

Erectile Dysfunction in clinical practice

*- With special focus on the correlation to myocardial infarction,
lower urinary tract symptoms(LUTS), treatment cost and
optimization -*

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To my dedicated and loving wife Christina for her unconditional support and persistent encouragement to complete this endeavour.

Abstract

The purpose of this thesis was to study and evaluate aspects of Erectile Dysfunction (ED) in clinical practice, with special focus on the correlation to myocardial infarction, LUTS (lower urinary tract symptoms), ED treatment costs and optimization.

A group of 100 patients under the age of 70 years who had suffered their first MI and an age matched control group without MI answered a questionnaire regarding ED and concomitant diseases. The aim was to evaluate the possible connection between ED and cardiovascular disease (CVD) in a more severe manifestation, myocardial infarction (MI) and if ED is a clinically useful predictor for MI.

A survey consisting of two questionnaires, IPSS (reflecting LUTS and the bother it causes) and IIEF-5 (reflecting ED) was sent to 2000 randomly selected men, 60-70 years old. The aim was to study the relationships between lower urinary tract symptoms (LUTS), the bother induced by LUTS, age and ED. The importance of the relationship between LUTS and ED for the care of the individual patient in clinical routine was given special attention.

A questionnaire was mailed to 132 men with ED, who 2 years earlier, when the drug was subsidised, had started Sildenafil (a selective PDE-5 inhibitor) treatment. The questionnaire, which was sent out when the subsidisation had been withdrawn, included questions regarding current ED treatment, frequency of Sildenafil use, reasons for change or discontinuation, effect of the treatment, partner relations and total income of the household. The aim was to study the compliance for ED treatment with Sildenafil in clinical practice, with special focus on the association between cost and consumption.

In a forth study outcomes of a treatment regime, where 186 eligible patients in clinical practice had the opportunity to try the three different PDE-5 inhibitors, were evaluated.

An association between CVD and ED was found, but ED as a single symptom does according to our judgment not justify an investigation of risk factors for coronary artery disease. If ED is to be a clinically useful predictor, it must also be a reason to seek medical attention, which rarely was the case. There was a correlation between LUTS (c.c. 0.3 $p > 0.001$), the bother induced by LUTS (c.c. 0.3 $p > 0.001$), age and ED. The relationships were as in other studies rather weak and consequently appear to be of less importance for the management of the individual patient seeking medical attention due to LUTS and/or ED. The treatment compliance for Sildenafil in clinical practice was just under 50% two years after treatment initiation. Cost appeared to be an important factor for both treatment abortion and rationing. A treatment regime that allows the patients to try out the three available PDE-5 inhibitors, at the highest recommended dose, is a feasible option in clinical practice which will lead to a exceptionally high response rate (89%) in both previously PDE-5 treated and naïve patients. More long acting drugs was not preferred more often and a fast acting effect was a factor of little importance for patient preference.

Key words: Erectile Dysfunction, Cardiovascular disease, LUTS, Cost, Treatment optimization, Preference, Clinical practice.

This thesis is based on the following papers, henceforth referred to by their Roman numerals:

Paper I:

”Is erectile dysfunction really a clinically useful predictor of cardiovascular disease?”

Ströberg P, Frick E and Hedelin H.

Scandinavian Journal of Urology and Nephrology, 2005; 39: 62 - 65.

Paper II:

“Relationships between lower urinary tract symptoms, the bother they induce and erectile dysfunction”.

Ströberg P, Boman H, Gellerstedt M and Hedelin H.

Scandinavian Journal of Urology and Nephrology, 2006; 40: 1 - 6.

Paper III:

“Is sex only for the healthy and wealthy?”

Ströberg P, Bergström A and Hedelin H.

Journal of Sexual Medicine; 2006; [on line early publication] (accepted Dec 2005).

Paper IV:

“Prescribing all PDE-5 inhibitors to a patient with Erectile Dysfunction (ED), a realistic and feasible option in everyday clinical practice -Outcomes of a simple treatment regime-”

Ströberg P, Hedelin H and Ljunggren C.

