The epidemiology and management of acute urinary retention: A study based on Hospital Episode Statistics and systematic literature review

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Statement of originality and involvement

I, James Armitage confirm that the work presented in this thesis has not previously been accepted in any substance for any degree and is not concurrently submitted in candidature for any degree.

This thesis is the result of my own investigations, except where otherwise stated. Other sources are acknowledged by explicit references and a bibliography is appended.

I hereby give consent for my thesis, if accepted, to be available for photocopying and inter-library loan, and for the title and abstract to be made available to outside organisations.

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Abstract

Acute urinary retention (AUR) is characterised by the sudden and painful inability to pass urine and is common in older men. It causes significant morbidity, frequently results in emergency hospital admission and often requires surgery. The aim of this thesis was to investigate ways of improving the management of men with AUR.

The Hospital Episode Statistics (HES) database of the Department of Health was used to investigate mortality after AUR. In 100,067 men with spontaneous AUR, the one year mortality was 4.1% in men aged 45-54 and 32.8% in those aged 85 and over. In men with spontaneous AUR aged 75-84, the most prevalent age group, the one year mortality was 12.5% in men without comorbidity and 28.8% in men with comorbidity.

The importance of comorbidity on mortality of men with AUR prompted the development of The Royal College of Surgeons of England (RCS) Charlson Score to improve comorbidity identification in HES. The RCS Charlson Score uses an explicit coding philosophy that is simple to use, more accurate than existing adaptations of the Charlson Score, reflects the current understanding of the prognostic impact of comorbidity and allows international comparisons.

Given that many men with AUR are elderly, have significant comorbidity and therefore have a high risk of death, minimally invasive treatment alternatives to surgery for AUR were evaluated. Systematic literature review defined the role of prostatic stents as an effective treatment for frail and elderly men. Although only observational data were available a specifically developed checklist to assess methodological quality gave context to the findings.

This thesis demonstrates that the management of AUR must focus not only on the prostate but also on the patient's overall health status. The urologist should

adopt a holistic approach when assessing and treating men with AUR to ensure the best possible outcomes.

Journal publications arising from this research

Identifying comorbidity in surgical patients using administrative data: the RCS Charlson Score
Armitage JN, van der Meulen JHP on behalf of The RCS Comorbidity Consensus Group
British Journal of Surgery 2010; **97**: 772-781

Mortality in men admitted to hospital with acute urinary retention: database analysis
Armitage JN, Sibanda N, Cathcart P, Emberton M, van der Meulen J
British Medical Journal 2007; **335**(7631): 1199-1202

Epithelializing stent for benign prostatic hyperplasia: a systematic review of the literature
Armitage JN, Cathcart P, Rashidian A, Emberton M, van der Meulen JHP
Journal of Urology 2007; **177**(5): 1619-24

The thermo-expandable metallic stent for managing benign prostatic hyperplasia: a systematic review
Armitage JN, Rashidian A, Cathcart P, van der Meulen JHP, Emberton M
British Journal of Urology International 2006; **98:** 806-810

Incidence of primary and recurrent acute urinary retention between 1998 and 2003 in England
Cathcart PJ, van der Meulen J, Armitage JN, Emberton M
Journal of Urology 2006; **176**(1): 200-4

Role of minimally invasive therapies in the management of benign prostatic hyperplasia

Armitage JN, Emberton M

European Pharmacotherapy. 2006 (www.touchbriefings.com)

Dynamic variables – novel and perhaps better predictors of progression in BPH

Armitage JN, Emberton M

British Journal of Urology International 2006; **97**(3): 439-441

Is it time to reconsider the role of prostatic inflammation in the pathogenesis of lower urinary tract symptoms?

Armitage JN, Emberton M

British Journal of Urology International 2005; **96**(6): 745

Presentations to learned societies arising from this research

An updated and validated approach to identify comorbidity in ICD-10 administrative data

SARS/Section of Academic Urology meeting

Bristol, 2009

Acute urinary retention is associated with an increased risk of mortality

British Association of Urological Surgeons annual meeting

Glasgow, 2007

Acute urinary retention is associated with an increased risk of mortality

American Association of Urologists annual meeting

Anaheim, 2007

Prostatic stents for benign prostatic hyperplasia: systematic literature reviews of the UroLume and Memokath devices

British Prostate Group autumn meeting

Cardiff, 2006

Memokath stent for the management of benign prostatic hyperplasia: a systematic review of the literature

British Association of Urological Surgeons annual meeting (satellite presentation)

Glasgow, 2005

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Section 1

Introduction and general overview

Chapter 1

Introduction

1.1 Introduction and objectives of thesis

This thesis describes work I undertook during a 28 month period as a research fellow at the Clinical Effectiveness Unit of the Royal College of Surgeons of England. It is divided into four sections, each sub-divided into chapters describing differing aspects of this work.

The overall aim of this thesis was to improve the management of men with acute urinary retention (AUR) by studying the epidemiology of AUR and evaluating its treatment options. The specific objectives of this thesis were three-fold. Firstly, to use administrative data from the Hospital Episode Statistics (HES) database of the Department of Health to investigate mortality rates after AUR and explore the effect of comorbid disease. Secondly, to develop an updated and improved comorbidity score that can be used to explore variations in surgical outcome using administrative data such as HES. Thirdly, to consider the management options for men with AUR, especially those who have a high risk of mortality.

Section one is a general introduction and provides the background to the thesis.

Section two considers the epidemiology of AUR. It includes an overview of our current understanding of the aetiology and epidemiology of AUR. The outcome of a man with AUR, in terms of risk of recurrence and the need for surgery, depends upon a number of factors including whether or not the retention episode occurred either spontaneously or after a precipitating event. However, the prognostic importance of AUR in terms of mortality had not been previously investigated. We hypothesised that AUR might be a marker of underlying comorbidity and that men who experience an episode of AUR might have a high risk of mortality. If this hypothesis were true it would have important implications regarding the management of AUR and the need to identify and treat comorbidity. Therefore, HES data are analysed to investigate the mortality of

men with AUR compared to men in the general population of England without AUR and to explore the effects of age and comorbidity.

When using administrative data such as HES for comparative purposes, accurate case-mix adjustment is essential, as differences in patient characteristics (for example, comorbidity) may contribute to observed variations in healthcare outcome. Therefore, a number of instruments have been developed to identify comorbidity in administrative data. A number of disadvantages with the existing comorbidity instruments prompted the development of an updated and simplified comorbidity score (The Royal College of Surgeons of England (RCS) Charlson Score). The RCS Charlson Score was developed by a consensus group of senior surgeons and epidemiologists having first established important general principles for identifying comorbidity in administrative data. The RCS Charlson Score was subsequently validated in patients undergoing a range of surgical procedures using HES data.

Section three concentrates on the definitive minimally invasive treatment options for men with AUR. While transurethral resection of the prostate (TURP) is still considered the most effective surgical treatment for AUR, it is associated with a risk of morbidity and mortality, especially in frail and elderly patients. [Mebust, 1989; Thorpe, 1994; Brierly, 2001; Nadu, 2004] Furthermore, TURP may confer even greater risk to men who have experienced AUR compared to those who have surgery for urinary symptoms alone. [Pickard, 1998] Therefore, a number of minimally invasive treatments have been developed as alternatives to TURP and these are considered in this section. One such treatment is to insert a stent (supportive tube) into the prostate of men with AUR thereby relieving obstruction and allowing spontaneous voiding once more. This section specifically evaluates the effectiveness, durability and safety of the two commonest types of prostatic stent.

The principle aim of this thesis was to investigate how the management of men with AUR could be improved. Section four considers the extent to which this objective has been addressed by the data and studies presented within this thesis. This thesis raises broader issues regarding the appraisal of minimally invasive treatments for AUR and the role of administrative data in the evaluation of the quality of healthcare and these are also discussed.

1.2   Background to thesis

1.2.1 Epidemiology of acute urinary retention

Acute urinary retention

AUR is characterised by the sudden and painful inability to pass urine. It is common in older men, representing a severe and unwanted complication of benign prostatic hyperplasia (BPH). With an ageing population, AUR represents a major public health issue in the Western world. The reported incidence of AUR in large population-based studies varies from 2.2 to 6.8 per 1000 men per year. [Jacobsen, 1997; Meigs, 1999; Verhamme, 2005; Cathcart, 2006] In one of these studies it was calculated that as many as one in ten men in their seventies may experience AUR if they survive for a five-year period. [Jacobsen, 1997]

AUR is a urological emergency that requires immediate treatment by insertion of a urinary catheter that allows the bladder to empty. Most men in the United Kingdom are then admitted to hospital although some patients are discharged immediately and specialist follow-up is arranged as an outpatient. [Manikandan, 2004]

Mortality after acute urinary retention

AUR usually occurs as a result of BPH and as such has often been considered a benign condition. However, AUR usually results in an emergency hospital admission and frequently requires surgery. Moreover, its incidence increases

strongly with age and several studies have also found associations with major morbidities. [McVary, 2006; Michel, 2004; Ozden, 2007] We therefore hypothesised that AUR may in fact be a seminal event that heralds a poor long-term prognosis rather than follow an indolent clinical course. This thesis investigates, for the first time, the risk of mortality in men with AUR and explores the impact of comorbidity.

The Hospital Episode Statistics database
The HES database is an administrative database which is funded and managed by the Department of Health. [Department of Health, 2000] Since 1989 records of all patients admitted to NHS hospitals in England have been added to the database. Each record includes information on the patient's demographic characteristics as well as details of the admission itself - dates of admission and discharge, and details of the patient's main and supplementary diagnoses and operations.

Although initially developed for administrative purposes, the HES database provides a rich source of clinical data that can be reliably used to investigate important research questions. [Roberts, 2003; Aylin, 2007] Moreover, the report from the inquiry into mortality in a paediatric cardiology department in Bristol suggested that 'the HES database should be supported as a major national resource which can be used reliably, with care, to undertake the monitoring of a range of healthcare outcomes'. [Bristol Royal Infirmary Inquiry, 2001] Consequently, the HES database was chosen to investigate mortality in men after AUR through linkage with mortality data from the Office for National Statistics. [Office for National Statistics]

Identifying comorbidity
When considering mortality after AUR, or indeed any other healthcare outcome, the presence and severity of comorbid disease are important prognostic factors. Several instruments have been developed for identifying comorbidity using

administrative data [Elixhauser, 1998; Ghali, 1996; von Korff, 1992] and of these adaptations of the Charlson Score are the most widely used and validated. [Charlson, 1987; Deyo, 1992; Halfon, 2002; Nuttall, 2006; Quan, 2005; Romano, 1993; Sundararajan, 2004] A version of the Charlson Score that has previously been validated in patients undergoing urological cancer surgery using HES data [Romano, 1993; Nuttall, 2006] was therefore used to identify comorbidity in patients with AUR and explore its influence on mortality.

However, a limitation of the Charlson Score, and indeed other comorbidity instruments, lies in its poor ability to distinguish conditions that existed prior to hospital admission from those that occurred at some point during the admission and represent complications of care rather than comorbidities. Furthermore, the Charlson Score was developed in a group of medical patients more than 20 years ago and the prognostic significance of many of the conditions which it describes has now changed considerably. Therefore, with the specific intention of developing an updated and improved version of the Charlson Score for use with administrative data, a consensus meeting was convened at the Royal College of Surgeons of England. Chapter 4 is a methodological chapter that describes the development and validation of the RCS Charlson Score.

1.2.2 Management of acute urinary retention

Treatment of acute urinary retention

After the acute period most men with AUR will be offered a 'trial without catheter' (TWOC) and about half will resume spontaneous voiding. [McNeill, 2004] Most men who fail a TWOC, experience a recurrent episode of AUR, or have moderate or severe lower urinary tract symptoms (LUTS) that are refractory to medical management will be considered for surgery.

TURP is still considered the 'gold standard' and is used as a reference against which other treatment modalities are assessed. After TURP, urinary symptoms are improved and objective increases in urinary flow rates are substantial. Long-

term outcomes are favourable with re-operation rates of only 1-2% per year. [Madersbacher, 2004] Technological and anaesthetic advances have considerably reduced the morbidity associated with TURP to low but not insignificant levels. A recent review of contemporary TURP series reported a very low incidence of perioperative complications (transfusion, 0.4%; TUR syndrome, 0%; urinary tract infection, 1.7%; and clot retention, 2%). [Rassweiler, 2006] The commonest late complications were urethral stricture (2.2-9.8%) and bladder neck stenosis (0.3-9.2%). Urinary incontinence was very rare (<0.5%).

However, the morbidity and mortality of TURP in frail and elderly patients is considerably higher [Mebust, 1989; Thorpe, 1994; Brierly, 2001; Nadu, 2004] and in those who have significant comorbidity surgery is not feasible at all. For example, a United Kingdom audit that included men aged over 80 years who had a TURP reported an early complication rate of 41% and a late complication rate of 22%. [Brierly, 2001] Another large audit in the United Kingdom found a significantly higher post-operative mortality rate after TURP in men with comorbidity than in those without. In men with ASA (American Society of Anesthesiologists) scores 3-4 mortality within 90 days of surgery was 8.8% (15/170 men) compared to only 2.0% in those with ASA scores 1-2 (10/458 men) (p<0.05). [Thorpe, 1994] Furthermore, men who died within 90 days of TURP were significantly older (75 years) than those who survived (71 years) (p<0.001). For these reasons minimally invasive treatments have been developed that aim to provide comparable effectiveness but lower morbidity than TURP.

The vast majority of these minimally invasive treatments are designed to reduce the bulk of the prostate by either ablating or removing the obstructing tissue. For example, transurethral microwave thermotherapy (TUMT) and transurethral needle ablation (TUNA) use thermal energy to cause coagulative necrosis and hence destruction of prostatic tissue. Similarly, lasers can be used at low power to ablate, or at higher power settings to resect or 'enucleate' the prostate. The prostate has been injected with various substances (water, ethanol, botulinum

toxin) and prostatic stents (supportive tubes) have been inserted into the prostate in an attempt to relieve obstruction. Unfortunately, the rapidity with which many of these technologies have been developed has often precluded adequate assessment of their effectiveness, durability and safety. Most have not been subjected to comparison with TURP in randomised controlled trials and instead we are often reliant on very limited research evidence of their performance. However, adequate evaluation of these technologies is essential so that the clinician can provide patients with accurate information and ensure that the most appropriate treatments are offered to them.

Perhaps the most appropriate next step in the evaluation of minimally invasive treatment alternatives to TURP is by systematic review. A systematic literature review is a summary of the research evidence that uses explicit methods to identify, appraise, select and synthesise relevant studies. It not only provides information on the effectiveness, durability and safety of a treatment but can also identify gaps in the evidence base and help to direct future research. This thesis includes two systematic reviews that evaluate the performance of the two commonest types of prostatic stent that are used in the treatment of AUR (Chapters 6 and 7).

In summary, this thesis for the degree of Doctor of Medicine (Research) aims to answer important questions regarding the epidemiology and management of AUR. This programme of work has the potential to improve the quality of care offered to the huge number of men who experience AUR - approximately 27,000 per year in the United Kingdom. [Armitage, 2007; Cathcart, 2006] It may also help to enhance the role of administrative databases such as HES as resources for healthcare monitoring and evaluation.

1.3 Practical considerations

The Clinical Effectiveness Unit (CEU) of the Royal College of Surgeons of England is an academic collaboration between the Health Services Research Unit of the London School of Hygiene and Tropical Medicine of the University of London and the Royal College of Surgeons of England. It was established in 1996 with a remit to study "the epidemiology of the quality of surgical care". It benefits from a unique combination of clinical and epidemiological expertise and since its inception has gained an international reputation as a leader in this field.

In 2005, the Director (Professor Jan van der Meulen) and the Clinical Director (Professor Mark Emberton) of the CEU appointed a research fellow (Mr James Armitage), who would be responsible for the day-to-day management and coordination of a two year research project to investigate the epidemiology and management of AUR. The entire study was funded by the Bob Young Research Fellowship, the Dunhill Medical Trust, and the Research Fellowship Scheme of the Royal College of Surgeons of England.

The vast majority of the work in this thesis has been undertaken by me. However, in the conduct of the research my supervisors, Professor van der Meulen and Professor Emberton, and I worked as a team whereby we each contributed ideas. I performed all of the analyses presented here, although statistical and methodological guidance was provided by Professor van der Meulen. All literature searches and background research were conducted by me, and the entire text has been written by me under the guidance of my two supervisors. This thesis represents original work, although some aspects of the work have been based on methods used by other workers, and where this is the case appropriate references have been provided.

Section 2

The epidemiology of acute urinary retention

Chapter 2

Description of the epidemiology of acute urinary retention

2.1   Objectives

The objectives of this chapter are to describe in brief our current understanding of the aetiology and epidemiology of AUR as well as the natural history of BPH as background information for readers of this thesis.

2.2   Description of the aetiology and epidemiology of acute urinary retention

2.2.1   Aetiology of acute urinary retention

The aetiology of AUR remains poorly understood although a number of factors may contribute to its occurrence. These can be broadly divided into three categories. [Choong, 2000] The first relates to mechanical or dynamic obstruction to the normal flow of urine. This usually occurs in men because enlargement of the prostate as a result of BPH causes obstruction of the bladder outlet. Secondly, interruption to the normal sensory innervation of the bladder wall or to the motor supply of the detrusor muscle can result in AUR. The third relates to situations where the bladder is allowed to over-distend. This classically occurs after surgery, especially if carried out under general anaesthesia, where the risk of AUR is often compounded by post-operative pain, an increased adrenergic outflow, and the use of opioid or anticholinergic medication.

The precise mechanisms leading to AUR are unclear. Prostatic infarction, increased alpha-adrenergic activity, a low ratio of stromal to epithelial tissue, various neurotransmitters, and more recently prostatic inflammation have all been implicated. [Spiro, 1974; Choong, 2000; Armitage, 2005]

For example, it is hypothesised that prostatic infarction leads to neurogenic disturbance in the peri-urethral zone with a subsequent failure of smooth muscle

relaxation. In a study that analysed the prostatectomy specimens of men who had undergone open surgery for either AUR or symptomatic BPH, histological evidence of prostatic infarction was present in 85% of the AUR specimens compared to just 3% of the BPH specimens. [Spiro, 1974] However, this observation was not supported by a later prospective study that found the rates of infarction in TURP specimens did not differ significantly between men who had and those who had not experienced AUR. [Anjum, 1998]

Prostatic inflammation has also been proposed as an aetiological factor in the occurrence of AUR. Until recently, most of the evidence to support this hypothesis was based on studies that have looked at histological specimens obtained after TURP. [Nickel, 1999; Soler, 1999] However, analysis of the outcomes of 1,197 patients enrolled in the Medical Therapy of Prostatic Symptoms (MTOPS) study who had transrectal prostate biopsy provides further evidence for the role of prostatic inflammation. [Roehrborn, 2005; McConnell, 2003] Overall, during the 4.5 years follow-up, patients with prostatic inflammation were significantly more likely to develop AUR than those without (2.4 vs. 0.6%, p=0.011). The finding that challenges current views on the pathogenesis of progression were in the placebo group, in which, in the presence of inflammation, 5.6% went on to develop AUR compared to none of the patients with no prostatic inflammation.

Benign prostatic hyperplasia
BPH is the commonest benign neoplasm in men and a major aetiological factor in the occurrence of AUR. The term BPH is, however, the source of considerable confusion. It is a histological diagnosis characterised by the presence of varying degrees of stromal and epithelial hyperplasia. Its prevalence increases with age such that approximately 60% of men in their fifties and 90% of men in their eighties have evidence of the disease. [Berry, 1984]

Hyperplasia of both stromal and epithelial elements of the prostate is thought to result from abnormal cellular proliferation and glandular apoptosis. [Zhang, 2006] Androgens are believed to play a permissive role, a fact supported by the observation that boys castrated before puberty do not develop BPH. [White, 1895] Dihydroxytestosterone is synthesised from testosterone predominantly by the stromal cells where it exerts autocrine and paracrine effects. It binds to androgen receptors in stromal and epithelial cells and signals the transcription of growth factors that are mitogenic to both of these cell types.

BPH may be evident anatomically as benign prostatic enlargement. Also, the relatively inflexible prostate capsule means that cellular proliferation in the peri-urethral and transitional zones can lead to compression of the urethra and therefore bladder outflow obstruction. This may result in the clinical manifestations of the disease such as lower urinary tract symptoms (LUTS) and AUR.

2.2.2 Incidence of acute urinary retention

Recent community-based studies have provided some insight into the incidence of AUR both in the general population and in men who have sought medical advice who are presumed to have BPH.

Incidence of acute urinary retention in the general population
A recent study based on the HES database estimated an incidence of AUR in England of 3.1/1000 men per year. [Cathcart, 2006] A Dutch epidemiological study, the only population-based study to date in which the incidence of AUR was estimated through direct access to a prospectively collected primary care database, reported a slightly lower incidence of 2.2/1000 men per year (95% confidence interval (CI), 2.0-2.4). [Verhamme, 2005] Two large community-based studies provided estimates of the incidence of AUR in the United States. The Olmsted County Study followed 2,115 community-dwelling men for a total of 8,344 person years. [Jacobsen, 1997] The overall incidence of AUR was

6.8/1000 men per year (95% CI, 5.2 to 8.9). During 15,851 person years of follow-up, the Health Professionals Study reported an incidence of 4.5/1000 men per year (95% CI, 3.1 to 6.2). [Meigs, 1999]

Incidence figures for AUR in community dwelling men therefore range considerably from 2.2/1000 men per year to 6.8/1000 men per year. The lowest incidence figure (2.2/1000 men per year) reported in the Dutch study may be explained by their strict case definition which required evidence both of a sudden inability to pass urine and of catheterisation. The higher incidences reported in the American studies may be explained by selection bias as these studies included only men who had responded to a detailed questionnaire. In other words, men with more bothersome urinary symptoms, and therefore a greater risk of developing AUR, [Jacobsen, 1997; Meigs, 1999; Roehrborn, 1999] are more likely to have completed a questionnaire enquiring about severity of LUTS.

Incidence of acute urinary retention in men with BPH
The incidence of AUR in men with clinically diagnosed BPH has been found to be appreciably higher than in men in the general population who have not sought a medical opinion for LUTS suggestive of BPH. [Barry, 1997; McConnell, 1998; McConnell, 2003; Verhamme, 2005]

A cohort of 500 men with clinical BPH who were candidates for prostatectomy but elected to be treated non-operatively were followed-up for four years although only 371 were evaluable at the end of the study period. [Barry, 1997] Forty men experienced AUR in 1,574 person-years of follow-up to give an incidence figure of 25/1000 men per year. The Dutch database study also evaluated the incidence of AUR in men with newly diagnosed LUTS or BPH. [Verhamme, 2005] The incidence of AUR in this cohort was 18.3/1000 men per year (95% CI, 14.5-22.8), considerably higher than the overall incidence of 2.2/1000 men per year.

