The Importance and Use of Registries for Performance and Safety Information on Medical Implants

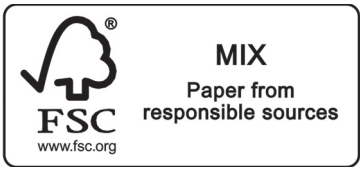
Laura M. de Vries

The work described in this thesis was conducted at the Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands.

Financial support by the the Dutch Health and Youth Care Inspectorate and the Erasmus University Rotterdam is gratefully acknowledged.

ISBN/EAN: 978-94-6233-796-1

Printed by: Gildeprint - Enschede



The Importance and Use of Registries for Performance and Safety Information on Medical Implants

Het belang en gebruik van registraties voor informatie over de prestaties en veiligheid van medische implantaten

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.A.P. Pols

en volgens het besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

woensdag 6 december 2017 om 11.30 uur

Laura Marieke de Vries
geboren te Zaanstad

ERASMUS UNIVERSITY ROTTERDAM

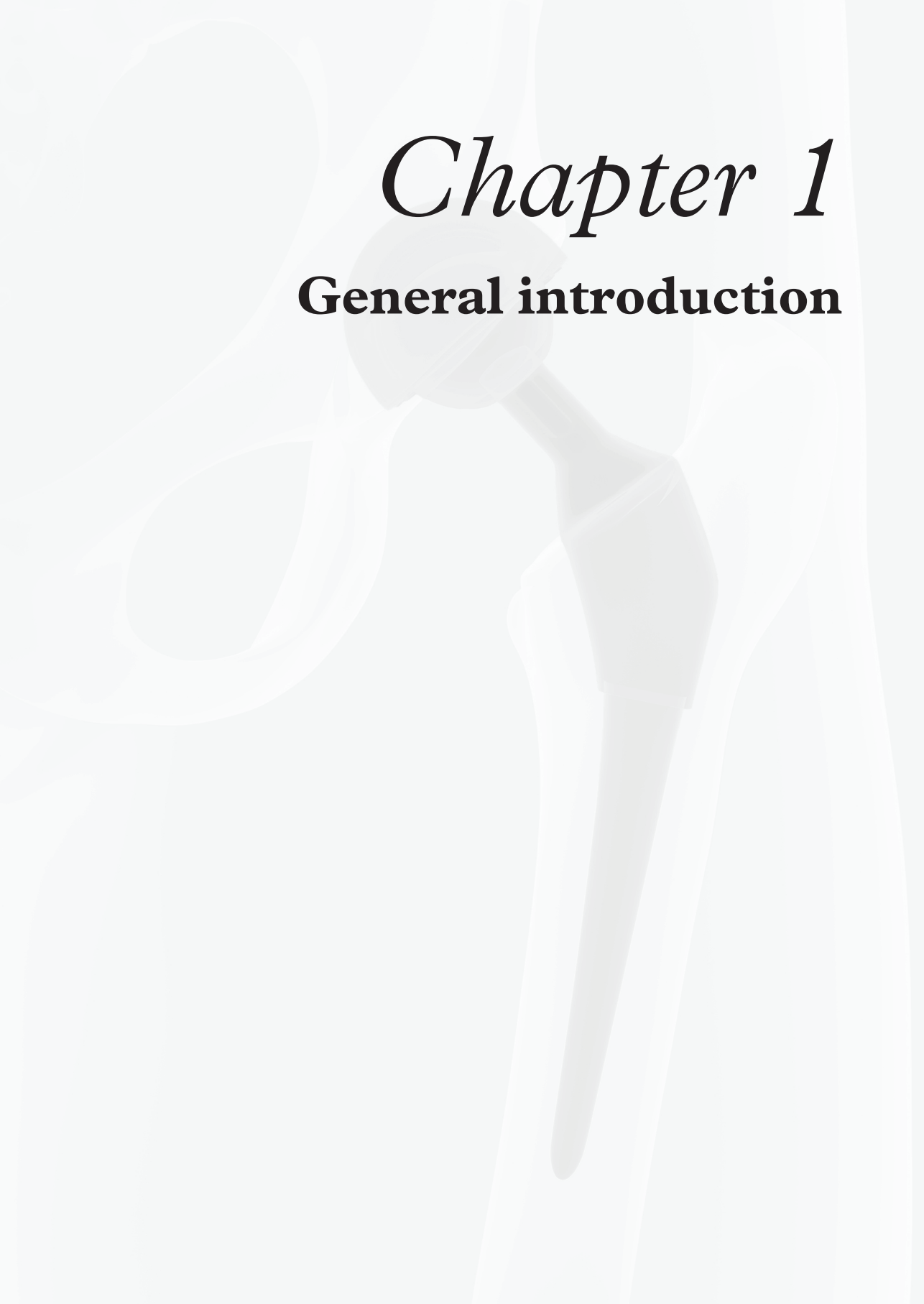
Promotiecommissie

Promotor:	Prof.dr. B.H.Ch. Stricker
Overige leden:	Prof.dr. C. Wagner
	Prof.dr. J.W. Deckers
	Prof.dr. J.A.N. Verhaar

Table of contents

Chapter 1

General introduction



The beneficial effects of modern health care are greatly dependent on medical technology. For an estimated 98% of all hospital admissions in the Netherlands, medical technology is used.[1] In the past decades, the technical developments have advanced and consequently, life expectancy and quality of life have increased. For example, cardiac implantable electronic devices have prolonged the lives of many patients worldwide because conduction disorders, atrial and ventricular fibrillation and subsequent heart failure can be treated by implantation of increasingly sophisticated pacemakers, ICD's and CRT-devices.[2-3] However, recent major incidents of deficient medical devices – mainly concerning implants – have illustrated that patient safety and trust in medical devices can be seriously affected by failures and recalls.[4] Consequently, there is a need to detect potential failures and complications as early as possible.

Patient safety became an issue after the publication of the Institute of Medicine report *To Err Is Human; Building a safer health system* in 1999[5]. This report addressed the effects of medical errors and their causes. The report led to several patient safety initiatives and comparable studies worldwide, among which in the Netherlands.[6-7] Where many studies focused on medical and medication errors, two Dutch studies also included adverse events related to the use of medical technology.[1, 8] These studies concluded that for 2.7-2.9% of all hospital admissions medical technology related injuries occurred. Placing of implants contributed relatively mostly to health care related injuries and included infections, bleeding and perforations. However, as product failures or long-term injuries following implantation were not included, the actual percentage of implant related injuries is expected to be higher.[1]

Device failures and related complications may not become apparent until the post-marketing phase, as was the case for many major incidents in the past. Examples are the metal-on-metal hip implants, Björk Shiley heart valves, the Sprint Fidelis leads from Medtronic and Riata leads from St. Jude.[9-13] Advisories and recalls of implants have major impact on the life of involved patients. If surgery is needed for replacing a defective implant, the risks of such surgery must be weighed against the risks of occurrence of device failure. In case a failure is life threatening, patients may have to live with a constant fear that their implant stops functioning.[14-16] which was illustrated by the problems with the Björk Shiley heart valve. A particular type of this heart valve appeared to have a risk of device fracture, leading to death in two thirds of the cases. The valve was recalled and class actions by worried patients and family of deceased patients followed.[12, 17]

Even if there are no failures, medical devices and particularly implants are never without risk. Device related injuries are not necessarily caused by device failures alone. Insufficient training of health care professionals, insufficient evidence based application of technologies and even negligence may contribute to complications and injuries.[18] Regarding the problems with the use of transvaginal mesh, incidents were at least partly also a consequence of the conduct of medical professionals; the implants were quickly incorporated into clinical practice without proper clinical evaluation by the field and insufficient consideration of alternative treatments.[19-21] Additionally, underlying co-morbidity and patient related factors such as age, predisposition to allergies and level of physical activity may also influence efficacy, effectiveness, and complication rates of device therapies. All these factors should be included in the decision-making process for the best applicable treatment and the expected positive effects must be carefully balanced against possible failures and complications of devices.

Regardless of the cause of major device related incidents and failures, they have made the public, media, politics, and regulatory authorities to

question the rigor of existing medical devices legislation and its ability to sufficiently protect patients. This discussion intensified after the problems with PIP breast implants emerged, where the manufacturer fraudulently used industrial silicone instead of medical grade silicone in their implants for several years while misleading the notified body during audits of the production process.[4, 22-25]

Market entry

In this context, a comparison with the US legislation is often made in favor of the US as it would be stricter and more protective for patients.[4, 24, 26] However, also in the US several major problems with implants have occurred, for example the insulation failures with Medtronic Sprint Fidelis leads and St. Jude's Riata leads, the problems with metal-on-metal hip implants, and with transvaginal pelvic floor mesh.[9, 10, 19] Due to the nature of medical devices and particularly implants, exhaustive clinical trials are not always possible and even in cases where clinical trials have been performed, failures and device related complications may not become apparent until after the devices have been used in a larger population and for a longer period of time.[27] Therefore, and contrary to pharmaceuticals, medical devices regulation puts more focus on post-market surveillance than on the pre-market approval regulations.

Medical devices are allowed on the European market when they comply with the essential requirements as laid down in the European Directives on medical devices and active implantable medical devices.[28-29] By applying the CE-mark to a device, the manufacturer claims such compliance. This Conformité Europeène marking is the device's passport which grants it access to all 28 Member States of the European Union and the European countries which are not Member States, but have implemented this legislation. These are the European Free Trade Associations (EFTA), comprising of Norway, Switzerland, Liechtenstein and Iceland.[30]

The medical devices directives seek harmonization of legislation across Europe in order to facilitate trade, while also setting a standard for safe and effective devices.[28-29, 31] In achieving a risk lever that is as low as possible, the essential requirements primarily focus on a safe device design. Any residual risks need to be mitigated preferably by alarms on the device itself and if this is not possible as is the case for several implants, they should be mentioned in the instructions for use. As part of the risk analysis, a manufacturer is required to identify all risks of normal use and of any reasonably foreseeable misuse of the device. This risk analysis must be continuously updated, also in the post-marketing phase. A trusted third party, the notified body, assesses the conformity of a device with the essential requirements. This process entails the assessment of the technical documentation that needs to be available for each device, audits of the production facilities and audits of the quality management system. In the post-marketing phase, manufacturers need to inform their notified body – but also relevant European competent authorities – of incidents, field safety corrective actions and relevant information emerging from the post-marketing surveillance activities. The Directives will be replaced by a single regulation which entered into force in May 2017 and will be fully applicable in 2020.[32] Contrary to the Directives, the regulation is applicable in all European countries without the need for implementation in national legislation. Important changes are more requirements regarding robust clinical evidence before and more rigorous post-marketing surveillance after market entry of a device.

In essence, the EU regulatory system does not differ to a great extent from that in the US; both systems have a market entry route via demonstration of equivalency with existing, similar devices and a pre-market approval route for high risk devices.[31, 33-34] Implants such as pacemakers and artificial hip prostheses are regarded as high risk medical devices and belong to the

group of most strictly regulated products, which have to follow a thorough pre-market approval or conformity assessment procedure. In the USA, a pre-market approval by the Food and Drug Administration (FDA) is necessary, although (minor) changes to a product already on the market may be approved via less extensive supplemental procedures.[35] In Europe, conformity to the essential requirements needs to be proven and in the case of high risk devices such as pacemakers and hip prostheses, an assessment of conformity with full design examination by a notified body is necessary. Providing clinical evidence is part of both procedures, but the type of information that is considered acceptable as clinical evidence differs.[30] The fact that in the US the pre-market approval assessment is performed by the governmental FDA, whereas in the EU conformity assessment is performed by notified bodies is an important difference between both systems. However, notified bodies oversee all high-risk devices, whereas high-risk devices that are allowed on the US market by equivalency via the 510(k) procedure are not assessed by the FDA.[31, 33-34]

During the market authorization process, a manufacturer must provide proof of conformity with the essential requirements. This proof is partially based on clinical data, which can either be (1) a critical appraisal of scientific literature of a device to which equivalence has been demonstrated, (2) the results of a clinical investigation or (3) a combination of both.[34] However, not all defects, failures and complications can be identified during such studies. Bench testing may not always be comparable to use in actual patients and clinical studies usually include only a limited number of participants. Furthermore, after marketing, the population in which the implant is actually used could significantly differ from the study population. Consequently, rare events and complications may only emerge after the device has been marketed and used in several thousands of patients. Therefore, post-market surveillance (PMS) is necessary for the evaluation of device performance in real-life.[27] Manufacturers are legally obliged to 'institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase, and to implement appropriate means to apply any necessary corrective action'. Unfortunately, legislation does not define how this should be done.[4, 34, 36] However, information for post-marketing surveillance can come from different sources. One used by all manufacturers is the collection and analysis of complaints and incident reports. However, this passive form of data collection is prone to underreporting and should be complemented with activities such as post-market clinical follow-up studies, enquiries, user panels and other pro-active sources.

Post-market phase

Post-market information is also relevant to the competent authorities overseeing the field of medical devices and its legislation. In case a device poses an unacceptable risk for patient safety, and is insufficiently addressed by the manufacturer, competent authorities can take measures such as requiring the manufacturer to take corrective actions or perform a recall. If a device should be removed from the market, the involved notified body can withdraw the CE-certificate.[30, 34] Ultimately, legislation allows competent authorities to remove a device from the market if the risk is severe and other measures are not sufficient or appropriate.[28-29, 34] Additionally, depending on national legislation authorities may impose fines, as is the case for France, the United Kingdom and the Netherlands.[37-39]

Competent authorities rely on several, mostly external, sources of information on device safety. These are their own market surveillance activities such as inspections of manufacturers and studies on products or product groups. The latter are generally based on technical files of products, literature studies and/or biocompatibility studies. Such activities may differ between competent authorities.

In general, clinical trials with devices are the responsibility of manufacturers as part of the pre-market authorization and post-market clinical follow-up processes. Other sources of information are the obligatory vigilance reports by manufacturers and depending on national legislation, mandatory and/or voluntary reports by health care professionals, and reports by patients.[34] Therefore, it is important that health care professionals realize that they have a role in reporting negative trends or experience with structurally deficient devices to manufacturers and competent authorities. Detection of device problems as early as possible is of paramount importance for authorities. Following incidents with metal-on-metal hip implants and transvaginal mesh, the Dutch competent authority advised to establish a register where patients can report adverse events and unwanted side-effects.[13, 21] Such a system has been established and started in July 2017, with a focus on reporting of events related to implants.[40]

Despite current initiatives, the availability of comprehensive registries that may be useful for information on device performance is limited to date and those that are available are often not accessible to manufacturers or competent authorities. Registers can provide data on long term safety, performance, and reliability and allow early identification of problems, which has been proven for the metal-on-metal hip implants in the past.[4] For the studies described in this thesis, existing registries have been used; a utilization register on pacemakers and a national hospital discharge records database. These databases are some of the few long-term registries that are available. Furthermore, data were used from a prospective population-based cohort study with up to 25 years of follow-up. Below, these databases are described in short.

CPPR-SPRN

The Netherlands Pacemaker Registry Foundation (CPPR-SPRN) was established in 1982 and the computerised Central Pacemaker Patients Registration was started. The aims of the registry were to get an overview of: 1) patient and implant characteristics; 2) trends in types of pacemakers and leads; and 3) the annual number of implants per clinic and nationwide. Furthermore, the objectives of the registry were to inform the participating clinics and recipients about quality issues with pacemakers and leads, to exchange information with other European countries, and to increase indirect patient care by furnishing information to clinics about pacemakers implanted elsewhere and to patients about pacemaker centers in other countries.[41-43]

Cardiologists and pacemaker technicians were requested to register the data on the patient, device and leads on the pacemaker card. Each recipient of a pacemaker was registered in the database. Data on symptoms, indication and diagnosis, brand of pacemaker and leads, type, follow-up visits, explantation, hospital transfer and death were registered according to European Registry Guidelines established in 1982 and later. When CPPR-SPRN ended its registration activities in December 2007, data on 174,405 first implantations and replacements, with 204,920 leads, had been recorded for 136,342 patients for 25 years.[41-43]

Until 1989, data were centrally registered by sending a carbon copy of the pacemaker card to the registry. From 1989 onwards, digitalised registration was used with automatic communication between the central registration computer and the local computer of the implanting centre. During the daily conversions into the database, multiple checks were performed on: missing data, conformation with already stored information and plausibility.[41] Additionally, the data were periodically returned to the clinics for correction purposes. A validation process in order to obtain better insight into the quality of the database was performed in 1997.[42]

National hospital discharge records database

The nationwide electronic database with hospital discharge records in The Netherlands (Landelijke Medische Registratie, LMR) covered admissions in all general and university medical centers.[44] The database included, among others, demographics, date of admission and discharge, main intervention (coded), type of medical specialist (coded), and the main and up to 9 secondary diagnoses at discharge, based on the International Classification of Diseases, 8th Revision, Clinical Modification (ICD-9-CM) coding system.[45] Registration of the main diagnosis was mandatory, the others were optional. Characteristics of all hospitalizations, polyclinical visits excluded, were registered by medical doctors on the basis of hospital discharge letters and coded by professional code clerks. The coding was independent of reimbursement of hospital or specialist. All diagnoses were submitted in the same format, mostly electronically.

The purpose of the registry was to provide medical-administrative information regarding hospital care in the Netherlands to support governmental and hospital policy. Additionally, it could provide bench-mark information to hospitals and medical specialists. The data was also available for scientific research. Unfortunately, the LMR-registry has been replaced by a new registry in 2006 which encompasses a system of 'diagnosis-therapy combinations' [diagnose-behandelcombinatie (DBC)]. The DBCs lack relevant epidemiologic information such as a coded diagnosis. Furthermore, the choice for a DBC may depend on reimbursement, and could therefore introduce the possibility of diagnostic information bias.[44, 46]

The Rotterdam Study

The Rotterdam Study (RS) is a large prospective population based cohort study on the occurrence and determinants of disease and disability in older persons. The study started in 1990, consisting of a cohort of inhabitants of Ommoord, a suburb of Rotterdam, who were 55 years or older and lived in Ommoord for at least one year. Initially, the study started with 7983 persons (78% of 10,215 invitees). In 2000 and 2006 two more cohorts were added, the latter also included all inhabitants aged 45-54 years. The overall response figure for all three cohorts at baseline was 72% (14,926 of 20,744 eligible subjects). In February 2016, a fourth cohort was started. The participants of the study are followed for a variety of diseases that are frequent in the elderly, such as cardiovascular, locomotor, respiratory, neurological and psychiatric diseases. Additionally, pharmaco-epidemiologic studies, and genomics, epigenetics, metabolomics and other biomarker studies were performed. The purpose of these epidemiologic studies was to gain insight in the etiology, prevention and prediction of disorders and diseases.[47] Medical implants are not registered in this study, but for several studies described in this thesis, the data were used for validation purposes.

Aim and outline of this thesis

The aim of this thesis was to gain more insight into the use of medical registries as a source of information on complications and failures of implants. For this purpose, we used two databases; the Central Pacemaker Patients Registration (CPPR-SPRN) containing all first pacemaker implantations and their replacements between January 1984 and December 2007, and the National Hospital Discharge Records Database (LMR) containing all hospital admissions and discharges from 2000-2005.

Part I contains studies based on the CPPR-SPRN registry. In chapter 2.1 we first describe the utilization of cardiac pacemakers in the Netherlands over a 20-year period. Secondly, we assessed the number and reasons of explantations, and the service time of the pacemaker generators (chapter 2.2). In this study,

we used the Rotterdam Study to validate the mortality data as registered in the CPPR-SPRN registry. Thirdly, in chapter 2.3 we analyzed the trends in service time of pacemaker leads, and the number and reasons for explantation. In part II we investigated the usability of the LMR registry for analysis of several clinical interventions using implants. First, in chapter 3.1 we analyzed the complications after hip arthroplasty, both after injury and for elective reasons. We have reviewed whether re-admissions due to complications are associated with hospital procedure volume. Furthermore, we have investigated the incidence of and treatments for subarachnoid hemorrhage (SAH), a devastating disorder which is caused by rupture of an intracranial aneurysm in the majority of cases (chapter 3.2). Finally, in chapter 3.3 we studied three invasive procedures for treatment of trigeminal neuralgia (TGN). We assessed the frequency of use and the failure of these treatments. In chapter 4 we reflect on our main findings and discuss the use of registries as source of information on implant performance. Chapter 5 contains a summary in both English and chapter 6 a summary in Dutch.

References

1. Langelaan M, Bruijne MC de, Baines RJ, et al. Monitor zorggerelateerde schade 2011/2012. Dossieronderzoek in Nederlandse ziekenhuizen. EMGO Instituut en NIVEL, 2013.

2. Raatikainen MJ, Arnar DO, Zeppenfeld K, et al. Statistics on the use of cardiac electronic devices and electrophysiological procedures in the European Society of Cardiology countries: 2014 report from the European Heart Rhythm Association. Europace. 2015;17:i1-i75.

3. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calender year 2009 – a World Society of Arrhythmia's project. PACE. 2011;34:1013-27.

4. Cohen D, Billingsley M. Europeans are left to their own devices. BMJ. 2011;342:d2748.

5. Institute of Medicine. To err is human: building a safer health system. Washington DC, 1999.

6. Cuperus-Bosma JM, Wagner C, Wal, G van der. Patient safety in hospitals. International Journal of Risk & Safety in Medicine. 2006;18(1);59-64.

7. Zegers M, Bruine MC de, Wagner C, et al. Adverse events and potentially preventable deaths in Dutch hospitals: results of a retrospective patient record review study. Qual Saf Health Care. 2009;18(4):297-302.

8. Langelaan M, Baines RJ, Broekens MA, et al. Monitor zorggerelateerde schade 2008: dossieronderzoek in Nederlandse ziekenhuizen. Utrecht: NIVEL, 2010

9. Maisel WH. Semper Fidelis – consumer protection for patients with implanted medical devices. N Engl J Med. 2008;358(10): 958-7.

10. Hauser RG, McGriff D, Kallinen Retel L. Riata implantable cardioverter-defibrillator lead failure: analysis of explanted leads with a unique insulation defect. Heart Rhythm. 2012;9:742-49.

11. MHRA. All metal-on-metal (MoM) hip replacements. Medical Device Alert MDA/2012/036. Juni 2012. https://assets.publishing.service.gov.uk/media/5485abf6ed915d4c10000273/con155767.pdf Last accessed: 17 May, 2017.

12. Harrison DC, Ibrahim MA, Weyman AE, et al. The Björk-Shiley Convexo-Concave heart valve experience from the perspective of the supervisory panel. Am J Cardiol. 2013;112:1921-31.

13. Inspectie voor de Gezondheidszorg. Metaal-op-metaal-heupimplantaten – de keten voor de kwaliteitsborging van medische hulpmiddelen moet beter functioneren. Mei 2013. https://www.igz.nl/Images/2013-05-20%20Rapport%20Metaal-op-metaal-heupimplantaten%20incl.%20bijlage%20RIVM-rapport_tcm294-341951.pdf Last accessed: 17 May, 2017.

14. Maisel WH. Physician management of pacemaker and implanable cardioverter defibrillator advisories. PACE. 2004;27:437-42.

15. Cavagna M, Strickberger SA. Management of recalled pacemakers and defibrillators. Expert Rev Cardiovasc Ther. 2006;4(5):601-3.

16. Amin MS, Matchar DB, Wood MA, et al. Management of recalled pacemakers and implantable cardioverter-defibrillators. JAMA. 2006;296(4):412-20.

17. Van der Graaf Y, De Waard F, Van Herweden LA, et al. Risk of strut fracture of Björk-Shiley valves. Lancet. 1992;339:257-61.

18. Expertgroep medische technologie. Medische technologie at risk? Onderzoek naar risico's bij medische technologie en mogelijkheden om deze te voorkomen of te reduceren. April 2011. http://prodb.zorgvisie.nl/PageFiles/76375/002_RBIAdam-download-ZVS12088D01.pdf Last accessed: 17 May, 2017.

19. Food and Drug Administration. FDA safety communication: update on serious complications associated with transvaginal placement of surgical mesh for pelvic organ prolapse. http://www.fda.gov/MedicalDevices/ Safety/

AlertsandNotices/ucm262435.htm. Published July 13, 2011. Last accessed: 17 May, 2017.

20. Myers E, Geller E, Crane A, et al. Estimating the early impact of the FDA safety communication on the use of surgical mesh. South Med J. 2013;106(12):684-8.

21. Inspectie voor de Gezondheidszorg. Bekkenbodemmatjes – ernstige complicaties vereisen terughoudend gebruik. Juli 2013. https://www.igz.nl/Images/Bekkenbodemmatjes_%20Ernstige%20complicaties%20vereisen%20terughoudend%20gebruik%20transvaginale%20mesh_tcm294-360255.pdf Last accessed: 17 May, 2017.

22. Wilmshurst P. The regulation of medical devices. Unsatisfactory, unscientific, and in need of a major overhaul. BMJ. 2011;342:d2822.

23. Godlee F. The trouble with medical devices. BMJ. 2011;342(13):d3123.

24. Heneghan C. The saga of Poly Implant Prosthèse breast implants. Urgent review of the regulation and postmarketing evidence requirements is needed. BMJ. 2012;344:e306.

25. Sedrakyan A. Metal-on-metal failures – in science, regulation, and policy. Lancet. 2012;379(9822):1174-6.

26. FDA. Unsafe and ineffective devices approved in the EU that were not approved in the US. 2012.

27. Blake K. Postmarket surveillance of medical devices: current capabilities and future opportunities. J Interv Card Electrophysiol. 2013;36:119-27.

28. Council Directive of 20 June 1990 on the approximation of the laws of the Member States relating to implantable medical devices. 90/85/EEC. Available via: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX-:01990L0385-20071011&from=EN. Last accessed: 4 August 2017.

29. Council Directive of 14 June 1993 concerning medical devices. 93/42/EEC. Available via: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:01993L0042-20071011&from=EN. Last accessed: 4 August 2017.

30. Fraser A, Daubert JC, Van de Werf F, et al. Clinical evaluation of cardiovascular devices: principles, problems, and proposals for European regulatory reform. Eur Heart J. 2011;32:1673-86.

31. Kramer DB, Xu S, Kesselheim AS. Regulation of medical devices in the United States and European Union. N Engl J Med. 2012;366(9):848-55.

32. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.

33. Kramer DB, Xu S, Kesselheim AS. How does medical device regulation perform in the United States and the European Union? A systematic review. PLoS Med. 2012;9(7):e1001276.

34. Van Drongelen A, Hessels J, Geertsma R. Comparison of market authorization systems of medical devices in USA and Europe. RIVM letter report 2015-0001, 2015.

35. Rome BN, Kramer DB, Kesselheim AS. Approval of high-risk medical devices in the US: implications for clinical cardiology. Curr Cardiol Rep. 2014;16:489, DOI 10.1007/s11886-014-0489-0.

36. Kramer DB, Tan YT, Sato C, et al. Postmarket surveillance of medical devices: a comparison of strategies in the US, EU, Japan, and China. PLoS Medicine. 2013;10(9):e1001519.

37. Wet op de medische hulpmiddelen. Wet van 15 januari 1970, houdende regelen met betrekking tot medische hulpmiddelen. Stb. 1970, 53. http://wetten.overheid.nl/BWBR0002697/2016-08-01. Last accessed: 5 August 2017.

38. Medicines and Healthcare products Regulatory Agency (MHRA). Medical devices: the regulations and how we enforce them. Guidance, 24 March 2017. https://www.gov.uk/government/publications/report-a-non-compliant-medical-device-enforcement-process/how-mhra-ensures-the-safety-and-quality-of-medical-devices. Last accessed: 5 August 2017.

39. Agence nationale de sécurité du medicament et des produits de santé (ANSM). La réglementation matériovigilance. http://ansm.sante.fr/Declarer-un-effet-indesirable/Materiovigilance/La-reglementation/(offset)/7 Last accessed: 5 August 2017.

40. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Meldpunt en expertisecentrum bijwerkingen implantaten van start. http://www.rivm.nl/Documenten_en_publicaties/Algemeen_Actueel/Nieuwsberichten/2017/Meldpunt_en_Expertisecentrum_Bijwerkingen_Implantaten_van_start Last accessed: 7 July 2017.

41. Dijk WA, Hooijschuur CA, Dassen WR. Central Pacemaker Registry in the Netherlands, a 10 year evaluation. Computers in Cardiology, Jerusalem 1989: IEEE Computer society: 293, doi: 10.1109/CIC.1989.130547.

42. Dijk WA, Kingma T, Hooijschuur CA, et al. Validation of the Netherlands Pacemaker Patient Registry. Comput Cardiol. 1997;24:653-6.

43. Hooijschuur CAM, Dijk WA. Impact of data collected on implanted devices and device recipients. Neth Heart J. 2008;16:S9-11.

44. Volksgezondheidenzorg.info, 2017: https://bronnen.zorggegevens.nl/Bron?naam=Landelijke-Medische-Registratie-(LMR), RIVM: Bilthoven. Last accessed: 13 May 2017.

45. Kupka K. International classification of diseases: 9th revision. WHO Chronicle. 1978;32:219–25.

46. Stricker BH, Herings, RM. Pleidooi voor et behoud van de Landelijke Medische Registratie voor betrouwbare informatie over de volksgezondheid en de gezondheidszorg. Ned Tijdschr Geneeskd. 2006;150(35): 1916-7.

47. Hofman A, Brusselle GG, Darwish Murad S, et al. The Rotterdam Study: 2016 objectives and design update. Eur J Epidemiol. 2015;30:661-708.

Part I

Utilisation registry on pacemakers: SPRN

Chapter 2.1

Utilisation of cardiac pacemakers over a 20-year period: results from a nationwide pacemaker registry

L.M. de Vries, W.A. Dijk, C.A.M. Hooijschuur,

M.J.G. Leening, B.H.C. Stricker, N.M. van Hemel

Published in Netherlands Heart Journal, 2017

Jan;25(1):47-55. doi: 10.1007/s12471-016-0880-0.,

PubMED PMID: 27561286

Abstract

Background

The implantation of cardiac pacemakers has become a well-established therapy for conduction disorders and sinus node dysfunction. In many countries pacemaker registries have been initiated in order to collect information on patient characteristics, trends in numbers and the types of pacemakers used, to identify problematic devices, and for safety monitoring.

Methods

For this utilisation study the Central Pacemaker Patients Registration (CPPR) from the Netherlands Pacemaker Registry Foundation (CPPR-SPRN) containing data collected for more than 20 years was used.

Results

During this period, nearly 97,000 first pacemakers were implanted. Analyses show an increase in the rate of implanted devices. The change in pacemaker type from VVI to DDD, followed by biventricular stimulation, is reflected by the number of simultaneously implanted leads, which is partly a consequence of cardiac resynchronisation therapy.

Conclusion

Our data demonstrate that indications for implantation and type of pacemaker are comparable with other European countries.

Advantages of cardiac pacing have been established in the past decades for conventional indications such as conduction disorders, and with new applications for treatment of arrhythmias and heart failure being added, clinical investigation is ongoing. Implantation of cardiac pacemakers has prolonged the lives and improved the quality of life of many patients.[1-3] Despite these advantages, implantation of devices is also inevitably associated with complications and may be prone to product defects. This was illustrated by several major cases and recalls in the past, such as the Accufix leads for cardiac pacemakers.[4-7]
In many countries device registries were initiated by individual cardiologists or national societies in order to gain insight into patient characteristics, trends in numbers and the types of pacemakers used, to inform participating centres about problematic devices, and to exchange information between countries.[8-10] However, most of these registries were restricted to a limited number of hospitals or geographical areas. In the Netherlands, registration with the intention to record every pacemaker implanted in Dutch hospitals was initiated in 1982. This registry, maintained by the Netherlands Pacemaker Registry Foundation (SPRN), was kept until 2008 after which the Netherlands Society of Cardiology started a new registration: the Dutch ICD and Pacemaker Registration (DIPR), which was recently integrated into the overarching National Cardiovascular Data Registry (NCDR).
The objective of the current analysis was to study changes in the utilisation of cardiac pacemakers for new implantations over a period of more than 20 years in a country with the nearly nationwide pacemaker registry CPPR-SPRN.

Methods

Setting

Data were retrieved from the Central Pacemaker Patients Registration (CPPR) from the Netherlands Pacemaker Registry Foundation (CPPR-SPRN). In 1982, CPPR-SPRN was established and the computerised Central Pacemaker Patients Registration was started. The aims of the registry were to get an overview of: 1) patient and implant characteristics; 2) trends in types of pacemakers and leads; and 3) the annual number of implants per clinic and nationwide. Furthermore, the objectives of the registry were to inform the participating clinics and recipients about quality issues with pacemakers and leads, to exchange information with other European countries, and to increase indirect patient care by furnishing information to clinics about pacemakers implanted elsewhere and to patients about pacemaker centres in other countries.
Cardiologists and pacemaker technicians were requested to register data on the patient, device and leads on the pacemaker card. Each recipient of a pacemaker was registered in the database. Data on symptoms, indication and diagnosis, brand of pacemaker and leads, type, follow-up visits, explantation, hospital transfer and death were registered according to European Registry Guidelines established in 1982 and later. When CPPR-SPRN ended its registration activities in December 2007, data on 174,405 first implantations and replacements, with 204,920 leads, had been recorded for 136,342 patients during 25 years.[8]

Monitoring and validation of data

Until 1989, data were centrally registered by sending a carbon copy of the pacemaker card to the registry. From 1989 onwards, digitalised registration was used with automatic communication between the central registration computer and the local computer of the implanting centre. During the daily conversions into the database, multiple checks were performed on: missing data, conformation with already stored information and plausibility.[11] Additionally, the data were periodically returned to the clinics for correction purposes. A validation process in or-

Table 1. Baseline characteristics of the patients at implantation of first pacemaker

	Women[a]	Men[a]	*p*-value for difference[b]	All first implantations
Total number of first implantations	45,661 (47,1)	51,164 (52.8)	<0.001[c]	96,900
Mean age, years (SD)	74.6 (12.6)	71.4 (13.2)	<0.001	72.9 (13.0)
Median age, years	77.0	74.0		75.0
Age ≥60 years, *n* (%)	41,457 (90.8)	43,637 (85.3)	<0.001	85,165 (87.9)
Age ≥80 years, *n* (%)	17,489 (38.3)	12,208 (23.9)	<0.001	31,569 (32.6)
ECG, *n* (%):				
Sick sinus syndrome	20,166 (44.2)	20,847 (40.7)	<0.001	41,026 (42.3)
Heart block	17,612 (38.6)	20,050 (39.2)	0.049	37,682 (38.9)
Bundle branch block	1537 (3.4)	2582 (5.0)	<0.001	4121 (4.3)
Normal sinus rhythm (with or without abnormal EPS) or not documented	940 (2.1)	1164 (2.3)	0.021	2104 (2.2)
Other	541 (1.2)	691 (1.4)	0.022	1232 (1.3)
Unknown/uncoded/unspecified	4865 (10.7)	5830 (11.4)	<0.001	10,735 (11.1)
Symptoms, *n* (%):				
Syncope	13,004 (28.5)	14,651 (28.6)	0.592	27,672 (28.6)
Dizzy spells	12,749 (27.9)	12,973 (25.4)	<0.001	25,728 (26.6)
Bradycardia	9,485 (20.8)	10,908 (21.3)	0.037	20,398 (21.1)
Dyspnoea/heart failure	2396 (5.2)	3064 (6.0)	<0.001	5462 (5.6)
None/prophylactic	751 (1.6)	1132 (2.2)	<0.001	1884 (1.9)
Tachycardia	866 (1.9)	876 (1.7)	0.031	1743 (1.8)
Other	215 (0.5)	267 (0.5)	0.260	483 (0.5)
Unknown/uncoded/unspecified	6195 (13.6)	7293 (14.3)	0.002	13,530 (14.0)
Aetiology, *n* (%):				
Conduction tissue disease	5219 (11.4)	5401 (10.6)	n.c.	10,623 (11.0)
Ischaemic	2100 (4.6)	2718 (5.3)	n.c.	4818 (5.0)
Therapy induced	1603 (3.5)	1978 (3.9)	n.c.	3583 (3.7)
Cardiomyopathy	1170 (2.6)	1400 (2.7)	n.c.	2572 (2.7)
Post myocardial infarction	716 (1.6)	1528 (3.0)	n.c.	2244 (2.3)
Congenital	394 (0.9)	348 (0.7)	n.c.	742 (0.8)
Other	182 (0.4)	446 (0.9)	n.c.	628 (0.6)
Unknown/uncoded/unspecified, *n* (%)	34,277 (75.1)	37,345 (73.0)	n.c.	71,690 (74.0)

EPS: electrophysiological study
[a] *For 75 patients the sex is unknown, for 38 males and 22 females age is unknown*
[b] *P-value was not calculated for aetiology because of large proportion of missing data (n.c.)*
[c] *For 1995-2005*

der to obtain better insight into the quality of the database was performed in 1997.[12]

Cohort

Based on the available data, an inception cohort of patients was formed containing all first implanted pacemakers during the period 1 January 1984 until 1 January 2006. A total of 353 implantations were excluded because of inconsistencies in the registered data, such as a new implantation being registered after the supposed date of death of a patient, or the same pacemaker registered more than once with different explantation dates, leaving 96,900 first implantations for analysis.

At the start of the registration in 1984, 120 hospitals participated, some of which were sub locations of the same hospital but participated independently. During the study period several locations and/or hospitals merged and the registry was continued under one account, leaving 101 participants in the registry. General population data were obtained from Statistics Netherlands (CBS, www.cbs.nl/en-GB/).

Analysis

We computed straightforward descriptive statistics for the aetiology, pacemaker types, and the prevalences of symptoms and ECG characteristics as percentages of all first implantations. For implantation rates, we calculated Poisson intervals. For the comparison of normally distributed continuous determinants, we used independent samples T-tests while categorical determinants were compared with chi-square statistics. All statistical analyses were performed in IBM SPSS Statistics version 20.0 (IBM Corp., Somers, New York, USA).

Results

Between 1 January 1984 and 1 January 2006, 96,900 first pacemakers were implanted (Table 1). This corresponds to an average number of implantations of more than 4600 devices per year, varying from a total of 3236 first implantations in 1984 (225 implants per million inhabitants) to 6901 first implantations in 2005 (423 implants per million inhabitants).

One hospital performed nearly 4000 first implantations during the study period, which is approximately 4% of the total number of first implantations. One hospital implanted more than 2600 first pacemakers (2.7%), 5 hospitals implanted between 1900 and 2500 pacemakers each (2-2.5%), another 36 hospitals

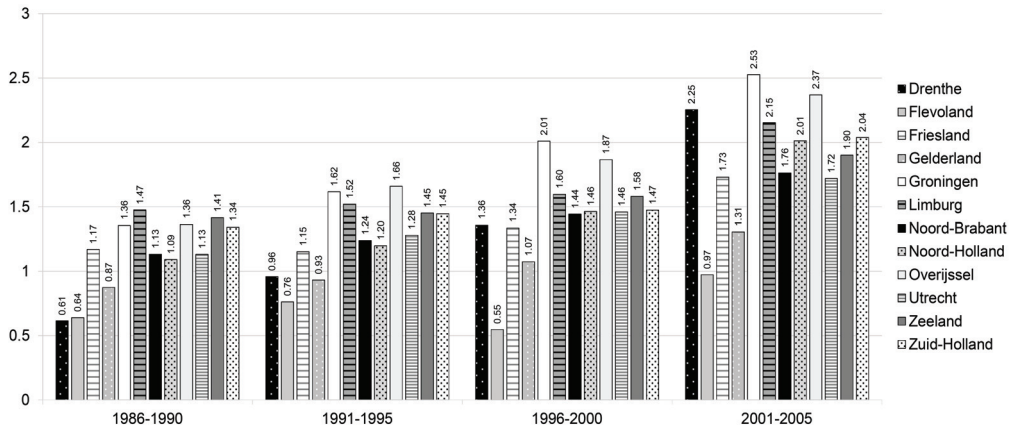


Figure 1. *Number of first implantations per 1000 inhabitants per province. 1984 and 1985 excluded to create equal time periods, additionally no population data are available for these years for Flevoland.*

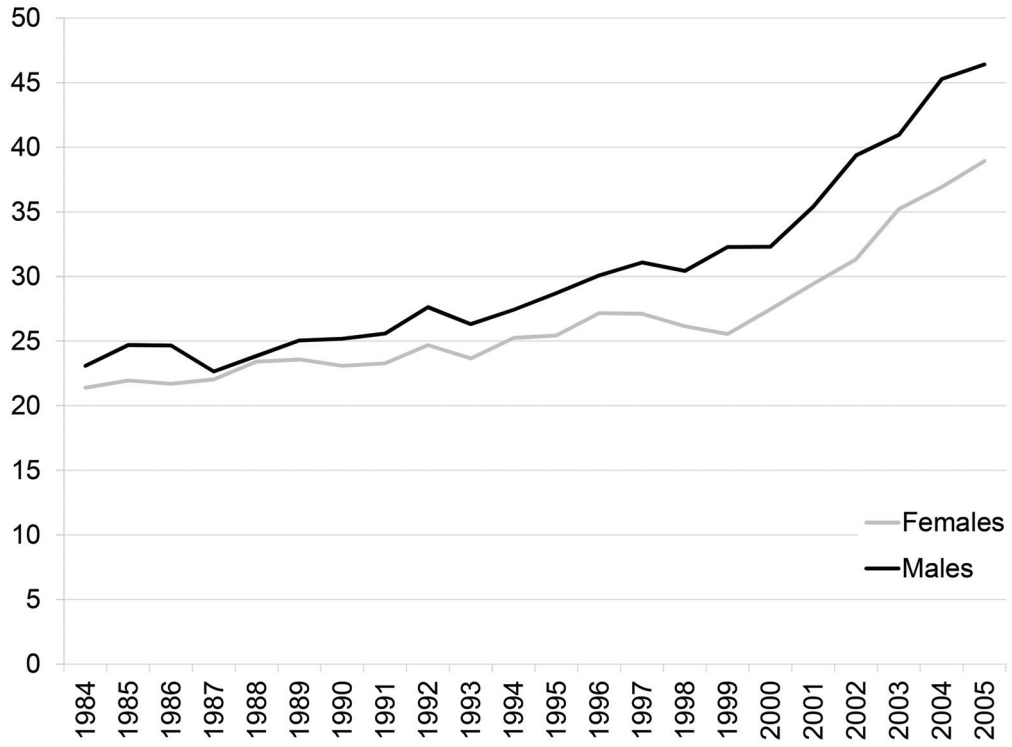


Figure 2. *Number of first implantations per 100,000 inhabitants by sex*

implanted between 900 and 1900 pacemakers each (1-2%). All other hospitals each implanted less than 1% of the total number of first pacemakers. Eight of these hospitals did not participate in the registration until the early 1990s. Six hospitals did not start until the late 1990s or early 2000s. Two hospitals implanted less than 10 first pacemakers per year. Most pacemakers per 1000 inhabitants were implanted in the province of Groningen, followed by the provinces of Overijssel and Limburg (Figure 1 and Table 2).