European Urology; 2006 Mar 9; [Epub ahead of print] (accepted Jan 2006).

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ABBREVIATIONS

- ED Erectile dysfunction
- LUTS Lower urinary tract symptoms
- BPH Benign prostatic hyperplasia
- NO Nitric oxide
- PDE-5 Phosphodiesterase- 5
- IIEF International index of erectile function
- SHIM Sexual health inventory of males
- EDITS Erectile Dysfunction Inventory of Treatment Satisfaction
- PAIRS Psychological And Interpersonal Relationship Scale
- GAQ Global assessment question
- SEP Sexual encounter profile
- MI Myocardial infarction
- CVD Cardiovascular disease
- EjD Ejaculatory disease
- IPSS International prostate symptom score
- cGMP Cyclic Guanosine Monophosphate
- NPT Nocturnal Penile Tumescence
- CAD Coronary Artery Disease
- OAB Overactive bladder
- BMI Body Mass Index

Introduction

Erectile dysfunction (ED) is defined as the consistent or recurrent inability of a man to attain and/or maintain a penile erection sufficient for sexual performance (1). It is an age-related, progressive condition, affecting, to some degree (mild, moderate or severe) over 50% of men aged 40-70 years, with the probability of complete ED increasing from about 5% at the age of 50 to 15% at 70 years (2).

Although a common condition, linked both to ageing and secondary to many medical conditions, i.e. diabetes, hypertension, dyslipidemia, depression and cardiovascular disease (Table I) (3-8), the treatment has in the past been conducted by a few specialists, mostly andrologists, urologists and sex therapists (1,9). The revolutionary introduction of oral therapy and the massive research concerning ED that followed, has led to a paradigm shift in ED treatment. This is no longer something done by a few for a few. It involves virtually all disciplines of medicine and more patients are being treated by more physicians (10).

Table I. *ED and its association with other disorders*

68% with hypertension have ED
60% with diabetes have ED
60% with ED have dyslipidemia
40% with ED have significant coronary occlusions
20% with ED have diabetes
11% with ED have depression

History

Dysfunction of the erectile ability has been and is a major concern for the male in all cultures from prehistoric ages and still is in today's modern world (11). Over the last millennium numerous reasons for the malfunction have been expressed and different treatments tried.

Last millennium

In *the Malleus Maleficarium (the "Witchhammer") 1486* (12) it was stated that ED was a sign of witchcraft and to be dealt with in an appropriate manner. Not until the late 19th century, impotence started to appear as a subject in the medical literature ("*Sexual Impotence in the Male*" -Hammond 1883).

During the 20th century we have witnessed a remarkable evolution of all aspects of ED, from basic science to treatment. In the beginning of the century impotence was considered to be

mainly an organic disorder (13). During this first “organic era” the first vacuum device was patented in 1914 (11). It was followed by the “psycogenic era” (~ 1920 - 1965) where erectile dysfunction (95%) was believed to be caused by psychologic or psychiatric disorders (14,15). Psychotherapy was considered the treatment of choice. The thoughts of men like Freud and Stekel had a substantial impact on how ED was managed.

The “sexual revolution” where sexual behaviour became a legitimate field of research started with the works *Human Sexual Response* (1966) and *Human Sexual Intimacy* (1970) by Masters and Johnson, later followed by Helen Singer Kaplan works *The New Sex Therapy* (1974) and *Disorders of Sexual Desire* (1975), where three components (desire, arousal and orgasm) of the sexual reaction were described (16,17).

Alongside the psychiatric approach to ED, surgical methods to treat the problem were developed. Modalities like penile implants from extra and intra corporal rigid rods to the inflatable penile prosthesis and vascular surgery were explored (18,19).

The second “organic era” of ED treatment started in the beginning of the 80-ties with the intracavernous pharmacotherapy (20,21). The famous lecture by Brindley at the 1982 annual American Urology Association (AUA)-meeting in Las Vegas, where he demonstrated, upon himself, the efficacy of penile injection therapy, made a huge impact in the world of urology. New diagnostic technologies were developed (Table II), all with the purpose to establish eventual organic causes for ED.