The placebo arms of the Proscar Long-term Efficacy and Safety Study (PLESS) and MTOPS trial also provide excellent opportunities to observe the natural history of clinically diagnosed BPH. [McConnell, 1998; McConnell, 2003] In PLESS, men were randomised to receive either finasteride (a 5-alpha reductase inhibitor) or placebo. In 1,376 placebo-treated men with enlarged prostates and moderate LUTS the incidence of AUR was 18/1000 men per year. In the placebo arm of the MTOPS study, the overall incidence of AUR was 2%, or 6/1000 men per year. However, the low figure reported in the MTOPS study is likely to be an underestimate of the true incidence of AUR for the following reasons. First, men who experienced other markers of BPH disease progression (worsening of International Prostate Symptom Score by ≥4 points, recurrent urinary tract infections, renal insufficiency, or incontinence) were censored and AUR, if it subsequently occurred, was not recorded. Second, the MTOPS trial excluded all men with precipitated AUR (urinary retention after a triggering event, see later) unless a TWOC was unsuccessful.

2.2.3   Risk factors for acute urinary retention

Several risk factors for the development of AUR have been identified. The Health Professionals Followup Study found that both age and baseline symptom severity increased the risk of AUR. [Meigs, 1999] In men with mild symptoms the incidence increased from 0.4/1000 men per year in men aged 45 to 49 years to 7.9/1000 men per year in those aged 70 to 83 years. In men with moderate or severe symptoms the incidence rates increased from 3.3/1000 men per year to 11.3/1000 men per year for the youngest and oldest age-groups respectively. Furthermore, each of the seven domains comprising the International Prostate Symptom Score (IPSS) was found to predict AUR. A sensation of incomplete voiding, urinary frequency and a poor urinary stream had the strongest predictive values.

Age, symptom severity, prostate volume, and urine flow rates were identified as independent risk factors for the occurrence of AUR in the Olmsted County Study.

[Jacobsen, 1997] The incidence of AUR increased from 2.6 to 9.3/1000 men per year for men in their forties to seventies if they had mild symptoms, and from 3.0 to 34.7/1000 men per year if they had moderate or severe symptoms. The relative risk (RR) of AUR increased for men with moderate or severe symptoms (RR 3.2), those with flow rates of less than 12ml/s (RR 3.9), and those with prostate volumes of greater than 30ml (RR 3.0), all compared to a baseline risk of 1.0 for the corresponding groups.

Data from the placebo arm of the PLESS study demonstrated that prostate volume, PSA and symptom severity were all predictors of AUR occurrence. [Roehrborn, 1999] In men with a serum PSA of less than 1.4ng/ml, the incidence of AUR increased from 5.6% for those with mild symptoms to 7.7% for those with severe symptoms, and in men with a PSA of more than 1.4ng/ml the respective incidences were 7.8% and 10.2%.

A pooled analysis of data from the placebo-treatment arms of PLESS [McConnell, 1998] and three other prospective randomised controlled trials each with 2 years follow-up [Anderson, 1995; Nickel, 1998; Marberger, 1998] was undertaken by Roehrborn. [Roehrborn, 2001] Serum PSA and prostate volume were found to be strong predictors of AUR. Interestingly, from more than 110 variables that were assessed, the logistic models with PSA alone performed almost as well as expanded models that included PSA, urinary frequency and hesitancy, flow rate parameters and urinary symptoms.

An individual's response to treatment has recently been identified as a predictor of the risk of BPH disease progression and AUR. [Armitage, 2005] In the Health Professionals Followup Study, the incidence of AUR was higher in patients whose overall or individual LUTS had worsened over a two-year period independent of baseline severity. [Meigs, 1999] This observation was supported by data from the Alf-One study in which 3,514 patients with LUTS were treated with the alpha-receptor blocker alfuzosin 10mg daily. [Emberton, 2005] A prior

episode of AUR was found to be the most important predictor of AUR (Hazard Ratio 6.35, 95% CI 2.31 to 17.40; p<0.01). However, the next strongest predictors of AUR were IPSS worsening of 4 or more points (HR 3.34, 95% CI 1.11 to 9.99; p=0.03) and a bother score greater than 3 at endpoint (HR 3.32, 95% CI 1.29 to 8.53; p<0.01). Deteriorating urinary symptoms were similarly associated with an increased risk of BPH surgery.

2.2.4 Spontaneous and precipitated acute urinary retention

AUR may be classified as occurring either spontaneously or after a triggering event. [Jacobsen, 1997; Roehrborn, 2000] Retention episodes preceded by surgery, anaesthesia, or ingestion of medications such as alpha-sympathomimetics, over-the-counter cold medications, antihistamines or anticholinergics may be classified as *precipitated* AUR. All other episodes of retention not preceded by a triggering stimulus may be considered to be *spontaneous* AUR. This is an important distinction as patients with spontaneous and precipitated AUR are likely to have different outcomes.

For example, almost half of the men who experienced AUR in the Olmsted County study were identified as having undergone a surgical procedure prior to retention, 90% of whom had had a general anaesthetic. [Jacobsen, 1997] Of these men with precipitated AUR, only 14% (eight patients) subsequently required surgery and only one patient experienced a further episode of retention within the four year study period.

In the PLESS study, of 1,503 placebo-treated patients, 99 experienced one or more episodes of AUR over the four-year follow-up period. [Roehrborn, 2000] Approximately equal proportions had spontaneous and precipitated AUR. Of the 52 patients who had spontaneous AUR, nine (17%) experienced a recurrent episode of retention. The recurrence rate after precipitated AUR was similar – 10 out of 47 patients (21%). However, a significantly greater proportion of

patients with spontaneous AUR went on to receive surgical intervention (75%) compared to those with precipitated AUR (26%).

Of the 344 patients who experienced AUR in the Dutch epidemiological study [Verhamme, 2005], more than 40% were considered to have had precipitated retention. AUR was preceded by a procedure (surgery, urological interventions, anaesthesia) in 77 cases (22%) and a further 72 cases (21%) were preceded by a urinary tract infection, the presence of a neurological disorder, or treatment with a drug that has been associated with AUR

2.2.5 Outcome of acute urinary retention

AUR is initially treated by inserting a urinary catheter. The catheter is usually introduced urethrally, although some urologists favour a suprapubic approach. [Desgrandchamps, 2006; Manikandan, 2004] The suprapubic procedure is more complex and requires an additional level of training that is usually only attained by urologists. Suprapubic catheterisation is associated with different morbidity compared to the urethral approach with bowel perforation the most feared complication. An audit of more than 200 patients who had a suprapubic catheter inserted under cystoscopic guidance (not for AUR) reported an overall complication rate of 29% within 30 days including a 2.4% incidence of bowel perforation. [Ahluwalia, 2006] Mortality in this series was 1.8%. Recent innovation in suprapubic catheter design, for example the Mediplus catheter which employs the Seldinger technique, aims to reduce the morbidity of the procedure.

However, for men with AUR who have not had previous abdominal surgery and where there is appropriate surgical expertise available, a suprapubic catheter may confer a number of advantages over a urethral catheter. For example, it may be associated with a lower incidence of urinary tract infection, [Horgan, 1992] and may be less uncomfortable, easier for the patient to manage, and more cost-effective than a urethral catheter. [Ichsan, 1987] What is more, a

suprapubic catheter can be clamped to assess whether or not a man can resume spontaneous voiding, negating the discomfort of removal and the trauma of catheter reinsertion if the patient is unable to pass urine.

Clean intermittent self-catheterisation after a short period of indwelling catheterisation has been advocated by some urologists. [Patel, 2001] Intermittent catheterisation has several advantages over an indwelling catheter. It allows a patient to restore normal bladder 'cycling', permits sexual activity, and reduces the incidence of bacterial colonisation of the urinary tract.

Trial without catheter
AUR on a background of LUTS attributable to BPH was once considered an absolute indication for surgery. Today, most men who experience AUR are first considered for a TWOC to determine whether or not they are able to resume spontaneous voiding. [Desgrandchamps, 2006; Manikandan, 2004] Men who are unable to pass urine when the catheter is removed are usually considered for TURP.

The administration of an alpha-receptor blocker has been shown to increase the chance of a successful TWOC. A recent randomised controlled trial reported a successful TWOC in 61.9% of men who were given a minimum of two doses of alfuzosin 10mg once daily prior to catheter removal compared to 47.9% who received placebo. [McNeill, 2004] Elderly patients (over 65 years) and those with residual urine volumes of more than one litre were less likely to have a successful TWOC but administration of alfuzosin almost doubled the likelihood of success.

A related study that reported longer follow-up (mean 7.2 months) of patients who had undergone a successful TWOC found that most (68%) required no further intervention. [McNeill, 1999] The other 32% experienced recurrent AUR or went on to have a TURP. Increased post-void residual urine after TWOC was found

to predict recurrent AUR and the need for surgery but no other prognostic factors, for example age or residual urine volume, were identified.

A successful TWOC and resumption of spontaneous voiding is desirable for a number of reasons. First, the morbidity and inconvenience associated with indwelling catheters is well documented. [Kohler-Ockmore, 1996] Second, catheter removal permits a thorough evaluation of a patient's symptoms and careful consideration of the merits of surgical intervention. Third, the absence of a catheter may reduce the incidence of sepsis if surgical intervention is required. [Hargreave, 1982; Cravens, 2000] Fourth, the morbidity and mortality associated with prostatectomy after AUR may be greater than that of surgery for urinary symptoms alone. [Mebust, 1989; Pickard, 1998]

It is not always straightforward to predict which patients will successfully void after catheter removal following AUR. Furthermore, consensus has not been reached on the optimal duration of catheterisation prior to TWOC. A recent study randomised 114 men presenting with AUR to one of three groups: 'in-and-out' catheterisation or TWOC at two days or seven days after catheter insertion. [Djavan, 1998] TWOC was successful in 44%, 51% and 62% of patients in the respective groups, suggesting that the success of TWOC increased with longer periods of catheterisation. This study also found that men aged less than 75 years, with retention volumes of less than 1000ml, and detrusor pressures at peak flow of greater than $35cmH_2O$ had better chances of successful voiding independent of duration of catheterisation. Patients with retention volumes of more than 1300ml had better outcomes with longer periods of catheterisation before TWOC.

Long-term outcome of acute urinary retention (recurrence and surgery)
The introduction of medical treatments for BPH, specifically alpha-receptor blockers and 5-alpha reductase inhibitors, in the Nineteen Nineties has revolutionised the management of LUTS and AUR. Both alpha-receptor blockers

and 5-alpha reductase inhibitors have been shown to improve urinary symptoms associated with BPH. Moreover, 5-alpha reductase inhibitors have also been shown to substantially reduce the risk of AUR. [Roehrborn, 2000; McConnell, 2003] Furthermore, there is good evidence that the number of TURPs being performed both in the United Kingdom and in the United States is falling and that this corresponds to the increased use of BPH drug treatments. [Cathcart, 2006; Logie, 2005; Wasson, 2000]

Prior to the regular use of BPH drug treatments, a prospective study of 228 men presenting with AUR found that 56% experienced recurrent retention within 1 week and 68% had recurrence within 1 year. [Klarskov, 1987] Factors that predicted AUR recurrence in this study were retention volumes of greater than 500ml, maximum urine flow rates of less than 5ml/s after catheter removal, and the absence of a precipitating event.

In the placebo arm of men recruited to the PLESS trial, 99 men experienced AUR. [Roehrborn, 2000] Of the 52 men who had spontaneous retention, 17% experienced recurrent AUR compared to 21% of the 47 men with precipitated AUR. However, 39 men (75%) with spontaneous AUR subsequently required surgery compared to just 12 (26%) of those with precipitated retention. For men treated with a 5-alpha reductase inhibitor (finasteride), four (20%) with spontaneous AUR and three (14%) with precipitated AUR experienced recurrent retention. There was a significant between-group difference in the incidence of surgery following spontaneous AUR - only eight of the 20 (40%) finasteride-treated patients who experienced spontaneous AUR required surgery compared to 39 of the 52 (75%) placebo-treated patients.

Recurrence after AUR was estimated in an English population through analysis of HES data. [Cathcart, 2006] Rates of recurrence within six months after AUR were higher after spontaneous (20%) than after precipitated (5%) retention. Similarly, the proportion of patients requiring surgery within six months after AUR

was higher after spontaneous retention (about 30%) than after precipitated AUR (about 6%).

2.2.6 Summary

Although the precise aetiology of AUR remains unclear, it often occurs in men as a complication of BPH. Several risk factors for AUR have been identified including patient age. Therefore, with an ageing population the high incidence of AUR in the Western world is likely to increase further still and represent a major public health issue.

The management of AUR has changed considerably since the introduction of medical therapy that has been shown to reduce the risk of developing AUR and to improve the chance of resuming spontaneous voiding in those men who do experience AUR. Effective medical therapy has therefore resulted in a decline in the number of TURPs that are now performed. The studies presented here also highlight an important differentiation between AUR that occurs spontaneously from that which occurs after a precipitating event. Patients with precipitated AUR are less likely to experience recurrent AUR or go on to require surgery. A distinction between spontaneous and precipitated AUR becomes apparent once more when mortality is investigated in Chapter 3.

Chapter 3

Exploring the hypothesis that acute urinary retention confers a high risk of mortality

3.1 Objectives

This chapter investigates the hypothesis that AUR may be a 'harbinger' of severe systemic disease and therefore predicts a poor long-term prognosis. We use administrative data from the Hospital Episode Statistics (HES) database of the Department of Health to investigate mortality rates after AUR and explore the effect of comorbid disease.

3.2 Methods

3.2.1 Data

We extracted data from the HES database, an administrative database of all admissions to National Health Service hospitals in England. [Department of Health, 2007] Admissions between 1st April 1998 and 31st March 2005 were included. A unique patient identifier allowed us to link records of different hospital admissions of the same patient. Each HES record contains diagnostic fields coded according to the International Classification of Diseases (ICD-10) [World Health Organisation, 1994] and operative procedure fields coded according to the UK Tabular List of the Classification of Surgical Operations and Procedures. [Office of Populations Censuses and Surveys, 1996] For all admissions after 1st April 1998, the HES database was linked to the mortality database of the Office for National Statistics. [National Centre for Health Outcomes Development] In 2.4% of men who were reported as having died after AUR, a record of a subsequent hospital admission was found. For these contradictory results, the information on death was considered to be erroneous and these men were therefore analysed as being alive until the end of the study period.

3.2.2 Definitions

A patient was considered to have had primary AUR (AUR for the first time), if there was no record in the HES database of a previous admission for AUR in at least the preceding 6 months. A period of 6 months was chosen because about 80% of men who experience recurrence do so within this time period. [Cathcart, 2006]

Furthermore, AUR was defined as spontaneous if AUR (R33) was recorded in the first diagnostic field, or if BPH (N40) was the primary diagnosis and AUR was recorded in another diagnostic field. All other cases of AUR were considered precipitated. [Cathcart, 2006; McNeill, 2004; Roehrborn, 2000]

3.2.3 Inclusion criteria

To identify admissions of men aged over 45 years who had primary AUR, we followed a step-wise process. First, we selected the records of all 229,089 men who were admitted at least once with an ICD-10 code indicating AUR (R33) in any of the first seven diagnostic fields between 1st April 1998 and 31st March 2005. Second, we sequentially deleted the records of 29,924 patients with an ICD-10 code indicating prostate cancer (C61), of 1,150 patients with a code indicating multiple sclerosis (G35), and of 6,380 patients with a code indicating Parkinson's disease (G20) in any diagnostic field of any record. Third, we excluded the records of 15,592 men who were admitted for AUR in the period between 1st April 1998 and 30th September 1998 in order to include only men with primary AUR.

3.2.4 Identification of comorbidity

We used an adaptation of the Charlson Score designed for use with administrative data. [Charlson, 1987; Romano, 1993] This score was validated in HES data for patients undergoing urological cancer surgery in England. [Nuttall, 2006] Comorbid disease was defined as present if it appeared in the

records of the index admission (the admission for primary AUR) or of hospital admissions that occurred in the 6 months preceding AUR.

3.2.5 Statistical analysis

The Kaplan-Meier method was used to estimate age-specific mortality within 90 days and 1 year after primary AUR. To compare mortality within the first year after AUR to that of men in the general population, standardised mortality ratios (SMRs) were calculated according to age and comorbidity. Age-group and calendar year-specific mortality rates of men in the general population of England in the years 1999 to 2005 were used as standard rates. The standardised rates were calculated by dividing the mid-year estimate of the number of men within an age-group alive in England and Wales by the number that died during that year. The confidence intervals for the SMRs were obtained using Byar's approximation. [Breslow, 1987]

3.3 Results

Between 1st October 1998 and 31st March 2005, 176,046 men were admitted to NHS hospitals with a diagnosis of primary AUR (Table 3.1). Of these men, 100,067 (56.8%) had spontaneous AUR and their mean age was 73.5 (SD 10.5) years. 75,979 men (43.2%) had precipitated retention and their mean age was 74.5 (SD 10.9) years. In all age-groups, men with precipitated AUR had a higher mortality than men with spontaneous AUR.

Overall, 14.7% of men with spontaneous AUR and 25.3% of men with precipitated AUR died within the first year (Table 3.1). Roughly half of these deaths (54.9%) occurred within the first 90 days.

In men with spontaneous AUR, 1-year mortality increased strongly with age from 4.1% in patients aged between 45 and 54, to 32.8% in those aged over 85 years

(Table 3.1). In men with precipitated AUR, 1-year mortality increased to a similar extent in the corresponding age-groups from 9.5% to 45.4%.

Although the highest 1-year mortality was observed in the oldest age-groups, the age-specific relative increase in mortality was highest in the youngest age-groups (Table 3.1). In men aged between 45 and 54 years with spontaneous AUR, there was a 10-fold increase and in men with precipitated AUR an almost 24-fold increase in mortality compared to the general population. In men aged over 85 years with spontaneous AUR, there was a 1.7-fold increase and in men with precipitated AUR a 2.4-fold increase.

More than one third of men with AUR were found to have at least one major comorbid condition as defined by the Charlson Score (Table 3.2). As expected, comorbidity was more prevalent in men with precipitated AUR (43.5%) than in men with spontaneous AUR (29.1%). The presence of comorbidity greatly increased mortality. For example, in men with spontaneous AUR aged between 75 and 84 years, the most frequent age-group, the presence of comorbidity more than doubled the 1-year mortality from 12.5% to 28.8%. In men with precipitated AUR in the corresponding age-group, the presence of comorbidity had a similar effect, and 1-year mortality increased from 18.1% to 40.5%.

Very high 1-year mortalities were observed in men with comorbidity in the oldest age-group (44.3% in men with spontaneous AUR and 54.7% in men with precipitated AUR). However, the age-specific relative increase compared to the general population is again highest in the youngest age-group (SMR of 36.5 in men with spontaneous AUR and 60.4 in men with precipitated AUR).

Even in men without comorbidity as defined by the Charlson Score, mortality within the first year after AUR was considerably higher than in the general population (Table 3.2). For example, in men with spontaneous AUR without comorbidity mortality was 4.4 times higher than in the general population in the

youngest age-group and 1.4 times higher in the oldest age-group. Similarly, in men with precipitated AUR without comorbidity, mortality was 8.4 times higher in the youngest age-group and 2.0 times higher in the oldest age-group.

3.4   Discussion

Mortality after primary AUR in men admitted to hospital is very high. Overall, we found that one in seven men with spontaneous AUR and one in four with precipitated AUR died in the first year. Mortality rates increased strongly with age and the presence of comorbidity. Consequently, about half of the men aged over 85 years with at least one comorbid condition died within the first year after AUR. Although mortality in men younger than 55 years without comorbidity is not as high, it was still at least 4 times higher than that observed in men of similar age in the general population.

3.4.1 Methodological limitations

We report the mortality of men with AUR who were admitted to hospital. Men who were treated within a primary care setting and those who were treated solely in a hospital emergency department were not considered. Those patients may have been in a better overall condition than the patients who were admitted. However, according to a recent survey, only 10% of UK urologists would not admit men who present with AUR to hospital. [Manikandan, 2004]   Also, a recent Dutch epidemiological study, the only population-based study to date in which the incidence of AUR was estimated through direct access to a prospectively collected primary care database, reported an incidence of 2.2 per 1000 men per year. [Verhamme, 2005] This is lower than the AUR incidence of 3.1 per 1000 men per year that we reported previously based on hospital admissions in England. [Cathcart, 2006] It is therefore unlikely that our study missed a substantial number of men with AUR.

The Charlson Score based on administrative data underestimates the prevalence of comorbid disease. [Romano, 1993a; Schneeweiss, 2000] Undetected comorbidity may account for our observation that AUR patients without comorbidity according to the Charlson Score still had a higher mortality than the general population. Nonetheless, we found that the Charlson Score identified at least one comorbid condition in more than a third of men with AUR and that mortality was most increased in this group. A more accurate instrument would have demonstrated an even more marked impact of comorbidity.

The mortality after AUR reported in this study is based on the linkage between the HES database of all admissions to NHS hospitals in England and the mortality database of the Office for National Statistics. 96% of patients had a date of death that was based on very robust linkage methods that relied on an exact match of at least two of the following three domains: NHS number (a unique 10 digit code allocated to an individual to enable identification for NHS healthcare), date of birth, and postcode. For these patients, we found contradictory linkage results (i.e. an admission date after a date of death) in only 0.3% of patients. In the remaining 4% of patients, a less robust linkage method (partial match of date of birth, and exact agreement of sex and postcode) was used and contradictory results were found in 54% of the patients. As explained before, men with contradictory mortality results were analysed as being alive until the end of the study period. Sensitivity analyses found that the mortality for all men within 1 year after AUR changed by less than 0.5 percent point, and in turn the relative increases in mortality compared to the general population did not change appreciably.