The cohort comprised 52.8% men (n=51,164). Starting in 1995 the number of implantations in men was significantly higher than in women ($p<0.001$) in each following year. In the period before 1995 the number of implants in men was only significantly higher in the years 1985, 1986 and 1992 (Table 1 and Figure 2). Mean age for the total cohort was 72.9 years (SD 13.0). The mean age at first implantation increased from 71.1 in 1984 to 72.3 in 2005 for men (mean difference 1.2 years, $p=0.003$) and from 72.8 to 75.1 for women (mean difference 2.3 years, $p<0.001$). The majority of the patients were over 60 years of age (87.9%) and pacemakers were most often implanted in the age group of 60 to 80-year-olds. The percentage of first implantations in octogenarians and nonagenarians is constant over the years. However, first implantations in these groups have been increasing since 2002. The most common indications were sick sinus syndrome (n=41,026; 42.3%) and heart block (n=37,682; 38.9%). This did not change over the years (Figure 3). The number of pacemaker implantations for both

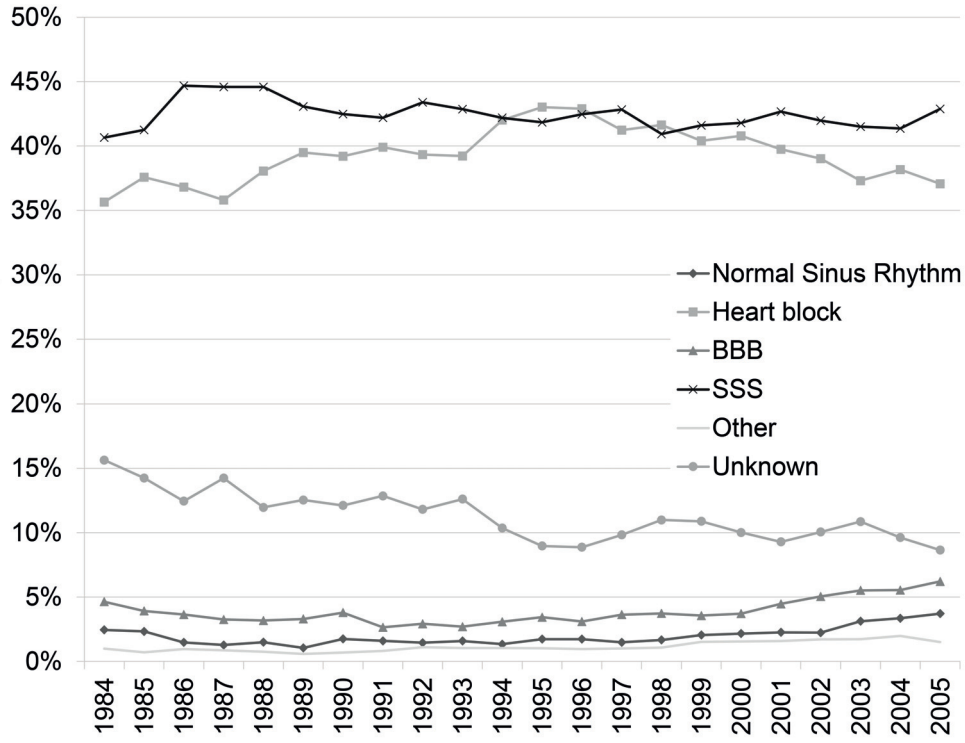


Figure 3. *Indication for first pacemaker implantation, adjusted for number of implantations per year. BBB = bundle branch block; SSS = sick sinus syndrome; normal sinus rhythm with or without abnormal electrophysiological study*

sick sinus syndrome and bundle branch block significantly differed between men and women (p<0.001). All baseline characteristics are provided in Table 1.

Pacemakers of 18 different manufacturers were implanted between 1984 and 2005. The ventricular pacing and sensing (VVI) and dual-chamber pacing and sensing, rate response (DDDR) types were the most commonly used pacemakers: 34.3% and 23.1%, respectively (Table 3). The other types, ventricular pacing and sensing, rate response (VVIR, 15.2%) and dual-chamber pacing and sensing (DDD, 16.1%), were used less often. However, during the early 1990s implantation of pacemaker types changed markedly from a mainly VVI type (single chamber systems) to a DDDR type (dual chamber systems) as depicted in Figure 4. At least 138,225 leads were implanted with the 96,900 first pacemakers. In two thirds of the cases the leads were placed in the ventricle. For 1024 implantations (1%) no leads were registered. For 83% of these implantations the type of pacemaker was also not registered. More than 80% of these pacemakers were implanted during the last 5 years of the study period.

Additionally, after the introduction of cardiac resynchronisation therapy (CRT) around 1995[13], the use of biventricular pacing increased between 2000 and 2005. This change of pacemaker type is also reflected by the number of first implantations with three leads (*n*=1269), 914 (72.3%) of which for the indication dyspnoea/heart failure and 65 (5.1%) for

Table 2. Number of implants per 1000 inhabitants and distribution of population >60 years over provinces

	1986-1990[a]		1991-1995		1996-2000		2001-2005	
	Number of implants per 1000 inhabitants per province (95% CI)	% of population >60 years[b]	Number of implants per 1000 inhabitants per province (95% CI)	% of population >60 years	Number of implants per 1000 inhabitants per province (95% CI)	% of population >60 years	Number of implants per 1000 inhabitants per province (95% CI)	% of population >60 years
Drenthe	0.61 (0.54-0.69)	3.1	0.96 (0.87-1.05)	3.2	1.36 (1.25-1.47)	3.3	2.25 (2.12-2.38)	3.4
Flevoland	0.64 (0.54-0.76)	0.9	0.76 (0.65-0.87)	1.1	0.55 (0.47-0.63)	1.3	0.97 (0.87-1.07)	1.4
Friesland	1.17 (1.09-1.26)	4.3	1.15 (1.06-1.24)	4.2	1.34 (1.25-1.43)	4.1	1.73 (1.63-1.83)	4.2
Gelderland	0.87 (0.83-0.92)	11.9	0.93 (0.89-0.97)	12.0	1.07 (1.02-1.12)	12.1	1.31 (1.26-1.36)	12.2
Groningen	1.36 (1.26-1.46)	4.1	1.62 (1.51-1.73)	3.9	2.01 (1.89-2.13)	3.8	2.53 (2.40-2.66)	3.7
Limburg	1.47 (1.40-1.55)	7.3	1.52 (1.45-1.59)	7.5	1.60 (1.53-1.67)	7.8	2.15 (2.07-2.24)	7.9
Noord-Brabant	1.13 (1.09-1.13)	12.8	1.24 (1.19-1.29)	13.4	1.44 (1.39-1.49)	14.2	1.76 (1.71-1.81)	14.7
Noord-Holland	1.09 (1.05-1.13)	16.7	1.20 (1.16-1.24)	16.2	1.46 (1.41-1.51)	15.7	2.01 (1.96-2.06)	15.5
Overijssel	1.36 (1.29-1.44)	6.8	1.66 (1.58-1.74)	6.8	1.87 (1.79-1.95)	6.8	2.37 (2.28-2.46)	6.8
Utrecht	1.13 (1.07-1.20)	6.3	1.28 (1.21-1.35)	6.4	1.46 (1.39-1.53)	6.4	1.72 (1.64-1.80)	6.4
Zeeland	1.41 (1.30-1.54)	2.8	1.45 (1.33-1.57)	2.8	1.58 (1.45-1.71)	2.8	1.90 (1.76-2.04)	2.8
Zuid-Holland	1.34 (1.30-1.38)	22.9	1.45 (1.41-1.49)	22.3	1.47 (1.43-1.51)	21.7	2.04 (1.99-2.09)	21.0

[a] *1984 and 1985 excluded to create equal time periods, additionally no population data are available for these years for Flevoland*
[b] *Calculated over the years 1988-1990, no population data available for 1986 and 1987*

bradycardia. The other first implantations with three leads were for various other indications (n=96, 7.6%) and unknown, uncoded or unspecified indications (n=190, 15.0%).

Discussion

In the Netherlands, the SPRN registry was operational for more than 20 years to collect pacemaker implantations with nearly complete nationwide coverage; almost 97,000 patients received a pacemaker for the first time between 1984 and 2006. The registry showed that the number of implanted pacemakers has increased steadily over the past few decades. This increase continued in later years (2003-2012).[14]

The number of first implantations per million Dutch inhabitants was below the European average: 314, 294, and 532 implantations per million inhabitants in 2001, 2005, and 2009, respectively, compared with an average of 390, 475, and 552 implantations per million inhabitants in Europe.[15-17] Stofmeel and colleagues[18] also reported that the Netherlands had a smaller number of implantations compared with other European countries over the period 1984-1997. This may be a consequence of reluctance to use pacemakers for indications for which there was limited evidence at that time, such as asymptomatic total AV-block or asymptomatic second-degree AV-block, type Wenckebach, or syncope which is not proven to be a consequence of a total AV-block in patients with a bifascicular or trifascicular block and other causes for syncope cannot be excluded. At that time, there was no agreement for those indications (class 2 indications), as was formulated in

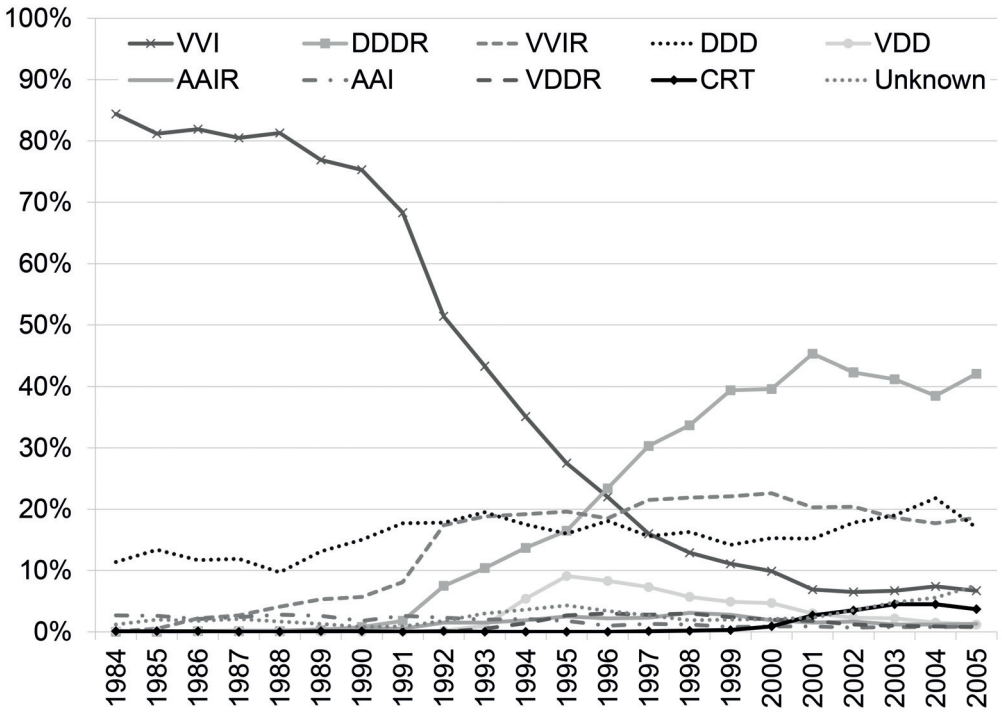


Figure 4. *Type of pacemaker at first implantation*

Table 3. Type of first pacemakers implanted in the period 1984-2005 in the Netherlands (*n*=96,900)

Pacemaker type	*n* (%)
VVI	33,241 (34.3)
VVIR	14,704 (15.2)
DDD	15,636 (16.1)
DDDR	22,424 (23.1)
AAI	1500 (1.4)
AAIR	1350 (1.4)
VDD	2677 (2.8)
VDDR	1123 (1.2)
Biventricular pacing	1269 (1.3)
Unknown	2,976 (3.1)

the 1999 Dutch pacing guidelines.[18,19]

The difference in implantation rates between provinces does not seem to be related to differences in the age of the population. Some provinces with a higher implantation rate have a younger population than provinces with a lower implantation rate. In some provinces one or two hospitals are responsible for more than half of the implantations performed in that province. These hospitals could be 'hot spots' that treat patients from a wider area than the province alone. When done on a regular basis, pacemaker implantation is safe. However, operator volume appears to count when it comes to quality of care. A concentration of procedures in centres where cardiologists implant at least 50 devices per year has therefore been suggested previously.[20]

Sick sinus syndrome and heart block were the major indications for pacemaker implantation. Sick sinus syndrome was significantly predominant in women. This could be attributed to the fact sick sinus syndrome occurs more often in female than in male individuals.[21] The indications for pacemaker implantations found in our study are in line with the major indications in other European countries. During the early 1990s physiological pacing and the use of adaptive pacing frequencies with dual chamber systems (DDD(R)) were increasingly used compared with single chamber systems (VVI(R)). From the more recent World Society of Arrhythmias (WSA) surveys it appeared that indeed virtually all countries had increased percentages of DDDR pacemaker implantations.[15-17, 22] A modest increase of implantation for bundle branch block is visible over the period 2000 to 2005, especially in men. This may be explained in part by the increased use of biventricular pacemakers for cardiac resynchronisation therapy. CRT devices with ICD function (CRT-D) were not registered in this database and are therefore not included in the current analysis. Internationally, an increase of non-bradyarrhythmic indications for cardiac pacing was projected, however remained a minor indication with approximately 5% or less in most countries.[15-17, 22] In the Netherlands this percentage remained less than 5% for a long time, but started increasing in the early 2000s.

Limitations

An important limitation of the data is that registration lies in many hands, which facilitates registration errors such as typographical errors and duplicate registrations of patients transferred to another hospital. We removed these duplicates whenever possible. However, some may have been overlooked due to unavailability of highly detailed patient-related data needed to distinguish duplicate records. Nevertheless, 99% of all implantations are registered[12, 18] and the data provide useful information; therefore, errors are expected to be random with regard to indication and pacemaker properties. In contrast to the ECG data and symptoms, information on aetiology is absent in most cases. However, in cardiology practice it appears to be very difficult to establish the precise cause of cardiac or non-cardiac disease that elicits rhythm or con-

duction disturbances. Additionally, the type of pacemaker was registered at baseline, but the actual setting could have been changed after implantation or during follow-up.

Conclusion

Maintaining a registry for implantable devices can serve many purposes. It provides insight into the patient population, trends regarding devices used and perhaps even more important: tracking and tracing of products in case of failures and recalls. Over the years the SPRN registry has provided input for several of these purposes, the most important being the tracking and tracing of patients in case of recalled devices. As some risks of implantable devices will only become apparent during the actual clinical use after marketing of the device, implant registries can serve a purpose in identifying those risks as well.

In conclusion, analysis of the SPRN database has shown that the frequency of first implantation of pacemakers has steadily increased in the Netherlands and that trends in indications for implantation and pacemaker type are in line with other European countries.

Acknowledgements

We would like to thank all cardiologists and allied professionals for their contributions to the SPRN database.

Both L.M. de Vries and B.H.Ch. Stricker also work for the Dutch Health Care Inspectorate, a governmental supervisory organisation for healthcare. The work described in this paper was explicitly not performed on behalf of the Inspectorate.

References

1. Heidbuchel H, Hindricks G. The year in cardiology 2014: arrhythmias and device therapy. Eur Heart J. 2015:36;270-8.

2. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2013:34;2281-329.

3. Van Hemel NM, Dijkman B, de Voogt WG, et al. Recommendations for pacemaker implantation for the treatment of atrial tachyarrhythmias and resynchronisation therapy for heart failure. A report from the task force on pacemaker indications of the Dutch working Group on Cardiac Pacing. Neth Heart J. 2004;12:18-22.

4. Maisel WH, Sweeney MO, Stevenson WG, et al. Recalls and safety alerts involving pacemakers and implantable cardioverter-defibrillator generators. JAMA. 2001:286:792-99.

5. Maisel WH, Moynahan M, Zuckerman BD, et al. Pacemaker and ICD generator malfunctions. Analysis of Food and Drug Administration annual reports. JAMA. 2006:295:1901-6.

6. Van Hemel NM, Defauw JJAMT, Ruiter J. Het Nederlandse antwoord op de baleinbreuk van de Accufix Atrial J-elektrode: eerste rapportage van de begeleidingscommissie. Cardiologie. 1996;3:72-8.

7. Van Hemel NM, Defauw JJAM, Ruiter JH. Second report of the Dutch committee for monitoring atrial-J retention wire fractures. Cardiologie. 1997;4:164-6.

8. Hooijschuur CAM, Dijk WA. Impact of data collected on implanted devices and device recipients. Neth Heart J. 2008;16:S9-11.

9. Gadler F, Valzania C, Linde C. Current use of implantable electrical devices in Sweden: data from the Swedish pacemaker and implantable cardioverter-defibrillator registry. Europace. 2015;17:69-77.

10. No authors listed. Danish pacemaker and ICD register. 1999. Pacing Clin Electrophysiol. 2000: 23:S1-93.

11. Dijk WA, Hooijschuur CA, Dassen WR. Central Pacemaker Registry in the Netherlands, a 10 year evaluation. Computers in Cardiology, Jerusalem 1989: IEEE Computer society: 293, doi: 10.1109/CIC.1989.130547.

12. Dijk WA, Kingma T, Hooijschuur CA, et al. Validation of the Netherlands Pacemaker Patient Registry. Comput Cardiol. 1997;24:653-6.

13. Daubert JC, Ritter P, Le Breton H, et al. Permanent left ventricular pacing with transvenous leads inserted into the coronary veins. Pace. 1998;21:239-45.

14. Leening MJG, Siregar S, Vaartjes I, et al. Heart disease in the Netherlands: a quantitative update. Neth Heart J. 2014;22:3-10.

15. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009 - a world society of arrhythmia's project. Pace. 2011;34:1013-27.

16. Mond HG, Irwin M, Morillo C, Ector H. The world survey of cardiac pacing and cardioverter defibrillators: calendar year 2001. Pace. 2004;27:955-64.

17. Mond HG, Irwin M, Ector H, Proclemer A. The world survey of cardiac pacing and cardioverter-defibrillators: calendar year 2005. An international cardiac pacing and electrophysiology society (ICPES) project. Pace. 2008;31:1202-12.

18. Stofmeel MA, Kelder JC, van Hemel NM, et al. Pacemaker implantation in the Netherlands, 1984-1997: numbers, types and patient characteristics. Ned Tijdschr Geneeskd. 2001;145:1254-1258 [Dutch].

19. Van Hemel NM, Bennekers JH, Bink-Boelkens MTE, et al. Richtlijnen elektrische hartstimulatie voor bradycardie. Cardiologie. 1999;2:270-84.

20. Van Hemel NM. Quality of care: not hospital but operator volume of pacemaker implantations count. Neth Heart J. 2014;22:292-4.

21. Tadros R, Ton AT, Fiset, C, et al. Sex differences in cardiac electrophysiology and clinical arrhythmias: epidemiology, therapeutics, and mechanisms. Can J Cardiol. 2014;30:783-92.

22. Vardas PE, Simantirakis EN, Kanoupakis EM. New developments in cardiac pacemakers. Circulation. 2012;127:2343-50.

Chapter 2.2

Trends in service time of pacemakers in the Netherlands: a long-term nationwide follow-up study

L.M. de Vries, M.J.G. Leening, W.A. Dijk,

C.A.M. Hooijschuur, B.H.C. Stricker,

N.M. van Hemel

Published in Netherlands Heart Journal, 2017

Aug 2. doi: 10.1007/s12471-017-1024-x.

[Epub ahead of print], PubMed PMID: 28770398

Abstract

Background

After decades of experience and strongly improved technology, service time of pacemaker generators is expected to increase. To test this hypothesis, we conducted a retrospective review of a large cohort of patients with a pacemaker.

Methods

We reviewed data collected between 1984 and 2006 in the first national Dutch pacemaker registry. This registry covered 96% of all generators implanted. We analysed the time of and reason for explantation of pacemaker generators. A 7-year follow-up interval after first implantation and following replacements was used to analyse changes over time.

Results

During 22 years of data collection, nearly 97,000 first pacemaker generators were implanted. A total of 27,937 (22.4%) generators were explanted within a mean of 6.3 (SD 3.3) years. Reasons for approximately 60% of these explantations were end of life of the pacemaker generator or elective system change. Complications or failures, such as infections and recalls, accounted for approximately 20% of the explantations. For the remaining 20%, the reasons for explantation had not been registered.

Conclusion

Despite progress in technology, a substantial proportion of pacemaker generators is explanted before its expected service time, with one in five generators being replaced due to technical failures, infections or other complications. Furthermore, the time interval between pacemaker implantation and explantation due to normal 'end of life' (battery EOL) decreased. Infections continue to rank highly as a cause for pacing system replacement, despite all current preventive measures.

Chronic stimulation of the heart with pacemakers for bradycardia and other indications has been applied worldwide in increasing numbers.[1-2] In the Netherlands, 3236 first pacemakers were implanted in 1984 (225 implants per million inhabitants),[3] while 10,389 pacemakers were implanted in 2011 (468/million inhabitants).[4]
Pacing devices have become technically more sophisticated to enable more options for sensing, pacing and monitoring, as well as sustainability for simultaneous use of other devices and techniques such as magnetic resonance imaging. At the same time, the devices got substantially smaller.[5-7] These developments required a more robust design of the device, IT facilities, and increased lifespan of the battery. The incremental need of remote monitoring to support an intense technical follow-up to optimise the care of the individual pacemaker recipient, also required technical innovations.
Because previous surveys showed a substantial complication rate,[5,6,8,9] we aimed to investigate trends in the duration of service time or longevity of pacemaker generators after first implantation and re-implantation. For this purpose, the reasons for replacement of pacemakers were studied. We anticipated that because of growing experience, guidelines and clustering of treatment facilities, service time of the devices would increase, and complication rates would gradually diminish over several decades.

Patients and Methods

Setting

Data were retrieved from the Central Pacemaker Patients Registration (CPPR) from the Netherlands Pacemaker Registry Foundation (CPPR-SPRN). The registry has been described in detail elsewhere.[3, 10] In brief: in 1982, CPPR-SPRN was established and the computerised registration began. Cardiologists and allied professionals were invited to voluntarily register data of each patient, pacemaker generator, and leads on the former European pacemaker card. Data on symptoms, indication and diagnosis, brand of pacemaker and leads, type, follow-up visits, explantation, hospital transfer and death were registered according to European Registry Guidelines established in 1982 and later.

Monitoring and validation of data

Until 1989, data was registered centrally; a carbon copy of the European pacemaker card had to be sent to the registry. From 1989 onwards, a digitalised registration was used with automatic communication between the central registration computer and the local computer of the implanting centre. During daily conversions into the database, multiple checks were performed on missing data, conformation with already stored information and plausibility.[11] Additionally, the data was periodically returned to the clinics for correction purposes. A validation process to obtain better insight into the quality of the database was performed in 1997. When the central registry was compared with patient files of participating hospitals and sales data from manufacturers, 95.7% of pacemaker generators could be retrieved.[12]

Cohort and outcome definition

Patients admitted for implantation of the first pacemaker between 1 January 1984 and 1 January 2006 were included in this nationwide cohort study. A total of 452 implantations were excluded because of inconsistencies in the registered data, e.g. a new implantation was registered after the supposed date of death of a patient, or the same pacemaker was registered more than once with different explantation dates. This resulted in a cohort with 96,900 patients having a first pacemaker implanted between January 1984 and January 2006, followed by 27,937 explantations (of which 27,659 replacement procedures) until January 2008. The years 2006 and 2007 were used for follow-up only. Additionally, for part of the analyses, the cohort was subdivided into three strata

Table 1. Baseline characteristics of patients in the nationwide CPPR-SPRN database having a first pacemaker implanted (*n*=96,900), the Netherlands 1984-2007

Patients[a]	**1984-1990**	**1991-1995**	**1996-2000**	**2001-2005**	**2006-2007**	**Total study period**
Mean age at first implantation, years (SD)	72.7 (13.0)	73.0 (13.0)	72.9 (13.2)	73.1 (12.9)	NA	72.9 (13.0)
Female gender, *n* (%)	11,628 (48.7)	9419 (47.9)	10,569 (46.6)	14,045 (45.8)	NA	45,661 (47.1)
Deaths, *n* (% of patients that received first pacemaker in this period)[b]	7245 (30.4)	6119 (31.1)	5849 (25.8)[c]	3721 (12.1)[c]	NA	22,934 (23.7)
Follow-up duration (range), years	17-23	12-16	7-11	2-6	NA	2-23
Pacemaker generators	**1984-1990**	**1991-1995**	**1996-2000**	**2001-2005**	**2006-2007**	**Total study period**
Implantations, *n* (% of total # implanted pacemakers during study period), of which:	24,952 (20.0)	23,451 (18.8)	29,789 (23.9)	41,569 (33.4)	4798 (3.9)	124,559 (100.0)
First pacemaker	23,870 (95.7)	19,659 (83.8)[c]	22,694 (76.2)[c]	30,677 (73.8)[c]	NA	96,900 (77.8)
First replacement	1004 (4.0)	3352 (14.3)[c]	5821 (19.5)[c]	8386 (20.2)	3571 (74.4)	22,134 (17.8)
Second replacement	73 (0.3)	389 (1.7)[c]	1050 (3.5)[c]	1930 (4.6)[c]	908 (18.9)	4350 (3.5)
Third or more replacement	5 (<0.1)	51 (0.2)[c]	224 (0.8)[c]	576 (1.4)[c]	319 (6.6)	1175 (0.9)
Explantation of pacemakers implanted in this period, *n* (%), of which:	7238 (29.0)	8402 (35.8)[c]	9250 (31.1)[c]	3000 (7.2)[c]	47 (1.0)	27,937 (22.4)
Explantation <7 years, *n* (%)	3233 (44.7)	4489 (53.4)[c]	5745 (62.1)[c]	NA	NA	16,514 (59.1)
Explantation <5 years, *n* (%)	1692 (23.4)	1972 (23.5)	2455 (26.5)[c]	NA	NA	8586 (30.6)
Explantation <3 years, *n* (%)	950 (13.1)	943 (11.2)[c]	1196 (12.9)[c]	NA	NA	4683 (16.8)
Without replacement/without immediate replacement, *n* (%)	41 (0.6)	33 (0.4)	66 (0.7)	181 (6.0)[c]	11 (23.4)	332 (1.2)
Mean duration of service time for explanted pacemakers, years (SD)	7.7 (4.0)	6.8 (3.0)[c]	6.0 (2.4)[c]	2.9 (2.0)[c]	0.5 (0.5)	6.3 (3.3)
Median duration service time for explanted pacemakers, years (IQR)	7.5 (5.2-10.0)	6.8 (5.1-8.6)	6.4 (4.9-7.6)	2.8 (1.0-4.7)	0.3 (0.1-0.7)	6.4 (4.4-8.2)

For 2006-2007 we used data on replacements only
SD standard deviation, NA not available.
[a] *For 75 patients, data on gender was missing. For 38 males and 22 females, data on age was missing*
[b] *Data on number of deaths is incomplete*
[c] *Significantly different compared to previous time interval (p=0.001), 2006-2007 not tested*

with 7 years of follow-up after each implantation, leaving 66,223 patients who received a first pacemaker between January 1984 and January 2001.

Exposure

The primary interest was the number of pacemaker replacements or explantations and the reasons for these interventions. In this study 'service time' is defined as the time between pacemaker implantation and replacement or removal of the generator.

Analysis

Analyses of explantations and replacements were performed on 1) the entire cohort of patients (*n*=96,900) having first and re-implantations during the study period irrespective of available duration of follow-up, and 2) on three strata (*n*=66,223 patients) to identify changes over time. Each implantation in these strata was followed for a maximum of 7 years or until explantation, whichever came first. For this purpose, first and re-implantations during the years 1984-2000 could be used, while data from 2001-2007 were used for follow-up only. We chose a 7-year follow-up period because the mean duration of follow-up for explanted pacemaker generators falls within this time interval, as also observed by Hauser et al.[13] Furthermore, with 66,223 first implantations during 1984-2000, two thirds of the cohort would remain available for analysis. *P*-values were calculated with chi-square analysis and independent samples *t* test.

Sensitivity analysis

To estimate the proportion of deaths that was (voluntarily) registered in SPRN, we performed a sensitivity analysis by looking up patients from the Rotterdam Study, a large prospective cohort study on inhabitants of the Ommoord area in Rotterdam,[14] in the SPRN database. First, we investigated on basis of gender and date of birth whether a participant from the Rotterdam Study was registered in SPRN. Subsequently, we validated each retrieval by using the pacemaker implant date. The date of death is registered for each participant of the Rotterdam Study.

Results

Between 1 January 1984 and 1 January 2006, 96,900 patients received a first pacemaker. Approximately 53% of the patients were men and the mean age at time of first implantation was 72.9 years (SD 13.0). Baseline characteristics are provided in Table 1.

Pacemaker generator replacements and removals

During the study period, 22,134 patients (22.8%) had at least one pacemaker generator replacement or removal and 4350 patients (4.5%) had more than one. In total, 27,937 pacemaker generators were replaced or removed (22.4% of total number of implants), including 332 pacemaker generators that were coded as a removal without replacement, although it appeared that some of these patients did receive a new pacemaker after several weeks to months (Table 1). The mean duration of follow-up to pacemaker generator replacement or removal (service time) during the whole study period was 6.3 (SD 3.3) years. Approximately 60% of the explantations occurred within 7 years after implantation, 30.6% within 5 years and 16.8% within 3 years (Table 1).

Approximately 19% of the pacemaker generators were replaced or removed following device failure or complications and in 20% the reason for explantation was not available (Table 2). Analysis of pacing systems stratified for the period in which a pacemaker was implanted and followed for a maximum of 7 years shows that the percentage of explantations within 7 years due to infection lies between 4.0-4.5% for pacemaker generators and did not significantly change over time. The percentage of recalled

Table 2. Reasons for pacemaker generator replacements in the nationwide CPPR-SPRN database, the Netherlands 1984-2007

Explantation of pacemaker generators within 7 years of follow-up, stratified for implantation period[a] *n* (% of explanted pacemakers):	**1984-1990**	**1991-1995**	**1996-2000**	**All pacemakers explanted during study period**[b] **1984-2007**
Device failure (sensing, programming, output, rate, connector)	126 (3.9)	151 (3.4)	105 (1.8)[c]	509 (1.8)
Recall	32 (1.0)	174 (3.9)[c]	270 (4.7)	583 (2.1)
Infection	149 (4.6)	176 (3.9)	248 (4.3)	884 (3.2)
Other complication (mechanical protrusion, erosion, wound pain)	31 (1.0)	31 (0.7)	39 (0.7)	153 (0.5)
Elective for system change	319 (9.9)	450 (10.0)	554 (9.6)	2775 (9.9)
System change – Haemodynamic reasons	90 (2.8)	261 (5.8)[c]	398 (6.9)	1513 (5.4)
System change – Electrode problem	182 (5.6)	325 (7.2)	178 (3.1)[c]	1003 (3.6)
System change – other reasons	37 (1.1)	53 (1.2)	61 (1.1)	214 (0.8)
Normal 'end of life', of which:	908 (28.1)	1800 (40.1)[c]	2678 (46.6)[c]	14,077 (50.4)
<7 years, *n* (% of all explantations <7 years[d])	908 (28.1)	1800 (40.1)[c]	2678 (46.6)[c]	6349 (38.4)
<5 years, *n* (% of all explantations <5 years[d])	202 (11.9)	393 (19.9)[c]	587 (23.9)	1759 (20.5)
<3 years, *n* (% of all explantations <3 years[d])	29 (3.1)	48 (5.1)	87 (7.3)	307 (6.6)
Premature 'end of life'	77 (2.4)	140 (3.1)	126 (2.2)	520 (1.9)
Reason uncoded, unknown or unspecified	1282 (39.6)	928 (20.7)[c]	1088 (18.9)	5706 (20.4)
Total	3233 (100.0)	4489 (100.0)	5745 (100.0)	27,937 (100.0)

[a] For each stratum, the duration of follow-up was maximised at 7 years. Hence, the years 2001-2007 were used for follow-up only. Consequently, numbers of the first three columns do not add up to the numbers in the fourth column
[b] Regardless duration of follow-up
[c] Significantly different compared to previous time interval (p=0.001)
[d] See Table 1

pacemaker generators within 7 years of implantation increased during the study period, whereas the percentage of device failures significantly decreased towards the end of the study period from 3.9% to 1.8% of the pacemaker generator replacements ($p \leq 0.001$; Table 2).

A total of 50.4% of pacemaker generators were explanted because of normal 'end of life' of the generator (Table 2). For these generators, the service time varied widely. When compared to the number of explantations within different periods of follow-up, 38.4% of the generators was explanted for normal 'end of life' within <7 years, 20.5% <5 years, and 6.6% <3 years. These percentages increased over time (Table 2).

Dual chamber systems were significantly more often explanted for normal 'end of life' <5 years and <7 years and technical reasons than single chamber systems (Table 3). Overall, dual chamber systems were significantly more often explanted than single chamber systems ($p \leq 0.001$; Table 3).

Sensitivity analysis

A total of 258 participants of the Rotterdam Study

Table 3. Comparison of specific replacement or explantation reasons between first pacemakers with NASPE codes VVI/VVIR and DDD/DDDR in the nationwide CPPR-SPRN database, the Netherlands 1984-2007

	VVI/VVIR		DDD/DDDR		
	n	**%**	***n***	**%**	***p*-value**
Number of first implantations of this pacemaker type[a]	47,945	49.5	38,060	39.3	-
Number of explantations of first pacemaker of this type	4391	9.2	5861	15.4	<0.001
Reason for explantation					
Recall	141	3.2	209	3.6	0.328
Complication	226	5.1	350	6.0	0.073
Failure	161	3.7	154	2.6	0.003
Premature end of life	123	2.8	164	2.8	0.993
Normal end of life <7 years	1302	29.7	2716	46.3	<0.001
<5 years	273	6.2	690	11.8	<0.001
<3 years	53	1.2	46	0.8	0.408

NASPE North American Society of Pacing and Electrophysiology
[a] % compared to all first pacemaker implantations between 1 January 1984 and 1 January 2006, n=96,900

were found in the SPRN database. During the study period, 148 (57.4%) died. Of these deaths, 60 (40.5%) were also registered in SPRN. We consider 92% of these registrations to be accurate (within 3 months from the registered date of death in the Rotterdam Study). Age at death and implanted pacemaker type did not statistically significantly differ between the group of patients registered as deceased and the group of patients not registered as deceased in SPRN (p=0.56 and p=0.90, respectively).

Discussion

Our results show that 22% of pacemaker generators were replaced or removed at least once between 1984 and 2008. Approximately one in five pacemaker generators were explanted due to technical failures or complications during 20 years of follow-up. Complication and failure rates for pacemaker generators did not improve during at least the first 15 years of the registry. Furthermore, we found that explantation of pacemaker generators for normal 'end of life' occurred at a decreasing follow-up time. The explantation rate found in the Danish Pacemaker Registry, which covers the same period, compares to ours.[15]

'Normal service time' of pacemaker generators includes the lifespan of the pacemaker generator in terms of the longevity of the battery and of the electronic components. Time intervals between pacemaker implantation and removal vary from a mean of 6.8 years for dual chamber devices and 9.7 years for single chamber devices in one study[16] and 7.3 years found in studies on several types and brands of devices.[13,17] Kindermann et al. found a median time interval to battery depletion of 8.2 years.[18] However, cohort size, study duration, number of participating hospitals and number and type of different pacemakers differed between these studies and differed compared to ours.

More ancillary functions and operational algorithms than standard pacing, sensing and communicating with the programmer, require

more battery capacity and may thus affect service time. This may cause newer models to offer shorter service time than expected.[17,19] Hauser et al. restricted service time to the battery life time ending with the appearance of the elective replacement indicator, considering a longevity of >3 years after implant as a minimal requirement.[13] They found that the average pulse generator was implanted for 7.3 years (SD 3.1). The almost twofold increase of the most frequently registered reason for pacemaker generator replacement in our study – normal 'end of life' – suggests that battery longevity did not improve during at least the first 15 years of the study. This underscores the need for longer service time of pacemaker generators by new battery technology that permits pacing for at least 10 years. A longer 'normal service time' of pacemaker generators would be more than welcome because replacement of pacemakers exposes patients to the risk of device infection.

Nearly one in five pacemaker generators was explanted following a complication or failure in our study. A review of reports submitted to the FDA and analysis of device registries published in literature show that pacemaker generator failures included acute or premature battery depletion, connector malfunctions, electrical problems such as short circuit, inappropriate high-current drains, or hermetic seal abnormalities. Such complications sometimes cause major clinical events.[5,6,13] Similar technical failures also emerged in our registry: premature 'end of life', electrode problems, recalls and device failures accounted for more than 9% of the replacements of pacemaker generators in our study. Furthermore, the percentage of explantations following a recall increased over time in parallel with medical device regulation and post-marketing surveillance. Nevertheless, studies have shown that, despite increasing complexity of the components of pacemaker generators over the past decades, the overall replacement rate for technical failures dropped.[5,6] However, technical defects may remain unnoticed despite regular follow-up, as a previous study implies.[20] This post-mortem study of pacemaker generators demonstrated that in 3.8% of patients, deceased after an average of 4 years of pacing, a life-threatening technical failure was present and in 3.0% a potentially life-threatening technical failure which may have caused their death.[20] The sensitivity analysis on the Rotterdam Study sub cohort showed that 50% the patients died within 3 years after implantation of the last registered pacemaker. We cannot rule out that a proportion of these patients died following pacemaker malfunction.

Limitations

In nearly 20% of the pacemaker generator replacements, the reason and time for replacement or removal remained unknown. Missing data could be ascribed to the voluntary participation in the registration; some hospitals (<5%) did not register data or did not register during the entire study period. Data were provided by each participating hospital individually. This may have led to differences in interpretation of the requested information. Relevant variables such as information on comorbidity, medication use, and cardiac function were not recorded at all. This precluded us from adjusting for potential clinical confounders. Furthermore, the registry did not include information on pacemaker setting, pacing threshold and lead impedance. These factors are known to influence battery longevity.[17,18]

Finally, detailed information on the proportion of patients that may have been lost to follow-up is unknown. Information on date of death was voluntarily registered and in 10% of the reported deaths no date of death was provided. Sensitivity analysis showed that approximately 60% of the deaths could be missing.

Conclusions

A substantial proportion of pacemaker generators is explanted before its expected service time, with one in five generators being replaced due to technical failures, infections or complications. Furthermore, the time interval between pacemaker implantation and explantation due to normal 'end of life' decreased. Our observations underscore the need to program only features of the pacemaker generator that have proven clinical benefit to avoid reductions of the service time of the device. The results of our study indicate that a continued highly detailed registry to identify risk factors for premature replacement is needed to maximise the service time of pacemakers.

Acknowledgements

The authors would like to thank all cardiologists and allied professionals for their contribution over many years to the SPRN database in Groningen, the Netherlands. The authors would also like to thank the study participants, the staff from the Rotterdam Study, and the participating general practitioners and pharmacists.

Ethical statement

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Screening Act: Rotterdam Study)". All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Both L.M. de Vries and B.H.Ch. Stricker also work for the Dutch Health Care Inspectorate, a governmental supervisory organisation for health care. The work described in this paper was explicitly not performed on behalf of the Inspectorate.

Appendix

We also performed a time-to-event analysis. For this analysis, the implanted pacemakers were divided into groups based on the type of generator that was registered at implantation: mono-chamber systems (AAI(R) or VVI(R)), dual-chamber systems (DDD(R) or VDD(R)), and cardiac resynchronization devices (CRT). Patients were followed for 7 years after the first pacemaker implantation until either one of the following events occurred: replacement/explantation, loss to follow-up, death that was reported to CPPR-SPRN, or end of follow-up, whichever came first. The 7-year follow-up interval after first and possibly successive pacemaker implantations was chosen to determine an assumed longevity (standard "end of life") of pacemaker generators of 5 years.

Cumulative incidence curves for pacemaker generator implants were estimated with competing risks analysis with death as a competing event.[21] Because deceased patients are no longer at risk for explantation, they cannot be considered as censored as the assumption that the censoring mechanism is independent of the probability of the outcome of interest (i.e. explantation), is no longer met.[22] We calculated proportional hazard ratios for sex, age, ECG indication and pacemaker type on the risk of explantation during 7 years of follow-up using Cox regression adapted for competing risk of death free from explantation [SAS 9.4, SAS Institute Inc., Cary, NC, USA].