Table II.

Diagnostic tools for evaluating ED

- Nocturnal Penil Tumescence (NPT)-test
- Rigiscan
- Angiogram
- Dynamic cavernosometry
- Doppler ultrasound

By the end of this decade approximately 80-90% of ED was considered to have an organic cause and the majority of the patients were treated by urologists.

In the 1990s much of today’s knowledge of ED regarding, aetiology, epidemiology, correlations to other ailments, treatment outcomes, patient and partner behaviour patterns was gained (22-26). New medications were registered to treat ED, e.g Alprostadil (CAVERJECT®) for intracavernous injections in 1994. The intraurethral application form of alprostadil (MUSE/BONDIL®) came on the market in 1996 and for the first time gave the General Practitioner a simple (but less effective) tool with which to treat ED (23,27). Two years later, the first effective oral remedy for ED was launched, a PDE-5 inhibitor - Sildenafil

(VIAGRA[®]). Alongside this remarkable development of pharmacological remedies, large epidemiological studies, such as the Massachusetts Male Aging Study (MMAS) in 1994 and the Cologne Male survey in 2000, were presented (3,4). These studies showed a high incidence of ED in the male population from the age of forty (Table III) and that only a minority (<8%) of those effected sought treatment.

Table III. *The prevalence of ED: Cologne Male Survey (N=4883)*

Age range (y)	ED (%)
30-39	2
40-49	10
50-59	16
60-69	34
70-80	53

The introduction of Sildenafil (VIAGRA[®]) attracted enormous mass medial attention; ED and the new treatment were on the front page all over the world, discussed on TV and the as well as being the topic of many jokes.

Along with this mass medial attention and the apparent large volume of individuals with untreated ED, the clinicians were faced with new dilemmas (28-30).

- Was there to be an increase in treatment seekers?
 - If so, - How to manage the increase?
- The economical impacts on society and health plans?
- Is ED to be considered as a disease or a part of the normal ageing?
- Was there to be a drug abuse or misuse?
- Did physicians (in general) have sufficient knowledge of different aspects of sexual medicine?

Present

At the beginning of the new millennium another two PDE-5 inhibitors became available Tadalafil (CIALIS[®]) and Vardenafil (LEVITRA[®]) together with Apomorphine (UPRIMA[®]). This raised new questions regarding the treatment. Which remedy is superior, and which one will patient prefer?

Parallel to the process of developing new treatment modalities for ED, extensive basic research was being performed on erectile function physiology. Studies were undertaken in order to acquire a better understanding of the problem from various angles such as; treatment seeking behaviours of patients and partners and treatment satisfaction qualities (8,31,32). Scores to quantify and measure erection quality, treatment satisfaction and self-esteem were developed and validated (33-36). Table IV.

Table IV. *Various validated scores to quantify different aspects of ED and treatment results*

Validated scores		Aspect
The international Index of Erectile Function	IIEF	Erection capability
Sexual Health Inventory of Males	SHIM	Erectile function
Global Assessment Question (GAQ)	GAQ	Over all assessment of erection
Sexual Encounter Profile	SEP	Erectile function
Erectile Dysfunction Inventory of Treatment Satisfaction	EDITS	Treatment satisfaction
Psychological And Interpersonal Relationship Scale	PAIRS	Self esteem and confidence

All this has led to a better understanding of all the aspects of erectile function and dysfunction (37,38). Not only to the etiology of dysfunction but to the correlation to other diseases (7), its role as possible predictor of other ailments (i.e. common pathological pathways to vascular disorders) and understanding of psychosocial aspects, treatment response and reasons for treatment discontinuation.

At the turn of the millennium the clinician was introduced to a whole field of knowledge regarding ED and a growing number of patients seeking treatment.