3.4.2 Comparison with other studies
This is the first study that specifically reports longer-term mortality after AUR. The only study to date that provides some evidence on mortality after AUR was carried out in 5 healthcare regions in the UK in the mid Nineties in 3,966 men who underwent prostatic surgery. [Pickard, 1998] This study demonstrated that

the 1,242 men who underwent a prostatectomy after AUR had a higher mortality in the first 90 days (3.0%) than the 2,724 men who had surgery for symptoms alone (0.7%). Other studies that report on outcomes after AUR tend to focus only on recurrence and the need for prostatic surgery. [Roehrborn, 2000; Cathcart, 2006]

AUR shares a number of characteristics with fractured neck of femur. Both are acute and serious age-related events that almost always result in hospital admission. Also, AUR like fractured neck of femur does not directly cause death. Two English studies have recently reported the 1-year mortality in men after fractured neck of femur to be just over 40%. [Roberts, 2003; Roche, 2005] The mortality clearly increased with age from 20% in men aged between 65 and 69 years to 50% in men aged between 85 and 89. [Roberts, 2003] Also for fractured neck of femur, comorbidity was found to be an important predictor of outcome. Mortality in the first year after fractured neck of femur was about 1.5 times higher in patients with at least one comorbid condition than in patients without comorbidity. [Roche, 2005]

The comparison with fractured neck of femur demonstrates that AUR constitutes a health problem of a similar magnitude. The overall 1-year mortality after AUR is 20% which is lower than that observed after fractured neck of femur. However, the incidence of primary AUR is 3.1 per 1000 men per year which is higher than the incidence of fractured neck of femur that can be estimated to be about 2.4 per 1000 men per year based on HES data. [Department of Health, 2007]

3.4.3 Explanations for the increased mortality

AUR is generally considered a urological emergency that if appropriately treated rarely has serious consequences. Our finding of a high mortality in the first year after AUR seems to contradict this. An obvious explanation for the increased mortality is that the occurrence of AUR exposes men to risks associated with

hospitalisation, catheter-related and other nosocomial infections as well as to invasive procedures that often need a general anaesthetic.

While these factors do play a role, the high mortality seems to be linked mainly to comorbidity for a number of reasons. First, the presence of comorbidity according to the Charlson Score substantially increased mortality within patients of similar age and with the same type of AUR. Second, mortality was also higher in patients with precipitated AUR than with spontaneous AUR. Per definition, precipitated AUR occurs after a triggering event that is unrelated to the prostate and therefore a further indication of comorbidity. Third, there appears to be a 'dose - response' relationship as the lowest mortality was found in patients with spontaneous AUR and no comorbidity according to the Charlson Score and the highest mortality in patients with precipitated AUR and comorbidity. Last, a detailed inspection of the diagnostic fields in patients with spontaneous AUR and apparently no comorbidity reveals that 58% of these patients had at least one non-prostate-related diagnosis not captured by the Charlson Score.

Of the patients who had comorbidity according to the Charlson Score, irrespective of the type of AUR, about 30% had cardiovascular disease, 25% diabetes, 25% chronic pulmonary disease, and 15% a malignancy. The relatively high prevalence of cardiovascular disease and diabetes is consistent with the findings of recent aetiological studies linking hypertension and metabolic syndrome with the progression of BPH. [Michel, 2004; Ozden, 2007]

3.4.4 Clinical implications

The high mortality that we observed in hospitalised men with AUR demonstrates that they are a vulnerable group of patients. These observations reinforce the importance to the clinician of adopting a multi-disciplinary approach when assessing and managing men with AUR. [Kirby, 2005] Men who experience AUR should undergo a comprehensive assessment for the presence of comorbid disease and where it is identified it should be treated appropriately. However, the extent to which mortality after AUR can be reduced will depend on the nature

and severity of the comorbidities involved and the effectiveness of the available treatments. For example, some patients will have comorbidity that is already optimally treated and for whom little further can be done.

Our observation that about half of the deaths after AUR occur within the first 90 days suggests that comorbidity assessment must occur promptly. Taking the need to be timely one step further, one could claim that to be most effective screening for other morbidities should start in men presenting with LUTS attributable to BPH before these patients have experienced AUR.

3.4.5 Research implications

The two most important unanswered questions relate to the way in which comorbidities can be identified and the extent to which their treatment will reduce mortality after AUR. In our view, research building on administrative databases, such as the HES database, enriched through linkage with additional clinical data seems to be the obvious next step to answer both questions. First, administrative databases can provide near complete follow-up in terms of further treatment as well as death. Clinical data, perhaps collected prospectively in a subgroup of patients and linked to the administrative data at individual patient level, will allow a further exploration of the impact of comorbidity according to its nature and severity. It can be envisaged that the results of this step will inform the development of treatment strategies. Second, these strategies can then be evaluated using research designs that build on combining administrative data with data derived from clinical trials.

3.5   Tables

Table 3.1: Age-specific mortality within 90 days and 1 year after spontaneous and precipitated primary AUR and standardised mortality ratios (SMR) against the general population of England

		Mortality				
	Total	**90 days**		**1 year**		
Age-group	**Admissions**	**Deaths**	**Rate % (95% CI)**	**Deaths**	**Rate % (95% CI)**	**SMR (95% CI)**
Spontaneous AUR						
45-54	5,580	119	2.2 (1.8-2.6)	216	4.1 (3.6-4.6)	10.0 (8.8-11.5)
55-64	13,918	329	2.4 (2.2-2.7)	692	5.3 (4.9-5.7)	5.0 (4.6-5.4)
65-74	30,661	1,301	4.3 (4.1-4.5)	2,822	9.7 (9.4-10.1)	3.3 (3.2-3.4)
75-84	36,086	2,752	7.8 (7.5-8.0)	6,070	17.9 (17.4-18.3)	2.3 (2.2-2.3)
>85	13,822	2,153	15.8 (15.2-16.4)	4,315	32.8 (32.0-33.7)	1.7 (1.6-1.7)
Total	**100,067**	**6,654**	**6.7 (6.5-6.8)**	**14,115**	**14.7 (14.5-14.9)**	**2.2 (2.2-2.3)**
Precipitated AUR						
45-54	4,979	276	5.6 (5.0-6.3)	453	9.5 (8.7-10.4)	23.6 (21.5-25.9)
55-64	8,736	625	7.2 (6.7-7.8)	1,043	12.5 (11.8-13.2)	12.0 (11.3-12.8)
65-74	20,461	2,095	10.3 (9.9-10.8)	3,492	17.8 (17.3-18.3)	6.1 (5.9-6.3)
75-84	28,148	4,551	16.4 (15.9-16.8)	7,711	28.7 (28.1-29.2)	3.7 (3.6-3.8)
>85	13,655	3,792	28.0 (27.3-28.8)	5,983	45.4 (44.6-46.3)	2.4 (2.3-2.4)
Total	**75,979**	**11,339**	**14.8 (14.6-15.1)**	**18,682**	**25.3 (24.9-26.3)**	**3.5 (3.5-3.6)**

Table 3.2: Age-specific mortality within 1 year after spontaneous and precipitated primary AUR and standardised mortality ratios (SMR) with and without comorbidity

Age-group	Men without comorbidity (Charlson Score=0)				Men with comorbidity (Charlson Score≥1)			
	Total	1 year			Total	1 year		
	Admissions	Deaths	Rate % (95% CI)	SMR (95% CI)	Admissions	Deaths	Rate % (95% CI)	SMR (95% CI)
Spontaneous AUR								
45-54	4,590	77	1.8 (1.4-2.2)	4.4 (3.4-5.4)	990	139	14.7 (12.6-17.2)	36.5 (30.7-43.1)
55-64	10,987	232	2.3 (2.0-2.6)	2.1 (1.9-2.4)	2,931	460	16.7 (15.4-18.2)	15.8 (14.4-17.4)
65-74	21,981	1,099	5.3 (5.0-5.6)	1.8 (1.7-1.9)	8,680	1,723	21.0 (20.1-21.9)	7.1 (6.8-7.4)
75-84	24,155	2,843	12.5 (12.1-13.0)	1.6 (1.5-1.6)	11,931	3,227	28.8 (27.9-29.6)	3.7 (3.5-3.8)
>85	9,268	2,400	27.3 (26.4-28.2)	1.4 (1.3-1.4)	4,554	1,915	44.3 (42.8-45.8)	2.3 (2.2-2.4)
Total	**70,981**	**6,651**	**9.9 (9.7-10.2)**	**1.6 (1.5-1.6)**	29,086	7,464	**27.2 (26.7-27.7)**	**3.7 (3.6-3.8)**
Precipitated AUR								
45-54	3,522	114	3.4 (2.9-4.1)	8.4 (6.9-10.1)	1,457	339	24.3 (22.1-26.6)	60.4 (54.2-67.2)
55-64	5,496	235	4.5 (4.0-5.1)	4.3 (3.8-4.9)	3,240	808	26.0 (24.5-27.6)	25.1 (23.4-26.9)
65-74	11,426	880	8.1 (7.6-8.6)	2.7 (2.6-2.9)	9,035	2,612	30.0 (29.1-31.0)	10.3 (9.9-10.7)
75-84	14,869	2,571	18.1 (17.5-18.8)	2.3 (2.2-2.4)	13,279	5,140	40.5 (39.6-41.3)	5.2 (5.1-5.4)
>85	7,578	2,778	38.0 (36.9-39.2)	2.0 (1.9-2.0)	6,077	3,205	54.7 (53.4-55.9)	2.8 (2.7-2.9)
Total	**42,891**	**6,578**	**16.1 (15.7-16.4)**	**2.3 (2.2-2.3)**	33,088	12,104	**38.1 (37.6-38.6)**	**5.0 (4.9-5.1)**

Chapter 4

Updating and improving comorbidity adjustment in HES

4.1 Introduction and Objectives

Many administrative databases have been developed throughout the world for health service planning and financial management. Although most were never intended to be used for research and performance assessment, they have been recognised as a unique data source for descriptive and comparative studies of surgical outcomes in many countries. [Aylin, 2007; Sundararajan, 2004; Quan, 2005; Jencks, 2003; Preen, 2006]

Since 1989, the records of all patients admitted to NHS hospitals in England have been registered in the HES database. Each record should include information on patients' demographic characteristics as well as their main and supplementary diagnoses and operations. Through linkage with mortality data from the Office for National Statistics, HES also contains information about date of death irrespective of whether patients died in hospital or after discharge. [Office for National Statistics; National Centre for Health Outcomes Development]

When using administrative data for comparative purposes, it is essential to adjust for case-mix, as differences in patient characteristics may contribute to observed variations in health outcome. [Quan, 2005; Nuttall, 2006] For this reason, a large number of instruments to identify comorbid conditions have been developed for use with administrative data. [Holman, 2005; Quan, 2005; Elixhauser, 1998; Fleming, 1999; von Korff, 1992] Many of these instruments are adaptations of a comorbidity score, developed in 1987 for adult patients by Charlson and co-workers, [Charlson, 1987] using diagnosis codes from either the 9th or 10th revisions of the International Classification of Diseases (ICD). [World Health Organisation, 1977; World Health Organisation, 1994]

Most of these Charlson-based instruments were developed and validated in the United States [Deyo, 1992; Romano, 1993] or Canada. [Quan, 2005] In these

countries, the main purpose of administrative databases is to guide reimbursement. This provides strong incentives to record patient characteristics that maximise the apparent severity of patients' health problems as well as to capture those procedures that are most financially rewarding. Until 2007 in the United Kingdom, these incentives were far less powerful which makes it likely that coding practice was different. Nevertheless, a recent study demonstrated that Charlson-based instruments that were derived in the United States – after translating ICD-9 into ICD-10 codes – were valid in identifying comorbidity in patients undergoing urological cancer surgery in England, although adjustment for comorbidity in this way had only a limited additional impact compared to adjusting for age and sex alone. [Nuttall, 2006]

Encouraged by the results of this recent English study, a consensus group was convened at The Royal College of Surgeons of England (RCS). The specific objectives of this consensus group were to agree general principles for identifying comorbidity in adult surgical patients and to develop the Charlson-based ICD-10 comorbidity instrument for patients undergoing surgery in the United Kingdom. [Nuttall, 2006]

In this chapter, we first present the comorbidity instrument developed by the consensus group (the RCS Charlson Score). Second, we describe the validity of this instrument in terms of its association with known risk factors for comorbidity as well as its ability to predict post-operative mortality after a variety of common surgical procedures.

4.2   Methods

4.2.1 RCS Consensus Group

A consensus group was convened in 2007 that consisted of five senior surgeons with a track record in research, audit and service evaluation representing

cardiothoracic, colorectal, orthopaedic, urological and vascular surgery, supported by methodologists with a background in clinical epidemiology and health services research (RCS Comorbidity Consensus Group; see Appendix 1). Before the meeting, the group received a document describing the 17 comorbid conditions that are included in the existing Charlson-based comorbidity instruments. This document also contained an overview of the codes used in each of the five existing ICD-10 versions of these instruments. [Halfon, 2002; Nuttall, 2006; Quan, 2005; Sundararajan, 2004]

The group's decisions on which ICD-10 codes to include in the RCS Charlson Score were almost always based on consensus achieved through discussion. When consensus could not be reached a majority view was taken. A draft of the RCS Charlson Score was sent to all group members and they were invited to suggest further revisions and as a result 19 minor changes were made.

4.2.2 General principles for identifying comorbidity

At the start of the meeting, the group discussed the challenges of identifying comorbidity using administrative data and the following general principles were agreed:

1. A comorbid condition should be defined as "a coexisting but unrelated condition that may affect a patient's prognosis in addition to the primary disease". [Elixhauser, 1998; Feinstein, 1970] By defining comorbidity based on its effect on a patient's prognosis, the group distinguished comorbid conditions deemed to be of prognostic significance from "unimportant conditions".

2. Whenever possible, only the first three digits of ICD-10 codes (giving the core disease category) should be used to identify comorbidity for three reasons: use of three-digit codes would enhance the international transferability of the RCS Charlson Score; it would reduce the impact of coding errors that are most likely to occur in the fourth digit of ICD-10 codes (reflecting aetiology, anatomic site or severity), [Surjan, 1999; Stausberg, 2008] and coding

definitions that only use three-digit codes are more practical and user-friendly.

3. The original Charlson disease categories distinguished between mild and severe conditions. This distinction is often difficult or even impossible to make on the basis of diagnosis codes available in administrative data and should therefore be avoided.

4. The prognostic importance of some diseases has changed. Therefore, comorbid conditions that were included in the original Charlson Score but that are no longer considered to have an important prognostic effect should be omitted. Similarly, the weights assigned to each of the comorbid conditions in the original Charlson Score, reflecting their prognostic importance in the 1980s, should not be used.

5. Comorbidity should be sought from diagnosis codes in the record of the index admission (the hospital admission during which the procedure of interest was carried out) as well as from codes in the records of previous admissions. [Preen, 2006]

6. Acute comorbid conditions (comorbidity with a sudden onset, such as acute myocardial infarction or stroke) should be sought in records of previous admissions only. If these codes are present in the record of the index admission, it is not possible to determine whether they represent comorbidity or complications that have arisen during the process of care.

7. Codes that represent very rare conditions (fewer than 10 hospital admissions in England each year) should not be used.

8. Codes that represent paediatric conditions should be omitted given that the RCS Charlson Score is being developed for adult patients only.

9. Procedure codes should not be used to identify comorbidity for two reasons: if comorbid conditions are clinically relevant it should be possible to identify them from the diagnosis codes alone; and procedure coding differs between countries and coding systems, and their inclusion would limit international applicability.

4.2.3 Development of RCS Charlson Score

At the time of the consensus meeting (2007), five versions of Charlson-based ICD-10 comorbidity instruments were available, all using different coding schemes to identify comorbid conditions. [Halfon, 2002; Nuttall, 2006; Quan, 2005; Sundararajan, 2004] The consensus group considered all individual ICD-10 codes of these five versions.

An inclusive approach was followed whereby ICD-10 codes were included in the RCS Charlson Score if they appeared in at least one of the five versions and were considered to comply with the general principles described above.

4.2.4 Validation of RCS Charlson Score

We investigated to what extent the presence of comorbidity identified by the RCS Charlson Score was associated with age, sex and type of admission (elective compared to emergency). We also investigated to what extent the presence of comorbidity was associated with poor outcomes such as increased length of hospital stay, augmented care use (time spent in a high dependency or intensive care unit), and in-hospital or 1-year mortality.

Data were extracted from the HES database for all patients aged 45 years and over recorded as having had repair of an unruptured abdominal aortic aneurysm (AAA), aortic valve replacement (AVR), total hip replacement (THR) or TURP between 1st April 1999 and 31st March 2005. These procedures were chosen as they are common, they are part of the Department of Health's *NHS Choices* initiative, they vary in complexity and risk, and they are mostly carried out in elderly patients who have a range of comorbid conditions. [NHS Choices, 2008]

We identified all patients who had AAA repair using the OPCS-4 (Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures – Fourth Revision) codes L18 (emergency replacement of aneurysmal segment of aorta), L19 (other replacement of aneurysmal segment

of aorta), L20 (other emergency bypass of segment of aorta) and L21 (other bypass of segment of aorta). [Office of Population, Censuses and Surveys, 1996] Because patients with a ruptured AAA have a poorer prognosis than those without, we excluded patients with evidence of vessel rupture using the following ICD-10 codes: I710 (dissection of aorta), I711 (thoracic aortic aneurysm, ruptured), I713 (abdominal aortic aneurysm, ruptured), I715 (thoracoabdominal aortic aneurysm, ruptured) or I718 (aortic aneurysm of unspecified site, ruptured).

We identified all patients who had AVR using the OPCS-4 code K26 (plastic repair of aortic valve). We excluded patients with evidence of congestive cardiac failure (CCF) in either the index or preceding hospital admissions using the following ICD-10 codes: I11 (hypertensive heart disease), I13 (hypertensive heart and renal disease), I255 (ischaemic cardiomyopathy), I42 (cardiomyopathy), I43 (cardiomyopathy in diseases classified elsewhere), I50 (heart failure) and I517 (cardiomegaly). CCF is considered a comorbid condition according to the Charlson Score, but for patients having AVR its presence reflects disease severity rather than comorbidity. [Elixhauser, 1998]

We identified all patients who had THR using the OPCS-4 codes W37 (total prosthetic replacement of hip joint using cement), W38 (total prosthetic replacement of hip joint not using cement) and W39 (other total prosthetic replacement of hip joint). We excluded all patients with an ICD-10 code indicating fractured neck of femur (S72) in any diagnosis field of the index admission.

We identified all patients who had a TURP for BPH using the OPCS-4 code M65 (endoscopic resection of male bladder outlet). We then deleted all admission records of patients with an ICD-10 diagnosis code C61 (prostate cancer) in any diagnosis field of any admission.

The index admission for all patients was defined as the first hospital admission with an episode that contained an OPCS-4 code for any of these procedures in the first four procedural fields. We abstracted the following data from the records of these episodes: age, sex, admission and discharge dates, admission method (elective or emergency), all primary and secondary diagnoses and procedures, status at discharge (alive or dead), and time spent in augmented care. A unique patient identifier in HES (HESID) allowed us to link admission records belonging to the same patient across different years. Mortality information from the Office for National Statistics allowed us to follow all patients until death or 31st March 2006. [Office for National Statistics]

A patient was considered to have a comorbid condition if an ICD-10 code included in the RCS Charlson Score was present in any of the first seven diagnosis fields of either the index admission or a hospital admission in the preceding year with the restriction that acute comorbid conditions (see Table 1) should have been recorded in previous admissions.

We compared the characteristics of the patients and the outcome of their procedures in patients with and without comorbidity according to the RCS Charlson Score using t-tests for means and chi-squared tests for proportions.

We used multivariable logistic regression to determine the importance of adjusting for comorbidity in prognostic models that predict in-hospital and 1-year mortality after surgery. Comorbidity was represented in the logistic models as the number of comorbid conditions (0, 1, 2, 3 or more) that were identified with the RCS Charlson Score. We also assessed the performance of models that only contained an indicator representing whether comorbidity was present or not (ignoring the number of comorbid conditions) as well as that of models that contained 14 indicators representing the presence of each of the individual comorbid conditions.

We evaluated the importance of adjusting for comorbidity by comparing the performance of four prognostic models:

1. A "basic model" that included only age and sex.
2. An "administrative model" that included age, sex, admission method (elective or emergency) and the number of emergency hospital admissions in the previous year. This model was intended to give an indication of the value of using administrative variables only.
3. A "comorbidity model": basic model plus RCS Charlson Score.
4. A "combined model": administrative model plus RCS Charlson Score.

The performance of these four pre-specified models was evaluated separately for each procedure using the HES datasets. The ability of each of the prognostic models to distinguish patients who died from those who did not ("discrimination") was evaluated using the c-statistic that corresponds to the area under the receiver operator characteristic curves. [Fawcett, 2006; Hanley, 1982] This c-statistic is equivalent to the probability that the model will rank a randomly selected patient who dies higher than a randomly selected patient who does not die. A c-statistic with a value of 0.5 indicates that the model discriminates no better than chance alone and a c-statistic with a value of 1.0 indicates perfect discrimination. The c-statistics of the models were compared using a significance test that recognises that they were derived from the same rather than a different set of cases. [DeLong, 1988]

The agreement between observed mortality and the expected mortality predicted by the prognostic models ("calibration") was assessed graphically and tested with the Hosmer-Lemeshow goodness-of-fit statistics. [Hosmer, 1989]

4.3   Results

4.3.1 Development of RCS Charlson Score

The RCS Charlson Score that was developed on the basis of the general principles agreed by the consensus group is presented in full in Table 4.1. It consists of 14 disease categories. The original versions of Charlson-based ICD-10 comorbidity instruments had 17 categories. [Halfon, 2002; Nuttall, 2006; Quan, 2005; Sundararajan, 2004] We omitted peptic ulcer disease because it was no longer considered to be of prognostic importance with the advent of effective pharmacological treatments. Mild liver disease and severe liver disease were combined as were diabetes with and without complications because these distinctions cannot be reliably made using HES data.

As a result of using three-digit ICD-10 codes as much as possible, the coding algorithm of the RCS Charlson Score contained far fewer codes than any of the other Charlson-based ICD-10 comorbidity instruments.

Seven acute conditions should only be counted as comorbidity if they occurred in the record of a previous hospital admission within the preceding 12 months (see codes indicated with an asterisk in Table 4.1).

4.3.2 Validation of RCS Charlson Score

The HES database contained records of 26,255 patients who had a repair of an unruptured AAA, 23,005 patients without evidence of CCF who had an AVR, 238,999 patients who had a THR, and 135,490 patients who had a TURP between 1st April 1999 and 31st March 2005. The characteristics of these patients as well as the outcomes of their surgery are presented in Table 4.2 according to whether comorbidity was present or not.