Adjusted for age, gender and indication the analysis showed that AAIR, VDD and DDDR-types had a higher probability of explantation or replacement than the reference group VVI-pacemakers (table A1, indication not shown). This outcome is most likely explained because VVI(R) implantation is in general a less complex procedure than AAI(R), VDD(R) and DDD(R). However, VVI(R) pacemakers are more often implanted in older individuals and patients with more extensive comorbidity.[23]

Table A1 *(continued on next page)*. Hazard ratios for explantation <7 years of follow-up after first implantation, adjusted for the competing risk of death in the nation-wide CPPR-SPRN database, the Netherlands 1984-2007

	1984-1990			**1991-1995**		
	***n* (%)**			***n* (%)**		
Number of first implantations	23,870			19,659		
Number of explantations	2918 (12.2)			3413 (17.4)		
Number of deaths	6689 (28.0)			5319 (27.1)		
	***n* (%)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**	***n* (%)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
Female	11,628 (48.7)	**0.92 (0.85-0.99)**	1.04 (0.96-1.11)	9,419 (47.9)	0.99 (0.93-1.06)	**1.13 (1.06-1.21)**
Age (per year increase)	23,824 (99.8)	**0.97 (0.97-0.97)**	**0.98 (0.97-0.98)**	19,647 (99.9)	**0.97 (0.97-0.97)**	**0.97 (0.97-0.98)**
Pacemaker type						
VVI	19,122 (80.1)	Ref	Ref	8763 (44.6)	Ref	Ref
VVIR	725 (3.0)	**2.64 (2.27-3.08)**	**2.10 (1.80-2.46)**	3296 (16.8)	**2.9 (1.89-2.32)**	**1.86 (1.68-2.26)**
DDD	2946 (12.3)	**4.00 (3.69-4.34)**	**3.05 (2.79-3.33)**	3472 (17.7)	**2.26 (2.05-2.49)**	**1.80 (1.62-1.99)**
DDDR	49 (0.2)	**8.00 (5.58-11.46)**	**5.32 (3.60-7.84)**	2004 (10.2)	**2.68 (2.41-2.98)**	**2.02 (1.81-2.26)**
AAI	577 (2.4)	**3.63 (3.08-4.27)**	**2.75 (2.31-3.27)**	424 (2.2)	**2.63 (2.14-3.23)**	**2.07 (1.67-2.56)**
AAIR	52 (0.2)	**3.14 (1.93-5.12)**	**2.09 (1.19-3.65)**	316 (1.6)	**4.07 (3.36-4.94)**	**2.97 (2.43-3.63)**
VDD	17 (0.1)	2.04 (0.66-6.33)	0.88 (0.27-2.87)	648 (3.3)	**2.40 (2.03-2.83)**	**2.08 (1.75-2.47)**
VDDR	1 (<0.1)	**22.59 (21.16-24.12)**	**21.38 (19.55-23.39)**	191 (1.0)	**4.26 (3.40-5.34)**	**3.47 (2.75-4.39)**
CRT	13 (0.1)	**3.89 (1.59-9.57)**	1.74 (0.60-5.05)	4 (<0.1)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Unknown	368 (1.5)	**1.66 (1.26-2.19)**	**1.52 (1.15-2.01)**	541 (2.8)	**1.76 (1.43-2.17)**	**1.49 (1.20-1.84)**

Values in bold font are significant

Table A1 *(continued from previous page).*

	1996-2000		
	n **(%)**		
Number of first implantations	22,694		
Number of explantations	4015 (17.7)		
Number of deaths	5457 (24.0)		
	n **(%)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
Female	10,569 (46.6)	0.96 (0.90-1.02)	**1.07 (1.00-1.14)**
Age (per year increase)	22,690 (~100.0)	**0.97 (0.97-0.97)**	**0.98 (0.97-0.98)**
Pacemaker type			
VVI	3250 (14.3)	Ref	Ref
VVIR	4843 (21.3)	**1.66 (1.43-1.93)**	**1.53 (1.31-1.78)**
DDD	3606 (15.9)	**2.80 (2.42-3.24)**	**2.41 (2.08-2.80)**
DDDR	7575 (33.4)	**3.16 (2.76-3.62)**	**2.55 (2.22-2.93)**
AAI	238 (1.0)	**3.10 (2.28-4.21)**	**2.38 (1.74-3.24)**
AAIR	562 (2.5)	**5.43 (4.48-6.58)**	**3.74 (3.06-4.58)**
VDD	1404 (6.2)	**2.36 (1.98-2.82)**	**2.30 (1.92-2.77)**
VDDR	593 (2.6)	**2.51 (2.01-3.14)**	**2.32 (1.85-2.92)**
CRT	74 (0.3)	**5.31 (3.40-8.30)**	**4.20 (2.67-6.59)**
Unknown	549 (2.4)	**3.91 (3.16-4.83)**	**3.33 (2.69-4.13)**

Therefore, this observation needs to be interpreted with caution.

When time-to-event analysis methods to compare the service time of several types of pacemakers with 7 years of follow-up were applied after the second, third and following implantations the outcome did not change, reason why only data of the analysis of the first implantations is presented in Table A1. Furthermore, it should be noted here that for 10% of the reported deaths no date of death was provided, hence for these records no follow-up time could be calculated; these records were excluded from the time-to-event analysis.

References

1. Raatikainen MJ, Ornar DO, Zeppenfeld K, et al. Statistics on the use of cardiac electronic devices and electrophysiological procedures in the European Society of Cardiology countries: 2014 report from the European Hearth Rhythm Association. Europace. 2015;17:i1-i75.

2. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009 - a world society of arrhythmia's project. PACE. 2011; 34:1013-27.

3. De Vries LM, Dijk WA, Hooijschuur CAM, et al. Utilisation of cardiac pacemakers over a 20-year period: Results from a nationwide pacemaker registry. Neth Heart J. 2016: doi:10.1007/s12471-016-0880-0. Epub ahead of print.

4. Leening MJG, Siregar S, Vaartjes I, et al. Heart disease in the Netherlands: a quantitative update. Neth Heart J. 2014;22:3-10.

5. Maisel WH, Moynahan M, Zuckerman BD, et al. Pacemaker and ICD Generator malfunctions. Analysis of Food and Drug Administration Annual Reports. JAMA. 2006;295:1901-6.

6. Maisel WH. Pacemaker and ICD Generator Reliability. Meta-analysis of Device Registries. JAMA. 2006;295:1929-34.

7. Eyal A, Roguin A. Magnetic resonance imaging in patients with cardiac implantable electronic devices. Circulation. 2015;132:e176-78.

8. Kirkfeldt RE, Johansen JB, Nohr EA, et al. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. Eur Heart J. 2014;35:1186-94.

9. Udo EO, Zuithoff NP, Hemel NM van, et al. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. Heart Rhythm. 2012;9:728-35

10. Hooijschuur CAM and Dijk WA. Impact of data collected on implanted devices and device recipients. Neth Heart J. 2008;16(Suppl 1):S9-S11.

11. Dijk WA, Hooijschuur CA, Dassen WR. Central Pacemaker Registry in the Netherlands, a 10 year evaluation. Computers in Cardiology, Jerusalem 1989: IEEE Computer society: 293, doi: 10.1109/CIC.1989.130547.

12. Dijk WA, Kingma T, Hooijschuur CA, et al. Validation of the Netherlands Pacemaker Patient Registry, Comput Cardiol. 1997;24:653-6.

13. Hauser RG, Hayes DL, Kallinen LM, et al. Clinicial experience with pacemaker pulse generators and transvenous leads: An 8-year prospective multicenter study. Heart Rhythm. 2007;4:154-60.

14. Hofman A, Brusselle GG, Darwish Murad S, et al. The Rotterdam Study: 2016 objectives and design update. Eur J Epidemiol (2015) 30:661–708.

15. Johansen JB, Jørgensen OD, Møller M, et al. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. Eur Heart J. 2011;32:991-98.

16. Hauser R, Hayes D, Parsonnet V, et al. Feasibility and initial results of an internet-based pacemaker and ICD pulse generator and lead registry. PACE. 2001;24:82-7.

17. Senaratne J, Irwin ME, Senaratne MPJ. Pacemaker Longevity: Are we getting what we are promised? PACE. 2006;29:1044-54.

18. Kindermann M, Schwaab B, Berg M, Fröhlig G. Longevity of dual chamber pacemakers: device and patient related determinants. PACE. 24:810-5.

19. Benkemoun H, Sacrez J, Lagrange P, et al. Optimizing pacemaker longevity with pacing mode and settings programming: results from a pacemaker multicenter registry. PACE. 2012;35:403-8.

20. Bartsch C, Irnich W, Junge M, et al. Post-mortem evaluation of 415 pacemakers: in situ measurements and bench

tests. Europace. 2005;7:175-80.

21. So Y, Lin G, Johnston G, SAS Institute Inc. Using the PHREG Procedure to Analyze Competing-Risks Data. 2014. Last accessed December 2015: https://support.sas.com/rnd/app/stat/papers/2014/competingrisk2014.pdf.

22. Putter H, Fiocco M., Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Statist Med. 2007;26:2389-2430.

23. Pyatt JR, Somauroo JD, Jackson M, et al. Long-term survival after permanent pacemaker implantation: analysis of predictors for increased mortality. Europace. 2002;4:113-9.

Chapter 2.3

Trends in service time of leads in the Netherlands: a long-term nationwide follow-up study

L.M. de Vries, M.J.G. Leening, W.A. Dijk,

C.A.M. Hooijschuur, B.H.C. Stricker,

N.M. van Hemel

Submitted

Abstract

Background

We aimed to investigate trends over time in longevity and reasons for replacement or extraction of pacemaker leads after first implantation.

Methods

Data collected between 1984 and 2006 in the national Dutch pacemaker registry were used. This registry covered 84.0% of sold leads. The time interval of, and reason for, replacement or extraction of leads implanted with a first pacemaker generator were analysed. A 7-year follow-up interval after first implantation was used to analyse changes over time.

Results

During 22 years of data collection 138.225 leads were implanted with a first pacemaker generator. Within a mean 5.4 (SD 4.5) years 8849 leads (6.4%) were replaced or extracted, the majority for insulation failures (14.7%), infection (11.8%), displacement (7.1%) or for elective reasons (10.2%). The number of insulation failures peaked during 1991-1995.

Conclusion

Despite improvements in pacing techniques and experience with cardiac devices, we found that insulation and conductor failures, and complications such as infections did not diminish over the 20 years of the registry. Continuing attention in clinical practice for the evaluation of these undesired outcomes and maintaining quality registries is warranted, whereas manufacturers should use this information to further improve their devices.

Cardiac implantable electronic devices (CIED) rely on implantable pacing leads to exert their benefit for many patients worldwide. Although new developments towards leadless pacemakers are underway,[1] the vast majority of devices that are currently in situ transfer the electronically generated pulses to the heart and receipt of cardiac and external signals through leads. In the early days of cardiac pacing lead longevity seemed long-lasting but this finding was merely caused because problems with pulse generators occurred before any failures with leads could be ascertained.[2-3] However later, the pacing lead was considered the 'weakest link' of the pacing system.[4]

The materials and shape of the conductors and insulation, the diameter and the polarity of the lead all play a crucial role in lead longevity.[3-5] Because of problems of any of these components, history shows that various lead types were particularly prone to failure and needed to be replaced following either abandonment or extraction.[5-9] For example in the 1980s and 1990s some specific bipolar leads were known to show a poor 5-year longevity rate.[9]

To identify CIED failures, a registry was set up in the Netherlands in the early 1980's; the Central Pacemaker Patients Registration (CPPR) from the Netherlands Pacemaker Registry Foundation (CPPR-SPRN).[10-11] This registry collected data over 25 years and allows for analysis of trends over time regarding the duration of service time or longevity of leads after first implantation.[12-13] For this paper, the reasons for replacement or extraction of leads were studied. We anticipated that because of growing experience, guidelines and clustering of treatment facilities, service time of the leads would increase, and complication and failure rates would gradually diminish over several decades of cardiac pacing.

Patients and Methods

Setting

Data were retrieved from the Central Pacemaker Patients Registration (CPPR) from the Netherlands Pacemaker Registry Foundation (CPPR-SPRN).[12] In brief, in 1982, CPPR-SPRN was established and the computerized registration was started. Cardiologists and allied professionals were invited to voluntarily register data of each patient, pacemaker generator, and leads on the former European pacemaker card. Data on symptoms, indication and diagnosis, brand of pacemaker and leads, type, follow-up visits, explantation, hospital transfer and death were registered according to European Registry Guidelines established from 1982 onward.[12-13]

Monitoring and validation of data

Until 1989, data was centrally registered by mailing a carbon copy of the European pacemaker card to the registry. From 1989 onwards, a digitalized registration was used with automatic communication between the central registration center and the local implanting center. During the daily conversions into the database multiple checks were performed on missing data, conformation with already stored information and plausibility.[10] Additionally, data was periodically returned to the clinics for correction and verification purposes. A validation process to obtain better insight into the quality of the database was performed in 1997. A total of 84.0% of the sold leads could be retrieved in the central registry when compared to patient files of participating hospitals and sales data from manufacturers.[11]

Cohort and outcome definition

Patients admitted for implantation of the first pacemaker between January 1, 1984 and January 1, 2006 were included in this study. A total of 452 implantations were excluded because of inconsistencies in the registered data, e.g. a

Table 1. Baseline characteristics of patients and leads in the nation-wide CPPR-SPRN database, the Netherlands 1984-2005

		Implantation period				Total study period
		1984-1990	1991-1995	1996-2000	2001-2005	1984-2005
Mean age at first implantation, years (SD)[a]		72.7 (13.0)	73.0 (13.0)	72.9 (13.2)	73.1 (12.9)	72.9 (13.0)
Female gender, *n* (%)[b]		11,628 (48.7)	9419 (47.9)	10,569 (46.6)	14,045 (45.8)	45,661 (47.1)
Follow-up duration (range), years		17-23	12-16	7-11	2-6	2-23
		1984-1990	1991-1995	1996-2000	2001-2005	Total study period 1984-2005
No. of first pacemaker generators, (% of total # implanted first pacemaker generators during study period)		23,870 (24.6)	19,659 (20.3)	22,694 (23.4)	30,677 (31.7)	96,900 (100.0)
Lead implantations, *n* (% of total # implanted leads during study period), of which:		27,030 (19.6)	25,479 (18.4)	34,374 (24.9)	51,342 (37.1)	138,225 (100.0)
Number of leads per first pacemaker, *n*= # of pacemakers (% of first pacemaker):	1	20,668 (86.6)	13,788 (70.1)[c]	10,869 (47.9)[c]	9475 (30.9)[c]	54,800 (56.6)
	2	3161 (13.2)	5839 (29.7)[c]	11,641 (51.3)[c]	19,166 (62.5)[c]	39,807 (41.1)
	3	12 (0.1)	3 (<0.1)	73 (0.3)[c]	1177 (3.8)[c]	1265 (1.3)
	4	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)	4 (<0.1)
	Unknown	28 (0.1)	28 (0.1)	110 (0.5)[c]	858 (2.8)[c]	1024 (1.1)
Lead position:	Ventricular, *n* (%)	23,120 (85.5)	18,772 (73.7)[c]	21,698 (63.1)[c]	30,338 (59.1)[c]	93,928 (68.0)
	Atrial, *n* (%)	3824 (14.1)	6694 (26.3)[c]	12,628 (36.7)[c]	20,993 (40.9)[c]	44,139 (31.9)
	Unknown, *n* (%)	86 (0.3)	13 (0.1)[c]	48 (0.1)[c]	11 (<0.1)[c]	158 (0.1)

[a] *For 60 patients, data on age was missing*
[b] *For 75 patients, data on gender was missing*
[c] *Significantly different compared to previous time interval (p=0.001)*

new implantation was registered after the supposed date of death of a patient, or the same pacemaker was registered more than once with different explantation dates. This resulted in a cohort with 96,900 patients having a first pacemaker implanted with 138,225 leads. The years 2006 and 2007 were used for follow-up only.

Exposure

The primary interest was the number of lead

Table 2. Lead replacements and duration of service time in the nation-wide CPPR-SPRN database, the Netherlands 1984-2005

	Implantation period				Total study period
	1984-1990	1991-1995	1996-2000	2001-2005	1984-2005
Replacements/extractions of leads implanted in this period, *n* (%)	2958 (10.9)	2627 (10.3)	1958 (5.7)[a]	1306 (2.5)[a]	8849 (6.4)
Mean duration of service time for replaced/extracted leads, years (SD)	7.6 (5.1)	5.9 (3.8)	4.1 (3.2)	1.5 (1.7)	5.4 (4.5)
Median duration of service time for replaced/extracted leads, years (IQR)	7.1 (3.7-10.9)	5.8 (3.2-8.7)	4.2 (0.8-6.9)	0.6 (0.1-2.4)	5.1 (1.3-8.2)
replacement/extraction <3 years, *n*	628	625	821		3126
(% of extracted leads)	(21.2)	(23.8)	(41.9)[a]	NA	(35.3)
(% of implanted leads)	(2.3)	(2.5)	(2.4)		(2.3)
replacement/extraction <5 years, *n*	981	1067	1099		4384
(% of extracted leads)	(33.2)	(40.6)[a]	(56.1)[a]	NA	(49.5)
(% of implanted leads)	(3.6)	(4.2)[a]	(3.2)[a]		(3.2)
replacement/extraction <7 years, *n*	1456	1613	1505		5875
(% of extracted leads)	(49.2)	(61.4)[a]	(76.9)[a]	NA	(66.4)
(% of implanted leads)	(5.4)	(6.3)[a]	(4.4)[a]		(4.3)

NA: Not applicable, only 2-6 years of follow-up available
[a] Significantly different compared to previous time interval (p=0.001)

replacements or extractions and the reason for this intervention. For this study 'service time' is defined as the time between lead implantation and replacement or extraction of the lead. Reasons for end of service time were categorized in several forms of technical failure of the lead itself (i.e. insulation or conductor failure) and infection.

Analysis

First, analyses of explantations and replacements were performed on the entire cohort of patients (n=96,900) having a first implantation during the study period irrespective of available duration of follow-up. Next, analyses were repeated on three strata (a total of n=66,223 patients) to identify changes over time. Each implantation in these strata was followed for a maximum of 7 years or until explantation, whichever came first. For this purpose, first implantations during the years 1984-2000 could be used, while data from 2001-2007 were used for follow-up only. We chose a 7-year follow-up period because the mean duration of follow-up for explanted pacemaker generators falls within this time interval.[14-15]

Descriptive data are presented as mean (standard deviation, SD), median (interquartile range, IQR), or frequencies (%) as appropriate. Characteristics were compared using independent sample t-tests for continuous variables and χ^2 tests for categorical variables, as appropriate. A 2-sided p-value ≤0.001 was considered as statistically significant. We used the SPSS version 20.0.0, statistical package (IBM, Armonk, NY, USA) for all analyses.

Results

A total of 52.9% of the patients were men and the mean age at time of first implantation was 72.9 years (SD 13.0) (Table 1). Depending on

Table 3. Reason for replacement or extraction of leads within 7 years after implantation in the nationwide CPPR-SPRN database, the Netherlands 1984-2007

	Implantation period			Total	Total all replaced/ explanted leads[a]
	1984-1990	1991-1995	1996-2000	1984-2000	1984-2007
Displacement	50 (3.4)	120 (7.4)[b]	184 (12.2)[b]	354 (7.7)	626 (7.1)
Exit block	29 (2.0)	78 (4.8)[b]	61 (4.1)	168 (3.7)	296 (3.3)
Undersensing	32 (2.2)	42 (2.6)	31 (2.1)	105 (2.3)	195 (2.2)
Insulation failure	214 (14.7)	395 (24.5)[b]	94 (6.2)[b]	703 (15.4)	1297 (14.7)
Conductor break	54 (3.7)	59 (3.7)	62 (4.1)	175 (3.8)	327 (3.7)
Other failure (e.g. connector failure)	10 (0.7)	16 (1.0)	18 (1.2)	44 (1.0)	103 (1.2)
Infection	162 (11.1)	170 (10.5)	261 (17.3)[b]	593 (13.0)	1046 (11.8)
Other complication (e.g. erosion, perforation)	15 (1.0)	3 (0.1)	54 (3.6)[b]	72 (1.6)	254 (2.9)
Elective replacement	133 (9.1)	165 (10.2)	143 (9.5)	441 (9.6)	905 (10.2)
Sealed	0 (0.0)	0 (0.0)	12 (0.8)	12 (0.3)	65 (0.7)
Reason unknown or unspecified	772 (53.1)	565 (35.0)[b]	585 (38.9)	1922 (42.0)	3735 (42.2)
Total replaced or extracted	1456 (100.0)	1613 (100.0)	1505 (100.0)	4574 (100.0)	8849 (100.0)

n (% of total replaced/extracted leads in corresponding implantation period)
[a] Regardless duration of follow-up
[b] Significantly different compared to previous time interval (p=0.001)

the year of implantation, patients were followed for 2 to 23 years after implantation.

The percentage of pacemakers implanted with a single lead diminished after 1990. However, the percentage of pacemakers implanted with both atrial and ventricular leads increased from 13.2% in 1984-1990 to 62.5% in 2001-2005 (p≤0.001). Furthermore, pacemakers implanted with 3 leads for cardiac resynchronization therapy increased to 3.8% over the years (p≤0.001). More than two thirds of the leads were ventricular leads. However, the percentage of atrial leads increased over time (p≤0.001). Missing information about lead insertion remained limited over the years: 0.1 to 0.5%, but increased after 2000 (Table 1).

For 8849 leads (6.4%) a replacement or extraction was registered. The mean duration of service time for explanted leads was 5.4 years (SD 4.5). Approximately two thirds of these leads (n=5875, 66.4%) were replaced or explanted within 7 years after implantation and nearly half (n=4384, 49.5%) was replaced or ex-

Next page:

Table 4. Simultaneous replacement of first pacemaker generators and leads in the nationwide CPPR-SPRN database, the Netherlands 1984-2007

Simultaneous replacement for 7 most frequently registered generator replacement reasons
EOL: end of life
[a] The denominator for the percentages in this row is the total number of replaced and permanently removed first pacemaker generators: n=22,410

	Reasons for generator explantation						
	Normal EOL	**Premature EOL**	**Elective**	**System change hemodynamic reasons**	**Electrode problem**	**Infection**	**Recall**
Number of explanted generators *n* (% of total number of explanted first generators)[a]	11,466 (51.2)	396 (1.8)	2221 (9.9)	1231 (5.5)	772 (3.4)	587 (2.6)	479 (2.1)
Number of leads implanted with these generators	17,188	600	3228	1726	1075	921	719
Number of generators simultaneously explanted with 1 or more leads *n* (% of explanted generators provided in top row)	1550 (13.5)	100 (25.3)	445 (20.0)	164 (13.3)	664 (86.0)	501 (85.3)	38 (7.9)
Number of leads sim. extracted with explanted generator *n* (% of implanted leads provided in 2nd row)	1693 (9.8)	111 (18.5)	510 (15.8)	188 (10.9)	789 (73.4)	768 (83.4)	40 (5.6)
Reasons for lead extraction, *n*=number of leads (% of number of leads simultaneously extracted with generator):							
Displacement	48 (2.8)	8 (7.2)	25 (4.9)	8 (4.3)	51 (6.5)	6 (0.8)	5 (12.5)
Exit block	50 (3.0)	11 (9.9)	20 (3.9)	7 (3.7)	42 (5.3)	0 (0.0)	1 (2.5)
Undersensing	33 (1.9)	3 (2.7)	11 (2.2)	7 (3.7)	38 (4.8)	2 (0.3)	3 (7.5)
Insulation failure	279 (16.5)	31 (27.9)	117 (22.9)	18 (9.6)	354 (44.9)	1 (0.1)	5 (12.5)
Conductor break	54 (3.2)	3 (2.7)	26 (5.1)	3 (1.6)	60 (7.6)	2 (0.3)	3 (7.5)
Connector failure	26 (1.5)	2 (1.8)	7 (1.4)	2 (1.1)	7 (0.9)	1 (0.1)	0 (0.0)
Infection	1 (0.1)	1 (0.9)	5 (1.0)	0 (0.0)	4 (0.5)	707 (92.1)	0 (0.0)
Erosion	106 (6.3)	3 (2.7)	30 (5.9)	13 (6.9)	10 (1.3)	2 (0.3)	1 (2.5)
Perforation	6 (0.4)	1 (0.9)	11 (2.2)	0 (0.0)	14 (1.8)	2 (0.3)	0 (0.0)
Elective	258 (15.2)	14 (12.6)	88 (17.3)	39 (20.7)	56 (7.1)	3 (0.4)	6 (15.0)
Other	27 (1.6)	3 (2.7)	16 (3.1)	4 (2.1)	11 (1.0)	2 (0.3)	0 (0.0)
Unknown	774 (45.7)	31 (27.9)	154 (30.2)	87 (46.3)	142 (13.2))	40 (5.2)	16 (40.0)
Number of generators simultaneously explanted with their leads within follow-up period of, *n (*% of number of generators simultaneously replaced with 1 or more leads):							
< 1 year	4 (0.3)	2 (2.0)	37 (8.3)	13 (7.9)	54 (8.1)	311 (62.1)	0 (0.0)
< 3 years	35 (2.3)	28 (28.0)	91 (20.4)	36 (22.0)	117 (17.6)	422 (84.2)	8 (21.1)
< 5 years	212 (13.7)	64 (64.0)	177 (39.8)	76 (46.3)	298 (44.9)	464 (92.6)	16 (42.1)
< 7 years	660 (42.6)	84 (84.0)	288 (64.7)	108 (65.9)	478 (72.0)	486 (97.0)	27 (71.1)

planted within 5 years after implantation (Table 2). When comparing the three implantation periods, the percentage of leads that were replaced or explanted within 3, 5, or 7 years decreased with later implantation years (p≤0.001) (Table 2). The most recent implantation period 2001-2005 could not be included because the available follow-up time was too short.

Reasons for lead replacements and extractions

In general, lead replacement was most frequently registered because of insulation failures (14.7%), infection (11.8%), and displacement (7.1%). Elective replacement, without further specification, was reported for 10.2% of the extractions (Table 3). Other failures and complications included conductor breaks (3.7%), exit block (3.3%), and undersensing (2.2%). For more than 40% the reason was unknown or unspecified (Table 3).

Analysis of implantation periods with 7 years of follow-up available showed that for 4574 leads a replacement or explantation was registered (Table 3). The percentage of extractions or replacements following infections increased over time from 10-11% for leads implanted between 1984 and 1995 to 17% for leads implanted between 1995 and 2000 (p≤0.001). Also, extractions because of lead displacement increased during the study period. Replacement or extraction for insulation failures (mean 14.7%) increased to nearly 25% for leads implanted between 1991 and 1996 (p≤0.001), but dropped to 6.2% for leads implanted during the era 1996-2000 (p≤0.001). Other complications such as exit block, undersensing failure, conductor break, erosion, perforation, and other technical lead failures had a low prevalence in the successive periods with percentages below 4%. The number of uncoded reasons for lead failures remained large over the successive periods, approximately 42% of all replaced or explanted leads (Table 3).

Reasons for simultaneous replacement of pacemaker generators and leads

For 13.0% of the replaced or explanted leads (*n*=1153) no pacemaker generator replacement was registered, whereas for 15,918 pacemakers (71.0%) only the generator was replaced without replacement of the leads. However, it also occurred that generators and leads were replaced independently of each other: 1620 leads (18.3%) were replaced with a mean of 4.3 years (SD 3.4) later than the generator. Additionally, 563 leads (6.4%) were replaced before the generator with a mean difference of 5.2 years (SD 3.3), (data not shown).

More than 62% of the leads were simultaneously replaced with replacement of the pacemaker generator (data not shown). Registration of simultaneous replacement occurred most often in case of infections. In those cases, 83.4% of the leads were also extracted. For 92.1% of these leads the reason for concomitant replacement was also classified as infection (Table 4). Infected systems were replaced within 1 year after implantation in 62.1% of the cases and within 3 years in 84.2% of the cases (Table 4). Secondly, simultaneous replacement of pacemaker generators and leads frequently occurred when electrode problems were registered as reason of pacemaker generator replacement. In these cases, 73.4% of the leads were replaced together with the generator. For 44.9% of these leads an insulation failure was registered (Table 4).

In case a pacemaker generator was replaced for premature 'end of life', for hemodynamic reasons, or a recall, 18.5%, 10.9% and 5.6% of the respective corresponding leads were simultaneously replaced. When pacemaker generators were replaced for normal 'end of life' or because of elective system change, 9.8% and 15.8% of the respective corresponding leads were also replaced. In those groups, insulation failures or elective replacement were most frequently registered as reason for lead replacement (Table 4).

Discussion

This large long-term follow-up study analysed the number and reasons of pacemaker lead replacements or explantation, and provides a comparison between three implantation periods with 7 years of follow-up. Registered replacements or explantations were highest in the first two periods. Insulation failures, conductor breaks and connector failures accounted for more than 19% of the registered lead explantations or abandonments within 7 years after implantation in our study. Furthermore, displacement and infections were common complications leading to lead extraction with 7 years after insertion. Both increased towards the end of the study period. Finally, explantations for elective reasons and for other failures remained stable over time.

Technical lead problems

Purely technical lead problems such as break of the insulation and of conductors and other failures of the lead constituted in approximately 20% of the cases the reason for registered lead replacement or explantation. In case of registered simultaneous replacements of pacemaker generators and leads, particularly insulation failures were a cause for lead replacement. Insulation defects have previously been described as regular causes of lead failure.[9, 14, 16] These technical failures can be attributed to material characteristics as well as to implantation techniques and lead fixation methods, bending of the lead in the pocket, site of insertion and so forth. In the 1980s and 1990s polyurethane insulated leads appeared to be more prone to defects due to metal ion oxidation or environmental stress cracking. [2, 5, 9, 14, 16] Another type of lead, the J-shaped lead, was prone to fractures of a retention wire. [5, 17] Lead failure is expected to occur in approximately 2-4% of implantations after an average of 5 years. Some studies reported failure percentages of up to 7 to 16%.[5] Hauser et al. found a median time to failure for all leads of 7.2 (SD 5.2) years. Despite differences in study design, we believe that our findings are similar to the described literature.[14]

Displacement

Lead displacement accounted for approximately 7% of lead replacement or explantation over the entire follow-up period. This figure varied between 3.4 and 12.2% over the years. However, lead dislodgement might have occurred more often when problems such as exit block (mean 3.3% over the entire period) and undersensing (mean 2.2% over the entire period) are considered manifestations of lead displacement. This includes that overall lead displacement should be considered in approximately 20% of registered lead replacement or explantation. With the preference towards active-fixation leads, also in the Netherlands, lead dislodgement is expected to have decreased during later years.[18-19] However, this is not yet visible during the periods covered by our study. A recent prospective Dutch study, performed in a subpopulation of the one described here, found lead dislodgement to be the most frequent lead-related complication that often occurred shortly after implantation, but was also not uncommon as a late problem.[20]

Infections

Infections of the pacing system consisting of pocket infection, migration along the leads and endocarditis resulted in approximately 12% of the replacements. In this condition pacemaker generator and lead(s) were most often simultaneously replaced. With 83.4% of the leads replaced, infection was the largest indication for simultaneous explantation. Complete device removal, including leads, is indeed the advised therapy in case of infection.[5, 21] Johansen et al. reported the highest infection rates at the earliest period in a registry comparable to ours but the prevalence of registered device infections in our survey clearly did not change over the years.[22] Procedure-related factors, such as

size of the implanting centre, the complexity of the procedure and the number of leads appeared not to be associated with infection rates in the Danish study.[22] The prospective FOLLOWPACE study confirmed this outcome and were unable to demonstrate any relationship between increasing age and complication rate.[20] Infections do not necessarily manifest themselves shortly after implantation, but may occur also at long-term follow-up.[23] In our study nearly two thirds of the explantations of the entire pacemaker system occurred within one year and within 7 years more than 95% of the infected systems were explanted.

Limitations

For approximately 70% of the leads no endpoint was registered, while for those that were registered more than 40% of the lead extractions, replacements and abandonments the reason for and date of replacement or removal remained unknown. We are aware that up to 60% of deaths have not been registered in SPRN.[15] Therefore, it is expected that a large proportion of patients may have died during follow-up. Furthermore, we hypothesize that at replacement of the pacemaker generator, old leads are re-connected to the new generator. However, the voluntary nature of the registry is likely to have caused underreporting of relevant endpoints.

Variables such as polarity, fixation mechanism, insulator material, and implantation route were not recorded at all. Therefore, we were not able to assess the influence of these relevant variables on the explantation and longevity of leads.

Implications

We anticipated that because of technical improvements, growing experience, guidelines and clustering of treatment facilities, the service time of the leads would increase, and complication and failure rates would gradually diminish over several decades of cardiac pacing. However, the percentage of complications and failures was higher than expected. Considering that extraction of leads has a relatively high incidence of serious complications,[5, 24-25] high percentage of lead failures and complications such as infections and displacement is cause for concern. Type and rate of complications are important indicators for the quality of health care and should contribute to the evaluation of protocols by health care professionals. Furthermore, for improvement of their devices, manufacturers are obliged to collect post-marketing surveillance information. For both purposes, device registries can be an important tool.

Conclusions

We expected a gradual decrease of lead complications requiring replacement or explantation over the 20 years of registry because of technological improvements, enhanced experience and training, and emergence of detailed clinical practice guidelines. However, lead displacement and infection (largely operator dependent complications) did not diminish and rates of registered explantation due to insulation and conductor failures (largely manufacturer dependent complications) were considerable. Further reduction of complications and failures is warranted.

Acknowledgements

The authors would like to thank all cardiologists and allied professionals for their contribution over many years to the SPRN database in Groningen, the Netherlands.

Both L.M. de Vries and B.H.Ch. Stricker also work for the Dutch Health Care Inspectorate, a governmental supervisory organization for health care. The work described in this paper was explicitly not performed on behalf of the Inspectorate.

References

1. Reynolds D, Duray GZ, Omar R. et al. A Leadless Intracardiac Transcatheter Pacing System. N Engl J Med. 2016;374(6):533-41.

2. Furman S, Benedek ZM. The implantable lead registry. Suvival of implantable pacemaker leads. PACE. 1990;13:1910-4.

3. Furman S, Benedek ZM, Andrews CA, Gross JN, Ritacco R. Long-term follow-up of pacemaker lead systems: establishment of standards of quality. PACE. 1995;18:271-85.

4. Voogt WG. Pacemaker Leads: performance and progress. Am J Cardiol. 1999;83:187D-91D.

5. Borek PP, Wilkoff BL. Pacemaker and ICD leads: strategies for long-term management. J Interv Card Electrophysiol. 2008;23:59-72.

6. Woscoboinik JR, Maloney JD, Helguera ME, Mercho N, Alexander LA, Wilkoff B, et al. Pacing lead survival: performance of different models. PACE. 1992;15:1991-5.

7. Helguera ME, Maloney JD, Pinski SL, Woscoboinik JR, Wilkoff BL, Castle LW. Long-tem performance of endocardial pacing leads. PACE. 1994;17: 56-64.

8. Møller M, Arnsbo P. The Danish Pacemaker Register. Appraisal of pacing lead performance from the Danish Pacemaker Register. PACE. 1996;19:1327-36.

9. Arnsbo P, Møller M. The Danish Pacemaker Register. Updated appraisal of pacing lead performance from the Danish Pacemaker Register: the reliablility of bipolar pacing leads has improved. PACE. 2000;23:1401-6.

10. Dijk WA, Hooijschuur CA, Dassen WR. Central Pacemaker Registry in the Netherlands, a 10 year evaluation. Computers in Cardiology, Jerusalem 1989: IEEE Computer society: 293, doi: 10.1109/CIC.1989.130547.

11. Dijk WA, Kingma T, Hooijschuur CA, Dassen WRM, Hoorntje JCA, Gelder LM van. Validation of the Netherlands Pacemaker Patient Registry, Comput Cardiol. 1997;24:653-6.

12. Hooijschuur CAM and Dijk WA. Impact of data collected on implanted devices and device recipients. Neth Heart J. 2008;16(Suppl 1):S9-S11.

13. De Vries LM, Dijk WA, Hooijschuur CAM, Leening MJG, Stricker BHC, Van Hemel NM. Utilisation of cardiac pacemakers over a 20-year period: Results from a nationwide pacemaker registry. Neth Heart J. 2017 Jan;25(1):47-55.

14. Hauser RG, Hayes DL, Kallinen LM, et al. Clincial experience with pacemaker pulse generators and transvenous leads: An 8-year prospective multicenter study. Heart Rhythm. 2007;4:154-60.

15. De Vries LM, Leening MJ, Dijk WA, Hooijschuur CA, Stricker BH, van Hemel NM. Trends in replacement and extraction of pacemaker leads in the Netherlands: a long-term nationwide follow-up study. Neth Heart J. 2017 Aug 2. doi: 10.1007/s12471-017-1024-x. [Epub ahead of print]

16. Hauser R, Hayes D, Parsonnet V, et al. Feasibility and initial results of an internet-based pacemaker and ICD pulse generator and lead registry. PACE. 2001;24:82-7.

17. Van Hemel NM, Defauw JJAM, Ruiter JH. Second report of the Dutch committee for monitoring atrial-J retention wire fractures. Cardiologie. 1997;4:164-6.

18. Mond HG, Irwin M, Morillo C, Ector H. The world survey of cardiac pacing and cardioverter defibrillators: calender year 2001. PACE. 2004; 27:955-964.

19. Mond HG, Irwin M, Ector H, Proclemer A. The world survey of cardiac pacing and cardioverter-defibrillators: calendar year 2005. An international cardiac pacing and electrophysiology society (ICPES) project. PACE. 2008; 31:1202-1212.

20. Udo EO, Zuithoff NP, Hemel NM van, et al. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. Heart Rhythm. 2012;9:728-35

21. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44):3075-128.

22. Johansen JB, Jørgensen OD, Møller M, Arnsbo P, Mortensen PT, Nielsen JC. Infection after pacemaker implanation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. Eur Heart J. 2011;32:911-8.

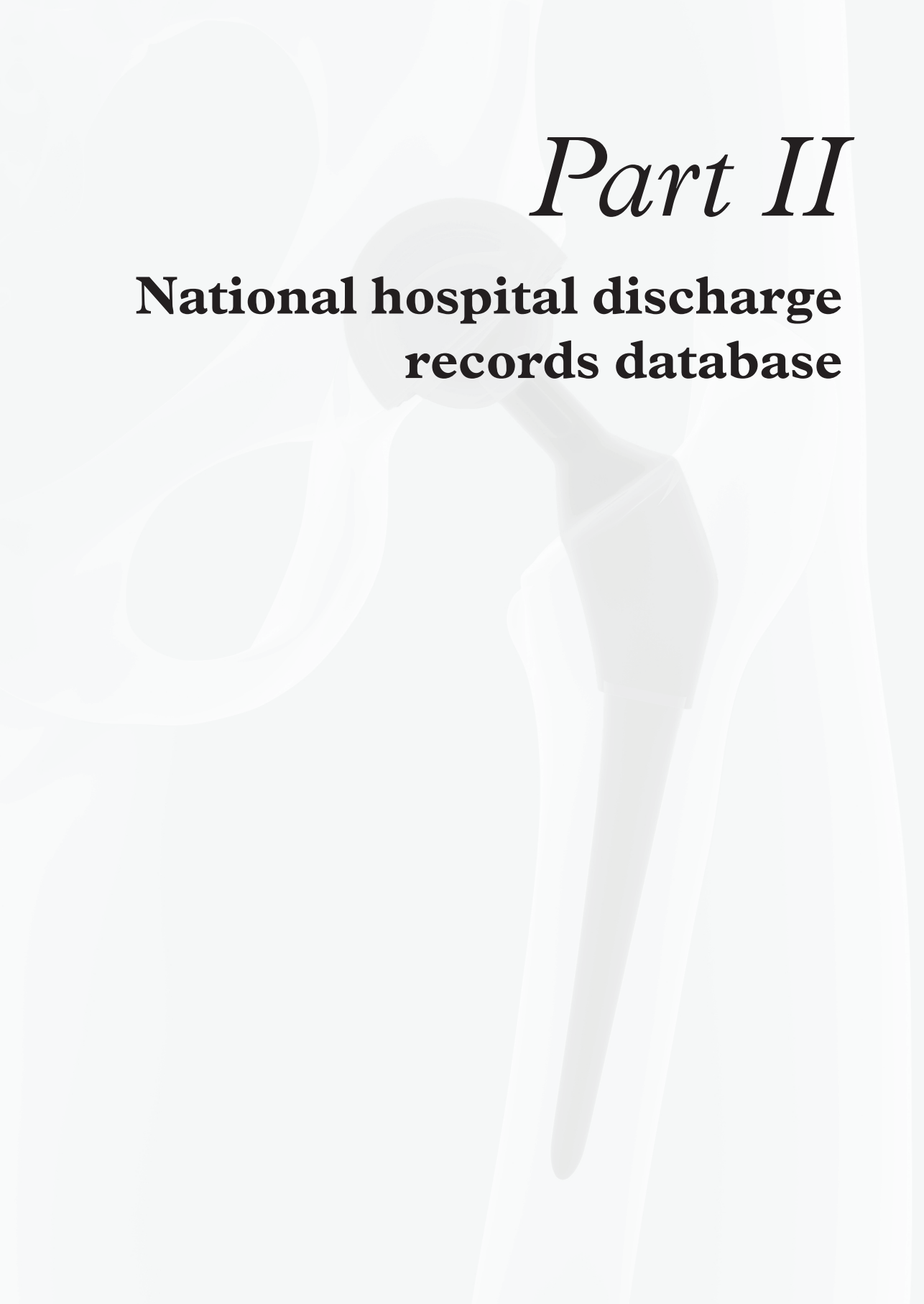
23. Chua JD, Wilkoff B, Lee I, Juratli N, Longworth DL, Gordon SM. Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. Ann Intern Med. 2000;133:604-8.