An important question is to what extent; this knew knowledge can be extrapolated into the everyday clinical work carried out by the non specialist. Many of the papers presented in the literature, particularly regarding treatment, are based on clinical trials sponsored by the pharmaceutical industry (39). It is well known; that the cohorts participating in these (multi-centre) studies have to a large extent, been specifically selected (40-42) and may not represent the general population handled in everyday clinical routines.

Physiology of Erectile Function

Penile erection is a hemodynamic event regulated by relaxation of arteriolar and trabecular smooth muscle cells in the corpora cavernosa mediated via the NO-cGMP pathway (43).

Following sexual stimulation neuronal impulses causes the release of NO into the corpora cavernosa. As a result of which the penile blood flow increases and sinusoidal spaces expand, preventing venous outflow and producing an erection (Figure 1).

The most common treatment today is the oral treatment with PDE-5 inhibitors (44). It is the only treatments that will be discussed in this dissertation, and their mode of action will be explained in greater detail.

The phosphodiesterase inhibitors used for ED treatment are selective competitive inhibitors of phosphodiesterase type 5 (PDE-5), an enzyme that breaks down cGMP the second messenger of NO (Figure 2). By inhibiting cGMP breakdown, PDE-5 inhibitors enhance the vasodilatory effect of NO and restore the ability to achieve an erection in patients with ED (Figure 2). PDE-5 inhibitors are thus only effective in case of a simultaneous sexual stimulation (43).

Figure 1. *The Cascade of events resulting in penile erection.*

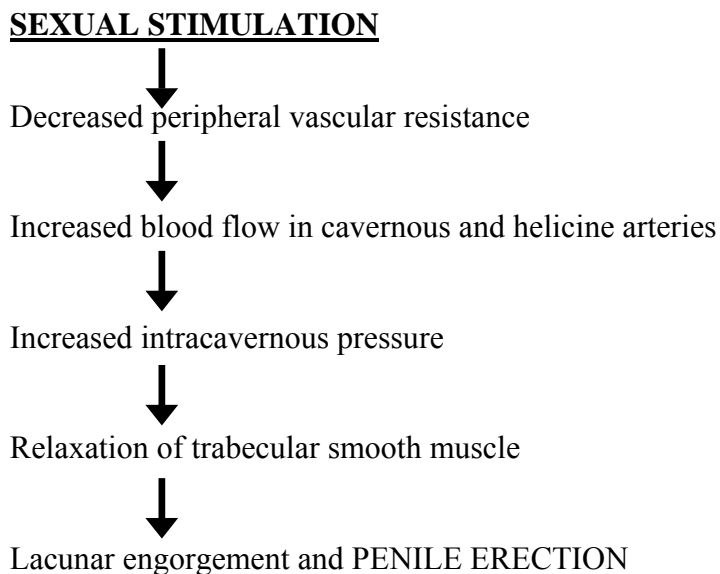
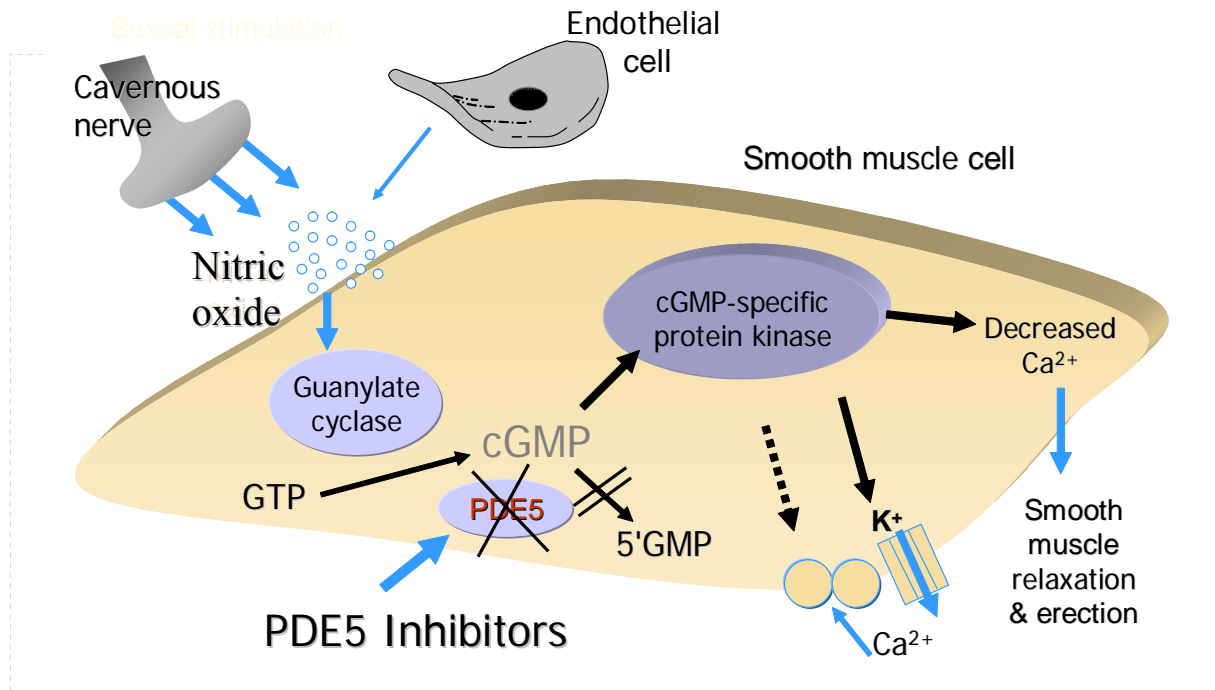