Prevalence of comorbidity

Of the patients who had AAA repair, 47.0% had at least one comorbid condition (29.0% had one, 11.8% two and 6.1% three or more) according to the RCS Charlson Score. Corresponding figures were 36.0% for AVR (28.0% had one, 6.7% two and 1.3% three or more), 19.4% for THR (16.2% had one, 2.6% two and 0.5% three or more), and 26.0% for TURP (14.7% had one, 7.8% two and 3.6% three or more).

Risk factors for comorbidity

With the exception of patients undergoing AAA repair, patients with comorbidity tended to be older and more frequently admitted as an emergency (Table 4.2). The percentage of patients who were male did not systematically differ between those with and without comorbidity.

Outcomes according to comorbidity

For all four surgical procedures, time spent in augmented care as well as length of hospital stay was longer in patients with comorbidity compared to those without, although the difference in time spent in augmented care was not statistically significant for patients with TURP (Table 4.2). For example, AVR patients with comorbidity spent on average more than one day longer in augmented care and almost three days longer in hospital than those without. Comorbidity seems to have the largest effect on time spent in augmented care in patients undergoing AAA repair and AVR and the strongest effect on length of stay in patients undergoing THR.

The presence of comorbidity increased in-hospital and 1-year mortality for all procedures (Table 4.2). Absolute differences in in-hospital mortality were considerably greater in patients undergoing AAA repair and AVR than in those undergoing THR and TURP. The relative increases were greater for patients having THR (8-fold) and TURP (5-fold) than for AAA (2-fold) and AVR (2-fold).

Absolute differences in 1-year mortality were similar in magnitude across all four surgical procedures.

Discrimination

Four multivariable logistic regression models were used to determine the importance of comorbidity in predicting in-hospital (Table 4.3a) and 1-year mortality (Table 4.3b). When adding comorbidity (represented as the number of comorbid conditions) to the basic and administrative models, we found that the c-statistics increased significantly for all four surgical procedures (p always < 0.001). For the basic model, increases of the c-statistic varied from 0.04 to 0.07 (compare basic and comorbidity models in Table 4.3a); for the administrative model corresponding increases varied from 0.03 to 0.04 (compare administrative and combined models in Table 4.3a). The discriminatory ability of the models predicting 1-year mortality also increased when the number of comorbid conditions was included, although the increases in the c-statistic were slightly smaller (Table 4.3b).

Calibration

Visual inspection of the calibration plots of observed versus expected mortality according to deciles of risk showed good agreement between observed mortality and that predicted by the "combined model" for all four surgical procedures. For patients having AVR, THR and TURP, the Hosmer-Lemeshow goodness-of-fit test confirmed good agreement with no statistically significant difference between observed and expected mortality (p>0.05). However, for patients having AAA repair there was a statistically significant difference between observed and expected in-hospital mortality (p=0.002). The large sample size resulted in a minor difference reaching statistical significance (see Figure 4.1).

4.3.3 Use of RCS Charlson Score information

The RCS Charlson Score is designed to be used as a count of the number of comorbid conditions (0, 1, 2, or 3 if there are three or more comorbid conditions).

When the comorbidity information was used in this way, we found moderate to very good discrimination of the combined models (c-statistics varied between 0.70 and 0.87 according to procedure). When comorbidity information was represented simply as the presence or absence of comorbidity (0 or 1), the discriminatory performance was slightly worse (c-statistics reduced by 0.01 for all four surgical procedures). When each of the 14 individual comorbid disease categories was incorporated into the "combined model", discrimination was slightly better (c-statistics increased by up to 0.02).

4.4   Discussion

The RCS Comorbidity Consensus Group developed and validated a comorbidity score for use with administrative data in the United Kingdom. The RCS Charlson Score has a number of advantages over existing comparable comorbidity scores. First, it is shorter and based on a simpler coding philosophy that enhances coding accuracy and international transferability. Second, it reflects our current understanding of the prognostic impact of comorbid disease. Third, it explicitly aims to avoid misclassifying surgical complications as comorbidity. We demonstrated using HES data for patients undergoing four common surgical procedures in England that the performance of this simplified score was at least as good as existing scores. [Quan, 2005]

The RCS Charlson Score was developed on the basis of general principles agreed by the consensus group in advance. The group felt that these principles should always be considered when existing instruments are updated or new ones developed.

4.4.1 Methodological limitations
Many of the comorbidity scores that have been developed for use with administrative data are based on the original Charlson Score. [Charlson, 1987]

As a result, a number of disease categories, such as neurological (for example, multiple sclerosis, Parkinson's disease) and endocrine (for example, thyroid) disorders, are not included. Although these diseases may be of significant prognostic importance, their prevalence is relatively low. The consensus group felt that this trade-off between comprehensiveness and parsimony should be explicitly addressed in the further development of comorbidity scores.

Secondly, the RCS Charlson Score was developed with surgical patients in mind and validated in patients undergoing elective surgery. These patients constitute a highly selected group as surgery is only offered to patients who are deemed fit for the procedure. Therefore, this score may perform differently in patients receiving other treatment and further evaluations of its performance are necessary.

A third limitation is that each disease category is given an equal weight in the RCS Charlson Score, as it was designed to be used as a simple count of comorbid conditions. We explored to what extent the performance of the RCS Charlson Score improved by assigning weights to each of the individual disease categories. Including the individual comorbidity information in this way resulted in small improvements of discriminatory performance (c-statistic increased up to 0.02).

Fourth, a clinical coding audit programme demonstrated errors in 16.5% of the primary diagnosis and procedure codes. [PbR data Assurance Framework 2007/08] Furthermore, another recent study demonstrated differences in coding practices among hospitals. [Mohammed, 2009] Our results are therefore likely to underestimate the strength of the associations between risk factors and prevalence of comorbidity and between comorbidity and clinical outcomes.

Lastly, we evaluated the performance of various prognostic models, including those with RCS Charlson Score comorbidity information, using c-statistics to

measure discrimination. However, for prognostic models that already contain standard risk factors and have reasonably good discriminatory power, very large independent associations of the new marker are required to produce meaningfully larger c-statistics. Therefore, new methods to evaluate model performance have been developed and these may have better demonstrated the importance of comorbidity information in models that predict mortality after surgery. [Pencina, 2008]

4.4.2 Validity of RCS Charlson Score

We found that the presence of comorbidity according to the RCS Charlson Score was associated with known risk factors for comorbidity, such as age and type of admission, and with increased length of time spent in augmented care and in hospital, as well as higher mortality. Inclusion of the RCS Charlson Score improved the performance of models for short-term outcomes (in-hospital mortality) as well as for outcomes in the more distant future (1-year mortality).

The validity of the existing comorbidity instruments for ICD administrative data was demonstrated in a similar way in administrative databases in the United States, [Deyo, 1992; Romano, 1993] Canada, [Quan, 2005] Australia [Sundararajan, 2004] and Sweden. [Halfon, 2002] Of these existing instruments, the most rigorously developed appears to be a Canadian version. [Quan, 2005] For example, its developers reviewed existing algorithms and extensively consulted clinical coders and clinicians. We examined the performance of this Canadian instrument in the same HES dataset that we used to validate the RCS Charlson Score. To ensure a fair comparison, we applied the ICD-10 codes in the Canadian instruments that relate to acute conditions only in records of preceding hospital admissions. The performance of the Canadian instrument was comparable to that of the RCS Charlson Score (results not shown). For example, discriminatory performance of models including comorbidity identified with the RCS Charlson Score or with the Canadian instrument differed at most by 0.01 in terms of the c-statistic. This result has to be interpreted in the context

that the Canadian instrument contains about 50% more data fields than the RCS Charlson Score and a greater number of four-digit codes. This comparison suggests that we have been successful in simplifying the comorbidity score for use in administrative data in the United Kingdom without diminishing its performance.

Most of the existing comorbidity scores do not consider comorbidity information derived from records of previous hospital admissions. [Halfon, 2002; Sundararajan, 2004; Quan, 2005] To improve the detection of comorbidity and to avoid using acute conditions that were recorded for the first time in the index admission, the consensus group felt that it was important to include the records of admissions in the preceding year. An important consideration in this context was that HES and equivalent administrative databases in the United Kingdom do not have a "diagnosis-type" indicator specifying the timing of the diagnosis which could be used to determine whether acute diagnoses recorded for the index admission are comorbid conditions or complications arising from the surgical treatment.

For example, in the 26,255 patients undergoing AAA repair, the RCS Charlson Score identified 974 patients (3.7%) with "old myocardial infarction" (I252) in the record of the index admission and 586 more patients (2.2%) with "acute myocardial infarction" (I21), "subsequent myocardial infarction" (I22) or "certain current complications following acute myocardial infarction" (I23) in records of hospital admissions in the preceding year. In total 1,560 patients (5.9%) were identified as having had a myocardial infarction before they had their operation. If we had identified patients with myocardial infarction by applying all of these codes to the index admission record only, we would have found 1,940 (7.4%). The difference between these two results (1,560 and 1,940) includes those patients who developed a myocardial infarction as a complication *during* or *after* their surgery.

4.4.3 Implications

A number of governmental initiatives in England emphasise the need to measure the quality of care of every provider in the NHS. [Darzi, 2008] For example, information on key performance indicators will be published to inform clinicians, managers and providers as well as patients and the public. It is generally accepted that this information needs to be robust, rigorous and risk-adjusted. HES has been recognised as a crucial data source for these "quality metrics" and the RCS Charlson Score should be considered as an instrument to identify comorbidity, especially when outcomes of surgical procedures are being evaluated.

It has been recognised that the performance of comorbidity scoring instruments using administrative data differs across countries. [De Coster, 2006; Sundararajan, 2007] We aimed to enhance the international transferability of the RCS Charlson Score by using three-digit codes as much as possible and avoiding the use of procedure codes. Given the results of our comparison of the RCS Charlson Score with the most rigorously developed comorbidity instrument to date, [Quan, 2005] we feel that the RCS Charlson Score should also be considered for international comparisons.

4.5 Tables

Table 4.1: The RCS Charlson Score indicating ICD-10 codes for 14 disease categories.

Disease category	ICD-10 codes
Myocardial infarction	I21*-I23*, I252
Congestive cardiac failure	I11, I13, I255, I42, I43, I50, I517
Peripheral vascular disease	I70-I73, I770, I771, K551, K558, K559, R02, Z958, Z959
Cerebrovascular disease	G45, G46, I60-I69
Dementia	A810, F00-F03, F051, G30, G31
Chronic pulmonary disease	I26, I27, J40-J45, J46*, J47, J60-J67, J684, J701, J703
Rheumatalogical disease	M05, M06, M09, M120, M315, M32-M36
Liver disease	B18, I85, I864, I982, K70, K71, K721, K729, K76, R162, Z944
Diabetes mellitus	E10-E14
Hemiplegia or paraplegia	G114, G81-G83
Renal disease	I12, I13, N01, N03, N05, N07, N08, N171*, N172*, N18, N19*, N25, Z49, Z940, Z992
Any malignancy	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C80-C85, C88, C90-C97
Metastatic solid tumour	C77-C79
AIDS / HIV	B20-B24

* Asterisked codes represent acute conditions that should be used to define comorbidity only if present in the record of a previous hospital admission within the preceding 12 months.

Table 4.2: Associations between comorbidity identified by the RCS Charlson Score and risk factors for comorbidity and clinical outcomes.

Procedure	No comorbidity (RCS Charlson Score = 0)		Comorbidity (RCS Charlson Score ≥ 1)		P-value
AAA (Unruptured)					
Patients, no. (%)	13,920	(53.0)	12,335	(47.0)	-
Mean age, years (SD)	71.7	(7.9)	70.7	(8.3)	<0.001
Male sex, no. (%)	11,446	(82.2)	10,096	(81.9)	0.434
Emergency admissions, no. (%)	2,830	(20.3)	2,368	(19.2)	0.021
Augmented care, mean, days (SD)	4.5	(5.5)	5.7	(7.8)	<0.001
Length of stay, mean, days (SD)	13.2	(12.4)	15.4	(15.7)	<0.001
In-hospital mortality, no. (%)	736	(5.3)	1,199	(9.7)	<0.001
*1-year mortality, no. (%)	1,265	(10.7)	2,024	(20.0)	<0.001
AVR (No CCF)					
Patients, no. (%)	14,719	(64.0)	8,286	(36.0)	-
Mean age, years (SD)	68.5	(9.5)	69.0	(8.9)	<0.001
Male sex, no. (%)	8,854	(60.2)	5,047	(60.9)	0.279
Emergency admissions, no. (%)	2,244	(15.2)	1,795	(21.7)	<0.001
Augmented care, mean, days (SD)	3.2	(3.8)	4.4	(7.6)	<0.001
Length of stay, mean, days (SD)	13.4	(11.7)	16.2	(15.7)	<0.001
In-hospital mortality, no. (%)	392	(2.7)	507	(6.1)	<0.001
*1-year mortality, no. (%)	762	(6.2)	838	(13.0)	<0.001
THR					
Patients, no. (%)	192,733	(80.6)	46,266	(19.4)	-
Mean age, years (SD)	69.8	(9.8)	71.3	(9.6)	<0.001
Male sex, no. (%)	72,339	(37.5)	18,749	(40.5)	<0.001
Emergency admissions, no. (%)	9,556	(5.0)	4,696	(10.2)	<0.001
Augmented care, mean, days (SD)	1.7	(2.1)	2.0	(2.3)	<0.001
Length of stay, mean, days (SD)	10.9	(9.8)	14.0	(15.7)	<0.001
In-hospital mortality, no. (%)	461	(0.2)	755	(1.6)	<0.001
*1-year mortality, no. (%)	3,559	(2.2)	2,946	(8.0)	<0.001
TURP					
Patients, no. (%)	100,199	(74.0)	35,291	(26.0)	-
Mean age, years (SD)	70.8	(8.6)	73.4	(8.1)	<0.001
Emergency admissions, no. (%)	7,987	(8.0)	3,472	(9.8)	<0.001
Augmented care, mean, days (SD)	0.7	(2.6)	0.9	(2.7)	0.433
Length of stay, mean, days (SD)	5.1	(4.9)	6.6	(9.4)	<0.001
In-hospital mortality, no. (%)	84	(0.1)	164	(0.5)	<0.001
*1-year mortality, no. (%)	2,325	(2.7)	2,701	(9.1)	<0.001

*1-year mortality is calculated after excluding patients in the final year of the study that did not have at least 1 year's complete follow-up.

Table 4.3a: Discriminatory ability of prognostic models that predict in-hospital mortality after each of the four surgical procedures.

	Basic Age and sex	Administrative Age, sex, admission method and number of emergency admissions in preceding year	Comorbidity Age, sex and RCS Charlson Score	Combined Age, sex, admission method, number of emergency admissions in preceding year and RCS Charlson Score
	c-statistic (95% CI)	c-statistic (95% CI)	c-statistic (95% CI)	c-statistic (95% CI)
AAA	0.62 (0.61-0.63)	0.66 (0.65-0.68)	0.66 (0.65-0.67)	0.70 (0.68-0.71)
AVR	0.61 (0.59-0.62)	0.67 (0.65-0.69)	0.67 (0.66-0.69)	0.71 (0.69-0.72)
THR	0.78 (0.76-0.79)	0.83 (0.81-0.84)	0.84 (0.83-0.85)	0.87 (0.85-0.88)
TURP	0.76 (0.74-0.79)	0.82 (0.79-0.84)	0.83 (0.80-0.85)	0.86 (0.83-0.88)

AAA = abdominal aortic aneurysm repair (unruptured), AVR = aortic valve replacement, THR = total hip replacement and TURP = transurethral resection of the prostate.

Table 4.3b: Discriminatory ability of prognostic models that predict 1-year mortality after each of the four surgical procedures.

	Basic Age and sex	Administrative Age, sex, admission method, number of emergency admissions in preceding year	Comorbidity Age, sex and RCS Charlson Score	Combined Age, sex, admission method, number of emergency admissions in preceding year and RCS Charlson Score
	c-statistic (95% CI)	c-statistic (95% CI)	c-statistic (95% CI)	c-statistic (95% CI)
AAA	0.62 (0.61-0.63)	0.66 (0.65-0.67)	0.67 (0.66-0.68)	0.70 (0.69-0.70)
AVR	0.61 (0.60-0.63)	0.65 (0.64-0.67)	0.67 (0.66-0.68)	0.69 (0.68-0.70)
THR	0.72 (0.72-0.73)	0.77 (0.77-0.78)	0.77 (0.77-0.78)	0.80 (0.79-0.80)
TURP	0.70 (0.70-0.71)	0.76 (0.75-0.77)	0.73 (0.73-0.74)	0.77 (0.76-0.78)

AAA = abdominal aortic aneurysm repair (unruptured), AVR = aortic valve replacement, THR = total hip replacement and TURP = transurethral resection of the prostate.

Figure 4.1: Comparison of observed (grey) and expected (black) in-hospital mortality in patients undergoing unruptured AAA repair according to deciles of risk. Expected mortality is predicted with the "combined model" (see text for further explanation).
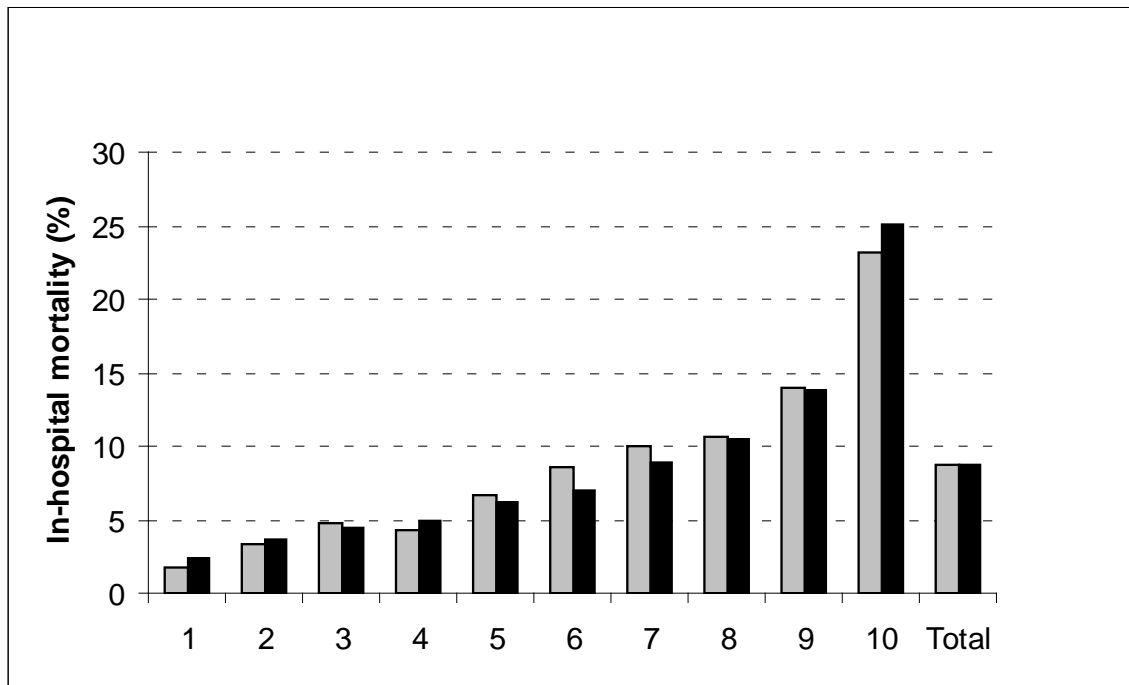
Section 3

Evaluating the management options for men with acute urinary retention

Chapter 5

Review of minimally invasive treatment of acute urinary retention

5.1 Objectives

To enable selection of the most appropriate treatment for a man with AUR it is important to understand the effectiveness, durability and safety of the available options. This chapter provides an overview of some of the minimally invasive treatment options for men with AUR, most of which have been recently subjected to evaluation by systematic literature review.

5.2 Minimally invasive treatment of acute urinary retention

5.2.1 Transurethral microwave thermotherapy

Heating of the prostate using microwaves causes tissue ablation thereby relieving bladder outlet obstruction secondary to BPH. [Yerushalmi, 1985] Early microwave devices heated the prostate to temperatures of between 40 and 45°C. Although patients reported some symptomatic improvement histological studies revealed that these temperatures were inadequate to cause cell death. [Montorsi, 1992] At temperatures greater than 45°C cellular apoptosis and necrosis occur. Therefore, the term hyperthermia is used to describe treatments producing prostatic temperatures of less than 45°C, and thermotherapy applied to those that achieve temperatures above this threshold. Histological studies have demonstrated that the amount of tissue necrosis is proportional to the temperature reached within the prostate and the duration for which it is sustained. [Devonec, 1993]

Several thermotherapy devices have been developed for the treatment of BPH. These include CoreTherm (ProstaLund, Sweden), Urowave (Dornier Medical Systems), Prostcare (HighTechCare, France), Prostatron (EDAP Technomed Medical Systems, France) and Targis (Urologix, United States). While these differ with respect to how they deliver the energy and monitor its effects, they are conceptually the same. All require the insertion of a specially designed urethral

catheter that locates a microwave antenna within the prostate. The antenna produces microwaves that pass into the prostate tissue where they are absorbed causing heat production and cellular destruction. Treatments typically last between 10 minutes and one hour with some devices tailoring the duration of treatment specifically to the individual. Thermotherapy causes a considerable amount of tissue oedema that requires a period of urethral catheterisation after the procedure, typically between one and two weeks.

A recent systematic review identified six distinct randomised controlled trials that compared thermotherapy to TURP in men with urinary symptoms attributed to BPH. [Hoffman, 2007] The pooled mean symptom score for men receiving thermotherapy decreased by 65% in 12 months compared to 77% for men undergoing TURP. A mean increase in peak urinary flow rate of 70% was noted following thermotherapy compared to 119% after TURP. While re-treatment rates were significantly higher after thermotherapy, adverse events were generally lower compared to TURP.

The same systematic review identified seven randomised controlled trials incorporating 850 patients that compared thermotherapy to sham treatment. [Hoffman, 2007] The pooled mean symptom score for men undergoing thermotherapy decreased by 50% in 3 to 6 months (21.4 to 10.8) compared to 41% (21.3 to 12.6) in men undergoing sham treatment. However, men undergoing thermotherapy were significantly more likely than those undergoing sham treatments to experience urinary retention, dysuria and haematuria.

A randomised controlled trial that compared thermotherapy to alpha-receptor blockade using terazosin demonstrated significant improvements in International Prostate Symptom Scores (IPSS), peak urine flow rates and quality of life scores in both groups at six months. [Djavan, 2001] The magnitude of the improvement was significantly greater in the thermotherapy group than in the terazosin group.

Furthermore, treatment failure rates in those receiving medical therapy were seven times those seen in the thermotherapy group at 18 months.