24. Bracke FA, Meijer A, van Gelder B. Endovascular extraction techniques for pacemaker and ICD lead extraction: Part 1. Neth Heart J. 2001 Apr;9(1):23-29.

25. Hauser RG, Katsiyiannis WT, Gornick CC, Almquist AK, Kallinen LM. Deaths and cardiovascular injuries due to device assisted implantable cardioverter-defibrillator and pacemaker lead extraction. Europace. 2010;12:395-401.

Part II

National hospital discharge records database



Chapter 3.1

Complications after hip arthroplasty and the association with hospital procedure volume

L.M. de Vries, M.C.J.M. Sturkenboom,

J.A.N. Verhaar, J.H. Kingma, B.H.C. Stricker

Published in Acta Orthop., 2011

Oct;82(5):545-52. doi: 0.3109/17453674.2011.618907.,

PubMED PMID: 21895498

Abstract

Background

It has been suggested that a higher procedure volume is associated with less complications after hip arthroplasty. In order to investigate the incidence of serious negative outcomes and a possible association with procedure volume, we performed a retrospective nationwide cohort study on total hip replacements in all Dutch hospitals.

Methods

All total hip replacements (n = 50,080) that were identified as primary intervention in all general and university medical centers between January 1, 2002 and October 1, 2004 were included. Primary endpoints of follow-up were mortality and complications during admission, and re-admission within 3 months due to complications. Variables that were assessed as potential risk factor were age, sex, duration of (preoperative) admission, specific diagnosis, acute/non-planned admission, comorbidity, and hospital procedure volume.

Results

Age, sex, and comorbidity were associated with complications and mortality. Additionally, acute admission was a risk factor for mortality but not for complications. There was no linear trend indicating that decreasing volume led to an increasing number of complications, and no statistically significant effect for mortality was found.

Conclusion

After adjustment for several risk factors, we found that the hospitals performing most hip procedures every year had fewer complications during index admission, but that they did not have a lower mortality than groups performing fewer procedures. The lack of a linear trend may be explained by the fact that almost all Dutch hospitals perform a high number of hip arthroplasties each year.

Approximately 20,000 total hip replacements are performed in Dutch general and university hospitals each year.[1] It is expected that this number will increase to more than 30,000 in 2030 and to more than 50,000 in the longer term.[2] Mortality, significant blood loss, postoperative infections, deep venous thrombosis (DVT), dislocations of the prosthesis, and instability are the most common early complications. Risk factors for complications are the type of intervention (hemiarthroplasty, total hip replacement, revision, trauma surgery), age, sex, and other patient-related factors such as obesity.[3] Furthermore, several studies have shown an association between complications on the one hand and experience of the surgeon and the hospital on the other, expressed as annual number of hip arthroplasties.[4-15]

Most studies have been performed in the United States, and due to differences in healthcare systems, it is not clear whether these results can be generalized to other countries. The aim of our retrospective nationwide cohort study was to gain insight into the incidence and risk of several serious complications of hip arthroplasty, both during the index hospitalization period and within the first 3 months after surgery. In addition, we assessed the importance of risk factors for complications such as the experience of the hospital, expressed as the number of interventions performed annually and corrected for several patient-related factors such as age, sex, co-morbidity, and diagnosis.

Patients and methods

Setting

Data were retrieved from a nationwide computer database of hospital discharge records, with complete coverage of all admissions in all general and university hospitals in the Netherlands (which has 16 million inhabitants). None of these hospitals is private. The university hospitals are owned by the government and the general hospitals are independent foundations, financed by public money. Private clinics did not perform THAs. The database includes (among other information) basic patient characteristics, date of admission and discharge, the main intervention (coded), the medical specialist (coded), and the main and secondary diagnoses at discharge, based on the ICD-9-CM coding system.[16] Characteristics of hospitalizations are registered by treating medical specialists or residents and coded by professional code clerks on the basis of hospital discharge letters. For every admission, one main diagnosis or diagnosis at discharge (mandatory) and up to 9 secondary diagnoses (optional) are registered. The coding is independent of reimbursement of the hospital or specialist. In addition, hospitals remain anonymous with the use of unique codes, instead of name and address data. All diagnoses are submitted in the same format, mostly electronically.

Cohort and outcome definition

All patients admitted for a first total hip arthroplasty between January 1, 2002 and October 1, 2004 were included in this nationwide cohort study (n = 50,080). This was the most recent dataset available, with sufficient power due to the large number of records. Each cohort member was followed only once from the day of the hip arthroplasty (index hospitalization) until the earliest of one of the following events: death during index admission, a complication, or end of the follow-up time of 3 months, whichever came first. Patients with an ICD-9 code indicating certain non-fatal complications related to the implant, such as mechanical loosening, dislocation, or infection of the implant during the index hospitalization were excluded since these complications may have been related to an earlier intervention and not to the index intervention that was performed during the study period. All interventions with codes indicating removal or revision of hip

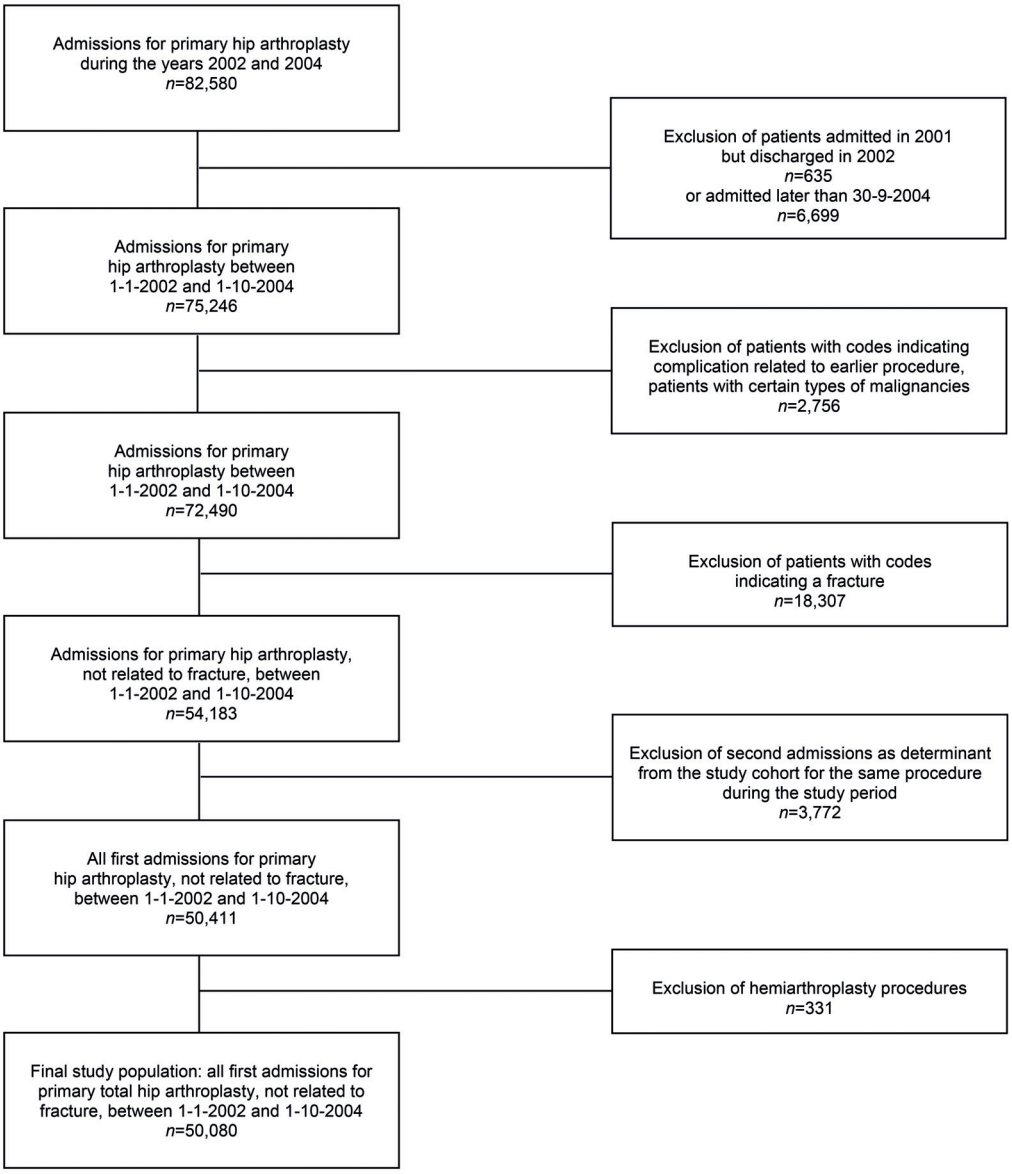


Figure 1. *Schematic representation of exclusion of patients from study population*

implants were excluded from the database, except when such removals or revisions occurred within 3 months after the index operation, as they may have indicated a complication.

In the total population, we identified 82,582 admissions for hemiarthroplasty and total hip arthroplasty in the period 2002-2004. After exclusion of patients who were admitted in 2001 but discharged in 2002, admissions later than Sep-

tember 30, 2004 to ensure at least 3 months of follow-up, patients discharged with codes indicating a complication from an earlier procedure, and patients with certain types of malignancies, fractures, and hemiarthroplasties, the study cohort consisted of 50,080 admissions for primary total hip arthroplasty.

In the Netherlands, most patients with a hip fracture have a hemiarthroplasty procedure, while patients with osteoarthrosis receive a total hip replacement. Patients with a fracture are clinically different from patients with osteoarthrosis. Thus, we excluded patients with fractures from the study cohort. Additionally, patients with osteoarthrosis or another diagnosis that was not fracture were excluded if they had hemiarthroplasty (see Figure).

We assessed the proportion of deaths and complications that occurred during the index hospitalization and the proportion of re-admissions as a result of a selected set of potential complications within 3 months of the index hospitalization. We searched the original database records over the period of April 1, 2002 to January 1, 2005 for admitted patients with the same date of birth, sex, postal code of their home address, and hospital identification code, as we found that almost all patients were re-admitted to the same hospital. Complications were identified based on the ICD-9 codes of the main discharge diagnoses and on literature.[4-5]

As complications during index hospitalization we considered ICD-9 codes describing pulmonary embolism, specific complications affecting specified body systems such as cardiac, vascular, respiratory, or urinary complications, complications of procedures, and complications of medical care. Reasons for re-admission that were considered as complications were: several types of infection, dislocation, vascular complications, and complications due to the procedure or implant. For this, we used a specific list, which was described earlier by Kreder et al. and Katz et al.[4-5] In addition, removal or revision of hip arthroplasty within 3 months of the index operation was also considered to be an indication of a complication and was therefore included as an endpoint.

Hospital volume

During the study period, the Netherlands had 88 general hospitals and 8 university medical centers. 2 of the 96 hospitals only performed hemiarthroplasties; therefore, 94 hospitals remained in the study. Some hospitals have more than one location, but for the purpose of our research they were considered as one organization. The Netherlands is a densely populated country with a relatively old population. The average number of hip procedures per hospital may therefore be higher than in other countries. Only 13 hospitals performed less than 100 total hip arthroplasties annually during the study period. When hemiarthroplasties and fractures were also considered, this number was even lower.

We divided the hospitals into 5 volume groups based on the mean number of total hip arthroplasties performed per year. The lowest volume group performed less than 100 procedures a year and the highest volume group performed more than 400 procedures a year. The number of patients in each of these groups (see Tables 3 and 4) is the number of patients from the total cohort who were in that group during the study period of 2.75 years.

Our data did not allow us to distinguish between individual surgeons. Orthopedic surgeons performed almost all of the total hip replacements (99.9%).

Covariables

As covariables, the following variables were considered for inclusion in the models: age and sex, surgical procedure volume per hospital, and co-morbidity in the year prior to the intervention that was severe enough for hospitalization and diagnosis. In order to assess co-morbidity a year before surgery, we searched the original database records over the period Jan-

Table 1. Baseline characteristics of the study cohort (n=50,080)

Characteristics Primary Total Hip Replacement	All admissions (*n*=50,080)	Males (*n*=14,966, 29.9%)	Females (*n*=35,114, 70,1%)
Mean age, *years (SD)*	68.7 (10.6)	65.9 (11.0)	70.0 (10.1)
Median age, *years (range)*	70 (15-99)	67 (15-99)	71 (15-99)
Median duration of admission, *days (range)*	9 (1-137)	8 (1-137)	9 (1-133)
Median duration of pre-operative admission, *days (range)*	1 (0-80)	1 (0-80)	1 (0-76)
Acute, non-planned admission, *n (%)*	504 (1.0)	132 (0.9)	372 (1.1)
Any co-morbidity, *n (%)*	3423 (6.8)	1164 (7.8)	2259 (6.4)
Specialist:			
Orthopedic surgeon, *n (%)*	50,038 (99.9)	14,956 (99.9)	35,082 (99.9)
General surgeon, *n (%)*	34 (0.1)	9 (0.1)	25 (0.1)
Other surgeon, *n (%)*	8 (<0.1)	1 (<0.1)	7 (<0.1)
Died during admission (all causes), *n (%)*	114 (0.2)	42 (0.3)	72 (0.2)
Complication during admission, *n (%)*	1115 (2.2)	350 (2.3)	765 (2.2)
Readmitted at least once within 3 months with a complication	1765 (3.5)	595 (4.0)	1170 (3.3)
Any unfavorable outcome[a]	2880 (5.8)	947 (6.3)	1933 (5.5)
Diagnosis			
Osteoarthritis, *n (%)*	48,313 (96.5)	14,260 (95.3)	34,053 (97.0)
Aseptic bone necrosis, *n (%)*	937 (1.9)	419 (2.8)	518 (1,5)
Congenital deformity of hip, *n (%)*	141 (0.3)	37 (0.2)	104 (0.3)
Rheumatoid arthritis, *n (%)*	121 (0.2)	31 (0.2)	90 (0.3)
Other, *n (%)*	568 (1.1)	219 (1.5)	349 (1.0)

[a] *Complication during index admission and/or re-admission to 3 times within 3 months of surgery*

uary 1, 2001 to January 1, 2005 for admitted patients who had the same date of birth, sex, and postal code. We classified co-morbidity according to the Charlson co-morbidity index as adapted by Deyo et al. for ICD-9 databases.[17-18] Furthermore, we considered the diagnosis, whether admission was acute and unplanned, duration of admission before surgery and total duration of admission.

Validation

We performed validation of procedures, complications, and mortality in a sample of our study material by linking it to the Rotterdam Study, a prospective population-based cohort study of chronic diseases in the elderly who live in the Ommoord district of the city of Rotterdam.[19] By matching according to date of birth, sex, and postal code of the home address, we identified 68 patients from the study cohort in the Rotterdam Study. These 68 patients had been admitted to 3 hospitals in Rotterdam and surrounding area. For 40 patients, the original file including the original discharge letter was available for review. For 17 other patients, information from their general practitioner could

Table 2. Characteristics of first three readmissions within three months after surgery

	First *n*=4364		Second *n*=759		Third *n*=167	
	n	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
2nd total hip replacement	423	9.7 (8.8; 10.6)	25	3.3 (2.0; 4.6)	3	1.8 (-0.2; 3.8)
Complication during index admission	156	3.6 (3.0; 4.1)	34	4.5 (3.0; 6.0)	6	3.6 (0.8; 6.4)
Readmission was acute/not planned	2534	58.1 (56.6; 59.5)	397	52.3 (48.8; 55.9)	72	43.1 (35.6; 50.6)
Mortality during readmission	83	1.9 (1.5; 2.3)	9	1.2 (0.4; 2.0)	5	3.0 (0.4; 5.6)
Readmission was due to complication	1765	40.4 (39.0; 41.9)	322	42.4 (38.9; 46.0)	70	41.9 (34.4; 49.4)
Complications specified:	1765	100	322	100	70	100
Mechanical complication of device	892	50.5 (48.2; 52.9)	212	65.8 (60.7; 71.0)	43	61.4 (50.0; 72.8)
Infection	526	29.8 (27.7; 31.9)	73	22.7 (18.1; 27.2)	20	28.6 (18.0; 39.2)
Dislocation	47	2.7 (1.9; 3.4)	10	3.1 (1.2; 5.0)	0	0.0 (0.0; 0.0)
Pulmonary embolism	58	3.3 (2.5; 4.1)	5	1.6 (0.2; 2.9)	1	1.4 (-1.4; 4.2)
Deep venous thrombosis	61	3.5 (2.6; 4.3)	4	1.2 (0.03; 2.5)	1	1.4 (-1.4; 4.2)
Other	180	10.2 (8.8; 11.6)	18	5.6 (3.1; 8.1)	5	7.1 (1.1; 13.2)

be accessed digitally, and no information was available for the other 11 patients.

Of all the procedures, diagnoses, and complications, 91% (CI: 84–99), 90% (CI: 82–97), and 80% (CI: 45–115), respectively, were confirmed. The remainder was missing and could not be judged. However, no procedures, diagnoses, or complications were false-positive.

Analysis

Descriptive analyses were conducted using SPSS software version 15.0. Statistical comparison of means and proportions consisted of independent samples t-tests (Student's), and chi-square tests. Because the precise delay between hip arthroplasty and complications during the index hospitalization was not available in the database, we used logistic regression analysis with the first occurrence of a complication as endpoint instead of a Cox proportional hazards model. Covariables that were considered as risk factors in the literature were tested in a univariable logistic regression analysis in order to obtain crude odds ratios. The final multivariable models were fitted by backward elimination regression based on the maximum likelihood ratio.[20] The effect of a variable on the risk of complication was expressed as an odds ratio with a 95% confidence interval (CI).

Table 3. Adjusted associations of all risk factors with mortality per hospital group

	Early mortality during index admission	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**
Hospital volume as # of total hip procedures[a]/yr		
>400 (n_h=7 / n_p=8,813)[b]	ref	ref
300-400 (n_h=12 / n_p=10,260)	0.94 (0.52; 1.70)	0.80 (0.44; 1.47)
200-300 (n_h=20 / n_p=12,413)	1.15 (0.67; 1.98)	1.05 (0.60; 1.83)
100-200 (n_h=42 / n_p=16,196)	0.91 (0.53; 1.56)	0.76 (0.44; 1.32)
<100 (n_h=13 / n_p=2,398)	0.18 (0.02; 1.30)	0.17 (0.02; 1.24)
Female sex	0.73 (0.50; 1.07)	**0.58 (0.39; 0.86)**
Age (quartiles of # of patients)		
<65	ref	ref
66-72	1.80 (0.81; 4.01)	1.97 (0.88; 4.42)
73-79	**5.61 (2.81; 11.19)**	**5.83 (2.88; 11.80)**
80<	**10.92 (5.52; 21.63)**	**10.87 (5.36; 22.07)**
Co-morbidity[c]		
Score 0	ref	ref
Score 1	**3.86 (2.32; 6.43)**	**2.69 (1.59; 4.61)**
Score 2	**6.80 (3.13; 14.76)**	**4.16 (1.86; 9.30)**
Score 3	**11.68 (4.70; 29.10)**	**5.99 (2.27; 15.85)**
Diagnosis		
Osteoarthritis	ref	ref
Aseptic bone necrosis	**3.31 (1.45; 7.57)**	**3.22 (1.37; 7.59)**
Congenital deformity of hip	-	-
Rheumatoid arthritis	4.28 (0.59; 30.91)	2.32 (0.29; 18.30)
Other	**12.02 (6.69; 21.59)**	**7.91 (4.09; 15.32)**
Acute, non-planned admission	**6.51 (3.02; 14.06)**	**3.03 (1.23; 7.22)**
Duration of index admission	**1.04 (1.02; 1.05)**	**0.97 (0.95; 1.00)[d]**
Duration of pre-operative admisison	**1.06 (1.03; 1.10)**	-[e]
Complication during index admission	**17.61 (11.66; 26.62)**	**13.23 (8.36; 20.93)**

Cut-off p≤0.05, odds ratios in bold font are significant
[a] Fractures and hemiarthroplasties excluded
[b] n_h = no. of hospitals in group / n_p = no. patients in group
[c] Charlson comorbidity index, adapted by Deyo et al. for ICD-9 databases
[d] Results with 3 decimals: 0.972 (0.947; 0.999)
[e] Not in final multivariable model

Results

Approximately half of the patients were older than 70 years, with a mean age of 69 years (SD 11), and about 70% were women. The median duration of admission was 9 days, with a median preoperative stay of 1 day. Most patients were admitted with a diagnosis of osteoarthritis (97%) and 7% had one or more co-morbidities. About 1% (n = 504) of the admissions were not planned. Most of these patients (n = 408, 81%) had osteoarthritis as the main diagnosis, 9.5% (n = 48) had other bone defects such as aseptic bone necrosis and malunion/nonunion of fracture, and another 9.5% (n = 48) had a variety of other diagnoses; 11 of the patients of this group had osteoarthritis as secondary diagnosis. The reason for these admissions being acute/unplanned was not mentioned. The mortality rate during the index admission was 0.2% (n = 114), and 2.2% (n = 1,115) of the patients had one or more complications. Including re-admissions during the 3 months after surgery, 5.8% (n = 2,880) of the patients had a complication, either during the index admission or after re-admission for that reason (Table 1).

Almost 9% (n = 4,364) of the patients were re-admitted at least once within 3 months of surgery. About 40% (n = 1,756) were readmitted with a complication of the procedure, most of which involved a mechanical complication of the device (51%, n = 892) or an infection (30%, n = 526). The second and third re-admissions within the same time frame showed a similar picture (Table 2). Of these 4,364 patients, about 10% were admitted for a second hip replacement.

Table 3 shows the univariable and multivariable analyses of all risk factors associated with mortality during the index admission. Age, male sex, co-morbidity, and certain diagnoses appeared to be associated with mortality. Furthermore, a complication during the index admission was a risk factor for mortality, with an adjusted odds ratio of 13 (CI: 8–21). Hospital groups performing fewer procedures appeared to be associated with a lower risk of mortality than the hospital group that performed most interventions. However, the odds ratios did not reach statistical significance.

Table 4 shows the univariable and multivariable analysis of several risk factors with complications during the index admission and the first 3 re-admissions within 3 months of surgery.

Age, male sex, co-morbidity, and diagnosis (aseptic bone necrosis and other) were statistically significantly associated with both endpoints. Hospital volume appeared to be associated with complications during the index admission, as all lower-volume groups had higher odds ratios than the high-volume group. However, it did not show the linear trend that would have been expected. For re-admissions due to complications, this association was not apparent.

Discussion

In this study, we found that during the index admission for total hip replacement, the percentage of complications was 2.2%. Almost 9% of the patients in the study cohort who were admitted between January 1, 2002 and October 1, 2004 for THA were re-admitted for any cause at least once within 3 months of surgery. However, 40% of these re-admissions were due to a complication that could be related to the implantation. Altogether, approximately 6% of the cohort of patients studied experienced a complication during index admission and/or within 3 months after the implantation. Acute admission appeared to be a risk factor for complications during index admission in the unadjusted analysis, but it was not selected as a risk factor in the final model. This may have been caused by adjustment for co-morbidity and diagnosis, variables that may confound the effect of acute admission.

The mortality during admission was 0.2% for patients with a total hip replacement. A complication during index hospitalization was strongly

Table 4. Crude and adjusted associations of all risk factors with complications during index admission and re-admissions

	Complication during index admission		Readmission due to complication	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Hospital volume as # of total hip procedures[a]/yr				
>400 (n_h=7 / n_p=8,813)[b]	ref	ref	ref	ref
300-400 (n_h=12 / n_p=10,260)[b]	**2.19 (1.74; 2.75)**	**2.15 (1.70; 2.72)**	**1.25 (1.08; 1.45)**	**1.25 (1.07; 1.45)**
200-300 (n_h=20 / n_p=12,413)[b]	**2.01 (1.61; 2.52)**	**1.93 (1.53; 2.43)**	1.04 (0.89; 1.20)	1.02 (0.88; 1.19)
100-200 (n_h=42 / n_p=16,196)[b]	**2.03 (1.63; 2.52)**	**1.83 (1.46; 2.29)**	0.96 (0.84; 1.11)	0.94 (0.82; 1.09)
<100 (n_h=13 / n_p=2,398)[b]	**2.31 (1.69; 3.16)**	**1.88 (1.35; 2.61)**	1.11 (0.88; 1.41)	1.10 (0.87; 1.39)
Female sex	0.93 (0.82; 1.06)	**0.78 (0.68; 0.90)**	**0.83 (0.75; 0.92)**	**0.79 (0.71; 0.87)**
Age (quartiles of # of patients)				
<65	ref	ref	ref	ref
66-72	**1.34 (1.13; 1.60)**	**1.22 (1.01; 1.46)**	1.06 (0.93; 1.21)	1.12 (0.98; 1.28)
73-79	**2.00 (1.69; 2.36)**	**1.51 (1.27; 1.80)**	**1.50 (1.33; 1.70)**	**1.61 (1.42; 1.83)**
80<	**2.63 (2.21; 3.15)**	**1.53 (1.26; 1.86)**	**1.71 (1.49; 1.96)**	**1.88 (1.63; 2.18)**
Comorbidity[c]				
Score 0	ref	ref	ref	ref
Score 1	**2.08 (1.70; 2.54)**	**1.67 (1.34; 2.07)**	**1.53 (1.28; 1.83)**	**1.39 (1.15; 1.68)**
Score 2	**2.51 (1.72; 3.67)**	**1.80 (1.20; 2.70)**	**1.72 (1.21; 2.44)**	**1.54 (1.08; 2.19)**
Score 3	**3.14 (1.85; 5.31)**	**1.89 (1.04; 3.41)**	**1.97 (1.18; 3.28)**	**1.77 (1.06; 2.95)**
Diagnosis				
Osteoarthritis	ref	ref	ref	ref
Aseptic bone necrosis	**2.11 (1.53; 2.90)**	**1.82 (1.29; 2.57)**	**1.78 (1.36; 2.33)**	**1.83 (1.40; 2.41)**
Congenital deformity of hip	-	-	0.19 (0.03; 1.37)	0.22 (0.03; 1.57)
Rheumatoid arthritis	1.17 (0.37; 3.69)	0.60 (0.16; 2.20)	**2.98 (1.64; 5.42)**	**2.57 (1.38; 4.81)**
Other	**3.87 (2.83; 5.29)**	**2.46 (1.71; 3.52)**	**1.75 (1.23; 2.48)**	**1.75 (1.23; 2.50)**
Acute, non-planned admission at index admission	**1.83 (1.17; 2.87)**	-[d]	**0.81 (0.49; 1.36)**	-[d]
Duration of index admission	**1.10 (1.09; 1.10)**	**1.10 (1.10; 1.11)**[e]	1.00 (1.00; 1.01)[f]	**0.99 (0.98; 1.00)**[g]
Duration of pre-operative admission	**1.04 (1.02; 1.06)**	**0.87 (0.84; 0.91)**	0.99 (0.96; 1.03)	-[d]
Complication during index admission	NA	NA	**1.99 (1.56; 2.52)**	**1.91 (1.49; 2.45)**

Cut-off p≤0.05, odds ratios in bold font are significant
[a] Fracturers and hemiarthroplasties excluded
[b] n_h = no. of hospitals / n_p = no. of patients in that group
[c] Charlson comorbidity index, adapted by Deyo et al. for ICD-9 databases[25,26]
[d] Not in final multivariable model
[e] Results with 3 decimals: 1.103 (1.095; 1.110)
[f] Results with 3 decimals: 1.004 (0.996; 1.012)
[g] Results with 3 decimals: 0.986 (0.977; 0.995)

associated with mortality. However, as might be expected, mortality could not be entirely related to the intervention, since age, co-morbidity, and acute admission (i.e. trauma) were also associated with it. The high-volume group had a higher risk of mortality than 3 of the lower-volume groups. This may be explained by the fact that complicated total hip replacements are usually referred to high-volume centers. However, we did not find that higher hospital volume was associated with lower mortality, as found in previous studies.[12, 14] Furthermore, we must note here that the data came from the Dutch National Medical Registration, which records all hospital admissions until discharge. Thus, only mortality during admission is registered in this database, and we were unable to monitor mortality after discharge. SooHoo et al. found a mortality rate of 0.7% and a complication rate of 3.8% within 90 days.[15] It is possible that the mortality rate is higher and shows more differences between volume groups when mortality that occurs after discharge is taken into account. Mortality within 3 months of surgery may still be related to the procedure, although the rate is rather low due to modern advances in surgery, anesthesia, and rehabilitation— and despite early discharges, operations on older and more fragile individuals, and earlier rehabilitation.[21-22]

In the past decade, several studies have been performed on the incidence of complications following surgery and the effect of hospital and surgical procedure volume.[4-5, 7-14] Many of these studies had a follow-up time of 3 months after surgery, since it appeared that the largest proportion of complications manifests itself within that time period, an extensive proportion of which occurred within a few days of surgery.[4-5, 23-24] Primary endpoints were mortality, infection, dislocation and/or instability, deep vein thrombosis, and pulmonary embolism. In our study, we investigated the occurrence of any complication, including the above-mentioned outcomes, and infection, dislocation, deep vein thrombosis, and pulmonary embolism separately.

Although hospital groups performing a lower number of THRs were more strongly associated with complications during the index admission than the highest-volume group, our study did not show a trend towards a lower proportion of complications when the number of interventions per hospital increased. Furthermore, there was no association between volume groups and re-admissions within 3 months. As the average number of hip arthroplasties per hospital was high in our study, this may have removed the potential difference between high-volume and low-volume hospitals. However, as in another study that did not find an effect of hospital volume on outcome,[25] and according to privacy legislation, our administrative data did not allow us to identify the surgeons who performed the intervention. Several other studies showed that a higher volume of hip arthroplasties resulted in a lower incidence of complications, and suggested that procedure volume per surgeon is the most important determinant.[7-8, 12-13, 26] This was questioned in other studies, where the authors concluded that hospital volume is an important factor.[9] It was also found that in patients who were operated by higher volume surgeons, higher hospital volume was independently associated with lower early failure rates but specialization of the hospital may also play a role.[7, 11] Furthermore, it has been suggested that the volume effect reaches a plateau and does not improve further regardless of increasing volume.[27] Thus, hospital volume may still be an appropriate indicator of quality.[28]

Finally, there may have been residual confounding caused by factors that could not be adjusted for in our analysis, such as type of prosthesis used, facilities in the operating room, and so on. As far as we know, our study is the first nationwide study in which all primary total hip replacements have been included, and involves a high average number of hip procedures per hospital in a densely populated country. Also, validation

of a sample showed that the quality of the registry is good. Furthermore, it is unlikely that there was selection bias, since Dutch inhabitants in need of hip arthroplasty are generally admitted to a Dutch hospital. Information bias due to knowledge of the research question was also unlikely, as the admissions were registered prospectively. However, false-negative misclassification of cases could be an issue because we only had access to data about mortality during hospitalization. Although a median length of stay of 9 days is rather long for this type of procedure, it is still likely that some mortality related to the procedure occurred after discharge. Additionally, although trained code clerks register hospital admissions, mistakes in coding and deviations between employees and hospitals cannot be excluded. However, given the high concordance between registered determinants and complications and medical records in our validation sample, we think that this is unlikely.

At least one additional diagnosis was mentioned in only 25% of the admissions. Possible complications may not have been registered because such registration is optional and only registration of the main diagnosis is mandatory. This may have led to underestimation of the number of complications.

In conclusion, in contrast with results from USA hospitals, volume does not fully explain the differences in mortality and complications between hospitals in the Netherlands. This might be explained in part by the fact that the average number of hip arthroplasties per hospital is high. This might mean that under such circumstances, other determinants become more important in explaining differences—such as volume per surgeon or technical considerations such as type of prosthesis, surgical technique, use of cement, conditions in the operating rooms, or patient related factors. Other options that may be interesting for further investigation are (1) the degree of orthopedic specialization of hospitals, as an association between this parameter and favorable outcome has been shown in a recent study,[29] and (2) the importance of standardization of the process, which was found to be strongly associated with better patient outcomes and more efficient use of resources in another study.[14]

Acknowledgements

The authors would like to thank J. Verkroost-Van Heemst for her assistance in the validation of the data and J. de Koning, MD, PhD and S.A. Romio, PhD, for their critical review of the manuscript.

Ethical statement

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Screening Act: Rotterdam Study)". All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

References

1. Prismant (service organization in health care) http://cognosserver.prismant.nl/cognos7/cgi-bin/ppdscgi.cgi?DC=Q&E=/Prisma-Landelijke-LMR/Landelijke+LMR-informatie+-+Verrichtingen. Last accessed: 09-11-2009.

2. Otten R, Roermund PM van, Picavet HSJ. [Trends in the number of knee and hip arthroplasties: considerably more knee and hip prostheses due to osteoarthritis in 2030]. Trends in aantallen knie- en heupartroplastieken. De vraag naar knie- en heupprotheses blijft voorlopig toenemen. Ned Tijdschr Geneeskd. 2010;154:A1534:1-7.

3. Lübbeke A, Stern R, Garavaglia G, et al. Differences in outcomes of obese women and men undergoing primary total hip arthroplasty. Arthritis Rheum. 2007;57(2): 327-34.

4. Kreder HJ, Deyo RA, Koepsell T et al. Relationship between the volume of total hip replacement performed by providers and the rates of postoperative complications in the State of Washington. J. Bone Joint Surg Am. 1997;79:485-94.

5. Katz JN, Losina E, Barrett J. et al. Association between hospital and surgeon procedure volume and outcomes of total hip replacement in the United States Medicare Population. J. Bone Joint Surg Am. 2001;83:1622-9.

6. Solomon DH, Losina E, Baron JA, et al. Contribution of hospital characteristics to the volume-outcome relationship: Dislocation and infection following total hip replacement surgery. Arthritis Rheum. 2002;46(9):2436-44.

7. Losina E, Barrett J, Mahomed, NN, et al. Early failures of total hip replacement. Effect of surgeon volume. Arthritis Rheum. 2004;50(4):1338-43.

8. Battaglia TC, Mulhall KJ, Brown TE, et al. Increased surgical volume is associated with lower THA dislocation rates. Clin Orthop Relat Res. 2006;447:28-33.

9. Doro C, Dimick J, Wainess R, et al. Hospital volume and inpatient mortality outcomes of total hip arthroplasty in the United States. J Arthroplasty. 2006;21(6 Suppl 2):10-6.

10. Judge A, Chard J, Learmonth I, et al. The effects of surgical volumes and training centre status on outcomes following total joint replacement: analysis of the hospital episode statistics for England. J Public Health (Oxf). 2006;28(2):116-24.

11. Cram P. Vaughan-Sarrazin MS, Wolf B, et al. A comparison of total hip and knee replacement in specialty and general hospitals. J Bone Joint Surg Am. 2007;89:1675-84.

12. Shervin N, Rubash HE, Katz JN. Orthopaedic procedure volume and patient outcomes. A systematic literature review. Clin Orthop Relat Res. 2007;457:35-41.

13. Manley M, Ong K, Lau E, et al. Effect of volume on total hip arthroplasty revision rates in the United States Medicare population. J Bone Joint Surg Am. 2008;90:2446-2451.

14. Bozic KJ, Maselli J, Pekow PS, et al. The influence of procedure volumes and standardization of care on quality and efficiency in total joint replacement surgery. J Bone Joint Surg Am. 2010;92:2643-52.

15. SooHoo NF, Farng E, Lieberman JR, et al. Factors that predict short-term complication rates after total hip arthroplasty. Clin Orthop Relat Res. 2010;468:2363-2371.

16. International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM). Michigan: Commission on Professional and Hospital activities, 1978.

17. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5): 373-83.

18. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45(6):613-19.

19. Hofman A, Breteler MMB, Duijn CM van, et al. The Rotterdam Study: 2010 objectives and design update. Eur J Epidemiol. 2009;24:553-72.

20. Sun GW, Shook TL, Kay GL. Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis. J Clin Epidemiol. 1996;49(8):907-16.

21. Pulido L, Parvizi J. Macgibeny M, et al. In hospital complications after total joint arthroplasty. J Arthroplasty. 2008;23(6 Suppl 1):139-45.

22. Aynardi M, Pulido L, Parvizi J, et al. Early mortality after modern total hip arthroplasty. Clin Orthop Relat Res. 2009;467:213-218.

23. Phillips CB, Barrett JA, Losina E, et al. Incidence rates of dislocation, pulmonary embolism, and deep infection during the first six months after elective total hip replacement. J Bone Joint Surg Am. 2003;85:20-6.

24. Parvizi J, Mui A, Purtill J, et al. Total joint arthroplasty: when do fatal or near-fatal complications occur? J Bone Joint Surg Am. 2007;89: 27-32.

25. Zhan C, Kaczmarek R, Loyo-Berrios N, et al. Incidence and short-term outcomes of primary and revision hip replacement in the United States. J Bone Joint Surg Am. 2007;89: 526-33.

26. Lavernia CJ, Guzman JF. Relationship of surgical volume to short-term mortality, morbidity, and hospital charges in arthroplasty. J Arthroplasty. 1995;10(2): 133-40.

27. Sharkey PF, Shastri S, Teloken MA, et al. Relationship between surgical volume and early outcomes of total hip arthroplasty. Do results continue to get better? J Arthroplasty. 2004;19(6):694-9.

28. Meredith DS, Katz JN. Procedure Volume as a quality measure for total joint replacement. Clin Exp Rheumatol. 2007;25(Suppl.47):S37-S43.

29. Hagen TP, Vaughan-Sarrazin MS, Cram P. Relation between hospital orthopaedic specialisation and outcomes in patients aged 65 and older: retrospective analysis of US Medicare data. BMJ. 2010;340:c165:1-8.

Chapter 3.2

Incidence, treatment, and case-fatality of non-traumatic subarachnoid haemorrhage in the Netherlands

R. Risselada*, L.M. de Vries*, D.W.J. Dippel,
F. van Kooten, A. van der Lugt, W.J. Niessen,
A. Firouzian, B.H.C. Stricker, M.C.J.M. Sturkenboom

* *Equal contribution*

Published in Clin Neurol Neurosurg., 2011
Jul;113(6):483-7. doi: 10.1016/j.clineuro.2011.02.015.,
PubMED PMID: 21420782

Abstract

Background

Non-traumatic subarachnoid haemorrhage (SAH) is a devastating disorder and in the majority of cases caused by rupture of an intracranial aneurysm. No actual data are available on the incidence of non-traumatic SAH and aneursymal SAH (aSAH) in the Netherlands and little is known about treatment patterns of aSAH. Our purpose was therefore to assess the incidence, treatment patterns, and case-fatality of non-traumatic (a)SAH within the Dutch general population.

Methods

Two population based data sources were used for this retrospective cohort study. One was the nationwide hospital discharge registry (LMR). Cases were patients hospitalized for SAH (ICD-9-code 430) in 2001-2005. The second source was IPCI, a medical record database allowing for case validation. Cases were patients with validated (a)SAH in 1996-2006. Incidence, treatment, and case-fatality were assessed.

Results

The incidence rate (IR) of non-traumatic SAH was 7.12 per 100,000 PY (95%CI: 6.94-7.31) and increased with age. The IR of aSAH was 3.78 (95%CI: 2.98–4.72). Women had a twofold increased risk of SAH; this difference appeared after the fourth decade. Non-traumatic SAH fatality was 30% (95%CI: 29-31%). Of aSAH patients 64% (95%CI: 53-74%) were treated with a clipping procedure, and 26% (95%CI: 17-37%) with coiling.

Conclusion

Non-traumatic SAH is a rare disease with substantial case-fatality; rates in the Netherlands are similar to other countries. Case-fatality is also similar as well as age and sex patterns in incidence.

Non-traumatic subarachnoid haemorrhage (SAH) is a devastating event, with a case-fatality of around 30%.[1-2] Incidence rates have been assessed in many countries and two patterns can be distinguished: countries with high incidence of around 20 per 100,000 person years (PY), such as Finland and Japan, and countries with low incidence of approximately 5-10 per 100,000 PY.[3]

Approximately 85% of non-traumatic SAH is a result of rupture of an intracranial aneurysm (IA), although it is not clear whether this percentage is the same over different age and sex categories.[1] Causes of spontaneous SAH from other origins include among others other vascular lesions, inflammatory and non-inflammatory lesions, tumours, and drug or substance use.[1, 4]

The diagnosis of SAH is primarily based on CT imaging and lumbar puncture, eventually followed by angiography; not only to identify an aneurysm as potential cause of the haemorrhage, but also to study the anatomical and morphological configuration of the aneurysm in relation to adjoining arteries, which allows optimal treatment selection.[1] Treatment of aneurysmal SAH (aSAH) consists mainly of either neurosurgical clipping or endovascular coiling. Other less frequently used treatment modalities comprise wrapping, stenting, or balloon occlusion.[5-7]

Given the fact that no recent data on age and sex specific incidence of non-traumatic SAH and aSAH in the Netherlands are available, we assessed the incidence of both conditions in the general Dutch population. Moreover, we studied case-fatality, and treatment modalities applied to aSAH patients. This was done in two population based databases; a national discharge database (LMR, Landelijke Medische Registratie) and a smaller medical record database (IPCI, Integrated Primary Care Information) which allowed for assessment of the presence of an aneurysm and treatment modality.

Materials and methods

LMR database

Hospital discharge diagnoses were obtained from the national registry of hospital admissions, the National Medical Registration (LMR), containing information on all admissions in general and academic hospitals throughout the Netherlands (base population: approximately 16.5 million subjects). The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used to classify hospital admissions in the Netherlands during the study period. Data used include hospital code, patient sex and age, ICD-9-CM coded discharge diagnosis, up to 9 diagnostic or therapeutic procedures (coded according to the LMR Classification of Diagnostic, Therapeutic, and Surgical Acts), and discharge destination ('home', 'old people's home', 'nursing home', or 'died in hospital').