Figure 2.

NO-cGMP Mechanism of Penile Erection

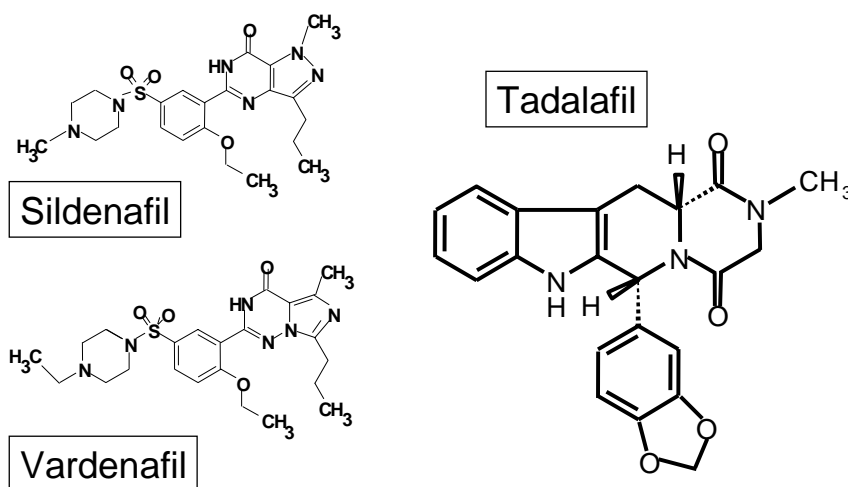


There are currently three different inhibitors available Sildenafil (45,46), Vardenafil (47) and Tadalafil (48,49) (Table V). As competitive inhibitors of PDE-5, the chemical structures of the substances are very similar to that of cGMP. Sildenafil and Vardenafil have a similar structure (50). Tadalafil, however, differs markedly from the other two in terms of its molecular structure, which also is reflected in pharmacokinetic difference as a substantially longer duration (Figure 3).

Table V. *Pharmacokinetic properties for the available phosphodiesterase inhibitors (45-49 and packet inserts).*

PDE-5-inhibitor	Time to onset	Effect duration	Side effects
Sildenafil	30-60 minutes	4-6 h	Headache, flushing, dyspepsia
Vardenafil	10-25 minutes	3-4 h	Headache, flushing, rhinitis
Tadalafil	15 min	18-36 h	Headache, dyspepsia, back pain

Figure 3. Chemical Structures of PDE-5 Inhibitors



Eardley I. *Int J Clin Pract.* 2002;56:300-304.