Thermotherapy appears to be an effective outpatient treatment for BPH that has fewer adverse events than TURP. However, TURP offers greater improvement in urinary symptoms and peak urine flow rates and fewer patients may require re-treatment than those who have thermotherapy.

5.2.2   Transurethral needle ablation

Transurethral needle ablation (TUNA) uses radiofrequency energy to cause heating and destruction of prostatic tissue. Radio waves are delivered to the prostate by means of two sheathed needles placed within the prostate. The procedure can be performed using local anaesthesia, often with sedation, in a similar manner to transrectal prostate biopsy. Preservation of the prostatic urothelium minimises irritative voiding, haematuria, and urinary retention after the procedure. A catheter is normally left in place for between 1 and 3 days after treatment to allow procedure-related oedema to resolve.

A recent meta-analysis assessed the effectiveness of TUNA. [Boyle, 2004] Two randomised controlled trials, two comparative studies and nine case series were identified and considered suitable for inclusion. A total of 1,244 patients had an evaluable IPSS and estimates of maximum urine flow rates were given for 1,331 patients. TUNA was found to reduce IPSS by a mean 12.1 points (standard error of mean (SEM) 0.43) and increase maximum urine flow rates by a mean 5.1ml/s (SEM 0.48) or approximately 70% from baseline at 1 year. However, significantly greater improvements in symptoms and urine flow rates were observed after TURP. IPSS decreased by 15.6 points (SEM 0.66) and maximum urine flow rates increased by 10.7ml/s (SEM 0.71). Assessment at 5 years suggested these improvements were durable.

Transient dysuria and haematuria are commonly reported after TUNA. A randomised controlled trial comparing TUNA with TURP reported fewer adverse events with TUNA. [Hill, 2004] Rates of retrograde ejaculation, erectile dysfunction, urinary incontinence and stricture formation were less after TUNA than TURP. However, re-treatment rates were higher after TUNA than TURP and 13.8% of TUNA patients required further intervention within 5 years.

A single treatment with TUNA may provide a level of efficacy approaching that of TURP but with fewer complications. TUNA may be performed using local anaesthesia, does not require hospitalisation and allows the patient to rapidly return to normal function. Symptomatic improvement after TUNA may not be as durable as TURP and high re-treatment rates may limit its cost-effectiveness. [Rosario, 2007]

5.2.3   Laser treatments

The use of lasers to treat BPH has been explored since the 1990s. Several different devices have been developed including the Neodymium:YAG, Holmium:YAG, and the Potassium-Titanyl-Phosphate (KTP) (GreenLight) lasers. Lasers produce two main tissue effects - coagulation and vaporisation. At lower power settings, prostatic tissue is heated to temperatures of up to 100°C which causes coagulation and subsequently sloughing of the necrotic tissue. Temperatures of 300-400°C are achieved at higher power settings with consequent vaporisation and the immediate reduction in prostate bulk.

The Neodymium:YAG laser is most commonly used for its coagulative effect although higher power settings do cause tissue vaporisation. Examples of treatments which utilise the neodymium laser include visual laser ablation of the prostate (VLAP), contact laser ablation of the prostate (CLAP), and interstitial laser coagulation of the prostate (ILCP).

The ability of the holmium laser to cause both cutting and coagulation of soft tissues has led to the development of resection and enucleation techniques in addition to laser ablation of the prostate (HoLAP). Holmium laser resection of the prostate (HoLRP) involves dissection of the gland to the capsule with its subsequent removal from the bladder in pieces. Holmium laser enucleation of the prostate (HoLEP) uses a retrograde approach to dissect the prostate as far as the capsule followed by the introduction of a mechanical morcellator which makes tissue retrieval easier. These techniques can be used to treat very large glands, up to 100ml and 200ml respectively.

A recent systematic review and meta-analysis assessed the safety and effectiveness of HoLEP compared to TURP. [Tan, 2007] The literature search and selection process identified four distinct randomised controlled trials that examined a total of 460 patients having either HoLEP (n=232) or TURP (n=228). Meta-analysis showed no statistically significant difference between HoLEP and TURP in terms of symptomatic improvement or urine flow rates at 6 and 12 months follow-up. While TURP was associated with reduced operating time, HoLEP was associated with significantly less blood loss, catheterisation time and length of hospital stay. However, the short follow-up of patients in these studies limited conclusions on the durability of HoLEP.

Another systematic review identified randomised controlled trials that compared laser prostate treatments to control interventions. [Hoffman, 2004] Laser treatments were compared to TURP in 16 randomised controlled trials, two trials compared laser prostatectomy to transurethral electro-vaporisation of the prostate (TUVP) and one study each compared laser surgery to thermotherapy and open prostatectomy. Urinary symptom scores were reduced by about 70% and flow rates generally doubled after laser treatment. These improvements were comparable to those seen following TURP although six studies found statistically better results after TURP. Hospital length of stay was significantly less following laser treatment compared to TURP and length of catheterisation

was less following contact laser treatments but longer after non-contact laser treatments than TURP. Adverse events including transfusion, clot retention, strictures and TUR syndrome occurred less frequently after laser therapy than TURP. Re-operation rates were, however, found to be greater after laser treatments than TURP within the first 12 months.

Photoselective vaporisation of the prostate (PVP) represents one of the latest developments in laser prostate surgery. The potassium-titanyl-phosphate (KTP) or GreenLight® laser emits laser energy that is absorbed by haemoglobin in red blood cells. This causes rapid heating and vaporisation of the targeted tissue as well as coagulation of blood vessels. The procedure requires general or spinal anaesthesia. Preliminary data from a recent randomised controlled trial that compared PVP to TURP showed equivalent improvements in urinary flow rates and symptoms with reduced length of stay, length of catheterisation and adverse events. [Bouchier-Hayes, 2006]

The heterogeneity of the various laser techniques and different laser devices makes generalisation of their safety and effectiveness difficult. Laser treatments do seem to confer a shorter length of hospital stay and have fewer complications than TURP. However, initial costs may be greater than those of conventional surgery and there is some evidence that re-treatment rates are higher. General or regional anaesthesia is usually required which may limit their role in treating frail patients or those with significant comorbidity. Laser resection and enucleation techniques have the advantage over other minimally invasive procedures of providing a specimen for histological analysis.

In summary, there appears to be a balance between the effectiveness and durability of minimally invasive prostate treatments on the one hand, and their associated peri-operative morbidity and safety on the other. Therefore, it is important to assess each patient's individual circumstances when considering treatment options. For example, an elderly patient with significant comorbidity

might be willing to accept a less durable and even less effective treatment if it allows spontaneous voiding and a quick return to normal activity. A young man may also choose a potentially less durable treatment, accepting the likely need for further intervention, if the risks associated with the more invasive alternative can be avoided or at least deferred.

The subsequent two chapters evaluate the effectiveness, durability and safety of prostatic stents and explore their role as a minimally invasive prostate treatment.

Chapter 6

The Memokath stent for benign prostatic hyperplasia: a systematic review of the literature

6.1   Introduction and Objectives

Many of the minimally invasive treatments described in Chapter 5 are designed to reduce the volume of the prostate and thereby relieve obstruction. An alternative to removing tissue is to use a prostatic stent to hold open the obstructing prostate and bladder neck.

In 1980, Fabian described a method of placing a stent in the prostatic urethra to relieve obstruction. [Fabian, 1980] Stents that allow epithelial incorporation were designed to provide a permanent treatment for BPH. Despite the theoretical advantages of stent incorporation, rates of infection, encrustation and migration remained high. [Bajoria, 1995] Also, epithelial in-growth can cause luminal narrowing to an extent that requires stent removal which can be difficult and usually requires general anaesthesia.

Consequently, another type of stent was developed. These stents, which sit freely within the prostatic urethra, were initially designed to provide short term relief from bladder outlet obstruction. [Fabian, 1980] More recently, some groups of patients with BPH at high surgical risk have been treated long-term using these non-epithelialising stents. The stent of this type most commonly used in practice is the Memokath.

The Memokath is manufactured from a nickel-titanium alloy that has the property of 'shape-memory'. 'Shape-memory' describes a process by which a deformed piece of the alloy is restored to its original shape by heating. When a Memokath stent is positioned in the prostatic urethra, it is flushed with warm saline which causes it to expand, thereby 'locking' it into position. Flushing with cold saline renders the stent soft which facilitates its removal. The first generation of Memokath stent expanded along its entire length but problems were experienced with migration. [Nordling, 1991] The second generation of Memokath has been available since 1992 and expands only at its distal end.

There have been a number of reviews of prostatic stents since their introduction 25 years ago. However, these reviews are not comprehensive and may present only the trial data which supports the author's opinion. An objective appraisal of the evidence can only be achieved by its systematic evaluation. A systematic review also allows deficiencies in the evidence base to be identified and serves to highlight areas where further research is required. This is the first systematic literature review to assess the safety, effectiveness and durability of the second generation Memokath stent for the management of BPH.

6.2   Methods

Inclusion and exclusion criteria. We included studies of any design that used the second generation Memokath stent in men with BPH. Only studies published after 1992 were included. We excluded review articles, comments, editorials and case reports, in-vitro or animal experiments, and studies pertaining to the exclusive use of other stents or describing alternative procedures using the Memokath.

Search strategy. We searched Medline and Embase databases for papers published before March 2005 (see Appendix 2). Additional literature was sought from the reference lists of all identified studies and the bibliographies of six recent review articles. [Harboe, 2004; Kapoor, 2000; Nordling, 1998; Oesterling 1995; Ogiste, 2003, Van Dijk, 2003] The manufacturer of the Memokath stent was asked to identify additional published or unpublished research. None of the additional references were published in journals that were indexed in the databases. No language restrictions were imposed.

Outcomes. We abstracted information on the frequency of complications that required stent removal, replacement or repositioning (treatment failure) as well as on the frequency of minor complications that did not require stent removal.

The severity of symptoms before and after stent insertion was assessed using urological symptom scores. Changes in urodynamic indices were also assessed before and after stent insertion.

Data extraction and assessment of methodological quality. Titles and abstracts identified by the search were independently assessed for inclusion by two reviewers (J Armitage and A Rashidian). All articles that were potentially relevant were obtained and the inclusion was assessed again after reading full papers. Data were then independently extracted by the same two reviewers and presented in structured tables. This data included information on study design, population characteristics and outcomes. Any disagreements were resolved by discussion and consultation with a third reviewer (J van der Meulen). Missing and additional information was sought from the authors.

The quality of identified studies was appraised using criteria developed from published frameworks for the assessment of methodological quality (see Appendix 3). [Downs, 1998; Khan, 2001; Lohr, 2004]

Analysis. We calculated immediate and subsequent treatment failure rates; the mean change in symptom score with stent insertion was presented graphically for each study.

6.3   Results

Literature search. The database search identified 526 articles, of which 497 were excluded after assessment of their titles and abstracts (Figure 6.1). The complete manuscripts of 29 studies were assessed, four of which met the inclusion criteria. [Kawakami, 2003; Matsuzaki, 2004; Perry, 2002; Poulsen, 1993] Bibliography review and communication with the stent manufacturer retrieved a further 33 studies. If these additional studies were presented in

abstract format only, the authors were contacted for further information. As a result, a further 10 studies were included in the review. [Booth, 1997; Eichenauer, 1998; Hamasaki, 2002; Itoh, 1999; Kiyota, 1994; Kuriki, 1995; Melissourgos, 1999; Mishra, 2004; Rathenborg, 2001; Sumura, 2002]

Characteristics of included studies. The literature search identified 14 case series (Table 6.1). [Kawakami, 2003; Matsuzaki, 2004; Perry, 2002; Poulsen, 1993; Booth, 1997; Eichenauer, 1998; Hamasaki, 2002; Itoh, 1999; Kiyota, 1994; Kuriki, 1995; Melissourgos, 1999; Mishra, 2004; Rathenborg, 2001; Sumura, 2002] Study size was generally small with less than 50 participants in 11 of the 14 case series.

Quality assessment. The methodological quality of the studies was poor. For example, few authors clearly outlined the study objectives or the outcomes in which they were interested. Statistical methods other than basic descriptive approaches were seldom employed and, if they were, insufficient detail was provided to allow the reader to be certain that their use was appropriate. Only five studies gave estimates of the statistical uncertainty of their results. The funding source was made explicit in only one study.

On the other hand, most studies made their inclusion criteria explicit and defined their study population characteristics. The majority defined recruitment periods clearly and reported major adverse events.

Patient demographics. In total, 839 patients were included and all of these seemed to be at high surgical risk. Stents were inserted for LUTS or urinary retention. Only one study clearly differentiated between acute and chronic urinary retention. [Mishra, 2004] The pathogenesis of bladder outlet obstruction was BPH in the majority of cases. Five studies included some patients with prostatic carcinoma (28% or less where stated). [Perry, 2002; Eichenauer, 1998; Hamasaki, 2002; Itoh, 1999; Sumura, 2002]

Treatment failure. All the studies reported treatment failure (complications which required stent removal, replacement or repositioning) as an outcome (Table 6.2). Immediate failure occurred in 11 of the 311 patients (4%) for whom this information was available. Immediate failure seemed to happen because of incorrect stent length or placement. [Poulsen, 1993; Eichenauer, 1998; Hamasaki, 2002] The frequency of subsequent stent failure could not be derived as insufficient information was given on the timing of failure. However, it was clear that stent migration was the most commonly reported cause of subsequent failure.

Reported failure rates varied widely across the studies. Two studies reported no stent failure after 8 weeks and 14 months (median) of follow-up. [Kawakami, 2003; Matsuzaki, 2004] The highest failure rate was 48% but the follow-up period in this study was not defined. [Mishra, 2004] The second highest failure rate was 41% with patients followed up for a mean of 7 months. [Kiyota, 1994]

Minor complications were inconsistently reported and little information was given on the timing of these events. Those most commonly reported appeared to be urinary incontinence, infection and haematuria.

Urological symptoms. Changes in urological symptom score associated with stent insertion were reported in seven studies. Five studies used the International Prostate Symptom Score (IPSS), [Matsuzaki, 2004; Perry, 2002; Eichenauer, 1998; Kiyota, 1994; Sumura, 2002] one used the Madsen-Iversen score, [Itoh, 1999] and one study [Kuriki, 1995] purported to have used the IPSS score but their reported values deviated from those accepted in the original definition. [Barry, 1992]

All seven studies reporting symptom scores noted a reduction in symptoms following stent implantation. Stent insertion was associated with a reduction in

IPSS of between 11 and 19 points, and a reduction in Madsen-Iversen score of 9 points, but assessment was made at different times after stent placement (Figure 6.2).

Only three of the five studies that used the IPSS reported statistical parameters. The first of these studies compared the mean IPSS of a group of 150 patients before stent insertion with the mean of another group of 151 patients after the procedure (within 3 months). [Perry, 2002] It reported a statistically significant reduction of 12 points, but seems to have used inappropriate statistical tests (paired t-test). This study also claimed that the reduction in IPSS was durable for those patients that were followed for longer periods. Another study reported a statistically significant reduction in IPSS of 11 points at 4 weeks compared with the pre-stent score ($p<0.05$) but said that the difference was no longer significant after 8 weeks. [Matsuzaki, 2004] Another observed a reduction in IPSS of 19 points which was reported as statistically significant at 12 weeks following stent placement ($p<0.05$) but not after 24 weeks. [Sumura, 2002]

Eight studies assessed changes in urodynamic indices. Changes in the maximum urine flow rate was reported in seven studies, [Matsuzaki, 2004; Poulsen, 1993; Eichenauer, 1998; Itoh, 1999; Kiyota, 1994; Kuriki, 1995; Melissourgos, 1999] in mean flow rate in two, [Matsuzaki, 2004; Itoh, 1999] in post-void residual in four [Matsuzaki, 2004; Itoh, 1999; Melissourgos, 1999; Sumura, 2002] and in total voided urine volume in one study. [Poulsen, 1993] Increases in maximum urine flow rate, mean flow rate and total voided urine volume, and decreases in post-void residual urine were noted in all studies reporting the particular outcomes. The increases in maximum urine flow rate associated with stent insertion ranged from 3 to 11 ml/sec although the time of assessment after placement varied.

6.4   Discussion

This is the first systematic literature review of the safety, effectiveness and durability of the Memokath stent in patients with BPH at a high surgical risk. The Memokath stent appears to be safe and effective. Only 4% of patients had an unsuccessful initial insertion of Memokath. The reduction in IPSS associated with the insertion of a Memokath is comparable to that seen after TURP. [Flanigan, 1998] However, the follow-up is inconsistent and unreliable which means that conclusions on the durability of the Memokath cannot be drawn.

There are no studies that compare the Memokath stent with alternative treatments for patients with LUTS or AUR. The studies that we could include in this review are case series of generally poor methodological quality.

At least 20 other types of prostatic stent can be identified. The quality of the evidence on their performance in men with BPH appears to be no better than for the Memokath stent. In the United States, most experience has been gained with the UroLume. The use of the Memokath stent has been confined to Europe. Bioabsorbable and silicone stents have also been used for men with BPH, but these may be considered more suitable for short-term use, for example, to evaluate the potential benefit of a TURP or to maintain luminal patency immediately after other minimally invasive treatments for BPH.

Our findings suggest that a patient can expect symptomatic improvement after Memokath stent insertion of a magnitude that is comparable to that seen after surgery. [Flanigan, 1998] However, the evidence on symptom improvement is incomplete and imperfect. For example, the timing of the IPSS measurements was sometimes not given, [Perry, 2002; Eichenauer, 1998] essential statistical parameters were not presented, [Matsuzaki, 2004; Perry, 2002; Eichenauer, 1998; Kiyota, 1994; Sumura, 2002] and different patients were included in IPSS results obtained before and after stent insertion. [Perry, 2002] Furthermore, one

study used IPSS estimated by the carers of patients with dementia, an approach that lacks validity. [Perry, 2002] Despite these limitations, the insertion of a Memokath stent seems to result in a substantial improvement in symptoms and this finding is consistent between the studies.

The studies included in this review looked at a heterogeneous group of patients. Patients were treated with a stent for both LUTS and urinary retention (acute and chronic). The pathogenesis of obstruction was predominantly BPH but five studies also assessed patients with carcinoma of the prostate. This heterogeneity may explain some of the observed differences between the studies' outcomes.

A feature that all the patients had in common was that they were all considered to be at high surgical risk and would probably have been offered a long-term catheter had they not been treated with a Memokath. The complications associated with long-term catheterisation are well documented [Kohler-Ockmore, 1996] and when considered in this context a Memokath stent may provide an attractive alternative for these patients.

Our review highlights the need for further research. First, a high quality observational study would provide information on the timing of treatment failure which would allow assessment of the durability of the Memokath stent. Furthermore, collection of detailed information on patient characteristics before insertion would contribute to the identification of patients who would benefit most from a Memokath stent. Second, a randomised controlled trial would provide valid evidence on the safety and effectiveness of a stent compared with other treatment modalities. However, the difficulties in designing such a trial should not be underestimated. These include the definition of the comparison group as well as the nature and timing of the outcome assessment. For example, should stents be compared with TURP? On the basis of the findings of this review a more appropriate comparator is likely to be an indwelling urethral or suprapubic

catheter. Also, how should the short-term morbidity associated with TURP or major stent complications be balanced against longer term symptom improvement?

6.5   Tables and figures

Figure 6.1: Summary of Memokath study selection process
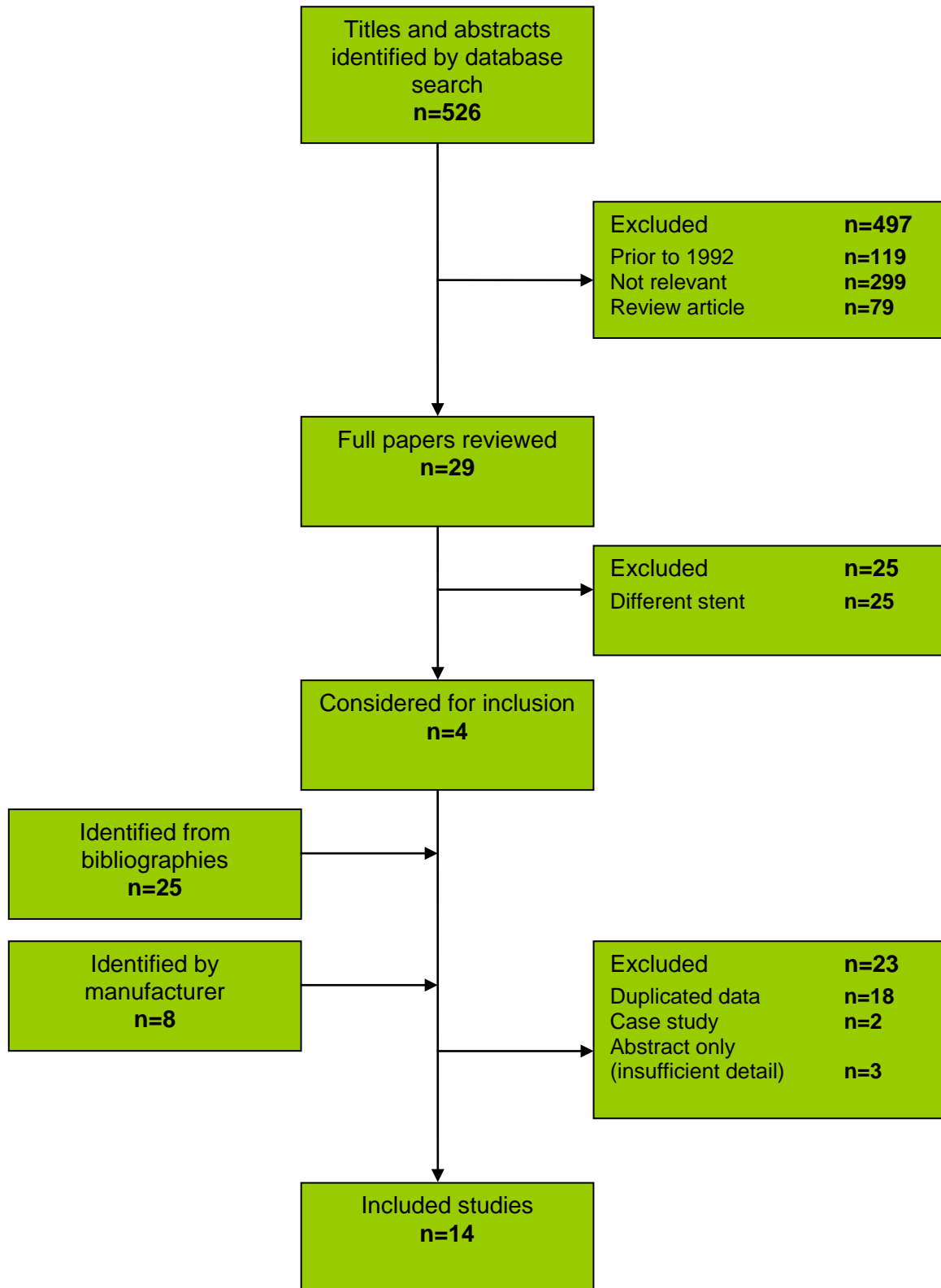
Figure 6.2: Changes in symptom score with Memokath insertion (A) IPSS, (B) Madsen-Iversen, indicating study size, the number of patients assessed if stated, and the time of assessment after stent insertion.