Non-traumatic SAH cases were all admissions with a primary discharge diagnoses (ICD-9-CM) 430 (subarachnoid haemorrhage) during the years 2001 through 2005. Case-fatality was defined as dying in the hospital during hospitalization for SAH.

The denominator for the incidence calculation was the annual mid-year population size as obtained from Statistics Netherlands (CBS, accessed through http://www.cbs.nl, as of 7 June 2010).

IPCI database

The Integrated Primary Care Information (IPCI) database is a general practice research database with electronic medical record data currently comprising more than one million patients throughout the Netherlands. The patient population is representative of the Dutch population regarding age and sex.[8] Details of the database have been described elsewhere.[9] The system complies with the European Union guidelines on the use of medical data for research and has been proven valid for epide-

miological studies.[9] The Scientific and Ethical Advisory Group of the IPCI project approved the study (Project No. 07/02). The database allows for validation of disease by requesting additional information from the general practitioner by questionnaire and copies of original specialist letters.

Potential cases of non-traumatic SAH and aSAH were identified from the IPCI database using an extensive narrative search; we identified potential cases in the computerized records by searching for International Classification of Primary Care (ICPC) codes of 'cerebrovascular accident' (K90), 'other diseases of peripheral arteries' (K92), or 'other diseases of the circulatory tract' (K99), and by free text searches on 'intracranial', 'aneurysm', 'subarachnoid', 'haemorrhage', or 'nimodipine'. In the Netherlands, nimodipine is exclusively prescribed as prophylaxis for delayed cerebral ischemia after aSAH. To further validate the diagnosis of SAH, a short questionnaire was mailed to the GPs. The questionnaire was used to confirm whether the person, according to the GP's judgment, indeed suffered from (aneurysmal) SAH, and whether the patient had been seen and diagnosed by a specialist. Copies of all specialist letters were requested. Specialist letters usually provide information about history, physical examination, lumbar puncture, and reports on imaging of the patient.

All cases were validated by manual review of the electronic medical record and subsequently by review of a questionnaire and specialist letters that were obtained from the GP for each case. The validity of the diagnosis was judged by a medical doctor (R.R.) and a neurologist (D.W.J.D. or F.K.). The judgment of the neurologist was decisive. Case-fatality was defined as dying within a period of 30 days after the date of onset of SAH (index date).

The denominator for the incidence calculation was the number of person years in the IPCI database during the study period (January 1996–September 2006).

Statistical analysis

The incidence rate of non-traumatic SAH and aSAH was calculated by dividing the number of incident cases (numerator), by the total number of accrued person years (IPCI) or persons (LMR) in the study population (denominator). Incidence rates (IR) were calculated in age and sex categories. Confidence intervals (95% CI) for each estimate were based on the Poisson distribution. To estimate case-fatality of aSAH in the IPCI database, Kaplan-Meier survival analysis was used. Incidence rates were used to calculate rate ratios of SAH and aSAH between females and males. All analyses were performed using SPSS software version 15.0 (Chicago, Ill., USA).

Literature review

To compare our Dutch findings with the existing literature on this topic, we performed a systematic review of the literature from October 2005 onwards, adding to the review of De Rooij and co-workers on the same topic, which ended in October 2005.[3] A similar Medline search was used: ("Stroke"[Mesh] OR "Subarachnoid Haemorrhage"[Mesh]) AND ("Epidemiology"[Mesh] OR "Population"[Mesh] OR "Incidence"[Mesh]) for the time period from October 2005 to May 2009. The papers thus obtained were abstracted manually by one researcher (R.R.). Our inclusion criteria were: (1) study population is representative of the population in general; and (2) for studies about stroke in general, SAH should be considered as a separate entity. We excluded papers reporting incidence rates in Finnish and Japanese populations, since these rates are consistently higher than in other populations and therefore add little to the comparison with our findings.[1]

Results

LMR: SAH

In the period 2001 to 2005 a total of 5,769 patients (64% female) were admitted to Dutch hospitals with discharge diagnosis 'non-trau-

Table 1. Incidence rates of SAH by age and sex in the LMR and IPCI databases

	LMR				IPCI				IPCI			
	SAH cases (*n*)	IR	95% CI	Fatality[a]	SAH cases (*n*)	IR	95% CI	Fatality[b]	aSAH cases (*n*)	IR	95% CI	Fatality[b]
Age												
< 40	570	1.33	1.23-1.45	19.47	15	1.28	0.75–2.06	20	12	1.02	0.56-1.73	8.3
40 to 64	3305	12.2	11.79-12.62	23.84	69	12.14	9.53–15.3	20.5	49	8.62	6.46-11.3	4.2
65 to 79	1396	16.52	15.67-17.40	37.75	20	12.34	7.78–18.7	36.2	12	7.4	4.04-12.5	9.1
≥ 80	498	18.05	16.51-19.69	58.23	3	9.64	2.67–25.7	100	0	0		
Sex												
Female	3674	8.98	8.69-9.27	31.16	75	7.7	6.10–9.60	29.4	52	5.33	4.03-6.94	7.7
Male	2095	5.23	5.01-5.45	27.26	32	3.34	2.32–4.65	16.5	21	2.19	1.40-3.28	0
Male												
< 40	218	1	0.88-1.14	19.72	3	0.5	0.14-1.34	0	3	0.5	0.14-1.34	0
40 to 64	1218	8.9	8.41-9.41	21.35	21	7.4	4.71-11.09	10	15	5.28	3.09-8.49	0
65 to 79	527	13.81	12.67-15.03	36.05	8	11.78	5.56-22.23	41.7	3	4.42	1.22-11.8	0
≥ 80	132	15.26	12.82-18.03	59.09	0	0			0	0		
Female												
< 40	352	1.68	1.51-1.86	19.32	12	2.09	1.14-3.54	25	9	1.57	0.78-2.86	11.1
40 to 64	2087	15.56	14.91-16.24	25.3	48	16.89	12.60-22.19	25.1	34	12	8.43-16.5	5.9
65 to 79	869	18.74	17.52-20.02	38.78	12	12.75	6.96-21.59	33.3	9	9.56	4.72-17.4	11.1
≥ 80	366	19.32	17.42-21.38	57.92	3	13.65	3.78-36.41	100	0	0		
Total	5769	7.12	6.94-7.31	29.75	107	5.53	4.56–6.66	25.5	73	3.78	2.98-4.72	5.6

[a] *during hospitalization;*
[b] *within 30 days, using Kaplan-Meier survival analysis*

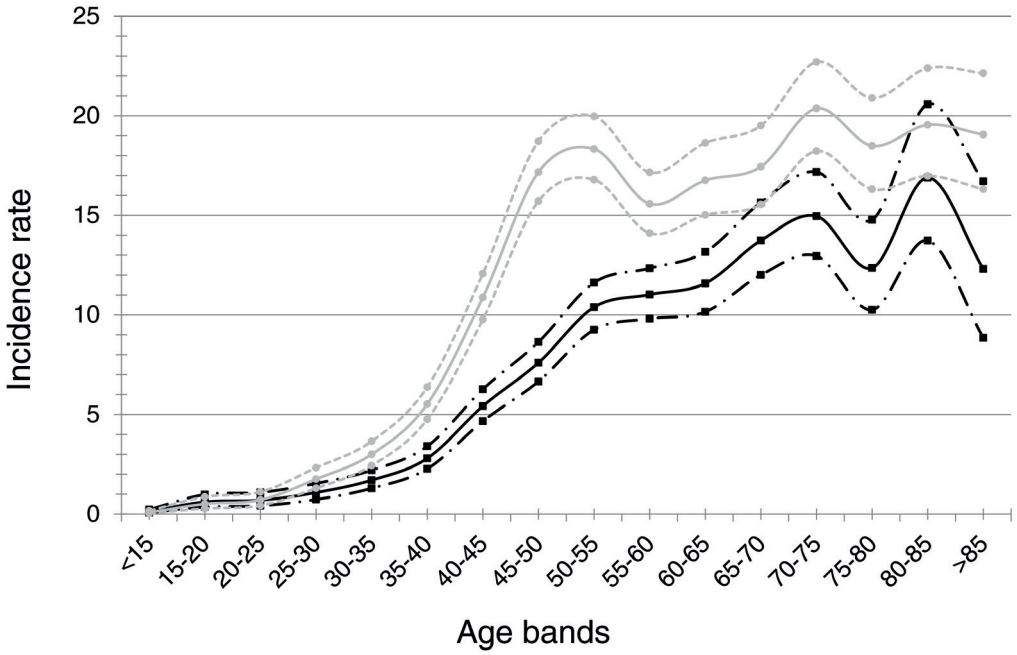


Figure 1. *Sex Specific Incidence Rates of SAH in 5-year age bands in LRM data. Solid lines are estimated rates, dashed lines the 95% confidence bands; grey line for women, black line for men*

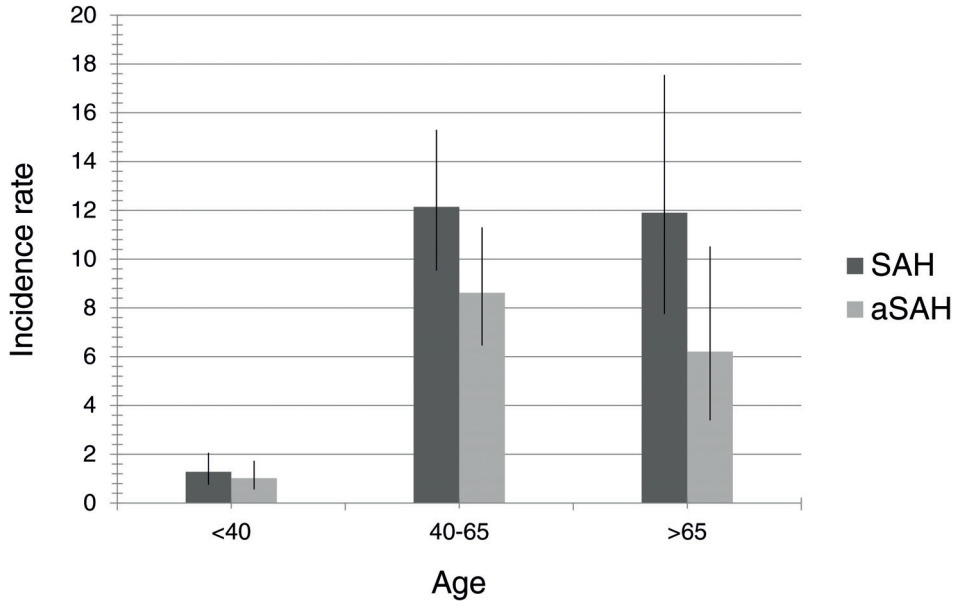


Figure 2. *Non-traumatic SAH and aSAH incidence rate by age (IPCI database)*

Table 2. Published incidence rates of non-traumatic SAH, overall and in sex strata

		All		Female		Male		All	
1st author	**Year**	**IR**	**95% CI**	**IR**	**95% CI**	**IR**	**95% CI**	**case-fatality**	**95% CI**
De Rooij[3]	2007	9.1	8.8-9.5	-	-	-	-	-	-
	2007[a]	10.5	9.9-11.2	11.5	10.6-12.6	9.2	8.4-10.2	-	-
Benatru[19]	2006	2.12[f,g]	1.04–3.21	-	-	-	-	26.1[c]	10.6–55.5
Feigin[20]	2006	10	8.0-12.0	10	7.0-13	10	7.0-13	-	-
Jiang[21]	2006	1.6[d]	0.8–4.1	1.5[d]	0.6–6.7	1.6[d]	0.6–6.5	-	-
Johansen[22]	2006	9	-	10	-	6	-	27.5[c]	25.5-29.5[b]
Labovitz[23]	2006	9.7	7.5–12.0	10.4	-	9	-	26.0[c]	16-40[b]
Engberg[24]	2007	13.6	-	-	-	-	-	22.7[e]	19.8-25.8[b]
Kozak[25]	2007	27	26-28	33	32-35	20	19-21	26.7	25.2-28.3
Smeeton[26]	2007	6[h]	5.0-8.0	-	-	-	-	-	-
Ishikawa[27]	2008	-	-	54.4	-	25.6	-	-	-
Islam[28]	2008	7[f]	4.0–12.0	7	3.0–15	7	3.0–16	25[c]	0.5–49.5
Koffijberg[17]	2008	12.4	12.2-12.6	14.4	14.2-14.7	10.3	12.2-12.6	31.7[c]	30.9-32.5[b]
Vaartjes[29]	2008	7.9[b]	7.4-8.3[b]	9.9	9.2–10	5.7	5.2–6.3	-	-
EROS[30]	2009	-	-	3.3[g]	0.7-9.2	4.8[g]	1.5-11.4	-	-
Sridharan[31]	2009	4.2[i]	2.2-6.1	-	-	-	-	-	-

[a] *Subset of 18 studies, reporting incidences for men and women separately*
[b] *Calculated from data in article*
[c] *Case-fatality within 28 days*
[d] *Beijing population only*
[e] *Case-fatality within 14 days*
[f] *Most recent period only*
[g] *Standardized to EU population*
[h] *White population only*
[i] *Age adjusted*

matic subarachnoid haemorrhage'. The overall nationwide incidence rate of non-traumatic SAH was 7.12 per 100,000 person-year (PY) (95% CI: 6.94-7.31) (Table 1). The incidence rate rapidly increased with age (Table 1, Figure 1). The overall incidence rate ratio (IRR) of SAH for women compared to men was 1.72 (95% CI: 1.63-1.81). This differential risk occurred gradually and was most pronounced in the fourth and fifth decade (Table 1, Figure 1). Case-fatality for SAH during hospitalization was 30% (95% CI: 29-31%), and increased with age, but did not differ between males and females (Table 1).

IPCI database: non-traumatic SAH and aSAH

In the initial source population of 488,118 persons, 107 incident cases of non-traumatic SAH (70% female) were identified after validation (Table 1). Based on these data the observed crude rate was 5.53 per 100,000 PY (95% CI:

4.56–6.66) (Table 1), which translates to a rate of 6.48 per 100,000 PY in the Netherlands after standardization to the Dutch age and sex distribution. The incidence rate increased with age and was similar to the LMR rates up until 64 years; rates were lower after that (Table 1).

In 68% of all IPCI derived non-traumatic SAH cases (*n*=73) an aneurysm had been diagnosed (95% CI: 59-76%). The proportion of aneurysms as cause of non-traumatic SAH diminished with age, although the trend is not statistically significant (Figure 2).

The crude observed incidence rate of aSAH was 3.78 per 100,000 PY (95% CI: 2.98–4.72), which would imply a rate of 4.26 per 100,000 for the Dutch population (age and sex standardized). Of the patients with an aneurysm the majority was treated by means of a neurosurgical clipping procedure (64%, 95% CI: 53-74%) and 26% (95% CI: 17-37%) by means of endovascular coiling. Five patients (7%) did not receive any treatment because of rapid deterioration and death. In the remaining 3% we could not find information on procedures.

Kaplan-Meier survival analysis showed that 26% of SAH patients died within 30 days (95% CI: 17-34%) (Table 1). Case-fatality in aSAH patients was 5.6% (95% CI: 0.31-10.9) (Table 1). Risks could not be estimated in separate treatment groups due to low numbers.

Discussion

We used two different population based databases: a hospital discharge database and an electronic medical record database to assess the occurrence, treatment, and case-fatality of non-traumatic SAH and aSAH in the Netherlands. We used both sources to profit from the size in the LMR and the quality of information and validation opportunities in the IPCI database. By using these data, we revealed various important observations: first, the crude national incidence rate of SAH was between 5 and 7 cases per 100,000 PY, putting the Netherlands in the low incidence countries. Second, about 70% of non-traumatic SAHs were of proven aneurysmal origin and this varied slightly by age (lower in high ages). Third, case-fatality of non-traumatic SAH was high: around 26% within one month and this increased with age. Fourth, a striking age and gender pattern was observed in the incidence rates. The incidence rates increased rapidly after age 40, but mostly so for women. Fifth, the incidence rates for aSAH increased less rapidly with age than for non-traumatic SAH overall, suggesting a difference in the percentage of aneurysms by age. Sixth, the majority of persons with an aSAH underwent surgical clipping.

Our findings on the rates and case-fatality were similar to previously published population-based studies from other countries. However, often the rates for aSAH are not available. The assumption that 85% of non-traumatic SAH is based on aneurysms, may therefore not hold true and certainly not for all age categories. Some of the previous studies have investigated sex specific rates and age-gender interaction, and also reported higher rates in women; however, the age dependent change in incidence for women compared to men was reported few times. The reasons for the overall higher incidence in women are not clear, but hormonal factors would be a first logical option.[10-11] Our finding that the preponderance of women becomes evident around the menopause, during which changes in oestrogen levels take place, further supports this suggestion. Previously, an increase in cardiovascular risk among women after menopause has been recognized,[12] for which declining endogenous oestrogen levels have been held responsible.[13] Declining levels of oestrogen might lead to impaired activation of nitric oxide,[14] which is hypothesized to be an important factor in the aetiology of SAH through its effects on the vascular endothelium.[15-16]

Being based on observational data the results of our study should be interpreted in the light of potential limitations, such as selection bias

and information bias. Selection bias in assessment of rates and case-fatality is negligible in this study since we used population based databases. Selection may have occurred because validation of the discharge diagnoses for the LMR was done only in our hospital. Results of this validation may not be generalizable to all other centres. Thus, the most important limitation is misclassification of the outcome. For a patient to be considered a case in our study, the diagnosis non-traumatic SAH had to be made. Patients who died before reaching medical care were not included in the LMR estimate and it is highly likely that they were also missed in the IPCI database due to lack of a proper diagnosis and specialist information. Previous studies have estimated the percentage of persons dying outside hospitals to be between 11 and 13%.[17-18] This means that the true incidence is potentially 10% higher than in our estimations (up to 8 per 100,000 PY). Another potential limitation is the accuracy of the registered diagnosis in the LMR database. Validation of discharge diagnoses in our own hospital showed that 10% of the cases were false positive (data not shown). Inclusion of these false positive cases in incidence estimates would lead to overestimation. In the IPCI database, false positives were unlikely, since cases were validated. In both databases, false negative misclassification has not been quantified. We think it is limited in the IPCI database as we applied a very sensitive search on codes and free text to identify potential cases and reviewed all potential cases manually.

Misclassification of mortality was an issue in the LMR database. Since the database only captures data during hospitalizations and is not linked to a death registry, it is not possible to obtain mortality data of patients once they are discharged from the hospital. We therefore chose to report on the mortality during hospital admission only. Nonetheless, the case-fatality is comparable to the case-fatality as estimated from the IPCI database that does capture follow-up and mortality data. This implies that most cases die often immediately and mostly during hospitalization. Case-fatality of aSAH patients is remarkably low and may not represent true fatality of an aneurysmal SAH (Table 1). Severe cases may have died before undergoing imaging; in that case an aneurysm could not be proven. Less severe cases will probably have survived the 30-day period.

The strength of this study is that two separate databases were used to address not only non-traumatic SAH but also aSAH. Both are observational and our study showed that they can be used complementary. Discharge databases are large which allows for fine stratification, but medical record databases allow for depth and more clinical insight. Together they have provided thorough insight in the occurrence, case-fatality, and treatment of non-traumatic (a)SAH.

Conclusion

In this study, we showed non-traumatic SAH incidence in the Netherlands is in the range of the low-incidence countries. We demonstrated that the incidence for both SAH and the subgroup of aSAH depends highly on age and sex but the patterns for aSAH might be slightly different than for non-traumatic SAH overall.

References

1. Van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. Lancet. 2007;369(9558):306-18.

2. Hop JW, Rinkel GJ, Algra A, et al. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. Stroke. 1997;28(3):660-4.

3. De Rooij NK, Linn FH, van der Plas JA, et al. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry. 2007;78(12):1365-72.

4. Rinkel GJ, van Gijn J, Wijdicks EF. Subarachnoid hemorrhage without detectable aneurysm. A review of the causes. Stroke. 1993;24(9):1403-9.

5. Sluzewski M, Brilstra EH, van Rooij WJ, et al. Bilateral vertebral artery balloon occlusion for giant vertebrobasilar aneurysms. Neuroradiology. 2001;43(4):336-41.

6. Choi DS, Kim MC, Lee SK, et al. Clinical and angiographic long-term follow-up of completely coiled intracranial aneurysms using endovascular technique. J Neurosurg. 2010;112(3):575-81.

7. Nussbaum ES, Madison MT, Goddard JK, et al. Peripheral intracranial aneurysms: management challenges in 60 consecutive cases. J Neurosurg. 2009;110(1):7-13.

8. Van der Lei J, Duisterhout JS, Westerhof HP, et al. The introduction of computer-based patient records in The Netherlands. Ann intern med. 1993;119(10):1036-41.

9. Vlug AE, van der Lei J, Mosseveld BM, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods inf med. 1999;38(4-5):339-44.

10. Longstreth WT, Nelson LM, Koepsell TD, et al. Subarachnoid hemorrhage and hormonal factors in women. A population-based case-control study. Ann intern med. 1994;121(3):168-73.

11. Mhurchu CN, Anderson C, Jamrozik K, et al. Hormonal factors and risk of aneurysmal subarachnoid hemorrhage: an international population-based, case-control study. Stroke. 2001;32(3):606-12.

12. Kannel WB, Hjortland MC, McNamara PM, et al. Menopause and risk of cardiovascular disease: the Framingham study. Ann intern med. 1976;85(4):447-52.

13. Colditz GA, Willett WC, Stampfer MJ, et al. Menopause and the risk of coronary heart disease in women. N Engl J Med. 1987;316(18):1105-10.

14. Caulin-Glaser T, Garcia-Cardena G, Sarrel P, et al. 17 beta-estradiol regulation of human endothelial cell basal nitric oxide release, independent of cytosolic Ca2+ mobilization. Circ res. 1997;81(5):885-92.

15. Ozum U, Bolat N, Gul E, et al. Endothelial nitric oxide synthase gene [G894T] polymorphism as a possible risk factor in aneurysmal subarachnoid haemorrhage. Acta neurochirur (Wien). 2008;150(1):57-61; discussion 62.

16. Risselada R, Straatman H, van Kooten F, et al. Withdrawal of statins and risk of subarachnoid hemorrhage. Stroke. 2009;40(8):2887-92.

17. Koffijberg H, Buskens E, Granath F, et al. Subarachnoid haemorrhage in Sweden 1987-2002: regional incidence and case fatality rates. J Neurol Neurosurg Psychiatry. 2008;79(3):294-9.

18. Huang J, van Gelder JM. The probability of sudden death from rupture of intracranial aneurysms: a meta-analysis. Neurosurgery. 2002;51(5):1101-5; discussion 1105-7.

19. Benatru I, Rouaud O, Durier J, et al. Stable stroke incidence rates but improved case-fatality in Dijon, France, from 1985 to 2004. Stroke. 2006;37(7):1674-9.

20. Feigin V, Carter K, Hackett M, et al. Ethnic disparities in incidence of stroke subtypes: Auckland Regional Community Stroke Study, 2002-2003. Lancet neurol. 2006;5(2):130-9.

21. Jiang B, Wang WZ, Chen H, et al. Incidence and trends of stroke and its subtypes in China: results from three large cities. Stroke. 2006;37(1):63-8.

22. Johansen HL, Wielgosz AT, Nguyen K, et al. Incidence, comorbidity, case fatality and readmission of hospitalized stroke patients in Canada. Canadian J Cardiol. 2006;22(1):65-71.

23. Labovitz DL, Halim AX, Brent B, et al. Subarachnoid hemorrhage incidence among Whites, Blacks and Caribbean Hispanics: the Northern Manhattan Study. Neuroepidemiology. 2006;26(3):147-50.

24. Engberg AW, Teasdale TW. [Epidemiology of non-traumatic brain injury of sudden onset in Denmark 1994-2002]. Ugeskr for laeger. 2007;169(3):204-8.

25. Kozak N, Hayashi M. Trends in the incidence of subarachnoid hemorrhage in Akita Prefecture, Japan. J Neurosurg. 2007;106(2):234-8.

26. Smeeton NC, Heuschmann PU, Rudd AG, et al. Incidence of hemorrhagic stroke in black Caribbean, black African, and white populations: the South London stroke register, 1995-2004. Stroke. 2007;38(12):3133-8.

27. Ishikawa S, Kayaba K, Gotoh T, et al. Incidence of total stroke, stroke subtypes, and myocardial infarction in the Japanese population: the JMS Cohort Study. J Epidemiol. 2008;18(4):144-50.

28. Islam MS, Anderson CS, Hankey GJ, et al. Trends in incidence and outcome of stroke in Perth, Western Australia during 1989 to 2001: the Perth Community Stroke Study. Stroke. 2008;39(3):776-82.

29. Vaartjes I, Reitsma JB, de Bruin A, et al. Nationwide incidence of first stroke and TIA in the Netherlands. Eur J Neurol. 2008;15(12):1315-23.

30. Heuschmann PU, Di Carlo A, Bejot Y, et al. Incidence of stroke in Europe at the beginning of the 21st century. Stroke. 2009;40(5):1557-63.

31. Sridharan SE, Unnikrishnan JP, Sukumaran S, et al. Incidence, types, risk factors, and outcome of stroke in a developing country: the Trivandrum Stroke Registry. Stroke. 2009;40(4):1212-8.

Chapter 3.3

A nationwide study of three invasive treatments for trigeminal neuralgia

J.S.H.A. Koopman, L.M. de Vries, J.P. Dieleman,

F.J. Huygen, B.H.C. Stricker, M.C.J.M. Sturkenboom

Published in Pain, 2011

Mar;152(3):507-13. doi: 10.1016/j.pain.2010.10.049.,

PubMED PMID: 21239113

Abstract

Background

Invasive procedures for treatment of trigeminal neuralgia (TGN) include percutaneous radiofrequency thermocoagulation (PRT), partial sensory rhizotomy (PSR) and microvascular decompression (MVD). Using a nationwide discharge registry from the Netherlands, we assessed the frequency of use, patient characteristics and evaluated treatment failure for each patient undergoing PRT, PSR or MVD from January 2002 through December 2004.

Methods

Only patients without a procedure in the year prior were included. Primary outcome was readmission for repeat procedures for TGN or known complications within one year. Comparability of patient populations was assessed through propensity scores based on hospital, age, sex and comorbidity. Conditional logistic regression matched on propensity score was used to calculate relative risks (RR) with 95% confidence intervals (95% CI) for repeat procedures or complications.

Results

During the study period, 672 patients with TGN underwent PRT, 39 underwent PSR and 87 underwent MVD. Hospital type was the predominant determinant of procedure type; age, sex and comorbidity were weak predictors. The RR for repeat procedures for PSR was 0.21 [95% CI: 0.07; 0.65] and for MVD 0.13 [95% CI: 0.05; 0.35] compared to PRT (RR 1). For complications, the RR of PSR was 5.36 [95% CI: 1.46; 19.64] and of MVD 4.40 [95% CI: 1.44; 13.42].

Conclusion

Sex, urbanization and comorbidity did not influence prognosis but hospital and surgical volume did. In conclusion, although PSR and MVD are associated with a lower risk of repeat procedure than PRT, they seem to be more prone to complications requiring hospital readmission.

Trigeminal neuralgia is a severe form of facial pain presenting with paroxysmal, unilateral pain in one or more branches of the fifth cranial nerve.[1] It has an estimated annual incidence of 12.6 per 100,000 person-years.[2] It can be either idiopathic or secondary to diseases such as tumors, infarction and multiple sclerosis.[3] Idiopathic trigeminal neuralgia is currently hypothesized to be caused by neurovascular contact between an aberrant vein or artery and the fifth cranial nerve at the root entry zone.[4] The three most common invasive modalities for the treatment of idiopathic trigeminal neuralgia are microvascular decompression (MVD), partial sensory rhizotomy (PSR) and percutaneous radiofrequency thermocoagulation (PRT). During MVD a teflon patch is placed between the nerve and vascular structure using an open brain surgical approach.[5] Partial sensory rhizotomy and PRT are both destructive techniques aiming to destroy a part of Gasserians ganglion by respectively a neurosurgical or a minimal invasive röntgen-guided approach.[6] Other possible procedures include glycerol injections, gamma-knife radiosurgery and balloon decompression. All procedures lack evidence of efficacy in randomized controlled trials.[7]

Partial sensory rhizotomy is sometimes used as an alternative for MVD if arterial contact cannot be found, but it is also an open neurosurgical procedure with risks comparable to those of MVD.[8] Although guidelines exist suggesting a longer duration of pain freedom after MVD compared to PRT, this advice should be regarded as an expert opinion.[9-10] A literature study describing long term outcomes of individual treatment modalities indicate that MVD has a better effectiveness than PRT, but also a higher rate of adverse events.[11] Studies included in this review concerned mainly cohort studies of individual procedures with more than five years of follow-up. These studies, however, have not been performed in one data source and therefore do not allow for a direct comparison of procedures.

At present the frequency of use of the individual invasive treatment modalities for trigeminal neuralgia in daily practice is not known and comparisons of the safety and effectiveness of the different treatment modalities on a population-based scale are lacking. Direct comparisons between the treatment modalities using one data source have not been reported. Furthermore, reports on prognostic factors for the success rate of individual treatment modalities remain contradictory.[12] To describe the frequency of use of MVD, PSR and PRT and to compare the complication and failure rate of these modalities on a nationwide scale, we performed a cohort study using a database with hospital discharge diagnoses with complete coverage of the population in the Netherlands.

Materials and methods

Source population

Data were retrieved from a nationwide electronic database with hospital discharge records, that covers admissions in all general and university medical centers in the Netherlands (Landelijke Medische Registratie). The database includes, among others, demographics, date of admission and discharge, main intervention (coded), medical specialist (coded) and the main and secondary diagnoses at discharge, based on the ICD-9-CM coding system.[13] Characteristics of hospitalizations are recorded by medical specialists or residents and coded by professional code clerks on the basis of hospital discharge letters. For every admission, one discharge/main diagnosis (mandatory), and up to nine secondary diagnoses (optional) are registered. This is done similarly for interventions. The coding is independent of reimbursement of hospital or specialist. Patients and hospitals are anonymized to allow for secondary use and processing of the data. All diagnoses are submitted in the same format, mostly electronically.

The database used for this study comprised data from 1 January 2001 up to and including 31 December 2005. More recent data are not available due to a change in the registration system in the Netherlands, which has resulted in incompleteness of the registry after 2005.

Cohort definition

For incidence rate calculations, the study base comprised the entire population of the Netherlands during the study period between 1 January 2002 and 31 December 2004. For all other analyses, we generated a cohort of patients admitted for MVD (ICD-9 codes: 5-014.0), PSR (intervention code (ICD-9 codes): 5-014.1, 5-014.2) or PRT (ICD-9 codes: 5-043.2) all with trigeminal neuralgia as main diagnosis during the study period. Patients who had one of the procedures in the year prior to study entry were excluded from the cohort. Each cohort member was followed until the earliest of one of the following events: admission for a complication, repeat procedure (any of the three studied) or end of a one-year follow-up period, whichever came first.

Outcome definition

The primary outcome parameters in this study were frequency of use, plus complications and treatment failure leading to hospital readmission within one year of the initial admission. Complications included hospitalizations for hearing loss, dysaesthesia, persistent neurological deficit, death, cerebrospinal fluid leakage, facial hypaesthesia, meningitis, ataxia, heamatoma, infarctions, pulmonary embolisms, herpes labialis, vertigo, tinnitus, an- or hypacusis, facial spasms, trochlear and acoustic palsy, facial paresis, severe brain damage, keratitis, sensory loss, corneal hypaesthesia, arteriovenous fistula, bleeding, loss of sight, corneal anesthesia, facial asymmetry and all ICD-9 codes specifically specifying complications of procedures (appendix 1).[5, 8, 11, 14-20] Complications were identified based on the ICD-9 codes of the main or secondary diagnoses. Treatment failure was defined as a readmission for one of the studied procedures for treatment of trigeminal neuralgia or for other reasons (e.g. pharmacological treatment) with trigeminal neuralgia mentioned as primary or secondary diagnosis. The index date for complications and failure was the date of hospital admission.

In addition to readmission rates for first complication or repeat procedure, we examined the duration of hospital stay of the initial procedure (index hospitalization) and in-hospital mortality of the index hospitalization as secondary outcomes. To evaluate complications and treatment failure after discharge, patients were linked by patient number (same hospital) and gender, date of birth and postal code (other hospitals).

Covariates

We considered the patient related (age, sex, urbanization level, comorbidity, specialism performing the procedure) and hospital related variables (surgical procedure volume per hospital, type of hospital) as potential confounders and prognostic factors. These factors might be related to treatment choice and outcome based on either clinical judgment or literature. Urbanization was chosen since it might reflect the accessibility to health care providers in the direct neighbourhood. The year prior to the index hospitalization was used to assess the presence of comorbidity (leading to hospital admission) on the basis of discharge diagnoses during that year. Comorbidity was categorized according to the Charlson comorbidity index adapted for ICD-9 CM.[21, 22] During the study period, there were 105 hospitals in the Netherlands, of which eight were university medical centers. To compare the experience with a specific procedure between hospitals we classified the surgical volume (i.e. number of procedures performed) for each procedure in each hospital into quintiles. Quintiles were based on the distribution of surgical volumes in the population. A surgical

volume category of one meant that the hospital belonged to the 20% hospitals with the lowest surgical volume in a certain procedure (including zero procedures). A score of five meant that the hospital belonged to the group of 20% hospitals with the highest surgical volume. The scores related to the three different procedures were then added together in one overall score ranging from 3 to 15, under the assumption that all types of procedures add to the experience of hospitals and surgeons.[14] Urbanization of the home address was evaluated using postal code data from Statistics Netherlands.[23] Very urban indicated more than 2500 houses per squared kilometer. Moderately urban is between 1500 and 2500, normal between 1000 and 1500, moderately rural between 500 and 1000 and very rural below 500 houses per squared kilometer.

Analysis

For each treatment modality, we calculated the incidence rate by dividing the number of procedures by the total Dutch population for that year according to Statistics Netherlands.[23]

Failure and complication risks were calculated for each type of intervention at 1 month, 1-2 months, 2-3 months and 3-12 months after the initial hospitalization by Kaplan-Meier analysis. Rates of failure and complication were calculated by dividing the number of readmissions by the total number of person years (patients could count multiple times). 95% Confidence intervals (95% CI) were calculated based on a binomial distribution.

To study whether we could compare outcomes between treatment groups we calculated propensity scores for each procedure with PRT as reference category.[24] Overlapping propensity scores of different procedures would indicate comparable treatment groups allowing for calculation of relative risks for complications and repeat procedures. Propensity scores were calculated for each procedure separately. The following variables were included in the model: the Charlson comorbidity score, sex, age and the type of treating hospital using logistical regression analysis. The final propensity score included all of these covariates for all procedures. Since we expected the treating hospital to be a very large predictor for type of procedure, we calculated a second propensity score model including age, sex and chronic disease score. Conditional logistic regression with matching on propensity score (including age, sex and comorbidity within bins of 0.1) was used to yield relative risks (RR) for PSR and MVD. Percutaneous radiofrequency thermocoagulation was taken as reference category. A Cox proportional hazards model was used to analyze prognostic factors for treatment failure.

A sensitivity analysis was performed including only specific complications described in literature (all of the above except the ICD-9 codes specifically specifying complications of procedures).[5, 8, 11, 14-20] Furthermore, to ensure complications were due to the index hospitalization and not due to other interventions after the index hospitalization a sensitivity analysis was performed in patients without hospitalizations between the index hospitalization and the first complication. Further sensitivity analyses included only patients operated in 2004, taking into account only complications and readmissions stated as primary discharge diagnosis (not as additional diagnoses). Hospitalization data only provide information on in-hospital death and death may impact on the failure rates. Therefore, we conducted a survival analysis with imputed survival data to take into account deaths occurring during follow-up. Survival data was imputed using the age and gender specific mortality data of the general Dutch population from 2003 as provided by Statistics Netherlands (CBS).[23] Imputation of survival data was done using R (version 2.7.12) (R Development Core Team, Vienna, Austria).[25] Five possible dates of death were imputed based on age and gender. The Kaplan Meier analyses were redone using this imputed sur-

Table 1. Baseline characteristics

	Percutaneous radiofrequency thermocoagulation (PRT)	Partial sensory rhizotomy (PSR)	Microvascular decompression (MVD)	Total posterior fossa approach	*p*-value[a]
n	672	39	87	126	-
Incidence rate / 1.000.000 persons per year [95% CI]	13.8 [12.8; 14.9]	0.8 [0.6; 1.1]	1.8 [1.4; 2.2]	16.4 [15.3; 17.6]	
Average age (SD)	67.3 (12.9)	58.0 (14.0)	57.8 (13.0)	57.9 (13.2)	<0.01
Male sex (%)	288 (42.8%)	15 (38.5%)	43 (49.4%)	58 (46.0%)	0.50
Mean duration of first Admission (SD)	1.52 (1.52)	10.44 (6.55)	7.59 (2.55)	8.47 (4.39)	<0.01
Urbanization					0.97
Very urban	107 (16.2%)	9 (23.1%)	10 (11.8%)	19 (15.3%)	
Moderately urban	148 (22.4%)	14 (35.9%)	13 (15.3%)	27 (21.8%)	
Normal	122 (18.4%)	10 (25.6%)	16 (18.8%)	26 (21.0%)	
Moderately rural	150 (22.7%)	6 (15.4%)	22 (25.9%)	28 (22.6%)	
Very rural	135 (20.4%)	0 (0.0%)	24 (28.2%)	24 (19.4%)	
Comorbidity index[b]					0.31
0 (%)	640 (95.2%)	39 (100.0%)	85 (97.7%)	124 (98.4%)	
1 (%)	21 (3.1%)	0 (0.0%)	1 (1.1%)	1 (0.8%)	
2 (%)	4 (0.6%)	0 (0.0%)	1 (1.1%)	1 (0.8%)	
3 (%)	7 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Type of specialist					<0.01
Neurosurgeon (%)	70 (10.4%)	39 (100.0%)	86 (98.9%)	125 (99.2%)	
Anesthesiologist (%)	601 (89.4%)	0 (0.0%)	0 (0.0%	0 (0.0%)	
Other (%)	1 (0.2%)	0 (0.0%)	1 (1.1%)	1 (0.8%)	
Type of hospital					<0.01
General (%)	653 (97.2%)	12 (30.8%)	37 (42.5%)	49 (38.9%)	
Academic (%)	19 (2.8%)	27 (69.2%)	50 (57.5%)	77 (61.1%)	

Between square brackets, the 95% confidence interval is given; [a] chi-square analysis for categorical analysis, t-test for continuous variables; [b] The comorbidity index is based on the Charlson comorbidity score

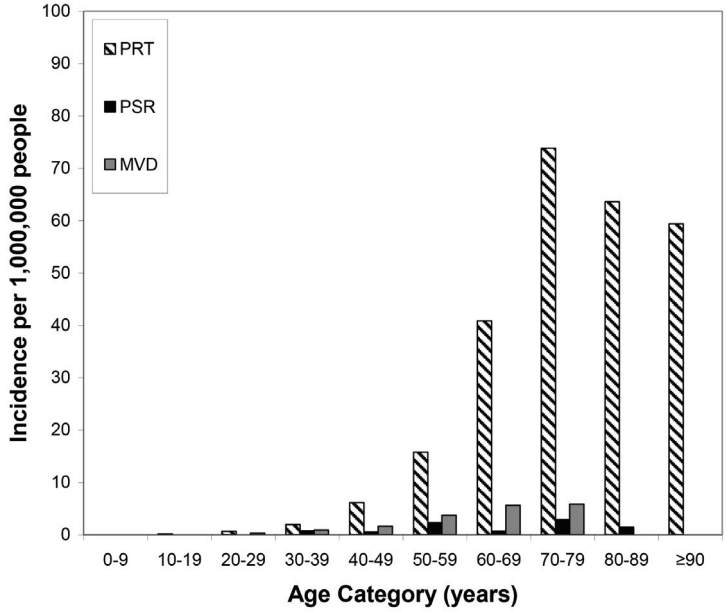
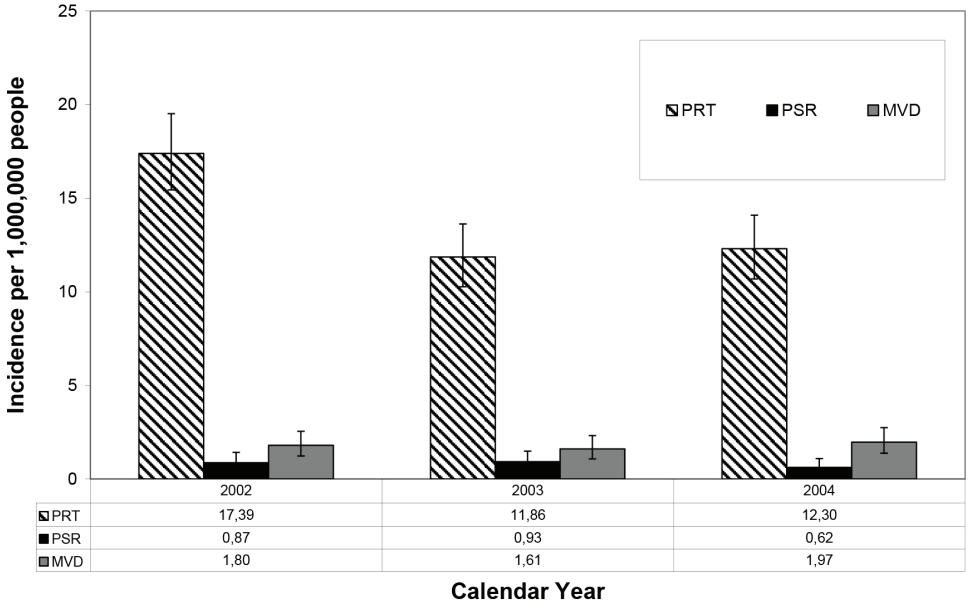


Figure 1A. *Incidence of individual treatments. The incidence per 1000,000 people per age category in The Netherlands. Treatments are applied more in older people, which is to be expected because the incidence of trigeminal neuralgia increases with age. Neurovascular treatment is not used after the age of 80.*



	2002	2003	2004
PRT	17,39	11,86	12,30
PSR	0,87	0,93	0,62
MVD	1,80	1,61	1,97

Figure 1B. *Incidence rate per calendar year. The y-error bars display the 95% confidence interval. The incidence rate of most treatment modalities is more or less stable over time. PRT, percutaneous radiofrequency thermocoagulation; PSR, partial sensory rhizotomy; MVD, microvascular decompression.*

vival data. In compliance with the method of multiple imputations the rates and the standard errors were averaged.[26] All statistical analyses were conducted in SPSS 15.0 (SPSS, Inc, Chicago, IL,USA).