Diagnosis and treatment of ED

Both the diagnosis and treatment of ED have some unique characteristics regarding the actual medical approach compared to other treatable conditions.

The patient approaches the physician saying he has a dysfunction of his erectile capacity and the physician will more or less have to take his word for it. No further test has to be performed to establish this fact, since the definition of ED is “the consistent or recurrent inability of a man to attain and/or maintain a penile erection sufficient for sexual performance”. A questionnaire, like the SHIM can be used to confirm, that he has an ED and to quantify the severity. However, these questionnaires are subjective and reflect the patient’s perception of his erectile capability and are not truly objective measurements. The aim of the treatment is thus to enable the patient and his partner to enjoy a satisfactory sexual experience. This means that the patient’s perception of an adequate erection is of major importance in the clinical situation, not the actual rigidity of the penis or the duration of erection as it might be in scientific research. In other words considerations whether one medication is more effective than another from a scientific perspective, may be of less clinical relevance.

Occasionally more sophisticated tools (NPT-test, angiogram, dynamic cavernosometry, doppler ultra sound) are used to establish an underlying cause of the malfunction. However, this is not necessary in routine management and their use is limited to clinical studies and to special centres of excellence (1).

Due to the high correlation between ED and other diseases, one of the tasks for the physician is to identify or rule out an underlying cause (diabetes, cardiovascular, depression, hyperlipidemia, and hormone deficiency). For example, if a concomitant disease is present and if it is untreated, further investigation of the disease and eventual disease specific treatment has to be considered (51). Furthermore, if the patient has a known chronic ailment under treatment and develops an ED, this might be an indication that the concomitant disease has progressed and/or is poorly regulated (52).

The ED treatment approach is also rather unique. The complexity and great variety of the human sex life will make almost impossible for a physician even with the most thorough history and work-up to be sure that he will select the optimal therapy for the couple (53). Only the patient and his partner are able to judge this and are the only ones who truly can evaluate the results of the treatment. There is no way in clinical practice to establish if the treatment has rendered satisfactory results apart from the patient's own report. With the exception of patient/partner questionnaires, we lack objective measurement of the actual treatment result. This creates a scenario, where the clinician is faced with the patient's statement that he has a problem and the judgment if the treatment is any good, without any truly objective means of verifying whether this is the case.

Cardiovascular disease and ED

Organic ED is considered to be mainly a vascular disorder (54-56). Vascular diseases and ED shares a similar pathogenic involvement of the NO pathway leading to early impairment of the endothelium-dependent vasodilatation and late obstructive vascular changes. Common risk factors for atherosclerosis (smoking, diabetes, obesity, hypertension and dietary factors) are frequently present in patients with ED (57,58). Furthermore, CVD (Cardio Vascular Disease) including CAD (Coronary Artery Disease), MI (Myocardial Infarction), hypertension, hyperlipidemia, peripheral vascular disease are closely associated with ED (57,59). One opinion today is that erectile dysfunction may be considered as the clinical manifestation of a disorder involving penile circulation in the same way as angina pectoris is the clinical manifestation of a disorder involving coronary circulation (60-64). Atherosclerosis, a systemic disorder, affects all major vascular beds. However, involvement rarely becomes clinically evident at the same time because of the different sizes of arteries supplying various vascular beds (65-68). Thus symptoms of ED should become manifest

before CAD symptoms, meaning that CAD prevalence in patients with ED should be low but ED prevalence in patients with CAD should be high (69-71). It has been suggested that ED represents an initial marker of a sub-clinical vascular disease early in the atherosclerotic process (72,73). However, whether impaired erectile function can be used as a clinical predictor for CAD, is largely dependent on whether men with ED seek medical attention (and to what extent) for their sexual dysfunction.

