investigating the outcome of dialysis patients after a survived OHCA documented a substantial survival benefit for those patients that received a prophylactic ICD.[26] Nonetheless, it should be kept in mind that these retrospective studies are subject to certain bias and that these results should be confirmed in prospective studies. Furthermore, those studies should also assess the cost-effectiveness and safety of this interventional strategy. Especially since several studies show a relationship between the incidence of ICD related complications and renal failure.[29, 30]

Complications of prophylactic ICD implantation

Although ICD implantation is associated with a significant survival improvement in various populations, it is associated with a certain number of, possible life threatening, complications. These complications can be divided into complications associated with the implantation procedure and complications associated with the device therapy itself. Pneumothorax and pericardial effusion (which in severe cases might lead to cardiac tamponade) are complications that can occur during the implantation procedure, whereas pocket hematoma formation usually occurs in the first 14 days after implantation. Lead dislodgement and cardiac device infection are complications that can occur early after implantation but also frequently occur during longer follow-up.[31-33] Cardiac device infections in particular should be considered an important complication of ICD therapy, since they have been associated with substantial morbidity and mortality.[34] In addition cardiac device infections also have been associated with substantial costs.[35] The current annual incidence of cardiac device incidence varies from ~1% up to 7% and unfortunately is has been reported that the incidence of cardiac device infections is increasing and has outpaced the increase in implantation rates.[32, 36-39] Complications that can be associated

with the device therapy itself are most importantly caused by malfunction of the device. The most prominent problem associated with device malfunction is the delivery of inappropriate shocks. Inappropriate shocks can occur in the event of misdiagnosing supraventricular tachycardias or in the case of lead failure and are not only painful and psychologicaly disturbing but might even be potentially arrythmogenic and thereby lead to increased mortality.[40-46] The current reported incidences of inappropriate ICD therapy vary to some extent however large studies report a 2 year cumulative incidence of around 10%.[45, 47, 48]

Currently only few studies have investigated the incidence of ICD complications and its relationship with renal failure and more importantly no prospective data assessing a true benefit-risk ratio are available. However, current data indicate that the incidence of complications might be higher among patients with renal failure and especially in those patients that require renal replacement therapy.[29, 30] Furthermore, it has also been documented that renal failure is associated with an increased incidence of cardiac device infections.[32] These findings underline the importance of assessing the safety of prophylactic ICD implantation in patients with renal failure, especially in patients with ESRD.

Objectives and outline of the thesis

The objective of this thesis is to investigate the prevention of sudden cardiac death in particular in patients with ESRD. With the ICD2 trial being the cornerstone of this thesis, special focus will be put on prophylactic ICD implantation in dialysis patients. Prophylactic ICD implantation is however associated with several major and minor complications, that may be particularly relevant also for patients with CKD. The second part of this thesis therefore focuses on the incidence and consequences of ICD related complications.

Part I: Prevention of Sudden Cardiac Death and identifying high risk patients

Part I starts with two extensive literature reviews regarding the current knowledge of prevention of SCD in patients with CKD (**chapters II and III**) followed by the study design of the ICD2 trial study protocol (**chapter IV**). In **chapter V** the incremental prognostic value of the spatial QRS-T angle in dialysis patients is discussed, followed by an analysis investigating modifiable echocardiographic parameters and their relationship with this electrocardiographic (vectorcardiographic) parameter (**chapter VI**). Another marker that has proven to have incremental prognostic value in dialysis patients, diastolic heart failure, has been studied in **chapter VII**. This chapter analyzes the determinants of diastolic heart failure as assessed with a novel echocardiographic measurement, using speckle tracking strain analysis. The final chapters of part I focus on diagnostic imaging tools to detect coronary artery disease, an important contributor to SCA, in dialysis patients. **Chapter VIII** describes the feasibility of CT-angiography to detect coronary artery disease in dialysis patients and in **chapter IX** the value of a plain X-ray of the abdominal part of the aorta to predict the presence of coronary artery disease in dialysis patients is described.

Part II: Implantable cardioverter therapy complications and troubleshooting

Part II starts with a review regarding the incidence of ICD implantation related complications (**chapter X**). In contrast to this chapter, that reviews data of clinical trials previously published, the next chapter (**chapter XI**) describes the incidence and predictors of ICD implantation related complications in a large clinically relevant population,

particularly focusing on the relationship between renal failure and the incidence of complications. The clinical consequences of the most prominent complication associated with ICD implantation is described in the next chapter: **chapter XII** discusses the survival outcome after cardiac device infection. The following chapter, **chapter XIII**, describes the outcome of manual lead extraction, an important part of treatment in the majority ICD related complications. The final chapter (**chapter XIV**) focuses on a novel device, the subcutaneously implanted ICD. This chapter describes the suitability of current ICD recipients for this novel device, that might have several advantages in overcoming ICD related complications.