	Perry 2002	Eichenauer 1998	Kiyota 1994	Matsuzaki 2004	Sumura 2002
When IPSS assessed	< 3 months	3-6 months	3 months	8 weeks	12 weeks
Study size	n=211	n=86	n=17	n=15	n=25
Number of patients assessed					
Before	n=150	?	?	n=7	n=12
After	n=151	?	?	n=7	n=9

	Itoh 1999
When symptoms assessed	< 3 months
Study size	n=22
Number of patients assessed	
Before	n=9
After	n=9
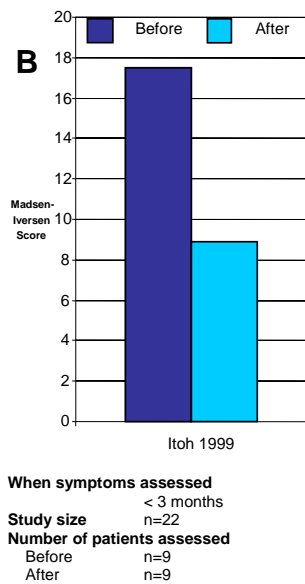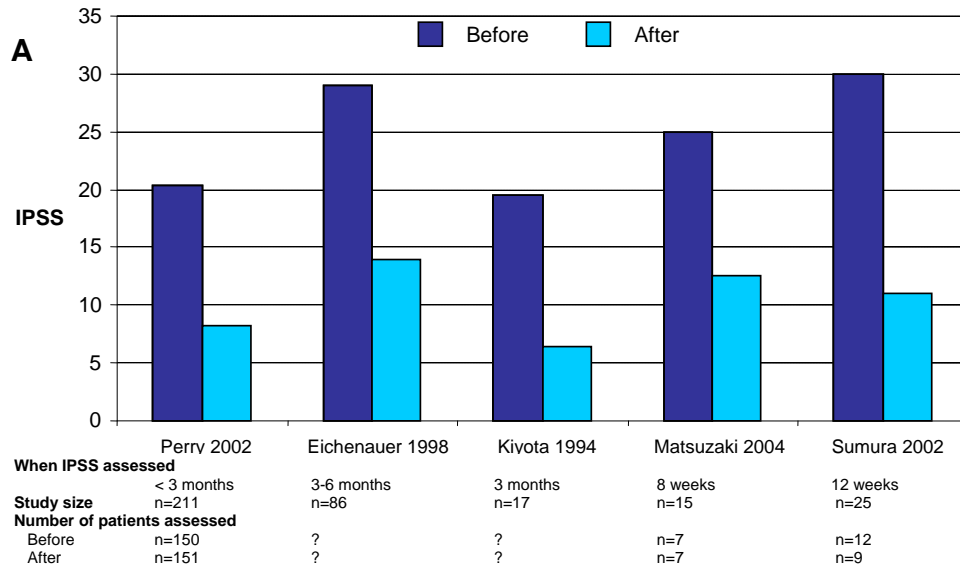
Table 6.1: Characteristics of included studies

Reference	Country	Type of publication	Quality score (max 18)	Number of participants	Mean/Median age (range)	Stent indication	Pathology	Mean/Median follow-up (range)
Booth 1997	UK	Journal Article	0	278 stents	(58-95)	UR and LUTS	BPH	Unclear
Eichenauer 1998	Germany	Journal Article	9	86	78.9 (64-93)	UR (n=58) LUTS (n=28)	BPH (n=68) CaP (n=18)	3-6 months
Hamasaki 2002	Japan	Journal Article	3	17	82 (54-92)	UR (n=15)	BPH or CaP (n=15) Neurogenic bladder (n=2)	21.2 (6-25) months
Itoh 1999	Japan	Journal Article	10	29	76.8 (61-85)	UR (n=19) LUTS (n=10)	BPH (n=22) CaP (n=7)	Unclear
Kawakami 2003	Japan	Journal Article	4	18	80 (65-92)	UR (n=18)	BPH	14 (3-18) months
Kiyota 1994	Japan	Conference Abstract	3	17	N/S	UR (n=15) LUTS (n=2)	BPH	7 (4-9) months
Kuriki 1995	Japan	Journal Article	8	32	74.9 (60-88)	UR (n=18) LUTS (n=14)	BPH	9.4 (1-25) months
Matsuzaki 2004	Japan	Journal Article	11	15	77.2 (69-87)	UR (n=8) LUTS (n=7)	BPH	8 weeks
Mellisourgos 1999	Greece	Conference Abstract	2	16	80.1	N/S	BPH	Unclear
Mishra 2004	UK	Conference Abstract	6	31	79.6 (61-94)	UR (n=18) LUTS (n=13)	BPH	Unclear
Perry 2002	UK	Journal Article	10	211	80.2 (54-103)	UR and LUTS	BPH (n=194) CaP (n=17)	7 years (max.)
Poulsen 1993	Denmark	Journal Article	6	30	79 (61-87)	UR (n=16) LUTS (n=14)	BPH	3 (0.2-9) months
Rathenbourg 2001	Denmark	Conference Abstract	3	28	80 (71-92)	UR and LUTS	BPH	30 (1-46) months
Sumura 2002	Japan	Journal Article	8	25	80.7	UR (n=20) LUTS (n=5)	BPH (n=18) CaP (n=7)	Unclear

UR   - Urinary retention   LUTS   BPH   - Benign prostatic hyperplasia   *All included studies were case series
      - Lower urinary tract symptoms   CaP   - Carcinoma of prostate

Table 6.2: Timing and cause of Memokath stent failure

Reference	Number of patients (n)	Mean / Median follow-up (range)	Number and timing of stent failures		
			Immediate failure n (%)*	Total failure n (%) in study period	Details on cause and timing of the failure
Booth 1997	(278$^\$$)	Unclear	-	88 (32)	No details on cause or timing of failure.
Eichenauer 1998	86	3-6 months	9 (10)	14 (16)	Incorrect stent length/placement was reported as the cause of immediate failure. Cause of subsequent failure not specified.
Hamasaki 2002	17	21.2 (6-25) months	1 (6)	1 (6)	Immediate failure: incorrect stent placement
Itoh 1999	29	Unclear	0	10 (34)	Migration (n=5); encrustation (n=3, at 6,10, and 12 months); dysuria (n=2).
Kawakami 2003	18	14 (3-18) months	0	0	
Kiyota1994	17	7 (4-9) months	-	7 (41)	Obstructive symptoms (n=7)
Kuriki 1995	32	9.4 (1-25) months	0	10 (31)	Migration (n=6, at 2 months); encrustation (n=4, at 6,16,18,21 months). 14 further stents were removed as they were no longer required.
Matsuzaki 2004	15	8 weeks	0	0	
Mellisourgos 1999	16	Unclear	-	6 (38)	Migration (n=6)
Mishra 2004	31	Unclear	0	15 (48)	Migration (n=5); retention (n=5); failure to improve symptoms (n=4); pain (n=1)
Perry 2002	211 (217$^\$$)	Unclear; up to 7 years (max.).	-	77 (36)	7 years follow-up reported for unclear number of patients, with no median or mean value reported. Reasons for removal included migration, worsening symptoms, encrustation, incontinence (n=44), repositioning for migration (n=33). 8 further stents were removed as they were no longer required.
Poulsen 1993	30	3 (0.2-9) months	1 (3)	4 (13)	Retention (n=2, at 2.5, 5 months); obstructive symptoms (n=1, at 3 months); incontinence (n=1, at 3 months). Immediate failure: incorrect placement.
Rathenbourg 2001	28	30 (1-46) months	0	7 (25)	Migration (n=3); incontinence (n=2); irritative symptoms (n=1); underactive detrusor (n=1). Median timing of failure at 8 (1-31) months.
Sumura 2002	25	Unclear	0	1 (4)	Encrustation (n=1, at 12 months)
Total n/N Total (%)	839 (100)		11/311 (4)	240/839 (29)	

*Immediate failure is given where explicitly indicated in the article $^\$$ (Number of stents used)

Chapter 7

The UroLume stent for benign prostatic hyperplasia: a systematic review of the literature

7.1   Introduction

The UroLume is the only prostatic stent which has been approved by the United States Food and Drug Administration (FDA) for the treatment of BPH. It is manufactured from a metal alloy which is woven to form an expandable tubular mesh. The UroLume stent can be inserted using local anaesthesia in the outpatient environment. When placed in the prostatic urethra the stent exerts a radial force which holds the lumen patent and permits spontaneous voiding.

The mesh structure of the UroLume stent allows epithelial incorporation, which confers theoretical advantages such as reduced rates of infection, stone formation and stent migration. Conversely, epithelial incorporation may permit prostatic regrowth which can lead to a recurrence of LUTS and make stent removal difficult if it is required.

The Memokath is an example of a different type of stent which does not allow epithelial in-growth, and is used predominantly in Europe. A systematic review of the Memokath stent for BPH showed that it is safe and that the improvement in symptoms is comparable to that seen after TURP (see Chapter 6).

In this Chapter we present the findings of a systematic literature review that assesses the effectiveness, durability and safety of the UroLume.

7.2   Methods

Inclusion and Exclusion Criteria. We included studies of any design, and with at least ten patients, that evaluated the UroLume stent in men with BPH. Case reports, editorials, and comments were excluded. Review articles were excluded although their bibliographies were searched for additional relevant literature.

Studies of the UroLume for indications other than BPH, and animal studies were also excluded.

Search Strategy. Medline and Embase databases were searched between 1989 (when the UroLume was first manufactured) and December 2005 using a comprehensive search strategy (see Appendix 4). The bibliographies of all included papers along with those of six review articles [Donnell, 2003; Kapoor, 2000; Lam, 2001; Oesterling, 1995; Ogiste, 2003; van Dijk, 2003] on stents were searched for additional literature. The manufacturer of the UroLume stent (American Medical Systems, Minnetonka, USA) was contacted for further published and unpublished research and subsequently provided a bibliography. No language restrictions were imposed and non-English papers were translated.

Outcomes. Effectiveness was assessed in three ways. First, by determining the proportion of catheter dependent men who were able to void spontaneously after insertion of the stent. Second, by determining symptom score reduction. Third, where possible, changes in uroflow parameters were assessed.

Safety was determined by the incidence of complications. These were divided into major complications which resulted in treatment failure (defined as the need for removal, replacement, or repositioning of the stent, or the need for another intervention to facilitate bladder drainage (for example, catheterisation, trans-urethral resection)), and minor complications which did not.

Data extraction and assessment of methodological quality. All titles and abstracts were independently assessed for inclusion by two reviewers (J Armitage and P Cathcart). Where there was insufficient detail the full paper was obtained. Where data was presented in abstract form only, the authors were contacted for further information. Data were independently abstracted from the literature by the same two reviewers and presented in structured tables for

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analysis. Disagreements were resolved by discussion and consultation with a third reviewer (J van der Meulen).

Methodological quality was appraised using criteria developed from published frameworks (see Appendix 3). [Downs, 1998; Khan, 2001; Lohr, 2004]

Analysis. Change in mean urological symptom score was presented graphically for each study. Treatment failure rates were calculated immediately after the procedure and again at one year.

7.3   Results

Literature search. 548 articles were identified by the database search of which 496 were excluded after reviewing their titles and abstracts (Figure 7.1). Of the remaining 52 articles where the full paper was obtained, only 15 could be included in the final analysis. [Adam, 1990; Amón-Sesmero, 1998; Bajoria, 1995; Bellinzoni, 1993; Clemente, 1997; Comeri, 1995; Goepel, 1997; Guazzoni, 1994a; Guazzoni, 1994b; Martorana, 1993; Masood, 2004; Milroy, 1993; Oesterling, 1994; Scarpone, 1992; Williams, 1993] For example, 15 studies reported duplicated data, and 12 pertained to the exclusive use of different types of stent and were therefore excluded. Two studies included less than ten patients and were excluded. One paper was not available through academic institutions in the UK. A further seven studies were identified by assessing the bibliographies of review articles, and three references were provided by the stent manufacturer. Together these contributed a further five discrete studies which were suitable for inclusion. [Gabellon, 1994; Chapple, 1995; Epstein, 1994; Shapiro, 2004; Yip, 1997]

Characteristics of included studies. 17 of the 20 studies were case series. Two studies compared the performance of the UroLume stent with TURP. [Chapple,

1995; Epstein, 1994] Although these trials were reported to be randomised they were only available as conference abstracts. After contacting the authors there remained insufficient detail to allow an assessment of methodological quality. One study compared the UroLume stent with transrectal hyperthermia and transurethral thermotherapy. [Bellinzoni, 1993] However, this study was not randomised and again insufficient information on patient demographics and poor methodology meant that meaningful comparisons were not possible. Therefore, only men from these studies who received a UroLume stent were included in this review.

Every effort was made to avoid the inclusion of duplicated data. However, despite contacting the authors, replication remains a remote possibility. [Guazzoni, 1994a; Guazzoni, 1994b] Where there were several reports from one group, [Masood, 2004; Oesterling, 1994] information was sought from all these sources, but only one study was cited in this review.

Eight studies included more than 50 patients, and three, more than 100 in their analyses (Table 7.1). The largest study included 135 patients. [Guazzoni, 1994a]

Quality assessment. The methodological quality of the studies was generally poor. For example, only 12 authors clearly outlined the study objectives. Only five studies clearly accounted for patients lost to follow-up during the study period. Statistical methods other than basic descriptive approaches were seldom employed and the funding source was made explicit in only two studies.

On the other hand, most studies accurately described the recruitment period, defined patient characteristics well, and reported major adverse events comprehensively.

Patient demographics. (see Table 7.1) A total of 990 patients were treated for bladder outlet obstruction with a UroLume stent. The aetiology of obstruction was BPH in all but 9 patients who had carcinoma of the prostate. About half of the patients were dependent on a urinary catheter for bladder drainage prior to UroLume insertion. 14 studies considered men who were mostly or exclusively at high operative risk, while 5 clearly stated that participants would normally have been considered suitable for surgery had they not been enrolled in the study.

Effectiveness.

Of the 990 patients included in the studies, 921 patients (93%) were able to void spontaneously following insertion of a UroLume stent (21 of these required a short period of suprapubic catheterisation). One should note that approximately half of these men were treated for LUTS only and were therefore able to void spontaneously prior to receiving a stent. Six studies included only patients who were dependent on a catheter prior to stent insertion. [Adam, 1990; Amón-Sesmero, 1998; Comeri, 1995; Martorana, 1993; Shapiro, 2004; Yip, 1997] 148 of the 176 men (84%) in these studies were able to void spontaneously after treatment with a UroLume.

Urological symptom scores were reported in 13 studies. [Amón-Sesmero, 1998; Bajoria, 1995; Bellinzoni, 1993; Guazzoni, 1994a; Guazzoni, 1994b; Masood, 2004; Milroy, 1993; Oesterling, 1994; Williams, 1993; Gabellon, 1994; Chapple, 1995; Epstein, 1994] Ten of these assessed symptoms before stent insertion in 440 men although one reported an estimated score, [Amón-Sesmero, 1998] the validity of which is questionable. All of these studies also reported reductions in symptom scores at some point in the first year after stent insertion, although the timing of assessment varied (Figure 7.2a). Madsen-Iversen scores were reduced by 7.9 to 14.3 points and IPSS by 10 to 12.4 points. These reductions in symptom score seemed stable in studies which reported longer follow-up although patient losses were often substantial. Men who had been reliant on a

catheter prior to stent insertion reported symptom scores similar to those of men who had been treated for LUTS.

Uroflow results were reported in 18 studies, 16 of which assessed mean peak urine flow rates. 11 studies assessed peak urine flow rates before and after stent insertion in men with LUTS (Figure 7.2b). All of these studies reported increases in mean peak flow rates following stent insertion of between 4.2 and 13.1ml/s. Mean peak urine flow rates after UroLume insertion in men who had been catheter dependent varied from 8.8 to 20ml/s. These improvements in flow rates appeared to become gradually less in studies which reported longer follow-up.

Durability.
666 patients were evaluable at one year in 12 studies which provided detailed information on the timing of stent failure, and reported a mean follow-up of 12 months or more. [Adam, 1990; Amón-Sesmero, 1998; Bajoria, 1995; Comeri, 1995; Goepel, 1997; Guazzoni, 1994a; Guazzoni, 1994b; Masood, 2004; Milroy, 1993; Oesterling, 1994; Gabellon, 1994] 104 stents (16%) failed during this period. The commonest complication leading to stent failure (removal, replacement, or repositioning of the stent, or the need for further intervention to facilitate bladder drainage) in the first year was stent misplacement or migration (38 stents (37%)). 15 stents (14%) failed because of recurrence of obstructive or irritative voiding symptoms. Furthermore 7 stents (7%) failed because of tissue hyperplasia, 5 (5%) due to stress incontinence, 4 (4%) as a result of chronic urinary retention, and 2 (2%) because of encrustation. The reason for stent removal was not given in 33 cases (32%). Accurate accounts of how these men were subsequently managed were not given.

Three studies which included 232 patients allowed yearly stent failure rates to be calculated up to 2 years. [Bajoria, 1995; Masood, 2004; Oesterling, 1994] A total of 33 stents failed in the first year (14%) and a further 16 stents failed in the

second year (8%). Two of theses studies went on to report explantation rates beyond two years. [Masood, 2004; Oesterling, 1994] The overall failure rate at 5 years was 27% (50/188 stents) although a substantial number of patients had been lost to follow-up or had died with their stent in-situ.

Safety

Sixteen studies including 894 patients described minor complications explicitly although the timing of these events was not always clear. [Adam, 1990; Amón-Sesmero, 1998; Bajoria, 1995; Bellinzoni, 1993; Clemente, 1997; Comeri, 1995; Goepel, 1997; Guazzoni, 1994a; Guazzoni, 1994b; Martorana, 1993; Masood, 2004; Milroy, 1993; Oesterling, 1994; Scarpone, 1992; Williams, 1993; Yip, 1997] All of these studies reported the occurrence of perineal pain or irritative symptoms in some patients immediately following stent placement. Furthermore, 12 studies that included 591 men, found that most or all men were affected. [Adam, 1990; Amón-Sesmero, 1998; Clemente, 1997; Comeri, 1995; Goepel, 1997; Guazzoni, 1994a; Martorana, 1993; Masood, 2004; Milroy, 1993; Scarpone, 1992; Williams, 1993; Yip, 1997] These symptoms settled spontaneously in the majority of patients but some, with irritative symptoms, required treatment with anticholinergic drugs. Out of all included patients 68 men (7.3%) were reported to have urinary tract infections and 3 (0.3%) epididymo-orchitis within the follow-up periods. However, the completeness of the reporting of infection is likely to be unreliable. Other minor complications were rare.

7.4   Discussion

Our review demonstrates that most men (84%) who were catheter-dependent voided spontaneously after insertion of a UroLume stent. The improvement in urinary symptoms was similar to that seen after TURP. [Flanigan, 1998] However, these results must be balanced against the one in six men who

required removal of the UroLume within 12 months of insertion and the occurrence of transient minor complications, such as pain and irritative voiding, immediately after insertion.

Our review could only consider case series, most of which were of low quality. Most studies provided limited long-term data and gave inadequate accounts of the patients that were lost to follow-up. This lack of long-term data limits the extent to which we can comment on durability beyond one year. Having said this, we included three relatively large, prospective, multi-centre studies which scored reasonably well on methodological criteria. [Guazzoni, 1994a; Oesterling, 1994; Williams, 1993] Furthermore, most included studies were explicit in their reporting of immediate changes in urological symptoms associated with stent insertion and treatment failure within one year.

It is worth noting that most patients in this review who received a UroLume stent had severe prostatic disease (approximately half were catheter dependent) and were at high risk of surgical complications. Our findings are therefore applicable to patients who are older, less fit, and more likely to have detrusor failure and bacterial colonisation of the urinary tract, than men traditionally allocated to a surgical intervention. None of the studies that were included in the systematic review undertook analyses according to any kind of stratification according to these risk factors.

In 1997, the FDA approved the use of the UroLume for men older than 60 years and for men less than 60 at high operative risk. This approval was based on the findings of only one study. [Oesterling, 1994] Given the results of our systematic review, there seems to be no justification for altering the FDA's decision. This review also supports the recommendation of the AUA that stents should be 'considered only in high-risk patients'. [AUA Guideline on the Management of Benign Prostatic Hyperplasia: Diagnosis and Treatment Recommendations]

This systematic review, together with our previous systematic evaluation of the Memokath stent (Chapter 6), allows a comparison of the literature on the two principal stents available for the management of BPH. The Memokath was designed to provide temporary relief of bladder symptoms, but is increasingly being used in Europe as a long-term treatment for BPH. [Madersbacher, 2006] The design of the UroLume allowing epithelial incorporation on the other hand was guided by the desire to prevent infection, encrustation and stent migration. The drawback of this design is that stent removal is more difficult and usually requires general anaesthesia.

On the basis of the current evidence, both stents appear to be equally effective at relieving bladder outlet obstruction due to BPH. The quality of the evidence on durability is better for the UroLume, so that treatment failure rates can be derived at one year for the UroLume but not for the Memokath.

No advice can currently be offered to men in relation to durability of prostatic stents beyond one year for the reasons described above. Future studies, on the UroLume or any other stent need to be designed in a way that long-term outcomes can be assessed. Perhaps the optimal way to do this would be via a registry as happens with other implantable materials.