LUTS (Lower Urinary Tract Symptoms) and ED

Lower Urinary Tract Symptoms (LUTS) is a term introduced by Abrams in 1994 to give an overall description the complexity behind the different etiologies that result in problems with voiding (74). It involves outlet obstruction, storage problems and various combinations of these entities. Benign prostatic enlargement, bladder neck obstruction and urethral strictures are disorders that primarily cause outlet obstruction (75). Overactive bladder (OAB), chronic interstitial cystitis, low bladder wall compliance and neurological disorders are frequently associated with storage problems (75).

Both LUTS and ED are highly prevalent disorders in men that increase with age (Figure 4 and Figure 5) (3,83) and have significant impact on the quality of life (76-78). Traditionally the correlation between both disorders has been seen as a factor of age and/or comorbidity (2).

Figure 4. Age distribution of ED

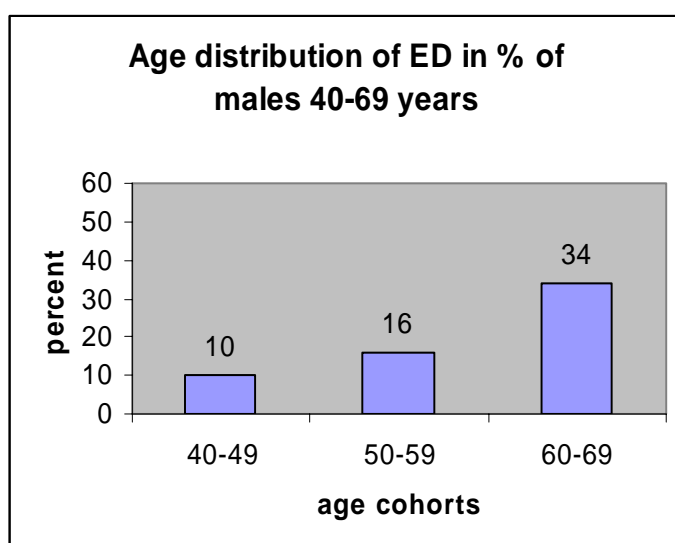
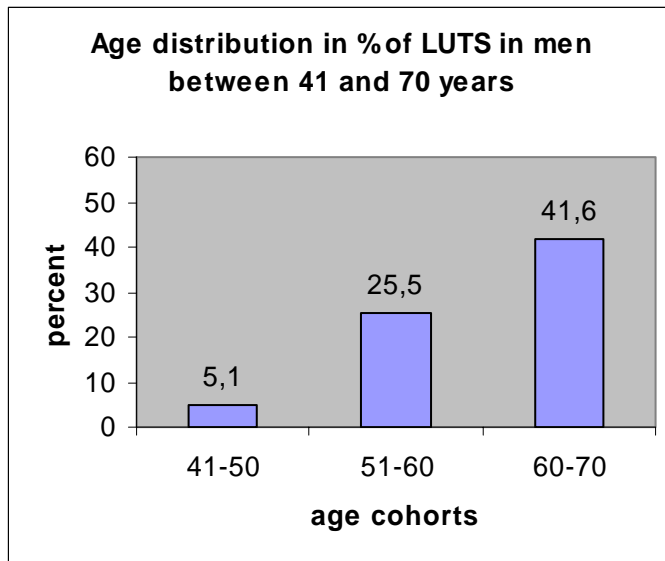


Figure 5. *Age distribution of LUTS*



Recently published studies have suggested that LUTS is an independent risk factor for the development of ED (79-83). In particular, voiding symptoms, nocturia, and the degree of the bother due to LUTS, are to be independently associated with ED.

Based on the results from these studies it has been suggested that in clinical practice men referred for LUTS should be interviewed regarding their sexual function and vice versa. Furthermore, the effect of any LUTS treatment on sexual function should be carefully discussed with the patient (79,83). However, as shown in several studies, the relationships are fairly weak (84-86) and the clinical value of this correlation, in the management of the individual patient seeking medical attention due to LUTS, is questionable.

Patient Preference

Several remedies administered by different routes are available for treating ED; oral pharmacotherapy represents the first-line option.