REFERENCE LIST

1. 1U.S. Renal Data System, USRDS 2006 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, *National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. 2006.*
2. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med 2005;353(3):238-48.*
3. Cheung AK, Levin NW, Greene T, Agodoa L, Bailey J, Beck G et al. Effects of high-flux hemodialysis on clinical outcomes: results of the HEMO study. *J Am Soc Nephrol 2003;14(12):3251-63.*
4. Cheung AK, Sarnak MJ, Yan G, Berkoben M, Heyka R, Kaufman A et al. Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. *Kidney Int 2004;65(6):2380-9.*
5. Pun PH, Smarz TR, Honeycutt EF, Shaw LK, Al-Khatib SM, Middleton JP. Chronic kidney disease is associated with increased risk of sudden cardiac death among patients with coronary artery disease. *Kidney Int 2009;76(6):652-8.*
6. Paoletti E, Specchia C, Di MG, Bellino D, Damasio B, Cassottana P et al. The worsening of left ventricular hypertrophy is the strongest predictor of sudden cardiac death in haemodialysis patients: a 10 year survey. *Nephrol Dial Transplant 2004;19(7):1829-34.*
7. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giacone G, Stancanelli B et al. Left ventricular mass monitoring in the follow-up of dialysis patients: prognostic value of left ventricular hypertrophy progression. *Kidney Int 2004;65(4):1492-8.*
8. Glassock RJ, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. *Clin J Am Soc Nephrol 2009;4 Suppl 1:S79-S91.*
9. Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, London GM. Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int 2003;63(5):1852-60.*
10. Converse RL, Jr., Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F et al. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med 1992;327(27):1912-8.*
11. Bleyer AJ, Hartman J, Brannon PC, Reeves-Daniel A, Satko SG, Russell G. Characteristics of sudden death in hemodialysis patients. *Kidney Int 2006;69(12):2268-73.*
12. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med 2009;360(14):1395-407.*
13. Volkova N, Arab L. Evidence-based systematic literature review of hemoglobin/hematocrit and all-cause mortality in dialysis patients. *Am J Kidney Dis 2006;47(1):24-36.*
14. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis 2007;49(2 Suppl 2):S12-154.*
15. Takahashi A, Takase H, Toriyama T, Sugiura T, Kurita Y, Ueda R et al. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis--a randomized study. *Nephrol Dial Transplant 2006;21(9):2507-12.*
16. Zannad F, Kessler M, Lehert P, Grunfeld JP, Thuilliez C, Leizorovicz A et al. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. *Kidney Int 2006;70(7):1318-24.*
17. Cice G, Ferrara L, D'Andrea A, D'Isa S, Di BA, Cittadini A et al. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol 2003;41(9):1438-44.*
18. Furgeson SB, Chonchol M. Beta-blockade in chronic dialysis patients. *Semin Dial 2008;21(1):43-8.*
19. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. *J Am Soc Nephrol 2012;23(6):1087-96.*
20. Culleton BF, Walsh M, Klarenbach SW, Mortis G, Scott-Douglas N, Quinn RR et al. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA 2007;298(11):1291-9.*
21. Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, Gassman JJ et al. In-center hemodialysis six times per week versus three times per week. *N Engl J Med 2010;363(24):2287-300.*
22. Hemmelgarn BR, Southern D, Culleton BF, Mitchell LB, Knudtson ML, Ghali WA. Survival after coronary revascularization among patients with kidney disease. *Circulation 2004;110(14):1890-5.*