Results

Incidence

Between 1 January 2002 and 31 December 2004, 87 MVD, 39 PSR and 672 PRTs were performed. The incidence rate of the three studied invasive procedures for trigeminal neuralgia in the Dutch population was 16.4 per million persons per year (95% CI: 15.3; 17.6) (Table 1). The rates were highest between the age of 70 and 79 for all procedures and the rate remained more or less stable over calendar time (Figure 1A and B).

Baseline characteristics

Patients undergoing an intervention for trigeminal neuralgia during the study period were on average 65.8 years of age (SD 13.4) and a minority was male (43%) (Table 1). Patients were generally healthy with a mean Charlson comorbidity index of zero. The average number of procedures performed per hospital per year was 5.54 (SD 8.94). Percutaneous radiofrequency thermocoagulation was the most widely applied procedure with a high average relative surgical volume level compared to that of PSR and MVD (1.17, 0.44 and 0.31 procedures per hospital respectively). Finally, patients undergoing PRT were on average older and had a shorter hospital stay than patients admitted for the other procedures. There were large differences in hospital and physician characteristics between the three procedures (Table 1).

Complications / therapeutic failure

In total, 33.8% of patients were readmitted for a repeat procedure (2.4%) or a complication (31.6%) within one year following the initial procedure (Table 2). The one-year readmission risk derived from Kaplan-Meier analysis was 34% (95% CI: 30% to 37%) for all procedures together. The one-year readmission risk was lowest with MVD (9%, 95% CI: 3% to 15%) and highest for PRT (38%, 95% CI: 34% to 42%) (Table 2, Figure 2).

Most complications occurred within the first month (31.6%) after the initial procedure. The risk of complications was lowest for PRT (2% vs 8% and 6%). The majority of complications were unspecific procedure complication codes (61%). Specified complications included Bell's palsy (11%), infections (5%), anaphylactic shock (6%), hemiplegia (6%), aspiration (6%), hematoma (6%) and respiratory complications (6%). Most repeat procedures took place between the third and ninth month (36.5%) after the initial procedure.

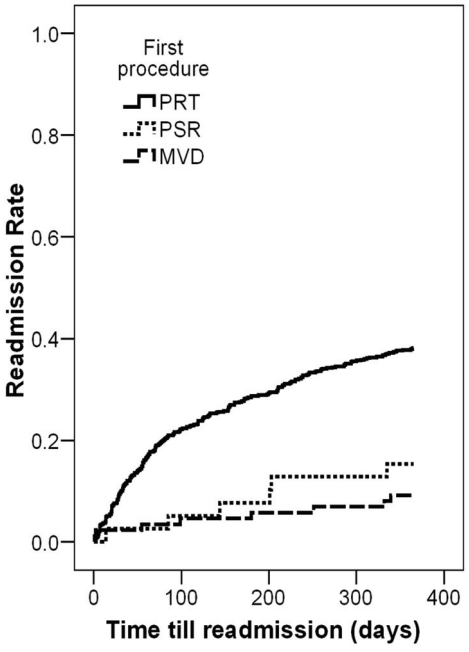


Figure 2. *Survival curve. Of the 3 studied treatment modalities, the percutaneous radiofrequency thermocoagulation had the highest risk of readmission. PRT, percutaneous radiofrequency thermocoagulation; PSR, partial sensory rhizotomy; MVD, microvascular decompression.*

Table 2. Characteristics of readmissions following initial procedure for trigeminal neuralgia

	PRT	PSR	MVD	Total
Readmission total (%)	256 (100%)	6 (100%)	8 (100%)	270 (100%)
Complication (%)	11 (4.3%)	3 (50.0%)	5 (62.5%)	19 (7.0%)
Repeat procedure (%)	245 (95.7%)	3 (50.0)	4 (37.5%)[a]	252 (93.0%)[a]
Repeat procedure				
Percutaneous Radiofrequency Thermocoagulation (%)	196 (80.0%)	0 (0.0%)	2 (50.0%)	198 (78.6%)
Partial Sensory Rhizotomy (%)	2 (0.8%)	2 (66.7%)	1 (25.0%)	5 (2.0%)
Microvascular Decompression (%)	6 (2.4%)	0 (0.0%)	1 (25.0%)	7 (2.8%)
Other or unspecified (%)[b]	41 (16.7%)	1 (33.3%)	0 (0.0%)	42 (16.7%)
One-year readmission risk[c]	38 [34-42]	15 [4-27]	9 [3-15]	34 [30-37]
One-year complication risk[c]	2 [1-3]	8 [0-16]	6 [1-11]	3 [2-4]
One-year risk for repeat procedure[c]	37 [33-41]	8 [0-17]	5 [0-9]	32 [29-35]

This table displays the prevalence and type of readmission within one year according to type of initial procedure for trigeminal neuralgia
PRT, Percutaneous radiofrequency thermocoagulation
PSR, Partial sensory rhizotomy
MVD, Microvascular decompression
[a] *There is one patient admitted for both a repeat procedure and a complication*
[b] *Admission for trigeminal neuralgia without a specific intervention listed. A reason for readmission without intervention can be drug treatment*
[c] *Calculated by using Kaplan-Meier analysis with days from discharge until readmission as follow-up time. Between square brackets are the 95% confidence intervals. SD = standard deviation*

A propensity score model based on hospital, age, sex and comorbidity could accurately predict which treatment was given (c statistic 0.99). There was, however, poor overlap. If hospital was excluded from the propensity score the model performed worse (c-statistic 0.70) but there was considerable overlap showing that actually the hospital was important for the decision which treatment to perform and not so much the patient. After matching on propensity score (not considering hospital), the relative risk of PSR for readmission (both complications or repeat procedures) was 0.40 [95% CI: 0.18 to 0.90], 5.36 [95% CI: 1.46 to 19.64] for complications and 0.21 [95% CI: 0.07 to 0.65] for repeat procedures. Microvascular decompression had a relative risk of 0.25 [95% CI: 0.12 to 0.52] for total readmission, 4.40 [95% CI: 1.44 to 13.42] for complications and 0.13 [95% CI: 0.05 to 0.35] for undergoing a repeat procedure. Most people undergoing a PRT underwent a PRT as repeat procedure, whereas most people undergoing a PSR underwent this procedure again as repeat procedure. In contrast, after MVD most people had a PRT as second procedure (Table 2).

Sensitivity analyses considering only patients operated in 2004, or only healthy patients (Charlson comorbidity index of zero), or only in literature specified complications, or only main diagnoses or using imputed survival data showed that the results and conclusions did not materially change (p>0.05).

Concerning our secondary outcomes; the admission duration of the index hospitalization was 2.62 days (SD 3.38). No patients died during hospital stay (95% CI: 0.0% to 0.4%).

Table 3. Prognostic factors

	PRT	PSR	MVD	Total
Age	0.92 [0.72-1.18]	1.30 [0.24-7.08]	7.18 [0.88-58.39]	1.01 [0.79-1.28]
Sex	1.01 [1.00-1.02]	0.96 [0.00-1.02]	1.00 [0.95-1.05]	**1.01 [1-1.02]**
Comorbidity index				
0	Ref	NA	Ref	Ref
1	1.21 [0.62-2.36]	NA	0.05 [0.00-∞]	1.33 [0.68-2.58]
2	**4.19 [1.34-13.12]**	NA	0.05 [0.00-∞]	2.92 [0.94-9.13]
3	0.73 [0.18-2.92]	NA	NA	0.85 [0.21-3.4]
Hospital				
University	Ref	Ref	Ref	Ref
General	**4.56 [1.13-18.32]**	0.03 [0-32.85]	**10.35 [1.27-84.12]**	**4.81 [2.47-9.34]**
Surgical volume				
1	Ref	NA	Ref	Ref
2	**1.49 [1.06-2.08]**	Ref	98257.15 [0.00-∞]	**1.54 [1.1-2.16]**
3	0.76 [0.33-1.78]	0.85 [0.05-13.68]	86540.31 [0.00-∞]	0.8 [0.38-1.68]
4	0.94 [0.60-1.48]	NA	NA	0.99 [0.63-1.56]
5	**1.50 [1.04-2.15]**	1.42 [0.15-13.64]	NA	**1.53 [1.07-2.2]**
6	0.49 [0.23-1.02]	0.19 [0.01-3.05]	15163.02 [0.00-∞]	0.29 [0.17-0.52]
Urbanization				
Very urban	Ref	Ref	Ref	Ref
Moderately urban	0.97 [0.66-1.44]	0.59 [0.08-4.20]	0.70 [0.10-4.99]	0.94 [0.64-1.36]
Normal	0.84 [0.55-1.29]	0.43 [0.04-4.80]	0.86 [0.14-5.16]	0.82 [0.54-1.22]
Moderately rural	0.88 [0.59-1.31]	0.68 [0.06-7.55]	0.20 [0.02-2.19]	0.82 [0.56-1.2]
Very rural	0.89 [0.59-1.33]	NA	0.00 [0.00-∞]	0.8 [0.54-1.19]

In bold are the statistically significant predictors of treatment failure
Ref is reference category, NA is not available (no cases in that group)
PRT, Percutaneous radiofrequency thermocoagulation
PSR, Partial sensory rhizotomy
MVD, Microvascular decompression

Prognostic factors

Sex, age, comorbidity, surgical volume, urbanization and hospital (aggregated) were evaluated as prognostic factors for treatment failure. Cox regression analysis, stratified by the type of first procedure showed surgical volume and type of hospital to be associated with failure (Table 3). Only the second and fifth group of surgical volume were associated with an increased risk of failure (OR: 1.54 (95% CI: 1.10 to 2.16) and 1.53 (95% CI: 1.07 to 2.20) respectively). However, no clear volume-success relationship (i.e. dose-effect) could be shown. Being treated in a general hospital was associated with an increased risk of failure (OR: 4.81 (95% CI: 2.47 to 9.34) compared to being treated in

a university hospital. There was no relationship between the comorbidity index, gender, age and being admitted for complications.

Discussion

This study showed that PRT was the most frequently applied invasive procedure for trigeminal neuralgia with 13.8 procedures per 1 million person-years per calendar year. The rate of invasive procedures did not materially change over time. Given an estimated prevalence of trigeminal neuralgia in the Netherlands of 1600 per 1 million persons approximately 1% of persons with trigeminal neuralgia undergo a first invasive procedure each year.[27] The type of procedures performed were strongly hospital, age and specialist dependent. Partial sensory rhizotomy and MVD were more likely to be carried out in specialized centers than PRT. Percutaneous radiofrequency thermocoagulation was mostly performed by anesthesiologists while PSR and MVD were almost exclusively carried out by neurosurgeons. One MVD procedure was performed by an ear/nose/throat specialist, although this might have reflected a coding error. One would expect the duration of stay to be similar for PSR and MVD since they are both neurosurgical procedures. The difference might be due to a lower efficacy or less familiarity of the treating specialist (or hospital) with the procedure. This latter might be reflected by the considerable difference in the absolute number of operation performed. Another noteworthy finding was the high degree of patients readmitted for unspecified repeat procedures. These might reflect patients being admitted for drug treatment. One would expect less PSRs being performed since these are usually reserved for patients in which no neurovascular contact could be shown. These operations might be performed in patients who underwent a previous destructive procedure thus lowering the success rate of MVD. This is less likely since we selected patients who were treatment naïve in the year preceding the index hospitalization. Alternatively, these patients might be selected based on absence of neurovascular contact. Given the spread in estimates of the presence of this contact, this might be plausible.[28-30]

Microvascular decompression had the lowest relative risk for readmission (either complications or repeat procedures), mainly because of a lower risk for repeat procedures. Microvascular decompression had, however, a higher complication risk compared to PRT. Readmission was not associated with sex, urbanization and comorbidity, which is in line with previous reports.[31] It was, however, positively associated with surgical volume (low and high) and receiving treatment in a general hospital. A previous paper reported a higher complication rate in hospitals and surgeons with a lower caseload.[32] Our finding that a lower caseload is associated with readmission is in line with this study. The association between a higher caseload and readmittance might occur because more severe or complicated patients are referred to the hospitals with a high caseload. Our finding that younger patients more frequently underwent MVD is in line with current practice.[33] This is presumably due to the allegedly longer effect of MVD and presence of comorbidity in older patients which makes it difficult to conduct that intervention.[33]

Percutaneous radiofrequency thermocoagulation showed the lowest absolute complication rate but the highest failure rate which is in line with recent reviews.[11-12, 20, 34- 35] One study compared MVD to PRT and reported an equal effect but a lower long-term complication rate for MVD.[36] Our study shows a difference in effect, but this may be because we only assessed serious complications requiring a readmission, which do not represent the total range of adverse events. Assuming that neurosurgical interventions

have a higher percentage of adverse events requiring hospitalization, this will lead to a selective underestimation favoring PRT. The high failure rate of PRT might have several reasons. Compared to MVD which is usually performed by experienced neurosurgeons, PRT is also performed by less experienced doctors. Furthermore, to avoid anesthesia dolorosa, doctors will be careful to apply too much coagulation. They prefer to conduct the operation in two stages instead of risking adverse events. The low complication rate of PRT is especially noteworthy since it is more often performed in high risk (older) patients.

Limitations

Being an observational study using a hospital registry we must consider the influence of potential misclassification and confounding. There are several sources of misclassification. Firstly, the failure rate may be an underestimation, since not every failure requires readmission as some recurrences may be treated conservatively. Our study did not focus on failure that could be addressed in an outpatient setting. Furthermore, it could be higher since patients dissatisfied after a procedure might not undergo a repeat procedure. Given the lower effectiveness of PRT, this might give rise to an underestimation of the relative risk for readmittance. Secondly, admission for complications after the intervention may have been the result of other hospitalizations during follow-up, this issue was explored by exclusion of patients with other hospitalization during follow-up. This did not change the results substantially. Thirdly, since the database only captures in-hospital deaths and not the outpatient deaths, people dying the year after readmission are lost to follow-up and cannot count in the numerator which may lead to an underestimation of risks. Due to differences in age, this is less likely to happen for MVD and more for the other interventions. People undergoing a MVD are younger and thus less likely to die out of the hospital. To minimize this bias, we imputed age and gender specific survival data from the general Dutch population, the relative risk estimated did not change substantially.

The fourth limitation of our study is the low number of prognostic variables and the lack of specific prognostic factors such as disease severity. We evaluated the type of hospital (university or general) as a proxy for disease severity, duration of pain etc., under the assumption that the patient population of university hospitals (tertiary centers) would differ from those of general hospitals (secondary centers). Previous destructive surgery, a known risk factor for an unfavorable outcome of MVD and PSR, could not be considered in our analyses since we only had one year of history available.[5, 8] Patients undergoing a destructive procedure in that year were excluded from the analysis to minimize possible confounding. To further limit residual confounding due to the fact that we had limited prior history data we performed a sensitivity analysis amongst people undergoing a procedure in 2004. For these persons, we had three years of prior history, the results in these patients were consistent with the main analysis showing that residual confounding due to a short availability of information is limited. Several factors are known to be prognostic factors for failure of (neurosurgical) procedures for trigeminal neuralgia. These include having a clear-cut and marked vascular compression at surgery, type of vessel compressing, duration of complaints, involvement of all three branches and postoperative pain relief.[8, 20, 31, 37-38] Unfortunately these could not be evaluated given the nature of our database. Despite its limitations the results of our study are unique in that they capture a large nationwide study sample which provides a comprehensive overview of the application of invasive procedures for trigeminal neuralgia in daily practice. The study further gives a valid estimate of the absolute and relative risks (com-

plications requiring admission) and effectiveness (re-admission for repeat procedure) of individual surgical procedures in patients with trigeminal neuralgia. Previous reports showing a higher success rate of MVD compared to PRT have now been confirmed in a single data source. Finally, we have shown that the choice for a certain treatment modality is, at least in the Netherlands, largely institutionalized practice and not based on a nationwide consensus.

Appendix

ICD-9	Complication
389	Hearing loss
34981	Cerebrospinal fluid rhinorrhea
7820	Disturbance of skin sensation
38861	Cerebrospinal fluid otorrhea
322	Meningitis of unspecified cause
321	Meningitis due to other organisms
320	Bacterial meningitis
047	Meningitis due to enterovirus
7813	Lack of coordination
368	Visual disturbances
998	Other complications of procedures, NEC
997	Complications affecting specified body systems, not elsewhere classified
996	Complications peculiar to certain specified procedures
054	Herpes simplex
7804	Dizziness and giddiness
3883	Tinnitus
3510	Bell's palsy
37853	Fourth or trochlear nerve palsy
3885	Disorders of acoustic nerve
78194	Facial weakness
854	Intracranial injury of other and unspecified nature
370	Keratitis
9961	Mechanical complication of other vascular device, implant, and graft
37181	Corneal anesthesia and hypoesthesia
V410	Problems with sight
E870	Accidental cut, puncture, perforation, or hemorrhage during medical care
E871	Foreign object left in body during procedure
E878	Surgical operation and other surgical procedures as the cause of abnormal reaction of patients, or of later complication, without mention of misadventrue at the time of operation
E879	Other procedures, without mention of misadventure at the time of procedure, as the Cause of abnormal reaction of patient, or of later complication
9954	Shock due to anesthesia
9950	Other anaphylactic shock
C2939	Unspecified transient mental disorder in conditions classified elsewhere
C3209	Meningitis due to unspecified bacterium
C3229	Meningitis, unspecified
C3429	Hemiplegia, unspecified
C3682	Diplopia
C3899	Unspecified hearing loss
C4340	Cerebral thrombosis
C5070	Due to inhalation of food or vomitus
C5990	Urinary tract infection, site not specified
C9973	Respiratory complications
C9981	Hemorrhage or hematoma or seroma complicating a procedure
C9985	Postoperative infection

References

1. Detailed description of pain syndromes. Book Detailed description of pain syndromes. City, 2006. pp. April 29, 2008.

2. Koopman JS, Dieleman JP, Huygen FJ, et al. Incidence of facial pain in the general population. Pain. 2009;147(1-3): 122-27.

3. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004;24 Suppl 1:9-160.

4. Krafft RM. Trigeminal neuralgia. American family physician. 2008;77(9):1291-96.

5. Jannetta PJ. Microsurgical management of trigeminal neuralgia. Arch Neurol. 1985;42(8):800.

6. Zakrzewska JM, Lopez BC, Kim SE, et al. Patient reports of satisfaction after microvascular decompression and partial sensory rhizotomy for trigeminal neuralgia. Neurosurgery. 2005;56(6):1304-11; discussion 1311-2.

7. Zakrzewska JJM, Linskey ME. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. Cochrane Database Syst Rev. 2011 Sep 7;(9):CD007312.

8. Young JN, Wilkins RH. Partial sensory trigeminal rhizotomy at the pons for trigeminal neuralgia. J Neurosurg. 1993;79(5):680-87.

9. Cruccu G, Gronseth G, Alksne J, et al. AAN-EFNS guidelines on trigeminal neuralgia management. Eur J Neurol 2008;15(10):1013-28.

10. Gronseth G, Cruccu G, Alksne J, et al. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. Neurology. 2008;71(15):1183-90.

11. Tatli M, Satici O, Kanpolat Y, et al. Various surgical modalities for trigeminal neuralgia: literature study of respective long-term outcomes. Acta Neurochir (Wien). 2008;150(3):243-55.

12. Toda K. Operative treatment of trigeminal neuralgia: review of current techniques. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106(6):788-805, 805 e781-86.

13. Kupka K. International classification of diseases: ninth revision. WHO chronicle. 1978;32(6):219-25.

14. Jannetta PJ. Neurovascular compression in cranial nerve and systemic disease. Ann Surg. 1980;192(4):518-25.

15. Kolluri S, Heros RC. Microvascular decompression for trigeminal neuralgia. A five-year follow-up study. Surg Neurol. 1984;22(3):235-40.

16. Linskey ME, Jho HD, Jannetta PJ. Microvascular decompression for trigeminal neuralgia caused by vertebrobasilar compression. J Neurosurg. 1994;81(1):1-9.

17. McLaughlin MR, Jannetta PJ, Clyde BL, et al. Microvascular decompression of cranial nerves: lessons learned after 4400 operations. J Neurosurg. 1999;90(1):1-8.

18. Sweet WH, Wepsic JG. Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers. 1. Trigeminal neuralgia. J Neurosurg. 1974;40(2):143-156.

19. Taha JM, Tew JM, Jr., Buncher CR. A prospective 15-year follow up of 154 consecutive patients with trigeminal neuralgia treated by percutaneous stereotactic radiofrequency thermal rhizotomy. J Neurosurg. 1995;83(6):989-993.

20. Tronnier VM, Rasche D, Hamer J, et al. Treatment of idiopathic trigeminal neuralgia: comparison of long-term outcome after radiofrequency rhizotomy and microvascular decompression. Neurosurgery. 2001;48(6):1261-67; discussion 1267-68.

21. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

22. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45(6):613-19.

23. Dutch statistics. Book Dutch statistics, Vol. 2009. City. pp. January 1, 2009.

24. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med. 1997;127(8 Pt 2): 757-63.

25. R Development Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2008.

26. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. Stat Med. 1991;10(4):585-98.

27. Sjaastad O, Bakketeig LS. The rare, unilateral headaches. Vaga study of headache epidemiology. J Headache Pain 2007;8(1):19-27.

28. Lorenzoni J, David P, Devriendt D, et al. Patterns of neurovascular compression in patients with classic trigeminal neuralgia: A high-resolution MRI-based study. Eur J Radiol. 2009.

29. Voros E, Palko A, Horvath K, et al. Three-dimensional time-of-flight MR angiography in trigeminal neuralgia on a 0.5-T system. Eur Radiol. 2001;11(4):642-47.

30. Yamakami I, Kobayashi E, Hirai S, et al. Preoperative assessment of trigeminal neuralgia and hemifacial spasm using constructive interference in steady state-three-dimensional Fourier transformation magnetic resonance imaging. Neurol Med Chir (Tokyo). 2000;40(11):545-55; discussion 555-6.

31. Sindou M, Leston J, Decullier E, et al. Microvascular decompression for primary trigeminal neuralgia: long-term effectiveness and prognostic factors in a series of 362 consecutive patients with clear-cut neurovascular conflicts who underwent pure decompression. J Neurosurg. 2007;107(6):1144-53.

32. Kalkanis SN, Eskandar EN, Carter BS, et al. Microvascular decompression surgery in the United States, 1996 to 2000: mortality rates, morbidity rates, and the effects of hospital and surgeon volumes. Neurosurgery. 2003;52(6):1251-61; discussion 1261-2.

33. Kabatas S, Albayrak SB, Cansever T, et al. Microvascular decompression as a surgical management for trigeminal neuralgia: a critical review of the literature. Neurol India. 2009;57(2):134-38.

34. Spatz AL, Zakrzewska JM, Kay EJ. Decision analysis of medical and surgical treatments for trigeminal neuralgia: how patient evaluations of benefits and risks affect the utility of treatment decisions. Pain. 2007;131(3):302-10.

35. Broggi G, Ferroli P, Franzini A. Treatment strategy for trigeminal neuralgia: a thirty years' experience. Neurol Sci. 2008;29 Suppl 1:S79-82.

36. Laghmari M, El Ouahabi A, Arkha Y, et al. Are the destructive neurosurgical techniques as effective as microvascular decompression in the management of trigeminal neuralgia? Surg Neurol. 2007;68(5):505-12.

37. Barker FG, 2nd, Jannetta PJ, Bissonette DJ, et al. The long-term outcome of microvascular decompression for trigeminal neuralgia. N Engl J Med. 1996;334(17):1077-83.

38. Li ST, Pan Q, Liu N, et al. Trigeminal neuralgia: what are the important factors for good operative outcomes with microvascular decompression. Surg Neurol. 2004;62(5):400-4; discussion 404-5.

Chapter 4

General discussion

An estimated number of 500,000 different medical devices are available on the European market, of which over 900 different types of implants.[1-2] However, as Europe is considered one internal market, individual countries are not always informed on the type and number of implants available on their national markets.[3] In Europe, medical devices have to comply with the Council Directive on Medical Devices, 93/42/EEC and active implantable devices with Council Directive on Active Implantable Medical Devices, 90/385/EEC.[4-5] Both will be replaced by a new Regulation on Medical Devices, which entered into force in May 2017 and will fully apply in 2020.[6] The European legislation establishes essential requirements for design, production, clinical investigation and evaluation, risk assessment, conformity assessment and post-market surveillance. Implants are considered high risk medical devices and in Europe must undergo a conformity assessment procedure by a notified body which includes audits of the production facilities, an evaluation of the technical file, a design examination, appraisal of the clinical evidence, and assessment of the risk analysis.[4-6] These steps in the life cycle of medical devices are depicted in Figure 1.

Before market-entry a manufacturer shall assess what the expected performance of an implant will be. Depending on the type of implant, these include characteristics such as expected longevity, wear and tear, calculated risks, foreseen complications and in case of active implants also available ancillary functions, programming, battery longevity, et cetera. Compliance to essential requirements for safety and performance must be substantiated by clinical evidence, which can comprise of a critical appraisal of available literature, bench testing, animal testing, clinical investigation or a combination of these activities.[7] These Directives not always require clinical trials; if substantial equivalence to a previously approved device can be proven, a critical appraisal of literature may suffice. However, for implantable devices and class III devices (highest risk class) clinical investigation is required, unless it is duly justified to rely on existing data.[4-5]

Contrary to medicinal products, regulatory oversight of medical devices puts more emphasis on post-market surveillance than on pre-market clinical studies. This has several reasons. There is a large number of medical devices on the market, which are more complex than drugs, more diverse and product development is more iterative combined with a relatively short product life cycle. In addition, there is a learning curve associated with technology adoption.[8-11] Even more important, clinical trials may not identify all risks and complications with implants, especially when they are rare or occur after several years of usage. This requires a larger group of study subjects than generally available in order to reach sufficient statistical power. Additionally, such studies tend to be expensive and would take many years, time that is not available for innovative technologies.[12-13] Other disadvantages are that investigators may be well trained and familiar with the device's characteristics and application. Trials are often conducted in an idealized physical environment and in a carefully selected population that can deviate from the population in which the device is actually used in the post-marketing phase. Additionally, physicians may use devices for other indications than those for which the clinical evaluation has been performed.[9-10, 14, 18] Therefore, clinical investigations have limitations and ongoing clinical evaluation and collection of post-market data after market-entry is essential.

Results from the analysis of post-market surveillance information should be used as feedback in a continuous cycle of improvement of the device, providing input for design improvements, risk analysis updates and adjustments of the instructions for use.[19] As some risks become apparent only after regular and/or long term clinical use, any unexpected malfunctions

may require more regular follow-up or even premature explantation. Legislation therefore requires manufacturers to actively follow their products during the post-market phase, investigate any unexpected events and report malfunctions to competent authorities in several countries. However, besides the mandatory reporting of incidents, legislation does not clearly describe which and how post-market surveillance activities should be performed.

A well-functioning post-market surveillance process depends on information sharing. However, the Dutch Health Care Inspectorate has observed that health care professionals and institutions are – often by order of their lawyers – reluctant to provide information or return defective medical devices to the manufacturer when they are involved in a litigation procedure, or the threat thereof. This hampers the PMS-process, which in the end is not beneficial for patients.

Recent major incidents with ICD leads, metal-on-metal hip implants, breast implants and vaginal mesh have led to a focus on device safety by media, politics and patients. Recurring questions in that context are: how many patients have received an involved implant and how to prevent such events in the future. This information is also relevant for competent authorities overseeing the medical devices field and regulations. In many countries, including the United States of America and Canada, initiatives were taken to improve the post-market surveillance of devices.[14-15, 20-22] In Europe, it is part of the revised legislation.[6] Meanwhile and pending the transitional phase from old to new legislation, an action plan has been established to strengthen the current legislative system. Following the major incidents in recent years the importance of maintaining registries is increasingly recognized. Establishing these implant registries is part of the joint action plan.[23] National device registries may contain relevant data to identify products with a lower than expected reliability and allows immediate identification of patients treated with specific models of implants in case of alerts or recalls from manufacturers, as was proven in Denmark for pacemakers and electrodes and Sweden regarding several orthopaedic implants.[12, 24] As such, the output of device registries is important for the quality chain of medical devices on one hand and for tracking and tracing purposes of patients on the other hand, notably when inadequate implants are involved. That is why efforts are being made by national governments to establish registries on implantable medical devices.

The main objective of this thesis is to examine the usability of a number of currently available and accessible registries for information on implant performance and complications of implant therapy. The current chapter first summarizes the main findings of the studies described in this thesis. Second, several methodological issues related to the studies are discussed, followed by a discussion of the role of registries in (post-)marketing surveillance of implantable medical devices. The chapter finalizes with future perspectives and concluding remarks.

Main findings

CPPR-SPRN – utilization and follow-up of implantable pacemakers

Duration of service time, cause of death, reasons for replacement and complications of pacemakers provide valuable information for both cardiologists and manufacturers. When these malfunctions are registered in the implant registry, this allows for trend analysis on the performance of the devices, and as such provides input for continuing improvement of implants. A study that performed a meta-analysis on several registries, showed that they proved very useful to assess pacemaker and ICD malfunctions.[25] Therefore, we aimed to assess service time and reasons for explantation of pacemakers and leads in the Dutch registry for pacemakers.

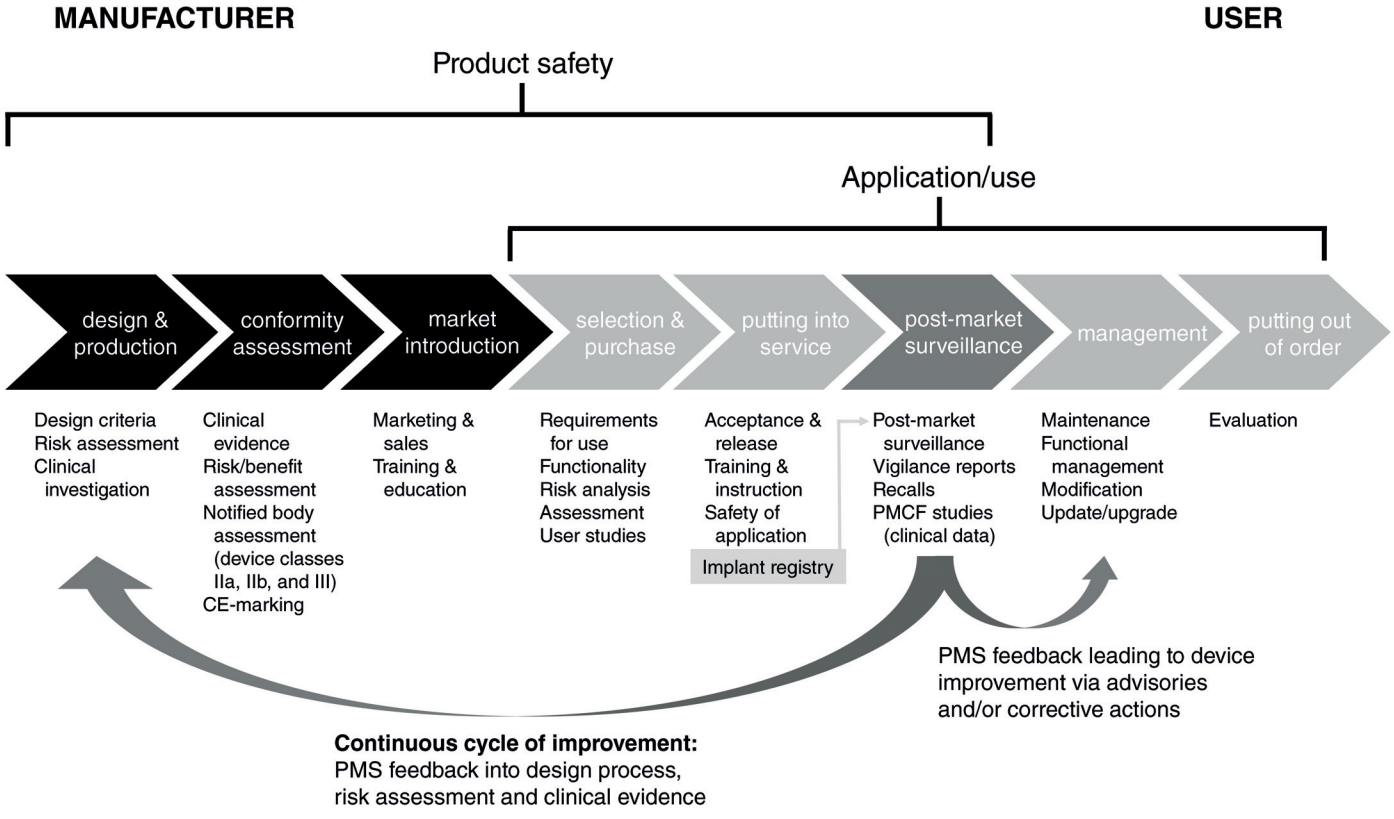


Figure 1. *Life cycle of medical devices and the continuous cycle of improvement. Based on a figure from the Dutch Health Care Inspectorate (used with permission)*

In chapter 2 we described the results of the analyses on the Central Pacemaker Patients Registration from the Netherlands Pacemaker Registry Foundation (CPPR-SPRN). This registry started in 1982 and contained data collected for more than 20 years. In chapter 2.1 we analysed pacemaker implanted between 1984 and 2006, which showed an increase in number of pacemakers used and an extension of the diagnosis for which pacemaker therapy is chosen. However, the implantation ratio in the Netherlands was below the European average. Furthermore, it showed that during the mid-1990s adaptive pacing frequencies with dual chamber systems (DDD(R) devices) were increasingly used. Around the millennium year, cardiac resynchronization therapy (CRT) was introduced, for which the data show an obvious increase in use.

In chapter 2.2 we aimed to investigate the trends in duration of service time of pacemaker generators and the reasons for explantation. We found that during the study period 22,134 patients (22.8%) had at least one pacemaker generator replacement or removal and 4350 patients (4.5%) had more than one. For approximately 1 in 5 pacemaker generators a replacement was registered. The mean duration of follow-up to pacemaker generator replacement or removal (service time) during the whole study period was 6.3 (SD 3.3) years. Nearly 20% of the explantations occurred following technical failures or complications, with insulation failures and infections being most abundant. Double chamber systems were significantly more often explanted than single chamber systems and they were also significantly more often explanted for normal 'end of life' within 5 and 7 years after implantations than single chamber systems.

Leads can be an important source of failures and complications of pacemaker therapy. Therefore, in chapter 2.3, we also studied the percentage of and reasons for explantations of leads as registered in the database. These analyses showed that 138,225 leads have been implanted with 96,900 first pacemakers, of which 8849 (6.4%) have been replaced or explanted. Main registered reasons for explantation were insulation failures, infections and displacements. Generally, in case of pacemaker generator replacement, the leads were not replaced. However, when simultaneous replacement of generator and leads occurred, this was most frequently done because of infections.

In general, the results from these chapters demonstrate that also with the older and now discontinued pacemaker registry, important information can be generated on the quality of medical devices.

LMR – national hospital discharge records database

The national hospital discharge records database was initially established for research purposes. Main advantages of this database are that it includes all admissions to Dutch academic and general hospitals and is independent of reimbursement.[26] As such, it provides a rich source of information on characteristics of hospital admissions. Since only a limited number of databases is available on medical devices and implants, we aimed to investigate treatment patterns and re-admissions for several implant-related therapies using this hospital admissions database.

In the study described in chapter 3.1 we investigated re-admissions following total hip arthroplasty (THA). A majority of the 50,080 patients admitted for THA had osteoarthritis as main diagnosis. Approximately 9% (*n*=4364) of the patients were re-admitted at least once within 3 months after the surgery, 40% of them for complications. More than half of the complications concerned mechanical problems and for another 30% an infection was reason for re-admission. A lower hospital procedure volume appeared to be associated with complications during index admissions, but

no such relation was found for re-admissions due to complications. Mortality during index admission was 0.2% and was higher during consecutive re-admissions. Having a complication appeared to be a risk factor for mortality during re-admission. Unfortunately, we did not have data on mortality of patients after they were dismissed from hospital. Therefore, the actual mortality within 3 months after surgery is unknown. Furthermore, we did not have information on the type of implant that was used or to what extent a complication was related to the implant itself.

In chapter 3.2 we studied the incidence and treatment of non-traumatic subarchnoid hemorrhage (SAH), a devastating event with high morbidity and mortality.[27-28] Based on the LMR data we found that 5769 patients were admitted to hospital for SAH as discharge diagnosis between 2001 and 2005. This corresponds to an incidence of 7.2 per 100,000 person-years (95% CI: 6.94-7.31). The main treatment options are clipping or coiling of the aneurysm. The first being an invasive neurosurgical procedure, while the latter is a less invasive endovascular procedure that can be performed by radiologists.[29] In the LMR data it appeared that coiling procedures could not be registered as such. Therefore, we were unable to compare treatment modalities based on these data. However, the Integrated Primary Care Information (IPCI) database, a general practice research database with electronic medical record data which we used for comparison, did contain information on treatment. In the initial source population of 488,118 persons, 107 incident cases of non-traumatic SAH were identified after validation. Analysis of these data showed that nearly two thirds (64%, 95% CI: 53-74%) of the patients was treated by clipping procedure and 26% (95% CI: 17-37%) were treated by endovascular coiling. The low numbers in each treatment group did not allow us to estimate the risk of mortality in each treatment group.

Finally, chapter 3.3 describes the results of our study on three most common invasive treatments for trigeminal neuralgia (TGN); microvascular decompression (MVD), partial sensory rhizotomy (PSR), and percutaneous radiofrequency thermocoagulation (PRT). We compared readmissions for repeat procedures and complications after these operations. TGN is a severe form of facial pain in one or more branches of the fifth cranial nerve.[30] During MVD a Teflon patch is introduced between the nerve and vascular structure that is in contact with the nerve, the other treatments are aimed at destruction of (part of) the nerve. In the LMR database we found 672 patients treated with PRT, 87 with MVD and 39 with PSR between January 1, 2002 and December 31, 2004. One third of the patients was readmitted within one year after surgery for either a complication (31.6%) or a repeat procedure (2.4%). The one-year readmission risk was lowest for MVD, whereas the risk for complications was lowest for PRT. After MVD most people had a PRT as repeat procedure, whereas for PSR and PRT the same procedure was performed again. The choice for procedure type appeared to be hospital dependent. Furthermore, Cox regression analysis, stratified by the type of first procedure, showed that surgical procedure volume and type of hospital were associated with failure. However, the relationship with volume only applied to the second and fifth groups of surgical procedure volume, there was no clear 'dose-effect' for the volume-success relationship.

Use of nationwide hospital admissions data proved useful for studying several types of implant-related procedures. It provides relevant information on re-admissions following complications and repeated procedures. Strengths are the nationwide coverage of the data and the coding of procedures and complications that is independent of reimbursement. Our institute also used the LMR database for several studies on adverse drug reaction-related hospi-

talizations.[31-34] However, analysis of these data proved to be most useful when other (external) data were available for linking or comparison, providing a denominator for calculating the ADR-hospitalization ratio. This data is not always available for implants and when it is, the utility depends on the availability of reliable parameters which can be used for linkage. For our studies, this appeared to be a major limitation. Furthermore, several of the ADR-studies identified the same limitations we found in our LMR based studies on implants: deaths may have occurred outside of the hospital, and adverse events may not have been recognized or were treated outside of the hospital.[31, 33-34] Finally, a limitation is that the LMR data do not contain any information on the implant that was used. This prevented us from studying associations of implant characteristics on re-admissions for complications and re-operations.

Methodological considerations

In general, the effects of medical interventions can be studied in two different ways: by (1) randomized, (double-)blind clinical trials or by (2) observational studies. In the first case, the investigators assign the treatment blinded and at random, whereas for the latter study type normal clinical practice is observed.[35] In case of clinical investigation of implants, randomized and blinded clinical trials are not always feasible or possible or may even be unethical. In such cases, observational studies are an important tool for studying the effects of devices and device therapy on disease. In the past decades, pharmaco-epidemiological studies focusing on the adverse effects of drugs have gained essential insight into the causes of adverse effects. Comparable studies with (implantable) medical devices are much more uncommon.

The epidemiological studies described in this thesis used data from two large registries: The Central Pacemaker Patients Registration from the Netherlands Pacemaker Registry Foundation (CPPR-SPRN) and the national hospital discharge records database (LMR). Both registries have been described in more detail in the respective studies and the introduction to this thesis. In this chapter, the methodological aspects of these databases and studies are discussed in more depth.

Study setting and design CPPR-SPRN

The SPRN-database was established to generate an overview of patient and implant characteristics; trends in types of pacemakers and leads; and the annual number of implants per clinic and nationwide. Additionally, the registry also served a purpose to warn hospitals in case of quality issues with pacemakers or leads.[36-38] We used the database to study the utilization of pacemakers and leads, and the service time and reasons for explantation of these devices.