7.5   Tables and figures

Figure 7.1: Summary of UroLume study selection process

Titles and abstracts identified by database search
n=548

After review of titles / abstracts
n=496

Full paper reviewed
n=52

Identified from bibliographies
n=7

Identified by manufacturer
n=3

Excluded

Duplicated data   n=15
Different stent   n=12
Review article   n=3
Study too small   n=2
Insufficient detail   n=2
Case report   n=1
Inadequate quality   n=1
Unable to obtain   n=1

Duplicated data   n=3
Insufficient detail   n=1

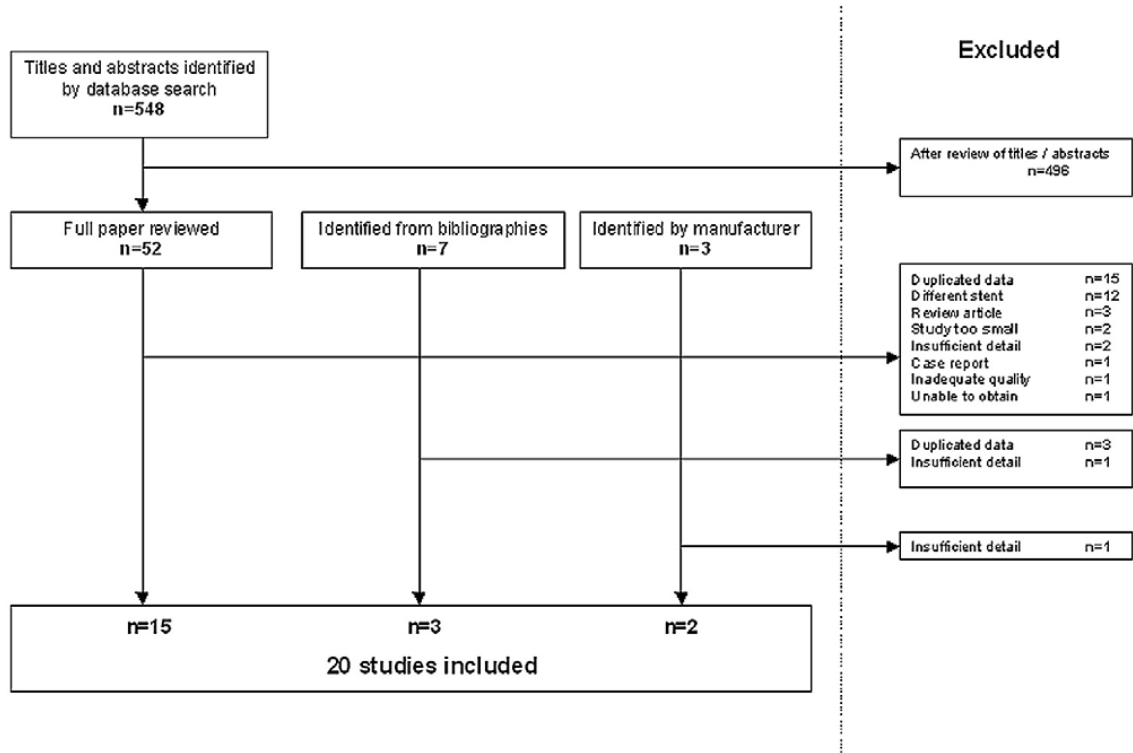Insufficient detail   n=1

n=15   n=3   n=2
20 studies included

Table 7.1: Included UroLume studies and patient demographics

Reference	Country	Type of publication	Quality score (max 18)	Number of participants	Mean/Median age (range)	Comorbidity	Stent indication	Pathology	Mean/Median follow-up (range)
				Participant characteristics					
Adam 1990	UK	Journal article	4	21	75 (65-90)	High risk	AUR=18 CUR=3	BPH=19 CaP=2	12-16 months
Amon-Sesmero 1998	Spain	Journal article	10	78	79.6 (62-93)	High risk	Indwelling catheter=48 AUR=26 Change stent=4	BPH	15.3 (3-38) months
Bajoria 1995	UK	Journal article	7	47	67.7 (50-80)	Fit for surgery	AUR=10 LUTS=37	BPH	2 years max
Bellinzoni 1993	Italy	Journal article	11	30	>70	High risk	LUTS	BPH	1 year
Chapple 1995	UK	Conference abstract	5	34	73 (65-90)	Fit for surgery	LUTS	BPH	3 months
Clemente 1997	Spain	Journal article	10	19	79.8 (72-93)	High risk	AUR=17 LUTS=2	BPH	8.2 (1-18) months
Comeri 1995	Italy	Journal article	11	34	74.5 (68-84)	High risk	AUR/CUR	BPH	14 (9-24) months
Epstein 1994	US	Conference abstract	3	32	69.4	Fit for surgery	LUTS	BPH	6-24 months
Gabellon 1994	Switzerland	Conference abstract	6	20	82.5 (70-93)	High risk	Indwelling catheter=17 LUTS=3	BPH	1 year
Goepel 1997	Germany	Journal article	8	37	79.4 (69-91)	High risk	AUR/CUR=15 LUTS=22	BPH	38.5 months
Guazzoni 1994a	Italy	Journal article	10	100	75.2 (62-93)	Most high risk	AUR=61 LUTS=39	BPH	2 years max
Guazzoni 1994b	Italy	Journal article	12	135	70.5 (50-85)	Fit for surgery	AUR=44 LUTS=91	BPH	18 months max
Martorana 1993	Italy	Journal article	6	21	77 (65-84)	High risk	AUR	BPH	Unclear
Masood 2004↑	UK	Journal article	13	70	67 (40-89)	Fit for surgery	LUTS	BPH	12 years max
Milroy 1993	UK	Journal article	8	54	75.7 (49-95)	Most high risk	AUR=34 CUR=12 LUTS=8	BPH=48 CaP=6	2 years max
Oesterling 1994†	US	Journal article	11	126	70	Not reported	AUR/CUR=31 LUTS=95	BPH	2 years max
Scarpone 1992	Italy	Journal article	6	14	78 (68-95)	High risk	Unclear	BPH=13 CaP=1	1 year
Shapiro 2004	US	Conference abstract	4	10	86	High risk	Indwelling catheter	Unclear	6 months - 3 years
Williams 1993	UK	Journal article	7	96	(52-95)	Most high risk	AUR=73 CUR=11 LUTS=12	BPH	3 years max
Yip 1998	China	Journal article	7	12	80 (72-92)	High risk	AUR	BPH	7 (2-18) months

AUR - Acute urinary retention   LUTS - Lower urinary tract symptoms   CUR - chronic urinary retention   BPH - Benign prostatic hyperplasia   CaP - Carcinoma of prostate

↑- Schneider and Anjum report earlier follow-up of these patients. †- Reports by Defalco, Shah, Marinkovic and Corujo as part of the North American UroLume study group contributed further information to this study.

Figure 7.2a: Change in urological symptom score associated with UroLume stent insertion

Figure 7.2a: Change in urological symptom score associated with UroLume stent insertion
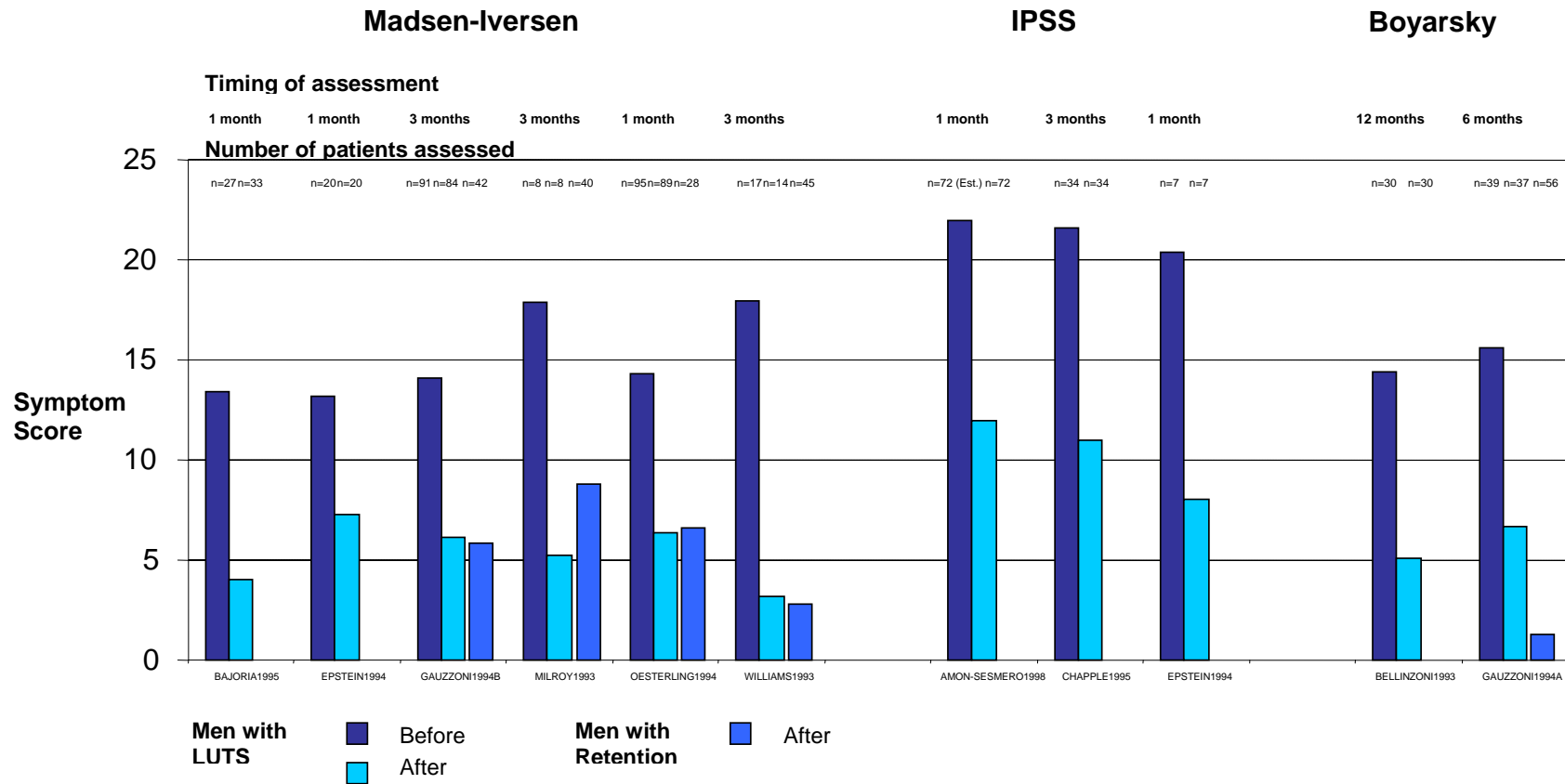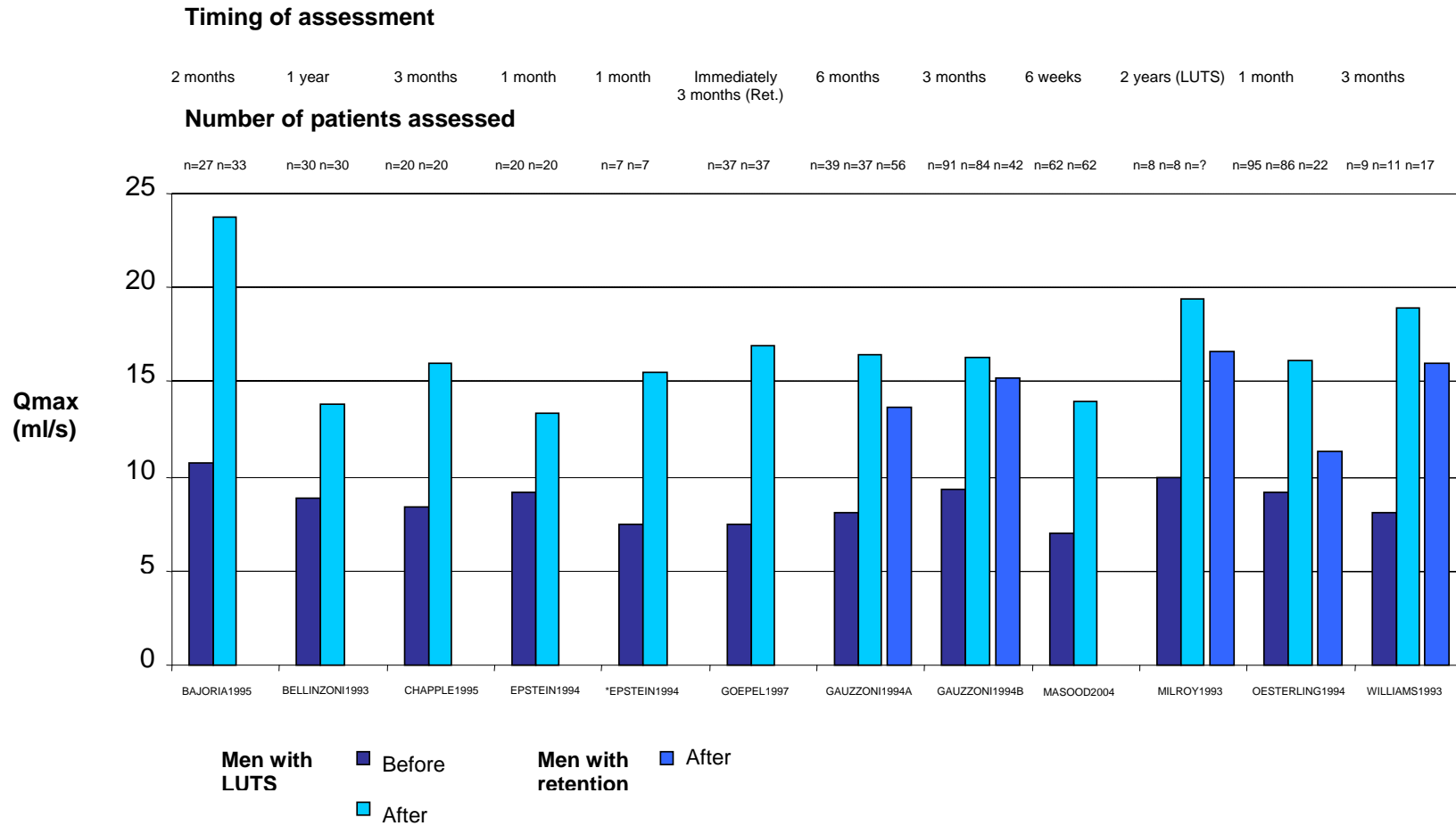
Figure 7.2b: Change in mean peak urine flow rates (Qmax) after UroLume stent insertion

Section 4

General discussion and clinical and research implications

Chapter 8

General discussion

8.1   Summary of thesis

Section one

Section one provided an introduction to and a general overview of this thesis. In Chapter 1 the objectives of the thesis were introduced, together with a description of how this programme of work commenced. The overall aim of this thesis was to investigate how the management of men with AUR could be improved. AUR was identified as a common and severe complication of BPH and interrogation of the HES database was proposed as a means of investigating mortality in men who experience an episode of retention. A lack of good quality evidence on the effectiveness, durability and safety of some minimally invasive alternatives to TURP was identified and systematic literature review was chosen as an appropriate next step in their evaluation.

Section two

Section two focused on the epidemiology of AUR. Chapter 2 summarised the epidemiology and initial treatment of AUR particularly for the benefit of non-urological readers of this thesis. In recent years, a number of risk factors for AUR have been identified including age, prostate size and the severity of LUTS. Also, the introduction of medical therapy for LUTS attributable to BPH appears to have had a considerable effect on the incidence of AUR, its management, and the subsequent requirement for prostate surgery.

Chapter 3 went on to investigate, for the first time, mortality rates after AUR using data from the HES database. Mortality after a first episode of AUR in men admitted to hospital was found to be very high. Overall, one in seven men with spontaneous AUR and one in four with precipitated AUR died within one year. Mortality rates increased strongly with age and the presence of comorbidity. Consequently, about half of the men aged over 85 years with at least one comorbid condition died within a year of their first episode of AUR. Although mortality in men younger than 55 years without comorbidity was not as high, it

was still at least four times higher than that observed in men of similar age in the general population. The high mortality that was observed suggests that these patients might benefit from early multi-disciplinary care to identify and treat comorbid disease.

The importance of comorbidity on the outcome of AUR together with recognition of the need for accurate case-mix adjustment when assessing and comparing healthcare outcomes prompted the development of an improved and updated version of the Charlson Score to identify comorbidity in administrative data. Chapter 4 described a consensus meeting of surgical and epidemiological experts that took place at the Royal College of Surgeons of England. The resulting RCS Charlson Score accounted for changes in the prognosis of some comorbid diseases since the Charlson Score was first developed 20 years ago. Furthermore, it was simplified to improve its accessibility and enhance its international transferability while taking into consideration the inherent limitations of routinely collected administrative data.

The RCS Charlson Score was subsequently validated in patients undergoing a range of common surgical procedures (abdominal aortic aneurysm repair, aortic valve replacement, total hip replacement and TURP) using HES data. The presence of at least one comorbid condition according to the RCS Charlson Score was associated with risk factors for comorbidity (for example, age, male sex and emergency admission) and with a poorer prognosis (for example, increased length of hospital stay, increased use of augmented care, and increased mortality). Furthermore, prognostic models that included the presence of comorbidity according to the RCS Charlson Score performed better at predicting mortality than models that relied on administrative variables alone.

Section three
This section considered treatment alternatives to TURP for men with AUR in whom a conservative management approach fails. These treatments are

generally considered to be less effective and less durable than TURP but on the other hand safer and associated with less morbidity. Some may be carried out under local anaesthesia in the outpatient department and are therefore often referred to as minimally invasive treatments. Chapter 5 introduced the minimally invasive treatment alternatives to TURP that are currently under evaluation within the context of clinical practice. Microwave thermotherapy (TUMT) and transurethral needle ablation of the prostate (TUNA) use microwaves and radiowaves respectively to heat and ablate the occlusive prostate. Lasers can be used in a similar manner to ablate or at higher power settings to resect prostatic tissue (for example, Holmium laser resection (HoLRP) or enucleation (HoLEP) of the prostate). Each of these minimally invasive treatments has recently been evaluated by systematic review. Both TUMT and TUNA were found to be less effective than TURP at reducing symptoms and increasing urinary flow rates but were associated with fewer adverse events. [Boyle, 2004; Hoffman, 2007] Some of the laser prostate treatments, for example HoLEP, were shown to offer comparable effectiveness to TURP [Tan, 2007] although the extent to which these procedures can be considered truly minimally invasive is questionable.

Inserting a prostatic stent to relieve bladder outlet obstruction in patients with AUR is an attractive concept as an alternative to surgery. Although the technology has existed for more than 25 years, prostatic stents have not found wide acceptance within the urological community. A perceived high complication rate has restricted their use to frail and elderly patients in whom surgery is deemed too dangerous. However, unlike some of the other minimally invasive treatment alternatives to TURP, the effectiveness, durability and safety of prostatic stents had not been adequately evaluated.

Chapters 6 and 7 presented systematic literature reviews of the Memokath and UroLume prostatic stents, those that are most commonly used in clinical practice today. These systematic reviews found that insertion of either stent type was

associated with a reduction in urinary symptoms comparable to that seen after TURP. Most men (84%) who were catheter-dependent voided spontaneously after insertion of a UroLume stent although one in six men required the stent to be removed within one year because of complications. Unreliable, inconsistent and limited follow-up meant that conclusions on durability beyond one year could not be made for either stent type. Therefore, the reviews support recommendations that the Memokath and UroLume stents should be considered only as treatments for elderly men and those at high operative risk. They highlighted the need for further studies with extended follow-up to determine the durability of the stents.

This thesis has provided important information on the long-term prognosis of men with AUR. It has also considered the role of minimally invasive treatment alternatives to TURP and provided a systematic evaluation of prostatic stents. These findings have significant implications for the management of men with AUR and these are considered in the discussion below.

8.2   Methodological challenges

8.2.1 Hospital Episode Statistics database

The Hospital Episode Statistics database is a unique data source because it provides information on all NHS hospital admissions in England. For these data to be used reliably in healthcare research they must be complete and accurate. A number of processes are in place to ensure good data quality. For example, a record submitted to HES will only be verified if it contains details of an appropriate hospital provider, details of the type of admission and if it also contains a date for the end of that episode which falls within the appropriate HES year. A process called 'autocleaning' ensures that data fields make sense both in isolation and also with reference to other fields. Incorrect fields are overwritten if the correct value can be derived from other data fields, for example, duration of

episode can be calculated if admission and discharge dates are known. In a further step called 'validation' all records are tested against a set of rules to identify problems that persist after autocleaning. A report on the quality of the submission is then generated. The performance of data providers may be assessed using this information and this process helps to maintain and improve data quality.

A number of studies have investigated the accuracy of HES data. A recent systematic review of studies that compared routine discharge statistics with medical casenotes found the median coding accuracy of more than 90% for diagnostic codes although this fell to 70% when procedural codes were considered. [Campbell, 2001] There is also evidence that the accuracy of coding has improved considerably over the last decade. [Hansell, 2001] A study that compared the accuracy of HES coding for varicose vein surgery to local audit data found that coding accuracy in 1989 was 45% compared to 98% in 1995. [Galland, 2000]

Clearly HES data must be complete and accurate but for any comparisons of healthcare performance to be reliable, robust interpretation of these data is also essential. This thesis has demonstrated the importance of precisely defining the study population. For example, in Chapter 3 we investigated the mortality of men with a first episode of AUR that had occurred as a result of BPH. Identifying these patients in HES required a step-wise process. First, the records of all female patients were excluded. Second, patients who had experienced AUR were identified using a single ICD-10 code (R33) that is unambiguous and therefore likely to be recorded accurately. Third, all of the records of patients who had prostate cancer or neurological disease were deleted. Patients with AUR in a record from the first year of the study period could not be included as these men may have had an earlier episode of AUR for whom this admission represented a recurrent episode rather than the first episode. Further categorisation according to whether AUR was spontaneous or precipitated was

important and required additional careful data manipulation. Similar rigorous consideration was given to each of the study populations defined in Chapter 4.

Researchers who use administrative data such as HES in health services research must also be alert to data quality issues that arise. In Chapter 3, for example, 2.4% of men who were reported as having died after AUR were found to have a record of a subsequent hospital admission. For these contradictory results, the information on death was considered to be erroneous and these men were therefore analysed as being alive until the end of the study period. Therefore, this thesis emphasises the importance of judicious interpretation and appropriate responses to any data inaccuracies within HES.

Ensuring adequate adjustment for case-mix is an essential component of any study that reports surgical activities or outcomes. Case-mix adjustment should include an estimate of the severity of the primary disease as well as determining the presence and severity of comorbid diseases (coexisting but unrelated conditions that may affect a patient's prognosis in addition to the primary disease). It presents a particular methodological challenge when administrative data are used because these sources frequently lack detailed clinical information.