23. Kumar N, Baker CS, Chan K, Duncan N, Malik I, Frankel A et al. Cardiac survival after pre-emptive coronary angiography in transplant patients and those awaiting transplantation. *Clin J Am Soc Nephrol 2011;6(8):1912-9.*
24. Herzog CA, Strief JW, Collins AJ, Gilbertson DT. Cause-specific mortality of dialysis patients after coronary revascularization: why don't dialysis patients have better survival after coronary intervention? *Nephrol Dial Transplant 2008.*
25. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, III, Freedman RA, Gettes LS et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol 2008;51(21):e1-62.*
26. Herzog CA, Li S, Weinhandl ED, Strief JW, Collins AJ, Gilbertson DT. Survival of dialysis patients after cardiac arrest and the impact of implantable cardioverter defibrillators. *Kidney Int 2005;68(2):818-25.*
27. Hreybe H, Ezzeddine R, Bedi M, Barrington W, Bazaz R, Ganz LI et al. Renal insufficiency predicts the time to first appropriate defibrillator shock. *Am Heart J 2006;151(4):852-6.*
28. Robin J, Weinberg K, Tiongson J, Carnethon M, Reddy M, Ciaccio C et al. Renal dialysis as a risk factor for appropriate therapies and mortality in implantable cardioverter-defibrillator recipients. *Heart Rhythm 2006;3(10):1196-201.*
29. Aggarwal A, Wang Y, Rumsfeld JS, Curtis JP, Heidenreich PA. Clinical characteristics and in-hospital outcome of patients with end-stage renal disease on dialysis referred for implantable cardioverter-defibrillator implantation. *Heart Rhythm 2009;6(11):1565-71.*
30. Hoffmeister JM, Estes NA, III, Garlitski AC. Prevention of sudden cardiac death in patients with chronic kidney disease: risk and benefits of the implantable cardioverter defibrillator. *J Interv Card Electrophysiol 2012;35(2):227-34.*
31. Lee DS, Krahn AD, Healey JS, Birnie D, Crystal E, Dorian P et al. Evaluation of early complications related to De Novo cardioverter defibrillator implantation insights from the Ontario ICD database. *J Am Coll Cardiol 2010;55(8):774-82.*
32. Lekkerkerker JC, van NC, Trines SA, van der Bom JG, Bernards A, van de Velde ET et al. Risk factors and time delay associated with cardiac device infections: Leiden device registry. *Heart 2009;95(9):715-20.*
33. Korte T, Jung W, Spehl S, Wolpert C, Moosdorf R, Manz M et al. Incidence of ICD lead related complications during long-term follow-up: comparison of epicardial and endocardial electrode systems. *Pacing Clin Electrophysiol 1995;18(11):2053-61.*
34. Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. *J Am Coll Cardiol 2007;49(18):1851-9.*
35. Ferguson TB, Jr., Ferguson CL, Crites K, Crimmins-Reda P. The additional hospital costs generated in the management of complications of pacemaker and defibrillator implantations. *J Thorac Cardiovasc Surg 1996;111(4):742-51.*
36. Wilkoff BL. How to treat and identify device infections. *Heart Rhythm 2007;4(11):1467-70.*
37. Klug D, Balde M, Pavin D, Hidden-Lucet F, Clementy J, Sadoul N et al. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. *Circulation 2007;116(12):1349-55.*
38. Voigt A, Shalaby A, Saba S. Rising rates of cardiac rhythm management device infections in the United States: 1996 through 2003. *J Am Coll Cardiol 2006;48(3):590-1.*
39. Voigt A, Shalaby A, Saba S. Continued rise in rates of cardiovascular implantable electronic device infections in the United States: temporal trends and causative insights. *Pacing Clin Electrophysiol 2010;33(4):414-9.*
40. Mark DB, Anstrom KJ, Sun JL, Clapp-Channing NE, Tsiatis AA, Davidson-Ray L et al. Quality of life with defibrillator therapy or amiodarone in heart failure. *N Engl J Med 2008;359(10):999-1008.*
41. Prudente LA. Phantom shock in a patient with an implantable cardioverter defibrillator: case report. *Am J Crit Care 2003;12(2):144-6.*
42. Schron EB, Exner DV, Yao Q, Jenkins LS, Steinberg JS, Cook JR et al. Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. *Circulation 2002;105(5):589-94.*
43. Vollmann D, Luthje L, Vonhof S, Unterberg C. Inappropriate therapy and fatal proarrhythmia by an implantable cardioverter-defibrillator. *Heart Rhythm 2005;2(3):307-9.*

44. Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH et al. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med 2008;359(10):1009-17.*
45. Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P et al. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. *J Am Coll Cardiol 2008;51(14):1357-65.*
46. Van Rees JB, Borleffs CJ, Bax JJ, Nagtegaal EM, van der Velde ET, van EL et al. Implementation of lead safety recommendations. *Pacing Clin Electrophysiol 2010;33(4):431-6.*
47. Germano JJ, Reynolds M, Essebag V, Josephson ME. Frequency and causes of implantable cardioverter-defibrillator therapies: is device therapy proarrhythmic? *Am J Cardiol 2006;97(8):1255-61.*
48. Klein RC, Raitt MH, Wilkoff BL, Beckman KJ, Coromilas J, Wyse DG et al. Analysis of implantable cardioverter defibrillator therapy in the Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial. *J Cardiovasc Electrophysiol 2003;14(9):940-8.*