Methodological strengths include the long period of follow-up of more than 20 years. Furthermore, the registry was nearly nationwide with most of the hospitals participating. Data was collected before and irrespective of the outcome, reducing the risk of information bias. A validation process to obtain better insight into the quality of the database was performed in 1997. 96% of pacemaker generators and 84% of the leads could be retrieved in the central registry when compared to patient files of participating hospitals and sales data from manufacturers.[37]

Available patient characteristics include date of birth, sex, symptoms of heart disease, diagnosis for pacemaker implantation, aetiology, date and reason of explantation of the pacemaker generator, and date and reason of death (voluntarily recorded). Additionally, several characteristics on the implanted pacemaker generators were available. Due to agreements made with manufacturers at the start of the registry we could not use brand names, therefore only the pacemaker type according to the North American Society of Pacing and Electrophysiology (NASPE) coding; VVI/VVIR, DDD/DDDR, AAI/AAIR, etc.,[39] could be included in our analyses.

Limitations of the data included the large proportion of loss to follow-up of the patients. Deaths were registered voluntarily. A validation study using data from the Rotterdam Study showed that approximately 60% of the deaths was not registered in SPRN. Age at death and implanted pacemaker type did not statistically significantly differ between the group of patients that was registered as deceased in SPRN and the group that was not. Furthermore, information on aetiology, reason of explantation, and diagnosis for implantation was unknown in the majority of cases, sometimes as high as 75% (aetiology). This reduced the usability of the data for more complex statistical analyses.

We performed three studies using the SPRN-data. Most of which had a descriptive study design. We also performed a cohort study to investigate the Cox proportional hazard rate for explantation of first pacemakers within 7 years of follow-up, between different pacemaker types with VVI-mode as reference type. This analysis calculates an accurate estimate of the relative risk with adjustment for available relevant confounding factors and competing risk of death. Selection bias is unlikely with this design, as all different exposure types were derived from the same prospective population-based cohort study.

Competing risks

We calculated the hazard ratio for pacemaker replacement adjusted for the competing risk of death as described by So et al.[40] Because deceased patients are no longer at risk for explantation, they cannot be considered as censored as the assumption that the censoring mechanism is independent of the probability of the outcome of interest (i.e. explantation), is no longer met.[41] However, as validation of mortality using the Rotterdam study showed that only an estimated 40% of deaths was registered in the SPRN-registry, the hazard ratio of pacemaker replacement is expected to be an underestimation of the true ratio because those who deceased without being censored are kept in follow-up until the end of the study period while reasons for explantation might also be causes of death.

Study setting and design LMR

The national hospital discharge records database was established in 1963. The purpose of the registry was to provide medical-administrative information regarding hospital care in the Netherlands to support governmental and hospital policy. Additionally, it could provide benchmark information to hospitals and medical specialists, but also serve research purposes.[42] Registered data include date of admission, coded main discharge diagnosis for admission (mandatory), up to 9 coded secondary diagnoses (optional), coded intervention, type of specialist who performed the intervention, date of birth of the patient, sex, and date of discharge. The diagnoses were coded using the ICD9 coding system,[43] whereas the intervention was coded using a national system. The strength of this registry is the nationwide coverage of admissions, as all hospitals provided information. The LMR was replaced by another system in 2005. At that time, reimbursed medical interventions were not yet performed in private clinics. Therefore, information on discharge diagnosis, type of intervention and outcome was available for each patient admitted to hospital.

We used this database for studies on three types of interventions: total hip arthroplasty (THA), non-traumatic subarachnoid haemorrhage (SAH) and trigeminal neuralgia (TGN) and assessed the incidence of the intervention and/or condition, and for the THA and TGN studies we also assessed re-admission due to complications within 3 months and 1 year respectively. We identified patients based on the intervention code (THA) or the discharge diagnosis (SAH and TGN). As interventions and discharge diagnoses are recorded similarly for each hospital and irrespective of reimbursement, data was collected before and irrespec-

tive of the outcome and thus not prone to information bias. Patient details are anonymized, and therefore re-admissions due to complications were linked based on date of birth, sex and postal code of the patient for the THA and TGN studies.

Anonymization of patient and hospital details had the disadvantage that validation of the data is cumbersome, or even impossible. For the SAH study we could only validate cases from our institution. This showed that for 10% the cases were false positive. For the THA study we used the Rotterdam Study by linking cases based on date of birth, sex and postal code. This validation showed that none of the procedures, diagnoses or complications were false-positive. Of the procedures, diagnoses and complications respectively 91%, 90% and 80% could be confirmed.

An additional disadvantage was that only death during admission could be included in the analyses. Furthermore, information on co-morbidity was scarcely available. We used the Charlson co-morbidity index to include co-morbidity in our analyses for the THA and TGN studies. This is a weighted index that takes the number and seriousness of co-morbidity into account. It was developed based on the 1-year mortality from an inception cohort study of 604 patients admitted to a New York hospital.[44] Diseases were assigned a weight based on their calculated relative risk for death within one year. The index appeared to be a significant predictor of 1-year survival. It was later adapted and validated for research based on databases using ICD-9-CM codes.[45] The co-morbidity index was added to the dataset as a variable, based on the ICD-9 codes provided for the secondary diagnoses fields. However, only co-morbidity for which hospitalization was required could be included as secondary diagnosis. As registration of these diagnoses was optional, information on co-morbidity was not always available.

The studies based on LMR-data are retrospective cohort studies. The THA study compared different groups of hospitals grouped by yearly volume of interventions and the effect this volume has on the occurrence of complications. As the time between the intervention and the complication during index admissions was unknown, we used logistic regression to calculate odds ratios. Similarly, the TGN study compared three treatment groups and their failure rates by analysing the re-admission rate after intervention. Prognostic factors were calculated using Cox regression analysis. Finally, the SAH study is a descriptive study, calculating the incidence and case-fatality rates of patients admitted to hospital for subarachnoid haemorrhage.

Bias and confounding

Contrary to randomized clinical trials, exposure in observational studies is decided on by doctors. Due to the lack of randomization, several (potentially) interfering factors are not controlled for. By choosing the correct study design and adjusting for the potentially interfering factors during the statistical analyses, the influence of these factors on the association found can be reduced.

The main biases that can be introduced in observational studies include selection bias, information bias and confounding. Bias undermines the internal validity of research.[46] Selection bias occurs when selection of patients in the groups that are compared coheres with the exposure or outcome. For cohort studies, this bias occurs when follow-up information is less likely to be collected on subjects who have better (or worse) outcomes.[47-48] This bias is considered negligible for the studies based on the SPRN-registry because of the population-based nature of the data. Nearly all patients receiving a pacemaker were included in the database. Contribution to the LMR-registry was obligatory for all Dutch hospitals. The completeness of the data is one of the main advantages of this registry. Exposure nor outcome is related to inclusion in both CP-PR-SPRN and LMR registries, because registration depended on having a pacemaker implanted

(CPPR-SPRN) or being admitted to hospital (LMR).

Information bias arises when collection of data on exposure and/or outcome is different for cases and controls. Examples of information bias are observer-bias, recall-bias, response-bias, classification-bias or measurement-bias.[46-47] It results from incorrect determination of exposure or outcome, or both and can be attributed to imperfect definition of a study variable or a flawed data collection procedure.[46, 48] Information on outcome should be collected in the same way for those exposed and those un-exposed (cohort studies) and data on exposure should be obtained in the same way for cases and controls (case-control studies).[46] Information bias can occur as differential or systematic misclassification or as non-differential or random misclassification. In the first case, the bias is one-directional which can lead to an over- or underestimation of the effect, whereas in the latter case misclassification is multi-directional and can obscure an association that is present.[46]

Our studies based on the CPPR-SPRN-data may contain information bias, because some hospitals did not contribute to the registry, or did not contribute during the entire study period. If these hospitals used other pacemaker types, our exposure of interest, than the hospitals included in the registry, this may have caused a bias. However, we believe that it is unlikely that the pacemaker types in these hospitals differed to a great extent. Furthermore, we do not believe that participation in the registry was related to the outcome of interest: replacement of the pacemaker generator and/or leads. Therefore, any misclassification is considered to be non-differential. Misclassification of outcome is non-differential if outcomes are assessed independently of exposure and patient co-morbidity.[47, 49] Furthermore, information bias does not apply to objective outcomes such as whether a patient with a pacemaker or hip implant required revision surgery.[48]

Information bias may have occurred in the studies based on the LMR-data. In our study on non-traumatic subarachnoid haemorrhage (SAH), we also studied case-fatality. By using the hospital discharge registry, we could only include those fatalities that occurred during hospital admission, whereas SAH-patients who died after discharge were not counted. In this case the bias may have been small, as comparison with the Integrated Primary Care Information (IPCI) database, which contains complete information on mortality, showed a similar case-fatality rate. In the total hip arthroplasty and trigeminal neuralgia studies we investigated complications during admission and re-admissions as primary outcomes. Complications that were not severe enough or led to death outside of hospital, were not included and may thus have affected incidence ratios and odds ratios. These ratios may have been an underestimation as we believe that the misclassification is random, because it is not related to the exposure.

Confounding occurs when the studied effects of exposure on the outcome of interest are altered by or blurred with the effects of other risk factors. A confounding variable is associated with both the exposure and the outcome, but is not a factor in the causational relationship between exposure and outcome.[46-48] Confounding can be controlled for by several methods before or after the study took place. Multivariate modelling by performing analysis using logistical or Cox proportional hazards regression analyses is one of these methods,[46] which has been mainly used to adjust for confounding in the studies described in this thesis. A pre-requisite is that potential confounding factors are known. Age and sex are two very common confounders, that are almost always included in multivariate statistical models. When information on such factors is available, they can be tested for their confounding effect by univariate analysis. When the point estimate changes by 10%, the factor

is considered to be a confounder by convention.[50]

In both the CPPR-SPRN and LMR databases only a limited number of potential confounders were available. Age and sex were known and included in studies on both databases. However, information on co-morbidity of patients, drug use and data on the applied implant were often not available. For example, the indication for which a pacemaker was implanted was registered and could be included in the multivariate analysis. However, several pacemaker settings were not available, whereas they are known to affect pacemaker longevity. In the LMR-database we derived co-morbidity from the secondary diagnoses of which up to nine could be registered. Registration of secondary diagnoses was optional, however, and not every hospital provided this information. Additionally, only the co-morbidity which led to (previous) hospital admissions were registered. Therefore, we were unable to completely control for confounding in the described studies, which may have affected the generalizability to other populations and thus the external validity of the studies.

Role of registries in post-market surveillance

Post-market surveillance (PMS) can provide information on the performance of a device in actual clinical care and identify risks and complications that have not yet been identified during pre-market clinical investigations. Professional societies, the medical device industry and national authorities for medical devices each have a role to play in establishing successful post-market surveillance.[51-52] Manufacturers must use information collected via PMS to update their risk analyses, product designs and clinical evidence.[7] Multiple sources for signalling of previously unidentified risks, hazards and complications are available and include: (1) post-market clinical follow-up studies, (2) (serious) adverse event reporting by health care professionals and voluntary adverse event reporting by patients, (3) annual performance reports by manufacturers, and (4) registries. However, each source of PMS has several serious challenges which are discussed below. We will pay particular attention to the usability of registries as a source for PMS.

Performing post-market clinical follow-up studies (PMCF) is a legal requirement. These are studies with CE-marked devices and intended for information collection on clinical safety and performance, including residual risks of a device which is used in accordance with its approved labelling. The objective is to confirm the clinical performance and safety throughout the expected lifetime of the device, the acceptability of identified risks and to detect emerging risks on the basis of factual evidence.[7] Limitations of clinical studies, such as relatively small samples and short follow-up, have been discussed previously.

The second source of PMS information is reporting of incidents. Manufacturers have the legal obligation to report incidents that have led or could have led to harm or death.[7] In general, reporting by health care professionals, either to competent authorities or to manufacturers, is voluntary. In the Netherlands, only those adverse events leading to serious harm or death are mandatory for health care professionals to report to the Dutch Health and Youth Care Inspectorate.[53] Less severe events and near-misses can be reported voluntarily. Structured follow-up on the performance of implants via reporting of incidents requires physicians to report malfunctions to the manufacturer of the device. Deaths and severe harm attributable to device malfunctions, but also device-related user failures, should be reported to both the manufacturer and the competent authority for medical devices in the country where the death or harm occurred.

Following the severe incidents with metal-on-metal hip prostheses and pelvic floor

repair systems containing mesh, the Inspectorate called for a facility where patients could report side-effects and adverse events that may be related to their implant.[54-55] In July 2017, a reporting and expertise centre on side-effects of implants has been established.[56] The purpose of this centre is to collect information on side-effects and complications that may be related to implants, and identify trends as early as possible. Both health care professionals and patients are invited to report. Results of the analyses are shared simultaneously with the Inspectorate and the public. This allows the Inspectorate to take regulatory measures when necessary, whereas health care professionals and manufacturers are also able to benefit from the information for their daily clinical practice and for PMS data collection respectively.[56]

While important, reporting has several limitations, the main of which is underreporting. Health care professionals are not always informed on what to report, consider the process to be burdensome, fear the consequences or are discouraged by a lack of feedback.[14, 18, 20, 22] Furthermore, statistical analysis and the determination whether reports represent a true safety signal or merely reflect an increase in reports from users are restricted because a reliable denominator – the number of implanted devices – is usually lacking.[20]

Third, information related to reporting of malfunctions that can provide a denominator is included in annual performance reports on implantable devices which the US FDA requires manufacturers to submit.[25, 57] These reports contain information on the number of implanted and explanted devices, and device malfunctions during the reporting period. This provides insight into malfunctions and trends in device reliability. While these reports without a doubt provide useful information on device performance and malfunction, they depend on health care professionals returning the device, which may not always happen.[58] When replacement of devices takes place under warranty, underreporting may be lower, because the device must be returned in order to receive a new device from the manufacturer.[59] Furthermore, the analyses of these reports do not always allow to account for explantations for other reasons than malfunction, such as infections, upgrades or recalls as they were not uniformly reported by manufacturers.[57] Moreover, devices are rarely evaluated after death of a patient with a device.[60] A study that investigated 415 pacemakers and 556 leads post-mortem for defects, revealed that 3.8% of the pacemakers had a life-threatening malfunction like a defect, battery exhaustion, ventricular lead failure, infection or bipolar sense with unipolar ventricular lead. Covering a study period of 4 years, the investigators calculated an annual complication rate of 0.95%.[61] Additionally, they found that 3.7% of the pacemakers had a potentially life-threatening malfunction such as an infection, a missing notch in ventricular leads or an indifferent screw that was not tightened. It appeared that lead defects were more frequent than generator defects.[61] Therefore, it seems feasible to undertake such studies for the purpose of collecting information on possible causal relationships between implant failures or complications and death.

The fourth source for PMS information and main focus of this discussion are registries, which present more opportunities for procedure and device-related outcomes data, and importantly: provide a denominator.[8, 20, 62] That clinical registries and remote monitoring databases have proven their added value has become clear with the recall of the Riata leads from St. Jude Medical,[52] but also international orthopaedic registries such as the Scandinavian and the Australian arthroplasty registers have successfully identified several product failures within a relatively short period of time. The Swedish arthroplasty register was the first to be established and is considered exemplary.[12, 63-64] Arthroplasty registers are

one of the most common types of registries in Europe, after registries in the field of cardiac implants.[63] In 2015 there were 11 registered nationwide arthroplasty registries worldwide.[12] However, the actual number may even be higher, since the successive Dutch cardiac implant registries were not included in this overview, and presumably other registries may not have been either.

Registries serve to inform several stakeholders like manufacturers, health care professionals, insurers and policy-makers, but can also be used for benchmarking purposes and improvement of patient management. Collaboration between these stakeholders is important for the development and maintenance of registries.[16, 62-63] Regardless of the advantages that registries have for post-market surveillance of devices, existing registries have not always served their purpose. For example, the breast implant registry in the UK took a lot of time and energy to initiate and maintain. When it came to interrogating the data, it was discovered that the dataset was so poor that no real benefit could be derived from it.[65] There are also disadvantages for several stakeholders. Besides functioning as a benchmarking tool, health care professionals may feel they are controlled. Furthermore, maintaining a registry adds to the administrative burden. Finally, registries may provide insight into the market shares of manufacturers and a ranking of their devices, which they often consider to be proprietary information.[63]

The usefulness of registries depends on the nature, size and extent of the details that are recorded. Many existing and past registries have been limited in size or limited in the number of participating centres, or were run by manufacturers individually without nationwide coverage or the ability to pool data, making it difficult to identify rare outcomes.[14-15, 66-67] Furthermore, outcomes are not only influenced by the device, but also by the surgical technique and by patient related factors.[65] Also, the purpose with which a registry was implemented may limit its use for other goals; a registry set up for tracking and tracing purposes or for measuring a particular outcome may not be suitable for other quality analyses.[65] Even cultural differences and differences in market shares of manufacturers between countries influence the generalizability of analyses on registries.[12]

Despite these drawbacks it is expected that the number and extent of registries will increase, partly due to the new European regulation.[64] In the United States, registries are considered to play a unique and prominent role in medical devices surveillance and the FDA believes that, within the boundaries of privacy protection, registries in selected product areas combined with routinely collected electronic health information containing unique device identification should serve as the foundation of a national medical device post-market surveillance system.[11]

Recognizing the strength of pooling data from smaller national registries, a plan was launched by the FDA in 2010: The International Consortium of Orthopedic Registries (ICOR). The purpose of ICOR is to provide a robust infrastructure to facilitate evidence-based decision-making on the performance of medical devices, by aligning several national registries and thus add to the knowledge of implant performance in order to support clinicians, device regulators, insurers, patients and industry.[8, 68] The Nordic Arthroplasty Register Association (NARA) is a major contributor to ICOR. This initiative compares registries from Norway, Sweden, Denmark and Finland. It pooled the data from the available national registries, which allowed comparison of different treatment strategies because of different treatment traditions among the countries. By combining the registries, numbers are high enough to compare implants and techniques.[69]

The data holders participating in ICOR remain owner and maintain full control of their data. They can contribute to studies they select by harmonizing data definitions and the processes for data collection and storage. Such inter-

national collaborations require agreements on data definitions, data collection procedures, and methods for making comparisons between interventions and overcome the limitations of individual registries. Particularly the device capture and classification at a level that allows device evaluation and assessment is critical. The minimum data set for device data collection is based on a unique device identifier (UDI). ICOR identified different stages at which collaboration with decentralised approaches is possible.[8, 68]

Some of the registries contributing to ICOR work together with their regulatory authorities, such as the Australian regulators, the MHRA in the UK and the FDA in the US. The integration of work of the registries into the regulatory process is considered helpful for advancing regulatory science.[8] Based on the ICOR initiative a similar international collaboration in the field of cardiovascular device evaluation and surveillance was considered for transcatheter aortic valve replacement (TAVR). The Dutch TAVR register is one of the participants.[70] The importance of registries in the field of medical devices is underlined by the International Medical Device Regulators Forum (IMDRF), a global co-operation in which several international markets are represented, including Europe. IMDRF drafted a proposed document on the essential principles of patient registries.[71] They define a registry as: *"An organized system with a primary aim to improve the quality of patient care that continuously collects relevant data, evaluates meaningful outcomes and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale (e.g. international, national, regional, and health system)"*.[71]

IMDRF envisages international collaboration to undertake medical device safety and performance evaluations, based on strong registries and collaborative distributed data consortia. International experience with devices can be brought together by various participating countries, while all countries may benefit from the results. Furthermore, IMDRF sees an essential role for regulators to initiate the engagement of their national registries.[71]

Future perspectives

Major device failures and recalls have highlighted the need for registries for 1) tracking and tracing of implants to a patient level, and 2) for quality assessment and performance data. For the first purpose, the Dutch government has set up an implant registry in cooperation with professional societies in the areas of orthopaedics, cardiology, plastic surgery and gynaecology. During the course of 2018, health care professionals and institutions will be obliged by Dutch legislation to cooperate with this governmental national implant registry.[72-73] However, as this registry serves tracking and tracing of implants following recalls or serious failures alone,[74-75] it is not intended nor suitable as a quality registry.

The current implant registries from the professional societies of four major health care specialties are more suitable for that purpose. Besides for traceability, they have been established for monitoring implant use, and complication registration. They include registries for cardiac implantable electronic devices – the National Cardiavascular Data Registry (NCDR);[75-76] orthopaedic implants – the Dutch Arthroplasty Register (Landelijke Registratie Orthopedische Implantaten – LROI);[75, 77] gynaecological implants such as mesh for pelvic organ prolapse – POMT; [72, 78] and breast implants – Dutch Breast Implant Registry (DBIR), which is also part of the international ICOBRA initiative.[75, 79] However, these registries are not accessible for authorities nor industry and some of them have only been established recently following incidents. Furthermore, only a limited number of high risk implants is registered and although the percentage of coverage is high, it is not yet nationwide.[75]

In terms of devices, the Netherlands is a relatively small market. This puts forward the question whether Dutch registries alone will obtain enough power to identify rare failures and complications for individual device types and models. Therefore, the Netherlands may benefit form participation in international collaborations and vice versa.

Furthermore, past observational studies regarding product use have mainly focused on complications of drugs, whereas such studies on implants have been limited. In addition to clinical investigations, post-market follow-up studies and registries, we also recommend that observational studies for surveillance of medical devices are set-up. Critical condition for such studies is the number of included subjects in order to have enough power for statistically significant associations that are clinically relevant. Registries may fulfil a need here as a source for study cohorts, while simultaneously providing a reliable denominator.

Finally, in several other countries such as Australia, the United Kingdom and United States, regulators are engaged in registry consortia, as is also envisaged by the International Medical Devices Regulators Forum. Whereas the Dutch authorities are involved in the National Implant Registry (LIR) aiming at tracking and tracing of implants, they are not involved in the clinical quality registries. A closer cooperation between stakeholders would be beneficial for the generation and use of market surveillance data.

Concluding remarks

Randomised clinical trials with implants are not always an option for reasons described in this chapter. Medical registries, in particular those dedicated to implants, can therefore be a useful tool for providing information on implant and patient characteristics, but also on clinical evidence and post-market surveillance data, such as safety, performance and complications. Despite the results we have obtained with the studies described in this thesis, the existing registries we have used have been established for other purposes. For the current need of information on device performance, these registries are no longer state-of-the-art. This underlines the importance of *a priori* definition of the purpose of the registry and data needed to be captured. When set-up according to pre-defined criteria and goals, registries can provide sufficient data and a denominator needed to draw clinically relevant conclusions. Additionally, national registries can deliver benchmarking information for clinicians, but since the Dutch market is relatively small, adherence to international collaborations for device evaluation and surveillance data is advisable. Finally, it is not only important that device registries are able to detect device problems early, but also provide the data that is necessary to guide patient care.

References

1. Http://www.gmdn.org. Last accessed: June 13, 2017.

2. MedTech Europe. The European medical technology industry in figures. http://www.medtecheurope.org/sites/default/files/resource_items/files/MEDTECH_FactFigures_ONLINE3.pdf Last accessed: 7 July 2017.

3. Cohen, D. Europeans are left to their own devices. BMJ. 2011;342:d2748.

4. Council Directive of 20 June 1990 on the approximation of the laws of the Member States relating to implantable medical devices. 90/85/EEC. Available via: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX-:01990L0385-20071011&from=EN. Last accessed: 4 August 2017.

5. Council Directive of 14 June 1993 concerning medical devices. 93/42/EEC. Available via: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:01993L0042-20071011&from=EN. Last accessed: 4 August 2017.

6. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. Available via: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2017:117:FULL&from=EN. Last accessed: 4 August 2017.

7. MEDDEV 2.7/1 rev. 4. Clinical evaluation: Guide for manufacturers and notified bodies. June 2016.

8. Sedrakyan A, Paxton EW, Phillips C, et al. The international consortium of orthopaedic registries: overview and summary. J Bone Joint Surg Am. 2011;93 Suppl 3(E): 1-12.

9. Resnic, FS, Normand SL. Postmarketing Surveillance of Medical Devices – Filling in the gaps. N Engl J Med. 2012;366(10):875-7.

10. Blake, K. Postmarket surveillance of medical devices: current capabilities and future opportunities. J Interv Card Electrophysiol. 2013;36:119-27.

11. FDA. Strengthening our national system for medical device postmarket surveillance. Update and next steps. Center for Devices and Radiological Health. 2013. https://wayback.archive-it.org/7993/20170406001015/https://www.fda.gov/downloads/MedicalDevices/Safety/CDRHPostmarketSurveillance/UCM348845.pdf. Last accessed: 4 August 2017.

12. Delaunay C. Registries in orthopedics. Orthop Traumatol Surg Res. 2015;101:S69-S75.

13. Brown T, Merten S, Mosahebi A, et al. Breast implant registries: the problem with ambition. Aesthet Surg J. 2016;36(2):255-59.

14. O'Shea, JC, Kramer JM, Califf RM, et al. Sharing a commitment to improve cardiovascular devices. Part I: Identifying holes in the safety net. Am Heart J. 2004;147(6):977-84.

15. Peterson, ED, Hirshfeld JW, Ferguson TB, et al. Part II: Sealing holes in the safety net. Am Heart J. 2004;147(6):985-90.

16. Hamill, S, Phurrough S, Brindis R. The national ICD registry: now and into the future. Heart Rhythm. 2006;3(4):470-3.

17. James, S, Daubert JC, Van de Werf F. Commentary: Use of registries to investigate the past and develop the future. BMJ. 2011;342:d2826.

18. Dhruva, SS, Redberg RF. FDA regulation of cardiovascular devices and opportunities for improvement. J Interv Card Electrophysiol. 2013;36:99-105.

19. Roszek B, Van Drongelen AW, Geertsma RE. Continuous Cycle of Improvement of medical devices. A questionnaire on experiences and procedures. RIVM Report 360050014/2009.

20. Rao, SV, Califf RM, Kramer JM, et al. Postmarket evaluation of breakthrough technologies. Am Heart J. 2008;156:201-8.

21. Platt, R. Wilson M, Chan KA, et al. The new Sentinel Network – improving the evidence of medical-product safety. N Engl J Med. 2009;361(7):645-7.

22. Gagliardi AR, Umoquit M, Lehoux P, et al. Identifying optimal postmarket surveillance strategies for medical and surgical devices: implications for policy, practice and research. BMJ Qual Saf. 2013;22:210-8.

23. European Commission, press release, 2012. http://europa.eu/rapid/press-release_IP-12-119_en.htm. Last accessed: 7 July 2017.

24. Møller M, Arnsbo P. Appraisal of pacing lead performance from the Danish Pacemaker Registry. PACE. 2002;19:1327-36

25. Maisel, WH. Pacemaker and ICD generator reliability. Meta-analysis of device registries. JAMA. 2006;295(16):1929-34.

26. Stricker BH, Herings, RM. Pleidooi voor et behoud van de Landelijke Medische Registratie voor betrouwbare informatie over de volksgezondheid en de gezondheidszorg. Ned Tijdschr Geneeskd. 2006;150(35): 1916-7.

27. Hop JW, Rinkel GJ, Algra A, et al. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. Stroke. 1997;28(3):660-4.

28. Van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. Lancet. 2007:369(9558):306-18.

29. Jalbert JJ, Isaacs AJ, Kamel H, et al. Clipping and coiling of unruptured intracranial aneurysms among medicare beneficiaries, 2000-2010. Stroke. 2015;46:2452-7.

30. IASP. Classificaiton of chronic pain, second edition (revised). Available from: https://www.iasp-pain.org/files/Content/ContentFolders/Publications2/ClassificationofChronicPain/Part_II-B.pdf. Last accessed: 5 August 2017.

31. Van der Hooft CS, Sturkenboom MC, van Grootheest K, et al. Adverse drug reaction-related hospitalisations: a nationwide study in The Netherlands. Drug Saf. 2006;29(2):161-8.

32. Rodenburg EM, Stricker BH, Visser LE. Sex-related differences in hospital admissions attributed to adverse drug reactions in the Netherlands. Br J Clin Pharmacol. 2011;71(1):95-104

33. Ruiter R, Visser LE, Rodenburg EM, et al. Adverse drug reaction-related hospitalizations in persons aged 55 years and over: a population-based study in the Netherlands. Drugs Aging. 2012;29(3):225-32.

34. Rodenburg EM, Stricker BH, Visser LE. Sex differences in cardiovascular drug-induced adverse reactions causing hospital admissions. Br J Clin Pharmacol. 2012;74(6):1045-52.

35. Grimes DA, Schulz KF. An overview of clinical research: the lay of the land. Lancet 2002;359:57-61.

36. Dijk WA, Hooijschuur CA, Dassen WR. Central Pacemaker Registry in the Netherlands, a 10 year evaluation. Computers in Cardiology, Jerusalem 1989: IEEE Computer society: 293, doi: 10.1109/CIC.1989.130547.

37. Dijk WA, Kingma T, Hooijschuur CA, et al. Validation of the Netherlands Pacemaker Patient Registry. Comput Cardiol. 1997;24:653-6.

38. Hooijschuur CAM, Dijk WA. Impact of data collected on implanted devices and device recipients. Neth Heart J. 2008;16:S9-11.

39. Bernstein AD, Daubert JC, Fletcher RD, et al. The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group. Pacing Clin Electrophysiol 2002;25:260.

40. So Y, Lin G, Johnston G, SAS Institute Inc. Using the PHREG Procedure to Analyze Competing-Risks Data. 2014. https://support.sas.com/rnd/app/stat/papers/2014/competingrisk2014.pdf Last accessed: December 2015

41. Putter H, Fiocco M., Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Statist. Med. 2007;26:2389-2430.

42. Volksgezondheidenzorg.info, 2017: https://bronnen.zorggegevens.nl/Bron?naam=Landelijke-Medische-Regis-

tratie-(LMR), RIVM: Bilthoven. Last accessed 13 May 2017.

43. Krupka K. International classification of diseases: 9th revision. WHO Chronicle. 1978;32:219–25.

44. Charlson, ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. 1987;40(5):373-83.

45. Deyo, R, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45(6):613-9.

46. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet 2002;359:248-52.

47. Vandenbroucke JP, Hofman A. Grondslagen der epidemiologie. Zesde druk, Elsevier gezondheidszorg, Maarssen 2000.

48. Hartz A, Marsh JL. Methodologic issues in observational studies. Clin Orthop. 2003;413:33-42.

49. Rothman KJ, Greenland S, Lash TL. Validity in epidemiologic studies. In: Modern Epidemiology. Rothman KJ, Greenland S, Lash TL. Third Edition. Wolters Kluwer, Lipincott Wiliams & Wilkins. Philadelphia, 2008.

50. Greenland S, Rothman KJ. Introduction to stratified analysis. In: Modern Epidemiology. Rothman KJ, Greenland S, Lash TL. Third Edition. Wolters Kluwer, Lipincott Wiliams & Wilkins. Philadelphia, 2008.

51. Platt R, Wilson M, Chan KA, et al. The new Sentinel Network – improving the evidence of medical-product safety. N Engl J Med. 2009;361(7):645-7.

52. Hauser RG, McGriff D, Kallinen Retel L. Riata implantable cardioverter-defibrillator lead failure: analysis of explanted leads with a unique insulation defect. Heart Rhythm. 2012;9:742-49.

53. Wet klachten, kwaliteit en geschillen zorg. Wet van 7 oktober 2015, houdende regels ter bevordering van de kwaliteit van zorg en de behandeling van klachten en geschillen in de zorg. Stb. 2015, 407.

54. Inspectie voor de Gezondheidszorg. Metaal-op-metaal-heupimplantaten – de keten voor de kwaliteitsborging van medische hulpmiddelen moet beter functioneren. Mei 2013. https://www.igz.nl/Images/2013-05-20%20Rapport%20Metaal-op-metaal-heupimplantaten%20incl.%20bijlage%20RIVM-rapport_tcm294-341951.pdf Las accessed: 17 May, 2017.

55. Inspectie voor de Gezondheidszorg. Metaal-op-metaal-heupimplantaten – de keten voor de kwaliteitsborging van medische hulpmiddelen moet beter functioneren. Mei 2013. https://www.igz.nl/Images/2013-05-20%20Rapport%20Metaal-op-metaal-heupimplantaten%20incl.%20bijlage%20RIVM-rapport_tcm294-341951.pdf Last accessed: 17 May, 2017.

56. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Meldpunt en expertisecentrum bijwerkingen implantaten van start. http://www.rivm.nl/Documenten_en_publicaties/Algemeen_Actueel/Nieuwsberichten/2017/Meldpunt_en_Expertisecentrum_Bijwerkingen_Implantaten_van_start. Last accessed: 7 July 2017.

57. Laskey W, Awad K, Lum J, et al. An analysis of implantable cardiac device reliability. The case for improved postmarketing risk assessment and surveillance. Am J Ther. 2012;19(4):248-54.

58. Maisel, W. Physician management of pacemaker and implantable cardioverter defibrillator advisories. PACE. 2004;27:437-42.

59. Maisel WH, Moynahan M, Zuckerman BD, et al. Pacemaker and ICD Generator malfunctions. Analysis of Food and Drug Administration Annual Reports. JAMA. 2006;295:1901-6.

60. Cavagna M, Strickberger SA. Management of recalled pacemakers and defibrillators. Expert Rev. Cardiovasc. Ther. 2006;4(6):601-603.

61. Bartsch C, Irnich W, Junge M, et al. Post-mortem evaluation of 415 pacemakers: in situ measurements and bench tests. Europace. 2005;7:175-80.

62. Sedrakyan A, Campbell B, Graves S. et al. Surgical registries for advancing quality and device surveillance. Lancet. 2016;388:1358-60.

63. Niederländer C, Wahlster P, Kriza C, et al. Registries of implantable medical devices in Europe. Health Policy. 2013;113:20-37

64. Labek G, Schöffl H, Meglic M. New medical device regulations ahead – What does that mean for arthroplasty registers? Guest editorial. Acta Orthop. 2015;86(1):5-6.

65. Brown T, Merten S, Mosahebi A, et al. Breast implant registries: the problem with ambition. Aesthet Surg J. 2016;36(2):255-9.

66. Furman, S, Benedek ZM. The Implantable Lead Registry. Survival of implantable pacemaker leads. PACE. 1990;13:1910-14.

67. Song, SL. The Bilitch Report. Performance of implantable cardiac rhythm management devices. PACE. 1994;17:692-708.

68. Sedrakyan A, Paxton EW, Marinac-Dabic D. Stages and tools for multinational collaboration: the perspective from the coordinating center of the international consortium of orthopaedic registries (ICOR). J Bone Joint Surg Am. 2011;93 Suppl 3(E):76-80.

69. Havelin LI, Robertsson O, Fenstad AM, et al. A Scandinavian experience of register collaboration: The Nordic Arthroplasty Register Association (NARA). J Bone Joint Surg Am. 2011;93 Suppl 3(E):13-9.

70. Sedrakyan A, Marinac-Dabic D, Holmes DR. The international registry infrastructure for cardiovascular device evaluation and surveillance. JAMA. 2013;310(3):257-8.

71. IMDRF. Methodological principles in the use of international medical device registry data. 2017. http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170316-methodological-principles.pdf Last accessed: 7 July 2017.

72. Het Landelijk Implantaten Register. https://bronnen.zorggegevens.nl/Bron?naam=Landelijk-Implantatenregister Last accessed: 7 July 2017.

73. Ministry of Health, Welfare and Sport. Letter from the Minister to Parliament (Tweede Kamer), 'Stand van zaken implantatenregister'. Reference: 343399-118356-GMT, 18 March 2014.

74. Ministry of Health, Welfare and Sport. Letter from the Minister to Parliament (Tweede Kamer), 'Eindrapport RIVM verkenning en pilot implantatenregister'. Reference: 692437-129772-GMT, 26 November 2014.

75. Van de Laar CWE, Van Berkel JJ, De Jong C, et al. Registratie van implantaten in Nederland. Inventarisatie en pilot. RIVM-rapport 2014-0089, 2014.

76. National Cardiovascular Data Registry (NCDR). http://www.ncdr.nl/registraties/pacemaker/ Last accessed: 7 July 2017.

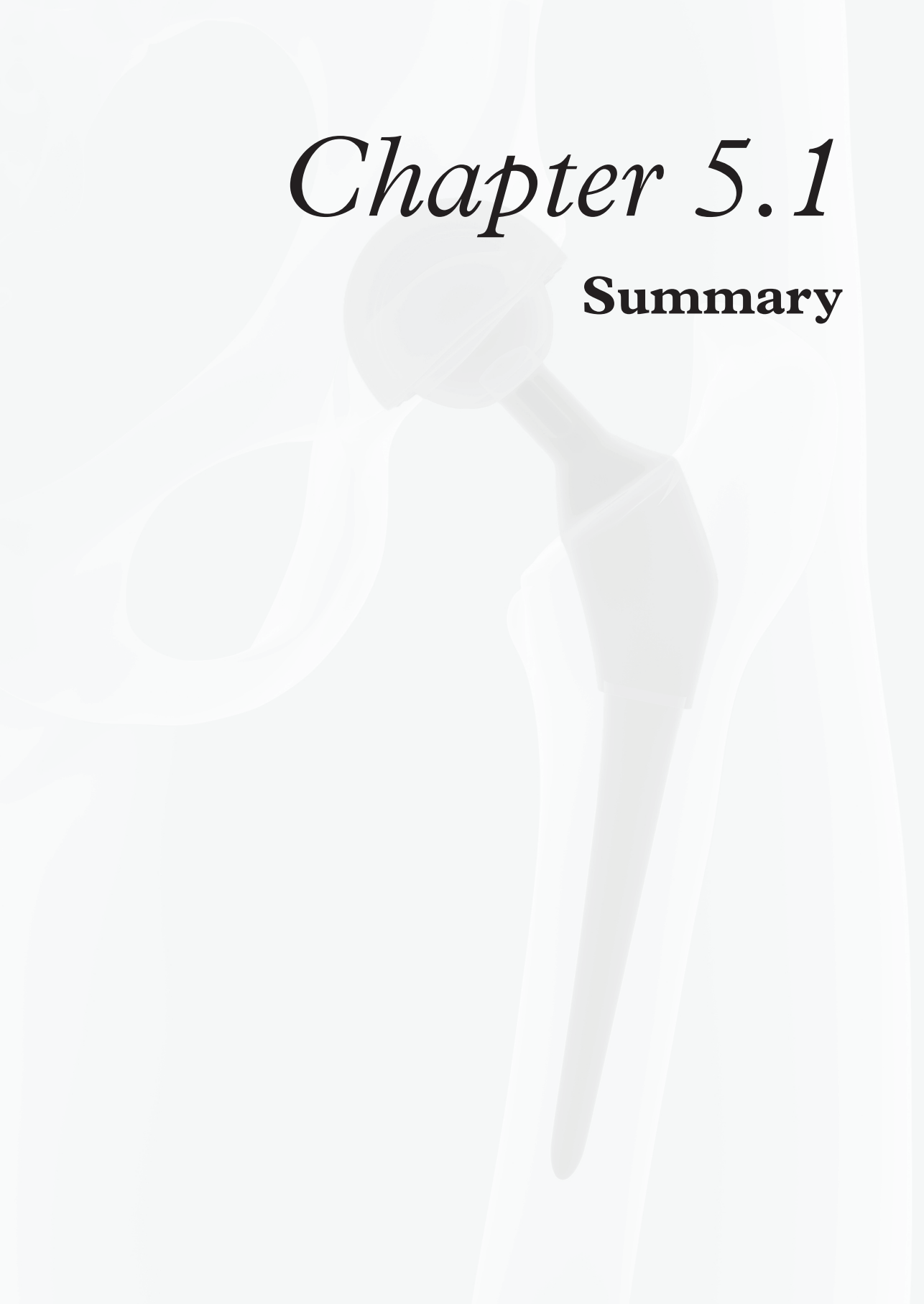
77. Van Steenbergen LN, Denissen GA, Spooren A, et al. More than 95% completeness of reported procedures in the population-based Dutch Arthroplasty Register. Act Orthop Scand. 2015;86(4):498-505.

78. Geomini PM, Hehenkamp WJ, Spaans WA, et al. POMT: Ruim drie jaar uniform registreren in de gynaecologie. NTOG. 2015;128:116-9. Accessed via: http://www.ntog.nl/dynamic/media/3/documents/NTOG_15_3_web.pdf. Last accessed: 23 August 2017.

79. Rakhorst HA, Mureau MAM, Cooter RD, et al. The new opt-out Dutch National Breast Implant Registry – Lessons learnt from the road to implementation. J Plast Reconstr Aesthet Surg. 2017; pii: S1748-6815(17)30156-0. doi: 10.1016/j.bjps.2017.04.003.

Chapter 5.1

Summary



It is estimated that at this moment approximately 500,000 different medical devices are marketed in the European union, ranging from devices such as plasters, needles, wheel chairs and surgical knives to blood glucose meters, MRI scanners, hip implants and cardiac implantable electronic devices. Technological development has advanced in the past decades, leading to increased life expectancy and improved quality of life. For example, implantable devices such as pacemakers and implantable cardioverter defibrillators (ICDs) have both prolonged as well as improved the quality of the lives of many patients. However, each surgical intervention has a risk of complications. This is particularly true for implants, which by definition are foreign objects that are introduced into the body. In some cases – especially when a patient's life depends on a functioning implant – failures and complications can be fatal. That is why implants are considered high risk devices and as such must comply with strict legal requirements and go through conformity assessment procedures before they are allowed on the market. However, patient safety and trust in medical devices have taken serious blows in the recent past after some major incidents.