A number of instruments have been used to identify comorbid disease in administrative data and of these, adaptations of the Charlson Score have been the most widely used and validated. Previous work has demonstrated that ICD-10 adaptations of the Charlson Score can be used to identify comorbid disease to an extent necessary to control for differences in case-mix between different patient populations. [Nuttall, 2006] In Chapter 4 of this thesis we developed the RCS Charlson Score that is a simple, valid and internationally applicable method for comorbidity adjustment in administrative data that builds on this earlier work. Furthermore, Chapter 4 identified important general principles for comorbidity adjustment in administrative data that may be used as a basis for further

research in this area. The utility of the RCS Charlson Score must now be demonstrated in further studies that include different patient groups.

8.2.2 Systematic reviews of observational studies

The validity and applicability of a systematic review depends on the quality of the primary studies that are included. A systematic review that includes only observational studies is subject to confounding, and selection and information biases that may lead to uncertainty in the estimates of treatment effect. Reviewers should be aware of these risks and users of systematic reviews that include non-randomised data should be careful not to over interpret their findings. [Deeks, 2003] An attempt must therefore be made to minimise these potential biases by including a methodological quality assessment of the studies that are included in a systematic review.

The systematic reviews of prostatic stents presented in Chapters 6 and 7 evaluated the methodological quality of all potentially relevant studies using an 18 point checklist developed from published frameworks specifically for the appraisal of non-randomised studies (see Appendix 3). [Downs, 1998; Khan, 2001; Lohr, 2004] These criteria hardly differed from those proposed in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement that has since been published. [von Elm, 2007] For example, both checklists highlighted the importance of stating the specific objectives of the study and clearly defining the outcomes of interest. They also identified the need for detailed reporting of the characteristics of included patients, how they were selected and an accurate account of those lost to follow-up. A discussion of the study limitations as well as the generalisability of the findings should also be included. A checklist such as the one developed in this thesis, or that which was published in the STROBE statement, provides important information on the quality of observational studies. The methodological assessment of the quality of observational studies included in a

systematic review helps to determine the validity and justifiability of its conclusions.

If the inherent limitations of non-randomised studies are recognised, their inclusion in a systematic review may contribute substantially to the evidence base for a particular intervention especially where randomised controlled trial evidence is lacking or indeed absent. Moreover, a recent review of empirical studies suggests that meta-analyses based on observational studies generally produce estimates of treatment effect similar to those from meta-analyses based on randomised controlled trials. [Shrier, 2007]

8.3   Clinical implications

8.3.1 Identifying and treating comorbidity in men with AUR

The high mortality of men with AUR reinforces the importance to the clinician of adopting a multi-disciplinary approach when assessing and managing men with AUR. We found that men with AUR who have comorbidity are at the greatest risk of death. Therefore, men who experience AUR should undergo a comprehensive assessment for the presence of comorbid disease and where it is identified it should be treated appropriately.

Our observation that about half of the deaths after AUR occur within the first 90 days suggests that assessment for comorbidity must occur promptly. Taking the need to be timely one step further, one could claim that to be most effective screening for other morbidities should start in men presenting with LUTS attributable to BPH before these patients have experienced AUR.

We found that about 30% of patients with AUR had co-existing cardiovascular disease, 25% had diabetes and 25% chronic pulmonary disease. The relatively high prevalence of cardiovascular disease and diabetes is consistent with the

findings of recent aetiological studies linking hypertension and metabolic syndrome with the progression of BPH. [Michel, 2004; Ozden, 2007] Furthermore, the high prevalence of these conditions implies that some men presenting with AUR will have undiagnosed comorbidity. Clinicians should specifically enquire about the presence of these diseases and their risk factors, and liase with the primary care physician to address their management. Perhaps all men with AUR should have their BMI (body-mass index) calculated, and have their blood glucose and blood pressure checked.

However, the extent to which mortality after AUR can be reduced will depend on the nature and severity of the comorbid diseases involved and the effectiveness of the available treatments. For example, some patients will have comorbidity that is already optimally treated and for whom little further can be done.

Perhaps the urologist should become an advocate for men's health in general. [Kirby, 2005] Men are often ignorant of the diseases at which they are most at risk and there is a general reluctance of men to seek medical advice. One of the first contacts with the medical profession may be with a urologist because of urinary symptoms or erectile dysfunction. This consultation provides a unique opportunity for the urologist to enquire about associated health issues, arrange investigation and institute appropriate management. For example, erectile dysfunction shares the same risk factors as ischaemic heart disease and cerebrovascular disease. [Thompson, 2005] Similarly, patients presenting to the urologist with LUTS who are found to have diabetes or hypertension may be commenced on treatment and smokers with urothelial carcinoma may be introduced to cessation programmes. The findings of this thesis support a holistic approach and suggest that patients presenting with LUTS or AUR undergo a thorough evaluation for the presence of comorbid disease.

8.3.2 Treatment options for men with AUR

The management of AUR has changed considerably in recent years. For example, the introduction of medical therapies for LUTS appears to have changed the natural history of BPH, with alpha-receptor blockers delaying disease progression and 5-alpha reductase inhibitors actually reducing the long-term risk of developing AUR. [McConnell, 2003] Moreover, whilst AUR was once considered an absolute indication for TURP, now most men with urinary retention will have at least one trial of voiding prior to considering surgery. Fears that this approach will merely delay the inevitable need for surgery appear to be unfounded in light of recent studies that have shown that the shift away from the surgical treatment of BPH has not resulted in an increase in AUR. [Cathcart, 2006]

For men with AUR who do not pass urine following a TWOC, have refractory LUTS, or experience complications of BPH such as a recurrent episode of AUR, there are now a number of minimally invasive treatment alternatives to TURP. This thesis has considered some of these minimally invasive treatments (see Chapter 5) and has evaluated the effectiveness, safety and durability of prostatic stents by systematic literature review (see Chapters 6 and 7). Minimally invasive treatments tend to be less effective and less durable but are generally associated with a lower risk of morbidity. These treatment-related factors constitute an important part of the discussion when counselling a man with AUR about his management options.

Many patient-related factors also influence the type of treatment that is offered to a man with AUR. For example, the size of the prostate, the retention volume and hence possible bladder dysfunction, the suspicion of malignancy, the use of anticoagulant medication, and the patient's expectations and attitudes towards the various treatments must all be considered. Also of significance, especially in light of the findings of the study presented in Chapter 3 of this thesis, are the patient's age and the presence of comorbid disease.

Older men with comorbid disease who experience AUR may be more appropriately offered a treatment with lower morbidity, accepting that it may be less effective and less durable than other options. For example, prostatic stents may represent a useful alternative to a long-term catheter in men with AUR who are deemed unfit for surgical procedures such as TURP.

Conversely, the morbidity associated with a procedure may be an important factor for young men with AUR who may wish to avoid, or at least defer, some of the risks associated with surgery while accepting a potentially less effective and less durable treatment. For example, laser ablation procedures may be associated with a lower risk of retrograde ejaculation than laser enucleation procedures or TURP.

8.4   Research implications

8.4.1 Extending the role of administrative databases in health services research

Administrative databases such as HES were not designed to answer specific research questions. However, because they contain patient-level data including identity, treatment and some health state or outcome data they are increasingly being used for healthcare research purposes. For example, in the UK HES data have been used to study the epidemiology of disease, [Cathcart, 2005; Roche, 2005] evaluate variations in healthcare outcomes [Nuttall, 2004; Aylin 2007] and in Chapter 3 of this thesis HES data were used to investigate mortality after AUR.

Studies that use administrative data to evaluate healthcare outcomes require adequate case-mix adjustment and the RCS Charlson Score presented in this thesis and discussed earlier in this chapter is an important component.

However, there are many other important factors in case-mix adjustment that are not readily derived from administrative datasets.

For example, the severity of the primary disease is another key determinant of outcome. This information is often not directly available from HES data although occasionally it may be inferred by association. For example, in patients undergoing aortic valve replacement the presence of congestive cardiac failure implies more severe disease (see Chapter 4).

Therefore, the utility of administrative data may be enhanced through linkage with other databases and registries that provide information on disease severity. For example, cancer registries often provide information on the severity of the disease by way of cancer staging (how advanced the cancer is). A US study that investigated mortality after radical prostatectomy for prostate cancer used routine data from Medicare linked to cancer staging data from the Surveillance, Epidemiology, and End Results (SEER) registry. [Begg, 2002] Linkage of HES data with the General Practice Research Database could provide important additional information on comorbidity that would help to define its effect on mortality after AUR. Conversely, the value of cancer registries may be increased through linkage with administrative data sources. A recent UK study found the reporting of ethnicity data in HES far better than in a regional cancer registry and suggested data linkage as a means of overcoming deficiencies in the registry data. [Jack, 2006]

Linkage of administrative databases with clinical databases and registries also provides important additional information on healthcare outcomes. For example, the linkage of the central cardiac audit database with mortality data from the Office for National Statistics database allowed indefinite tracking of mortality of cardiac patients. [Keogh, 2005] More recently HES data have been linked to the ONS mortality database making studies such as that presented in Chapter 3 of this thesis that assessed mortality rates after AUR possible. HES linked ONS

mortality data now include not only date of death but also cause of death which could help to explain the reasons for the high mortality after AUR. Detailed information on the incidence of complications as well as important outcomes such as health-related quality of life might also be obtained through linkage with clinical databases.

Research building on administrative databases, such as HES, enriched through linkage with additional clinical data may be used to further define the importance of comorbidity in patients with AUR and investigate the extent to which its treatment will reduce mortality. First, administrative databases can provide near complete follow-up in terms of further treatment as well as death. Clinical data, perhaps collected prospectively in a subgroup of patients and linked to the administrative data at individual patient level, will allow a further exploration of the impact of comorbidity according to its nature and severity. It can be envisaged that the results of this step will inform the development of treatment strategies. Second, these strategies can then be evaluated using research designs that build on combining administrative data with data derived from clinical trials.

The linkage of databases therefore provides a powerful way of extending their utility and also permits cross validation of data. For example, The Clinical Effectiveness Unit of The Royal College of Surgeons of England has linked prospective data from the National Joint Registry with HES data at hospital level. [National Joint Registry for England and Wales. 4th Annual Report] This study allowed the determinants of outcomes such as mortality and length of stay after hip and knee replacement to be investigated. The generation of electronic patient records may in time allow data from clinical and administrative databases to function as one, with each acting as a source of validation and corroboration of the other. [Connecting for health, NHS Care Records Service. http://www.connectingforhealth.nhs.uk/systemsandservices/nhscrs]

In the UK there have been recent failures of the medical profession to identify poor performance of both individual medical practitioners [The Shipman Inquiry - Final Report, 2005] and hospital providers. [Learning From Bristol - Bristol Royal Infirmary Inquiry, 2001] Therefore, there is an increasing requirement for openness, public accountability and the transparent provision of high quality healthcare. As part of this, the Department of Health believes that the publication of survival rates after surgery will provide an incentive to the medical profession to maintain and improve standards and at the same time reassure the public that these efforts are being made. This is a view that is supported by The Royal College of Surgeons of England which believes that the publication of outcomes as a combination of patient reported outcomes measures, routinely collected administrative data and the results of clinical audits will lead to improving the quality and standards across surgery. [Royal College of Surgeons response to Lord Darzi's NHS Next Stage Review, 2008]

Since 2005 mortality data that has been voluntarily supplied by cardiac units for all cardiac surgeons in the UK have been made publicly available. More recently in 2008 the Department of Health published mortality rates for abdominal aortic aneurysm repairs (elective and emergency), elective hip replacements and knee replacements, information that was derived from the HES database. [NHS Choices, 2008]

Publication of these data is still controversial. For example, it has been suggested that it may lead surgeons to refuse difficult cases or may result in surgeons and healthcare providers being penalised unfairly if data are inaccurate. It is therefore imperative that these data are reliable and measures taken to provide accurate adjustment for differences in case-mix. This thesis has shown that HES data can be reliably used to answer important healthcare questions and through the development of the RCS Charlson Score will hopefully extend the utility of this valuable data source.

8.4.2 Appraisal of minimally invasive prostate treatments

Recently, traditional surgical techniques have been challenged by numerous minimally invasive treatment alternatives to TURP. Some of these have been introduced into clinical practice and continue to undergo evaluation in this context, while others have been abandoned because of concerns over their effectiveness, durability and safety. Unfortunately, the rapidity with which many of these technologies have been developed has often precluded their adequate assessment, as demonstrated in Chapters 6 and 7 with prostatic stents. However, rigorous evaluation of these interventions is essential so that clinicians can provide patients with accurate information and ensure that the most appropriate treatments are offered to them. Some of the challenges facing researchers when evaluating new minimally invasive prostate treatments are now considered.

Limitations of randomised controlled trials

Randomised controlled trials (RCTs) have been considered by many to be the only reliable means of evaluating healthcare interventions. This study design ensures that the comparison groups differ only in their exposure to the intervention and may therefore provide the best estimate of treatment effect. However, when evaluating surgical procedures, such as minimally invasive prostate treatments, RCTs are sometimes unnecessary or unfeasible and in these situations observational studies may be more appropriate. Furthermore, there is increasing recognition that the two approaches - RCTs and observational studies - have complementary roles in the assessment of healthcare interventions.

An important limitation of RCTs is that their external validity (the generalisability of their findings) may be limited. [Black, 1996; McKee, 1999] For example, RCTs are frequently conducted by experienced clinicians under optimal conditions and do not therefore reflect real life practice. Furthermore, stringent inclusion and exclusion criteria may result in a highly selected study group that is not

representative of the population for whom the intervention is ultimately intended. Therefore, the effectiveness of an intervention in everyday clinical practice may be better assessed by population-based observational studies. Such studies will be representative of all patients but control of confounding will be limited to those factors that are recognised as important and are measured. The issue of generalisability is particularly pertinent in surgery where outcomes are very dependent on the experience and expertise of the surgeon and of the unit where the procedure is carried out.

For RCTs to be ethical there must be sufficient doubt about the relative merits of the different treatment options. Where clinicians do not accept that there is uncertainty about the effectiveness of different interventions RCTs are inappropriate. This is often the case for minimally invasive prostate treatments that are not designed to provide comparable effectiveness to TURP. For example, we showed in Chapters 6 and 7 that prostatic stents are effective at restoring spontaneous voiding in most men with AUR but that their use should probably be restricted to a subgroup of patients who are not fit for surgery. Therefore, an RCT comparing prostatic stents to TURP would not be appropriate.

The role of data registries
Data registries can be used to evaluate healthcare technologies that are already in clinical use. Registries only record data that are derived from the administration of routine clinical care. Therefore, these patients should be representative of those for whom the intervention is intended in 'real-life' practice. The ethical concerns facing clinicians when enrolling patients in clinical registries are also fewer because patients receive only the treatment that they would normally be given. Clinical registries are relatively cheap and may therefore be maintained for many years thus providing important information on rare and late complications and on the durability of treatments.

There are many examples of clinical registries in the UK. For example, the National Joint Registry (NJR) was established in 2003 with the aim of collecting data on all joint replacements carried out in England and Wales. [National Joint Registry] The NJR appears to fulfill its specific objectives that are to improve clinical care through identifying best practice in orthopaedic units and to provide information on the performance of the various implants.

The introduction of a clinical registry may therefore be the most appropriate next step in the evaluation of prostatic stents and other minimally invasive prostate treatments. The systematic reviews of prostatic stents presented in Chapters 6 and 7 identified a lack of long-term data on the durability of prostatic stents. The challenge of maintaining a clinical trial for a prolonged period to collect information on durability is compounded by the age and frailty of the patients who are typically treated with prostatic stents. A stent registry would provide good evidence of durability as well as additional information on safety and effectiveness.

Importance of evaluating short-term morbidity versus long-term benefit
When considering the morbidity associated with minimally invasive prostate treatments, factors such as the inconvenience of the procedure, post-operative pain and discomfort, and the time to recovery of functional status are also important. However, it can be difficult to accurately assess this short-term morbidity. For example, generic surgical complications such as fever, urinary tract infection, wound infection and bleeding are often poorly defined. Moreover, a recent systematic review found inconsistency in the quality of reporting of post-operative adverse events, limiting accurate comparison of rates over time and between institutions. [Bruce, 2001] A reliable and valid approach to assess short-term morbidity would be of great value when assessing minimally invasive prostate treatments as this information may influence a patient's decision when selecting treatment.

The Postoperative Morbidity Survey (POMS) is the only published prospective method that attempts to capture the short-term morbidity associated with major surgery. [Bennett-Guerrero, 2001] This instrument aims to provide a simple means of identifying short-term morbidity of a type and severity that could delay discharge from hospital. It contains 18 items that address nine domains of post-operative morbidity and is starting to be used in both outcomes [Bennett-Guerrero, 2001] and effectiveness research. [Wakeling, 2005] A recent study that assessed short-term morbidity in patients undergoing elective major orthopaedic, gastrointestinal and urological surgery in a UK teaching hospital found the POMS to be valid and reliable. [Grocott, 2007]

Harder still are estimations of the degree and duration of post-operative pain and of the impact of surgery on a patient's functional status. A number of generic and disease-specific instruments to measure health related quality of life have been developed. These 'patient reported outcome measures' are an essential part of the evaluation of healthcare interventions and also allow the comparison of healthcare providers. [Browne, 2008] Future studies that assess minimally invasive prostate treatments that may sacrifice some effectiveness for improved safety and quicker recovery, should attempt to quantify short-term morbidity and assess patient reported outcomes.

8.5   Concluding remarks

This thesis has demonstrated that the mortality of men with AUR is high and increases strongly with age and the presence of comorbid disease. When assessing patients with AUR urologists are in a unique position where by actively seeking comorbidity and by instituting appropriate management they may help to reduce its associated mortality.

The important influence of comorbidity on mortality of men with AUR prompted the development of The RCS Charlson Score to improve comorbidity identification in HES. The RCS Charlson Score uses an explicit coding philosophy that is simple to use, more accurate than existing instruments, reflects the current understanding of the prognostic impact of comorbidity and allows international comparisons. It was developed on the basis of sound general principles for identifying comorbidity that should extend the role of administrative data such as HES in health services research. Moreover, through linkage with clinical data sources it is hoped that HES data may be used to enhance our understanding of the epidemiology and optimal management of AUR.

Given that many men with AUR are elderly, have significant comorbidity and therefore have a high risk of death, minimally invasive treatment alternatives to surgery for AUR were considered. Systematic literature review defined the role of prostatic stents as an effective treatment option for frail and elderly men. Although only observational data were available a specifically developed checklist to assess methodological quality gave context to the review findings. This thesis has also highlighted the importance of reliable evaluation of new technologies such as minimally invasive treatment alternatives to TURP.

The overall aim of this thesis was to investigate how to improve the management of men with AUR. Its principle finding is that the management of AUR must focus not only on the prostate but also on the patient's overall health status. The urologist should adopt a holistic approach when assessing and treating a man with AUR to ensure the best possible outcome.

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Appendices

Appendix 1

Updating and improving comorbidity adjustment in HES

Members of the RCS Comorbidity Consensus Group

Mr James Armitage	Urological Research Fellow Clinical Effectiveness Unit The Royal College of Surgeons of England
Professor Nick Black	Professor, Health Services Research Unit London School of Hygiene and Tropical Medicine
Dr David Cromwell	Senior Lecturer London School of Hygiene and Tropical Medicine
Professor Sina Dorudi	Consultant Colorectal Surgeon The Royal London Hospital
Professor Mark Emberton	Professor of Urological Oncology and Consultant Urological Surgeon Institute of Urology and Nephrology, London Clinical Director, Clinical Effectiveness Unit The Royal College of Surgeons of England
Professor Paul Gregg	Consultant Orthopaedic Surgeon South Tees Hospital NHS Trust
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Professor Sir Peter Morris	Director, Evidence Based Transplant Centre The Royal College of Surgeons of England
Mr Thomas Palser	Upper Gastrointestinal Surgery Research Fellow Clinical Effectiveness Unit The Royal College of Surgeons of England
Professor Tom Treasure	Consultant Cardiothoracic Surgeon Guy's and St. Thomas's NHS Foundation Trust
Professor Jan van der Meulen	Professor of Health Services Research London School of Hygiene and Tropical Medicine Director, Clinical Effectiveness Unit The Royal College of Surgeons of England

Appendix 2

Memokath systematic literature review search strategy (Medline)

Population terms

1   exp. prostatic hyperplasia#
2   exp. prostate#
3   ((hypertroph$3 or hyperplas$3) near prostat$3)
4   adenoma near prostat$3
5   prostatism
6   intraprostatic
7   (bladder near (outflow or outlet) near obstruct$3)
8   exp. bladder-neck-obstruction#
9   LUTS
10   lower adj urinary adj tract adj symptoms
11   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

Intervention terms

12   exp. stents#
13   stent$3
14   memokath$
15   prosthes$
16   spiral
17   12 or 13 or 14 or 15 or 16

Combined terms

18   11 and 17

Appendix 3

Checklist for the assessment of methodological quality of observational studies

Criterion	Yes	No	Unclear	N/A
1. Is the aim/objective of the study clearly described?				
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?				
3. Are the inclusion/exclusion criteria explicit?				
4. Are the characteristics of the patients included in the study clearly described?				
5. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?				
6. Did all individuals enter the study at a similar point in their disease progression?				
7. Was patient selection consecutive?				
8. Was data collection prospective?				
9. Was the recruitment period clearly defined?				
10. Does the study provide estimates of the random variability in the data for the main outcomes?				
11. Were the main outcome measures used accurate (valid and reliable)?				
12. Have all important adverse events that may be a consequence of the intervention been reported?				
13. Are the main findings of the study clearly described?				
14. Were the statistical methods used to assess the main outcomes appropriate?				
15. Do the analyses adjust for different lengths of follow-up of patients?				
16. Have the characteristics of patients lost to follow-up been described and have these losses been taken into account?				
17. If comparisons of sub-series are being made was there sufficient description of the series and the distribution of prognostic factors?				
18. Was the funding source made explicit if applicable?				

Appendix 4

UroLume systematic literature review search strategy (Medline)

Population terms

1   exp. prostatic hyperplasia#
2   exp. prostate#
3   ((hypertroph$3 or hyperplas$3) near prostat$3)
4   adenoma near prostat$3
5   prostatism
6   intraprostatic
7   (bladder near (outflow or outlet) near obstruct$3)
8   exp. bladder-neck-obstruction#
9   LUTS
10   lower adj urinary adj tract adj symptoms
11   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

Intervention terms

12   exp. stents#
13   stent$3
14   urolume$
15   prosthes$
16   spiral
17   12 or 13 or 14 or 15 or 16

Combined terms

18   11 and 17