As described in **chapter 1**, and partly in chapter 4, manufacturers have to provide proof that the device is safe and effective, and that it complies with the essential requirements as laid down in European Directives for medical devices. These requirements focus on a safe device design. Manufacturers must make an inventory of all possible risks that normal use and any reasonably foreseeable misuse of the device may generate. Any residual risks need to be mitigated preferably by alarms on the device itself and if this is not possible – as is the case for several implants – they should be mentioned in the instructions for use. A notified body will evaluate if the device is in conformity with the legal requirements. This is an organisation that has the expertise to assess medical devices and as such is appointed by its national authority. As part of this process, manufacturers have to provide clinical evidence on the performance and safety of their device. For high risk devices (i.e. hip implants and pacemakers) they usually have to perform clinical studies. However, for several reasons, not all defects, failures and complications can be identified during such studies. Consequently, rare events and complications may only emerge after devices have been used for a longer period of time and in several thousands of patients. Therefore, post-market surveillance (PMS) is of major importance for the evaluation of device performance in real-life. During the PMS phase manufactures must actively collect information on the use of their devices in order to implement appropriate measures for improvement, correct any failures when necessary, and report any incidents to the competent authorities of European Member States.

Competent authorities are governmental organisations responsible for market surveillance and law enforcement in the field of medical devices. Whereas marketing safe and effective devices, and taking every measure necessary in case of problems and failures, is primarily the responsibility of manufacturers, competent authorities are also allowed to prevent or suspend the marketing of devices or take other measures in case of severe (public) health threats. In contrast to medicinal products, regulatory oversight of medical devices puts more emphasis on post-market surveillance than on pre-market clinical studies. This has several reasons. There is a large number of medical devices on the market, which exceeds the number of registered drugs. Also, medical devices are more complex, more diverse and product development is more iterative combined with a shorter product life cycle. Additionally, there is a learning curve associated with technology adoption.

Accordingly, early detection of device problems is of great importance to authorities. They rely

on different sources of information regarding device safety. Examples are market surveillance activities such as inspections of manufacturers and studies on products or product groups, but also obligatory vigilance reports by manufacturers, and, depending on national legislation, mandatory and/or voluntary reports by health care professionals and patients. Clinical (device) registries are another important source of information. They may contain relevant data to identify products with a lower than expected reliability and are able to identify patients who have been implanted with an inadequate implant.

Therefore, the main objective of this thesis was to examine the usability of a number of currently available and accessible registries for information on implant performance and complications of implant therapy. For the studies described in this thesis, existing registries have been used: a utilization register on pacemakers (CPPR-SPRN) and a national hospital discharge records database (LMR). These databases are some of the few long-term registries available in the Netherlands.

Chapter 2 describes the studies that are based on the CPPR-SPRN database. The Netherlands Pacemaker Registry Foundation (CPPR-SPRN) was established in 1982 and at the same time the computerised Central Pacemaker Patients Registration was started. The registry aimed to collect information on patient and device characteristics, trends and annual numbers of implanted devices. Another purpose of the registry was to inform health care professionals and patients about quality issues with pacemakers and leads. The results from our studies on this database showed that the registry provided important information on pacemaker therapy.

In **chapter 2.1** we studied the number and types of pacemakers that have been implanted between 1984 and 2006. The data showed that during this period nearly 97,000 patients received their first pacemaker. The number of first pacemakers used in the Dutch population gradually increased over the years: from 225 implants per million inhabitants in 1984 to 423 implants per million inhabitants in 2005. The type of pacemaker that was mainly implanted changes from VVI to DDD. In case of VVI sensing and pacing both take place in the right ventricle; the pacemaker responds by inhibiting its activity when it detects a spontaneous heart signal. With DDD sensing and pacing take place in both the atrium and the ventricle and the pacemaker can respond by either inhibiting its activity or by triggering.

Furthermore, we studied the trends in duration of service time of pacemaker generators and the reasons for explantation as described in **chapter 2.2**. We found that during the study period 22.8% of the patients had at least one pacemaker generator replacement or removal and 4.5% had more than one. These explantations occurred after a mean of nearly 6.5 years and were done because of technical failures or complications in approximately 20% of the cases. In addition to problems with the pacemaker generator, the leads that conduct the electrical pulse to the heart can also be a source of failures and complications. In **chapter 2.3** we therefore studied the percentage and reasons for explantations of leads. Our analysis showed that nearly 6.5% of the 138,225 leads that were implanted with first pacemaker generators have been replaced or explanted. The main reasons for this were insulation failures, infections and displacements. Infections were also the main reason for simultaneous explantation of the pacemaker generator and its accompanying leads. In general, it appeared that in more than 70% of the generator replacements, the leads were not explanted.

For the studies described in **chapter 3**, we used the national hospital discharge records database (Landelijke Medische Registratie, LMR). This database was established for research purposes and contains all admissions to Dutch academic and general hospitals be-

tween 1986 and 2006. Because registry of interventions and diagnoses was mandatory, provided in codes, and independent from reimbursement, it provides a rich source of information on hospital admissions. We studied three interventions that use medical devices and implants: total hip arthroplasty, clipping and coiling of subarchnoid haemorrhage and three treatments for trigeminal neuralgia.

In the study described in **chapter 3.1**, we investigated re-admissions following complications and/or re-operations within three months after total hip arthroplasty (THA). Approximately 9% of the 50,080 patients were re-admitted of whom 40% for complications. These consisted mainly of mechanical problems and infections. Furthermore, we studied whether hospital procedure volume was associated with a higher risk of re-admissions. A lower procedure volume appeared to be associated with complications during index admissions, but such a relation was not found for re-admissions due to complications. We could only study mortality during admission, which was 0.2% during index admission and increased with each following re-admission. The actual mortality within 3 months was unknown, because we did not have information on the number of deaths that occurred outside the hospital.

Chapter 3.2 describes the incidence and treatment of non-traumatic subarachnoid haemorrhage (SAH). We found an incidence of SAH of 7.2 per 100,000 person-years. This type of haemorrhage can be treated by clipping or coiling of the aneurysm. The first treatment is an invasive neurosurgical procedure, while the other one is a less invasive endovascular procedure that can be performed by radiologists. We found that coiling procedures were not registered as such in the LMR data. By using data from the Integrated Primary Care Information (IPCI) database, we found that 64% of the patients were treated by clipping of the aneurysm, while 26% was treated by coiling. Due to the limited size of the patient groups, we could not estimate the risk of death for each group.

Trigeminal neuralgia (TGN) is a severe form of facial pain in one or more branches of the fifth cranial nerve. In **chapter 3.3** we studied readmissions for repeat procedures and complications of the three most common invasive treatments of TGN. These are microvascular decompression (MVD), partial sensory rhizotomy (PSR), and percutaneous radiofrequency thermocoagulation (PRT). During MVD a teflon patch is introduced between the nerve and vascular structure that is in contact with the nerve, the other treatments are aimed at destruction of (part of) the nerve. Most patients (84%) underwent PRT, 11% MVD and 5% PSR. Nearly 34% of the patients was re-admitted within one year primarily for complications, but also for a repeat procedure. The risk for readmission was lowest for MVD, whereas the risk for complications was lowest for PRT. After MVD most people had a PRT as repeat procedure, whereas for PSR and PRT the same procedure was performed again. Hospital procedure volume was partly associated with failure. However, this relationship only applied to the second and fifth groups of surgical procedure volume.

Finally, **chapter 4** provides a general discussion of the results, including methodological considerations that need to be addressed with regard to epidemiological studies, future perspectives and a general conclusion. We also described several sources of post-market information that are relevant for detection of complications and failure of devices. Recent failures and recalls of implants have highlighted the need for registries for the purpose of tracking and tracing implants to patient level, but also for quality assessment and performance data. Although several registries already existed, mainly in the field of orthopaedics and cardiology, new registries in other fields have been initiated recently. They serve to inform several stakeholders, such as health care professionals, manufacturers, insurers and health authorities, for the benefit of patient safety and man-

agement. Successful use of registries requires collaboration between these stakeholders, authorities included.

The data in our studies clearly support the vital role registries on implants and implant therapies play in modern day health care. In addition, registries may fulfil a need as source for the formation of study cohorts and providing a reliable denominator for observational studies regarding implant use. In comparison to studies on drugs, such studies have been limited in the field of medical devices. However, the registries we have used were established for other purposes and can no longer be considered state-of-the-art. An important limitation was that several implant characteristics relevant for such analyses were not always included in the data. This illustrates the importance of a priori definition of the purpose of the registry and the data needed to be registered. Additionally, adherence to international collaborations, which have already been initiated in some areas, is at least advisable to be able to identify rare complications and failures, whereas it is also important that registries are able to provide data that is necessary to guide patient care.

Chapter 5.2

Samenvatting

Naar schatting zijn er thans in de Europese Unie ongeveer 500.000 verschillende medische hulpmiddelen op de markt. Deze variëren van pleisters, naalden, rolstoelen en chirurgische mesjes tot bloedglucosemeters, MRI-scanners, heupimplantaten en implanteerbare elektronische hulpmiddelen voor het hart. In de afgelopen decennia is de technologische ontwikkeling enorm toegenomen, waardoor zowel de levensverwachting als de kwaliteit van leven zijn toegenomen. Implanteerbare hulpmiddelen zoals pacemakers en implanteerbare cardioverter defibrillatoren (ICD's) hebben bijvoorbeeld het leven van vele patiënten zowel verlengd als verbeterd. Elke chirurgische ingreep heeft echter een risico op complicaties. Dat geldt vooral voor implantaten, waarbij per definitie een vreemd object in het lichaam wordt gebracht. In sommige gevallen – vooral wanneer het leven van een patiënt afhankelijk is van een functionerend implantaat – kunnen gebreken en complicaties fataal zijn. Daarom beschouwt men implantaten als hoogrisico hulpmiddelen en moeten ze voldoen aan strenge wettelijke eisen en een conformiteitbeoordelingsprocedure doorlopen voordat de EU-lidstaten ze toelaten tot de markt. Als gevolg van enkele recente en ernstige incidenten zijn de patiëntveiligheid en het vertrouwen in medische hulpmiddelen echter ernstig geschaad.

Zoals beschreven in **hoofdstuk 1**, en deels ook in hoofdstuk 4, moeten fabrikanten bewijzen dat het hulpmiddel veilig en effectief is en dat het voldoet aan de essentiële eisen uit de Europese Richtlijnen voor medische hulpmiddelen. Deze eisen richten zich op een veilig ontwerp van het hulpmiddel. Fabrikanten moeten een inventarisatie maken van alle mogelijke risico's die normaal gebruik en elk redelijk misbruik van een hulpmiddel met zich mee kan brengen. Elk resterend risico moeten ze vervolgens zoveel mogelijk inperken door alarmen op het hulpmiddel zelf en als dat niet mogelijk is – zoals bij verschillende implantaten – moeten fabrikanten ze vermelden in de gebruiksaanwijzing. Een aangemelde (keurings) instantie (*notified body*) zal evalueren of het hulpmiddel voldoet aan de wettelijke eisen. Een notified body is een organisatie die de expertise heeft om medische hulpmiddelen te beoordelen en daarvoor door zijn nationale autoriteit is aangewezen. Als onderdeel van deze procedure moeten fabrikanten klinisch bewijs leveren over de geclaimde prestaties en veiligheid van hun hulpmiddel. Voor hoogrisico hulpmiddelen (bijvoorbeeld heupimplantaten en pacemakers) moeten zij doorgaans klinische studies uitvoeren. Echter, om verschillende redenen is het niet altijd mogelijk om alle defecten, gebreken en complicaties tijdens zulke studies te identificeren. Als gevolg daarvan zullen zeldzame incidenten en complicaties pas bekend worden nadat hulpmiddelen voor een langere tijd en in enkele duizenden patiënten toegepast zijn. Daarom is *post-market surveillance* (PMS), het intensief volgen van hulpmiddelen nadat ze in gebruik genomen zijn, van groot belang voor de evaluatie van de prestaties van het hulpmiddel in het dagelijks gebruik. Tijdens de PMS-fase moeten fabrikanten actief informatie verzamelen over het gebruik van hun hulpmiddelen om het product te verbeteren, waar nodig gebreken te herstellen, en incidenten melden aan de bevoegde autoriteiten van de Europese Lidstaten.

Bevoegde autoriteiten zijn overheidsorganisaties die verantwoordelijk zijn voor markttoezicht en handhaving op het gebied van medische hulpmiddelen. Fabrikanten zijn primair zelf verantwoordelijk voor het in de handel brengen van veilige en effectieve hulpmiddelen en het nemen van elke benodigde maatregel in geval van problemen en gebreken. Dat neemt echter niet weg dat bevoegde autoriteiten de mogelijkheid hebben om de handel van hulpmiddelen te voorkomen of op te schorten, of andere maatregelen te nemen als die hulpmiddelen een gevaar voor de (publieke) gezond-

heid vormen. In tegenstelling tot geneesmiddelen, richt het overheidstoezicht op medische hulpmiddelen zich meer op de fase nadat de producten in de handel gebracht zijn dan op klinische studies vooraf. Dit heeft verschillende redenen. Het aantal verschillende soorten medische hulpmiddelen dat op de markt is, betreft het honderdvoudige van het aantal geneesmiddelen. Daarnaast zijn medische hulpmiddelen complexer en meer divers, en verloopt de productontwikkeling veel sneller gecombineerd met een kortere levenscyclus dan bij geneesmiddelen. Daarnaast is er sprake van een leercurve bij het introduceren van nieuwe technieken.

Als gevolg daarvan is het snel opsporen van problemen met hulpmiddelen van groot belang voor toezichthoudende autoriteiten. Ze zijn voor productveiligheid afhankelijk van verschillende informatiebronnen. Voorbeelden zijn toezichtsactiviteiten zoals inspecties bij fabrikanten en onderzoeken naar producten of productgroepen, maar ook de verplichte incidentmeldingen door fabrikanten en, afhankelijk van nationale wetgeving, de verplichte en/of vrijwillige meldingen door zorgverleners en patiënten. Een andere belangrijke bron van informatie zijn de klinische (hulpmiddelen) registraties. Deze kunnen relevante gegevens bevatten om producten met een lagere dan verwachte betrouwbaarheid op te sporen en kunnen patiënten identificeren die een gebrekkig implantaat hebben gekregen.

Het belangrijkste doel van dit proefschrift was daarom om de bruikbaarheid te onderzoeken van verschillende beschikbare en toegankelijke registraties voor informatie over de prestaties van en complicaties van behandelingen met implantaten. Voor de studies die in dit proefschrift zijn beschreven, zijn bestaande registraties gebruikt: het kwaliteitsregister van pacemakers (SPRN) en de Landelijke Medische Registratie (LMR). Dit zijn enkele van de langetermijnregistraties die in Nederland beschikbaar zijn.

Hoofdstuk 2 beschrijft de studies die gebaseerd zijn op de SPRN-database. De Stichting Pacemaker Registratie Nederland (SPRN) is in 1982 opgericht en in dat jaar is de geautomatiseerde Centrale Pacemaker en Patiënten Registratie van start gegaan. De registratie had tot doel om informatie te verzamelen over patiënten- en pacemakerkenmerken, trends en het aantal pacemakers dat jaarlijks geïmplanteerd werd. Een ander doel van de registratie was om zorgverleners en patiënten te informeren over kwaliteitsproblemen met pacemakers en leads. De resultaten van onze studies op deze database lieten zien dat de registratie belangrijke informatie opleverde over de behandeling met pacemakers.

In **hoofdstuk 2.1** hebben we het aantal en de typen pacemakers onderzocht die tussen 1984 en 2006 geïmplanteerd zijn. De gegevens lieten zien dat in deze periode bijna 97.000 patiënten hun eerste pacemaker kregen. Het aantal eerste pacemakers dat artsen bij patiënten in de Nederlandse bevolking toepasten, nam over de jaren geleidelijk toe: van 225 implantaten per miljoen inwoners in 1984 naar 423 implantaten per miljoen inwoners in 2005. Het meest geïmplanteerde type pacemaker veranderde in die periode van VVI naar DDD. In het geval van VVI vinden het meten van hartactiviteit (sensing) en het stimuleren van het hart (pacing) allebei in de rechter hartkamer plaats; de pacemaker reageert door zich in te houden (**I**nhibit) als hij een spontaan signaal van het hart zelf waarneemt. Bij DDD vinden sensing en pacing plaats in zowel de bezoem als het ventrikel, en kan de pacemaker afhankelijk van de hartactiviteit zowel een puls afgeven als inhouden.

Verder bestudeerden we de trends in de werkingsduur van pacemaker generatoren en de redenen voor explantatie, zoals beschreven in **hoofdstuk 2.2**. We vonden dat tijdens de studieperiode 22,8% van de patiënten tenminste één vervanging of verwijdering van de pacemaker heeft ondergaan en 4,5% meer dan één. Deze explantaties vonden gemiddeld 6,5 jaar na implantatie plaats en waren in on-

geveer 20% van de gevallen het gevolg van technische gebreken of complicaties. Naast problemen met de pacemaker generator, kunnen ook de leads problemen geven. De leads zijn de geleidedraden die de elektrische puls van de pacemaker generator naar het hart overbrengen. In **hoofdstuk 2.3** hebben we daarom het percentage en de redenen voor explantatie van leads onderzocht. Onze analyses toonden aan dat bijna 6,5% van de 138.225 leads die met een eerste pacemaker generator geïmplanteerd waren, zijn vervangen of verwijderd. De belangrijkste redenen hiervoor waren gebreken aan de isolatielaag van de draden, infecties en ongewenste verschuiving van de leads. Infecties waren ook de belangrijkste reden voor gelijktijdige explantatie van de pacemaker generator en de bijbehorende leads. In het algemeen bleek dat bij meer dan 70% van de vervangingen van de generator de leads niet verwijderd werden.

Voor de studies beschreven in **hoofdstuk 3** hebben we gebruik gemaakt van de Landelijke Medische Registratie (LMR). Deze database is voor onderzoeksdoeleinden opgezet en bevat alle opnames in Nederlandse academische en algemene ziekenhuizen tussen 1986 en 2006. Aangezien registratie van behandelingen en diagnoses verplicht was, deze vastgelegd werden in codes en dit onafhankelijk was van vergoeding, vormt de LMR een rijke bron aan informatie over ziekenhuisopnames. We bestudeerde drie behandelingen waarbij medische hulpmiddelen en implantaten gebruikt werden: totale heupvervanging, clippen en coilen van subarachnoïdale bloedingen, en drie behandelingen voor aangezichtspijn.

In de studie die beschreven is in **hoofdstuk 3.1** onderzochten we heropnames als gevolg van complicaties en/of heroperaties binnen drie maanden na een totale heupvervanging (total hip arthroplasty, THA). Bijna 9% van de 50.080 patiënten werden opnieuw opgenomen, waarvan 40% voor complicaties. Deze bestonden voornamelijk uit mechanische problemen en infecties. Daarnaast bestudeerden we of het aantal ingrepen per ziekenhuis geassocieerd was met een hoger risico op heropname. Een lager aantal ingrepen bleek geassocieerd te zijn met complicaties tijdens de indexopname, maar een dergelijke relatie vonden we niet voor heropnames als gevolg van complicaties. We konden alleen de sterfte tijdens opname onderzoeken; deze bedroeg 0,2% tijdens de indexopname en nam toe met elke volgende heropname. De daadwerkelijke sterfte binnen drie maanden was onbekend, omdat we geen informatie hadden over het aantal sterfgevallen buiten het ziekenhuis.

Hoofdstuk 3.2 beschrijft de incidentie en behandeling van niet-traumatische subarachnoïdale bloedingen (SAH). We vonden een incidentie (aantal nieuwe gevallen) van SAH van 7,2 per 100.000 persoonsjaren. Dit type bloeding kunnen artsen behandelen door een clip op het aneurysma te plaatsen of er een draad in te brengen die zich opkrult (coil). De behandeling met een clip is een invasieve neurochirurgische procedure, terwijl de andere een minder invasieve endovasculaire behandeling is die een radioloog kan uitvoeren. We vonden dat de behandeling met coiling niet als zodanig geregistreerd was in de LMR-data. Door data te gebruiken van de Integrated Primary Care Information (IPCI, een database van huisartsen), vonden we dat 64% van de patiënten werd behandeld met clipping van het aneurysma, terwijl 26% werd behandeld door coiling. Vanwege de beperkte grootte van deze patiëntengroepen konden we het risico op overlijden binnen elke groep niet berekenen.

Aangezichtspijn, of trigeminusneuralgie (TGN), is een ernstige vorm van gezichtspijn in een of meerdere takken van de vijfde aangezichtszenuw. In **hoofdstuk 3.3** hebben we de heropnames bestudeerd voor herhaalprocedures en complicaties van de drie meest voorkomende behandelingen van TGN. Dit zijn microvascular decompression (MVD), partial sensory rhizotomy (PSR) en percutaneous

radiofrequency thermocoagulation (PRT). Bij MVD brengen artsen een teflonschijfje in tussen de zenuw en het bloedvat dat de zenuw raakt; de andere behandelingen richten zich op vernietiging van (een deel van) de zenuw. De meeste patiënten (84%) ondergingen PRT, 11% MVD en 5% PSR. Bijna 34% van de patiënten kwam binnen een jaar terug voor heropname als gevolg van complicaties, maar ook voor herhaalingrepen. Het risico op heropname was het kleinst bij MVD, terwijl het risico op complicaties het kleinst was voor PRT. De patiënten die MVD hadden ondergaan, kregen het vaakst PRT als herhaalingreep, terwijl na PSR en PRT dezelfde procedure opnieuw gedaan werd. Het aantal ingrepen per ziekenhuis was deels geassocieerd met het falen van de indexingreep. Dit verband gold echter alleen voor de tweede en vijfde volumegroep van aantal ingrepen.

Tot slot bevat **hoofdstuk 4** de algemene discussie van de resultaten, inclusief methodologische overwegingen die van belang zijn bij epidemiologische studies, verkenningen voor de toekomst en een algemene conclusie. Daarnaast hebben we verschillende bronnen voor PMS-informatie beschreven die relevant zijn voor het opsporen van complicaties en gebreken van hulpmiddelen. Recente gebreken en terugroepacties van implantaten illustreren de noodzaak voor registraties met als doel het herleiden van implantaten tot op patiëntniveau, maar ook voor gegevens over prestaties en ten behoeve van kwaliteitsbeoordeling. Ondanks dat er al verschillende registraties bestaan, voornamelijk in de orthopedie en cardiologie, zijn recentelijk op andere gebieden nieuwe registraties opgezet. Zij dienen voor het informeren van verschillende belanghebbenden, zoals zorgverleners, fabrikanten, verzekeraars en toezichthouders, ten bate van de veiligheid en behandeling van patiënten. Succesvol gebruik van registraties vereist samenwerking tussen deze belanghebbenden, inclusief toezichthouders.

De resultaten van onze studies leveren een duidelijke onderbouwing van de essentiële rol die registraties van implantaten en behandelingen in de moderne gezondheidszorg spelen. Daarnaast blijkt dat registraties een noodzaak vervullen als belangrijke bron voor de vorming van studiecohorten en het leveren van een betrouwbare noemer voor observationele studies over het gebruik van implantaten. In vergelijking met studies op geneesmiddelen is het aantal studies op het gebied van medische hulpmiddelen beperkt in aantal. De registraties die wij gebruikten zijn echter voor andere doeleinden opgezet en zijn niet langer state-of-the-art. Een beperking was dat verschillende gegevens over de implantaten die relevant zijn om mee te nemen in de analyses, niet altijd beschikbaar waren. Dit onderschrijft het belang om vooraf het doel van de registratie en de benodigde gegevens daarvoor te definiëren. Daarnaast is het op zijn minst te adviseren om aan te sluiten bij internationale samenwerkingsverbanden, die op sommige terreinen al tot stand gekomen zijn, om zeldzame complicaties en gebreken te kunnen opsporen. Tot slot is het belangrijk dat registraties in staat zijn om gegevens te leveren die nodig zijn om te adviseren over de zorg voor patiënten.

Chapter 6

Dankwoord

Mijn promotietraject heeft lang geduurd, daar zal ik niet omheen draaien. Een combinatie van een afwijkende constructie, weinig tijd naast werk, tijdrovende databewerking, en niet in de laatste plaats mijn karaktereigenschappen. Een perfectionist die werk, onderzoek en relaties allemaal op het hoogste niveau wil uitvoeren en onderhouden, maakt het zichzelf niet gemakkelijk. Zo dat is eruit! Maar nu ligt het boekje er toch maar mooi en ik ben heel tevreden met het eindresultaat. Door eerdergenoemde constructie van een promotie naast een vaak veeleisende baan, voelde het voor mij vaak als een eenzaam traject. Echter, je doet zoiets nooit helemaal alleen. Daarom wil ik diverse mensen bedanken voor hun bijdrage en steun. Omdat dat in de loop van de jaren best veel mensen zijn geweest, en ik zoals de meesten van jullie weten zelden kort van stof ben, zal dit dankwoord meerdere pagina's in beslag nemen.

In de eerste plaats wil ik prof.dr. B.H.Ch. Stricker en prof.dr. J.H. Kingma bedanken. Beste Bruno, nadat de plannen voor een promotietraject begonnen uit te kristalliseren, ben ik onder jouw hoede gekomen. Als toch wat vreemde eend in de bijt, een medisch technoloog tussen de geneesmiddelenbewakers, schoof ik aan bij jouw onderzoeksgroep voor farmacovigilantie. Ik heb bepaald geen standaard promotietraject doorlopen, zelfs in vergelijking met je andere promovendi die zowel in Rotterdam als bij de inspectie werk(t)en. Ik weet ook niet of ik anderen deze constructie kan aanbevelen. Maar ik wil je bijzonder hartelijk danken dat je het al die jaren met me volgehouden hebt. Ik ben blij en dankbaar met alles wat ik van je heb geleerd op het gebied van epidemiologie en statistiek. Op momenten dat het moeizaam ging, heb je me altijd op het hart gedrukt om niet te stoppen, en hoewel dat soms een aanlokkelijke optie was, heb ik dat nooit serieus overwogen. Ik heb altijd volgehouden dat ik 'A' heb gezegd en dus ook 'B' zou doen. Het heeft lang geduurd, maar het resultaat ligt er nu. Ik denk dat we daar allebei een goed gevoel over hebben.

Prof.dr. Kingma, beste Herre, hoewel onze wegen nu gescheiden zijn, was deze promotie er zonder jou waarschijnlijk niet gekomen. Gedurende je positie als Inspecteur-Generaal van de Inspectie voor de Gezondheidszorg wilde je ook enkele promovendi begeleiden. Ik wilde me naast mijn werk ook op dit gebied graag verder ontwikkelen, dus één en één was twee. Dank dat je dit mogelijk hebt gemaakt.

Een bijzonder woord van dank voor prof.dr. N.M. van Hemel is op deze plek zeker gerechtvaardigd. Ik ben ontzettend dankbaar voor wat u voor mij en mijn promotie heeft betekend. Tijdens het hele proces van analyseren, schrijven, submitten en reviseren heb ik heel veel gehad aan onze (veelal telefonische) overleggen. Dat ik zelf geen arts ben, maakte dat ik soms twijfelde over de interpretatie van de resultaten en opmerkingen van reviewers. Onze besprekingen gaven me altijd weer het vertrouwen dat we op de goede weg waren. Veel dank voor uw betrokkenheid, ook wat betreft de afronding van mijn proefschrift!

Graag wil ik op deze plek ook de commissieleden bedanken voor het plaatsnemen in de commissie. Prof.dr. C. Wagner, prof.dr. J.W. Deckers en prof.dr. J.A.N. Verhaar in de kleine commissie en naast prof.dr. N.M. van Hemel ook prof.dr. I.P. Leistikow en prof.dr. K.G.M. Moons in de grote commissie.

Prof.dr. A. Hofman, voormalig hoofd van de afdeling epidemiologie van de medische faculteit van het ErasmusMC en grondlegger van de ERGO-studie, wil ik van harte bedanken voor het feit dat ik via een gastvrijheidsaanstelling werkzaam mocht zijn bij de afdeling. Ik heb enorm veel bewondering voor wat u heeft bereikt met ERGO. Er zijn al veel belangrijke wetenschappelijke inzichten en promoties uit deze populatiestudie voortgekomen. Daarnaast heb ik met plezier deelgenomen aan uw colleges tijdens de NIHES-master. Prof.dr. A. Ikram, het huidige hoofd van de afdeling ep-

idemiologie, wil ik eveneens bedanken voor de gastvrijheid. Arfan, hoewel we weinig met elkaar te maken hebben gehad, heb ik ook voor jou veel bewondering met wat je op jonge leeftijd al hebt bereikt. Veel succes met het voortzetten van het belangrijke en mooie werk van de afdeling.

Hoewel mijn onderzoek zich niet op ERGO gericht heeft, heb ik voor de validatie van gegevens bij enkele studies wel gebruik gemaakt van de ERGO-data. Daarom wil ik bij deze de deelnemers uit Ommoord bedanken, evenals de medewerkers die de ERGO-studie mogelijk hebben gemaakt. Speciale dank voor Jolande Verkroost voor de hulp bij het valideren en opzoeken van informatie. Jouw werk vindt wat meer op de achtergrond plaats, maar is o zo belangrijk! Nano wil ik hartelijk bedanken voor de ICT-ondersteuning.

Drie artikelen uit mijn proefschrift zijn gebaseerd op de SPRN-registratie. Dat was zonder Carla en Arnold niet mogelijk geweest. Veel dank voor het beantwoorden van mijn vragen en het meedenken. Ik waardeer het zeer dat jullie een aantal keren 'even' vanuit Groningen naar Utrecht zijn afgereisd voor overleg. Verder ben ik alle professionals die aan SPRN hebben bijgedragen zeer erkentelijk.

En dan kom ik nu bij iemand die een cruciale rol gespeelt heeft voor zowel mijn carrière bij de inspectie als in de beginfase van mijn promotie-onderzoek: dr. J. de Koning, of 'ome Han' zoals ik u stiekem noem. Als stagiaire kwam ik in 2000 onder uw begeleiding bij de inspectie werken en na dat half jaar nam u me als projectmedewerker in dienst voor het project bloedgebruik in ziekenhuizen. Daarna stroomde ik door naar de afdeling medische technologie, waar ik nog steeds zit. In de beginjaren heeft u me ook begeleid bij mijn onderzoek. U heeft een paar keer het verhaal verteld over uw eigen promotietijd en het Sinterklaasgedicht dat sprak over die vermaledijde promotie en dat vermaledijde proefschrift. Ik begrijp de strekking daarvan maar al te goed… Heel veel dank voor uw begeleiding, ik heb er veel van geleerd en denk nog regelmatig terug aan de begintijd op de 13e verdieping van de D-toren in de Resident! In de beginjaren heb ik ook begeleiding gehad van Prof.dr. M. Sturkenboom van de afdeling medische informatica van het ErasmusMC. Beste Miriam, dank daarvoor.

Van mijn leidinggevenden bij de inspectie heb ik altijd veel steun gehad om aan mijn onderzoek te werken. In de eerste jaren ook in de vorm van tijd. Mijn direct leidinggevenden in de loop der jaren ben ik hiervoor zeer erkentelijk. Daarbij wil ik Paul 'sr.', Rob, Hans ter S., en Jos bij naam noemen. Ook de Inspecteurs-Generaal die na Herre Kingma kwamen, prof.dr. G. van der Wal en (de huidige IG) dr. R. van Diemen-Steenvoorde, en voormalig hoofdinspecteur Josée Hansen wil ik hartelijk bedanken, zowel voor de mogelijkheid om onderzoek te doen als voor de persoonlijke belangstelling.

Dan mijn collega's van de inspectie. Mijn teamgenoten wil ik danken voor hun belangstelling en steun. G., met jou werk ik het meest samen, we hebben geregeld onze handen vol aan onze gezamenlijke implantatendossiers. Ik zeg het waarschijnlijk niet vaak genoeg, als ik het al een keer gezegd heb, maar ik ben heel blij met een collega zoals jij! Collega's van de IVD-vakgroep, samen zorgen we ervoor dat er genoeg aandacht blijft voor de IVD's. Het is fijn samenwerken met jullie, dank ook voor jullie belangstelling. Kees, jij in het bijzonder, fijn om af en toe even mijn verhaal kwijt te kunnen en de ervaringen uit jouw promotietraject te horen. Het zorgde ervoor dat ik weer even kon relativeren. Daarom ben ik blij dat je op 6 december als paranimf naast me staat!

Andere collega's en oud-collega's van de afdeling medische technologie ook dank voor jullie belangstelling. Het is een eer om met zoveel fijne collega's te mogen samenwerken! Voor de nieuwe collega's die op het moment dat ik dit schrijf net de afdeling zijn komen versterken: ik

kijk uit naar onze samenwerking!
Ook (oud-)collega's van andere afdelingen dan medische technologie wil ik bedanken voor hun belangstelling. Een bijzonder woord van dank is voor Irene H.: jou wil ik hartelijk bedanken omdat je mij bij professor Van Hemel geïntroduceerd hebt. Op een moment dat ik zoekende was naar de verdere richting van mijn onderzoek en dacht aan een studie op het gebied van de cardiologie, pakte jij meteen de telefoon en belde jouw voormalige opleider Norbert van Hemel. Een afspraak was snel gemaakt en het resultaat zit in dit boekje in de vorm van drie artikelen over pacemakers en leads. Ik kan dus wel stellen dat jij op een kruispunt in mijn promotietraject een belangrijke rol hebt gespeeld! Dank ook voor je interesse. Beste Janneke van L., bedank voor de fijne samenwerking. Aan het begin van mijn promotie hebben we bij de inspectie samen onderzoek gedaan voor de Staat van de Gezondheidszorg. Jammer dat we het artikel dat daaruit voortkwam niet hebben kunnen publiceren.
Van de afdeling epidemiologie en medische informatica van de medische faculteit ErasmusMC, wil ik co-auteurs Maarten, Seppe en Roelof heel hartelijk danken voor de samenwerking. Maarten, ik heb groot ontzag voor jouw kennis en inzicht. Ik vreesde stiekem de momenten dat ik manuscripten met jouw commentaar terugkreeg, maar ze werden er (uiteraard) altijd beter van! Seppe, vrolijke noot bij medische informatica, je filmpjes voor collega's die gingen promoveren zijn volgens mij legendarisch. Roelof, het was een plezier om met jou aan het SAB-artikel te werken. Het was prettig om af en toe even frustraties te kunnen delen. Dank daarvoor! Belangstelling, gezelligheid en een klankbord waren er in Rotterdam ook bij kamergenoten (waarvan sommigen tevens inspectiecollega's waren).
Thuis zeggen we voor de grap weleens tegen elkaar "we hebben te veel vrienden", maar we zijn natuurlijk gewoon geluksvogels met zoveel lieve mensen om ons heen! Ik wil ze allemaal bedanken voor hun belangstelling, steun en vriendschap. Jullie weten wie jullie zijn! Marit, wat fijn dat je mijn paranimf wilt zijn!
Jos, ik heb jou als leidinggevende al bedankt voor je steun, maar naast leidinggevende beschouw(de) ik je ook als mijn mentor. Ik heb veel van je geleerd en dat doe ik nog steeds. Na je vertrek bij de inspectie hebben we contact gehouden en ik ben blij met deze bijzondere vriendschap. Ik weet dat je er soms een hard hoofd in had, maar nu is het af. Ik weet dat je trots op me bent en dat betekent veel voor me. Ik reken op nog meer goede gesprekken in de toekomst!
Mijn schoonouders, mijn zwagers en schoonzus, en mijn 'schoonoma' wil ik heel hartelijk bedanken voor hun belangstelling, steun en gezelligheid. Het was fijn om op de momenten dat we samen waren voor feestdagen, vakantieweekjes, verjaardagen of gewoon zomaar, even mijn gedachten te verzetten. Ik ben gezegend met een schoonfamilie zoals jullie! Ooms en tantes, ook die uit mijn schoonfamilie, en de vrienden van mijn ouders wil ik bedanken voor hun belangstelling hoe het met mij en mijn onderzoek ging in de loop der jaren.
Lieve pap en mam, het is goed gebruik om de belangrijkste mensen aan het eind van het dankwoord te noemen. Jullie vonden het weleens moeilijk om te vragen hoe het met mijn onderzoek ging, omdat jullie wel zagen dat het me niet altijd gemakkelijk afging. Het was ook inderdaad niet altijd mijn favoriete gespreksonderwerp. Ik wil jullie uit het diepst van mijn hart bedanken voor jullie steun en de mogelijkheden die jullie mij geboden hebben. De oma's hebben nog meegemaakt dat ik hieraan begonnen ben, ze zien het me niet meer afmaken, maar ze zouden vast trots geweest zijn op hun enige kleindochter.
Mijn allerliefste echtgenoot, vriend, klankbord, studiegenoot en maatje, al 22 jaar samen. Dat dit proefschrift er ligt is voor een heel groot deel aan jou te danken, en

niet alleen omdat je de opmaak en de cover gedaan hebt (die er beiden geweldig uitzien!). Gedurende dit hele traject was je mijn rots in de branding. Je hebt me door moeilijke periodes heen geholpen en stond altijd klaar om te helpen met praktische zaken als ik het druk had of tegen deadlines aan zat, of door er samen op uit te gaan. Ik prijs mezelf gelukkig met iemand zoals jij. Ik hou van je!

Het dankwoord in deze digitale versie is op sommige punten ingekort.

Chapter 7

Bibliography

Manuscripts based on the studies in this thesis

Chapter 2.1

Utilisation of cardiac pacemakers over a 20-year period: Results from a nationwide pacemaker registry.
De Vries LM, Dijk WA, Hooijschuur CA, Leening MJ, Stricker BH, van Hemel NM.
Neth Heart J. 2017 Jan;25(1):47-55. doi: 10.1007/s12471-016-0880-0.

Chapter 2.2

Trends in service time of pacemakers in the Netherlands: a long-term nationwide follow-up study.
De Vries LM, Leening MJ, Dijk WA, Hooijschuur CA, Stricker BH, van Hemel NM.
Neth Heart J. 2017 Sep;25:581–591. doi: 10.1007/s12471-017-1024-x. [Epub ahead of print]

Chapter 2.3

Trends in replacement and extraction of pacemaker leads in the Netherlands: a long-term nationwide follow-up study.
De Vries, Leening MJ, Dijk WA, Hooijschuur CA, Stricker BH, van Hemel NM.
Submitted

Chapter 3.1

Complications after hip arthroplasty and the association with hospital procedure volume.
De Vries LM, Sturkenboom MC, Verhaar JA, Kingma JH, Stricker BH.
Acta Orthop. 2011 Oct;82(5):545-52. doi: 10.3109/17453674.2011.618907.

Chapter 3.2

Incidence, treatment, and case-fatality of non-traumatic subarachnoid haemorrhage in the Netherlands.
Risselada R, de Vries LM*, Dippel DW, van Kooten F, van der Lugt A, Niessen WJ, Firouzian A,* Stricker BH, Sturkenboom MC.
Clin Neurol Neurosurg. 2011 Jul;113(6):483-7. doi: 10.1016/j.clineuro.2011.02.015.
**These authors equally contributed to this paper.*

Chapter 3.3

A nationwide study of three invasive treatments for trigeminal neuralgia.
Koopman JS, de Vries LM, Dieleman JP, Huygen FJ, Stricker BH, Sturkenboom MC.
Pain. 2011 Mar;152(3):507-13. doi: 10.1016/j.pain.2010.10.049.

Other published manuscripts

IVD Classification – Proposal for a European Rule-based Decision Model.
Hollestelle M, De Bruijn A, De Vries LM, Kraus JJ.
RAJ Devices. 2007;(nov/dec):373-9.

Chapter 8

PhD portfolio

Research skills

2005 – 2006:	Master or Science in Clinical Epidemiology, Netherlands Institute for Health Sciences, Erasmus University, Rotterdam
2006:	Additional courses during the Erasmus Summer Programme
2016:	Workshop Systematic Literature Retrieval in Pubmed
2016:	Workshop Systematic Literature Retrieval in other databases (i.e. Embase)

Teaching

2006:	Supervising medical students during a NIHES course, Erasmus University Medical Center, Rotterdam, the Netherlands

Other

In her capacity as Inspector for Medical Technology at the Dutch Health and Youth Care Inspectorate, she has been involved in several activities regarding the market surveillance of medical devices, amongst others the following:

- Market surveillance activities and studies on implants
- Contribution to the development and implementation of the new medical devices regulations (2012-current)
- Member of the IVD Technical Group and its predecessor; an expert group of European Member States, the European Commission, industry and other stakeholders on regulatory issues regarding in-vitro diagnostic medical devices (2002-current)
- Manager of a project on cosmetic care (2015-current)
- Presentation on cosmetic devices and treatments at the meeting of Competent Authorities on Medical Devices (CAMD) in Amsterdam (2016)
- Several presentations on IVDs, medical technology and legislation for stakeholders

Chapter 9

About the author

Laura Marieke de Vries (1977) did a Master's study in medical biology at the Free University (VU) in Amsterdam. Her first internship was at the Free University Medical Center, department of clinical genetics and antropogenetics, in the research group of prof.dr. Hans Joenje.

This internship was followed by a second internship at the municipal health service GGD Amstelland-De Meerlanden, under supervision of Nicole Penterman. At the GGD, she developed an educational program on public health screening for breast cancer aimed at women of Turkish and Moroccan descent.

In her final year at the university, she followed the graduation course Policy & Management in Healthcare. Part of this course was a six-month internship at the Dutch Healthcare Inspectorate. During this internship, she studied the reports on medical incidents that occurred in hospitals between 1993 and 2000, under supervision of dr. J. de Koning.

In 2005, she also started the work described in this thesis, under supervision of prof.dr. Bruno Stricker. In the same year, she followed the NIHES master Clinical Epidemiology, for which she obtained a certificate in 2006.

She still works at the Inspectorate (which is now called Dutch Health and Youth Care Inspectorate), currently as Coordinating/Specialist Inspector. She is involved in market surveillance and law enforcement activities in the areas of implants and in-vitro diagnostic medical devices. Additionally, she contributed to the development, and is involved in the implementation, of the new regulations on medical devices.