The presence of the three phosphodiesterase inhibitors, has initiated studies aiming to evaluate them regarding patient preference. Such studies regarding ED treatment are controversial, difficult to design scientifically correct and hard to interpret (87,88) as their results are rather conflicting. Studies sponsored by the industry tend to suggest that their own drug has the best preference (89-91). Investigations not supported by the industry fail to demonstrate a clinically significant difference between the three agents (92-96) (Table VI). Accordingly, so far no study has shown that one drug is clearly superior to the other. On the contrary no major difference is present in patient preference between the three drugs (88,97). In clinical practice,

this means that there is at least a 40% chance that the drug prescribed is not be the best remedy for that particular patient (97).

There is however a tendency for younger men to chose Tadalafil, because it gives them an extended opportunity over a prolonged time , while older men tend to prefer Vardenafil or Sildenafil (92). This could be decision data used when choosing among the PDE-5 inhibitors, another option being to let the patient try the available agents and make his own choice (97). However, presently, no clinically feasible treatment regime to do this has been suggested.

Table VI.

Presented PDE-5 Preference Studies

Percentage of Patients Who Expressed a Treatment Preference					
	Author	N	Tadalafil	Sildenafil	Vardenafil
Sponsored	Govier	190	66%*	34%	-
	Stroberg	147	90%*	10%	-
	Von Keitz	181	73%*	27%	-
Independent	Claes – naive patients	418	32%	32%	36%
	Porst – 3 Arm	149	45%*	13%	30%
	Porst – 2 Arm	226	66%*	21%	-
	Sommer – low dose	47	19%	34%	47%
	Sommer – high dose	86	40%*	17 %	43%*

*Significantly preferred treatment.

Treatment and cost

There are several aspects regarding medical treatment that relates to all forms of treatment, including treatment of ED with PDE-5 inhibitors. Erectile dysfunction and oral treatment meet these criteria (Table VII), but one question that remains to be answered is: Is it affordable? If not patients will not seek treatment. Also of interest for the patient, physician and the society is if the ailment addressed might be a forbearer for a more severe condition, which might have major impact on individual’s health status. If that is the case, it might be important to screen for the condition (98,99), thus enabling early intervention. For this to become a reality, information regarding these risks must be known to all those involved. Furthermore, the above mentioned statements regarding treatment must, at least to some degree, be met otherwise the patient will not seek treatment nor will the physician institute such a regime. As shown in Table VII oral treatment with PDE- 5 inhibitors meet several of the criteria proposed. The cost for these drugs remains a debatable issue, and seems to be important for the patient in his motivation to seek and continue treatment (100,101).

Table VII. *Important aspects of medical treatment in general and how these aspects are addressed in ED treatment with PDE-5 inhibitors.*

Aspects Of Medical Treatment	Oral ED treatment of (PDE-5 inhibitors)
<ul style="list-style-type: none"> • First and foremost should do no harm. 	<ul style="list-style-type: none"> • Has good safety profile
<ul style="list-style-type: none"> • Secondly the treatment must be effective. (The optimal remedy is one that cures the disease). 	<ul style="list-style-type: none"> • Is effective, does not cure.
<ul style="list-style-type: none"> • It should be easy to administrate and interfere as little as possible with normal life. 	<ul style="list-style-type: none"> • Is easy to administrate • Does not interfere with normal life.
<ul style="list-style-type: none"> • An untreated condition should have a substantial impact on the individual's wellbeing. 	<ul style="list-style-type: none"> • An untreated condition might have substantial on the individual's quality of life.
<ul style="list-style-type: none"> • Treatment should be affordable. 	<ul style="list-style-type: none"> • ?

It has been suggested that ED may be a predictor for severe manifestations of cardiovascular disease, such as myocardial infarction, and stroke (72). If this is the case, and if it is to be a clinically useful tool, patients and physicians must to a larger extent bring forward the subject of ED. This is not the case at present (31). Furthermore, the cost benefit of screening for a concomitant disease, with the intention of early detection, intervention and possible reduction of a patient's overall morbidity, must be considered.

Introduction Epilogue

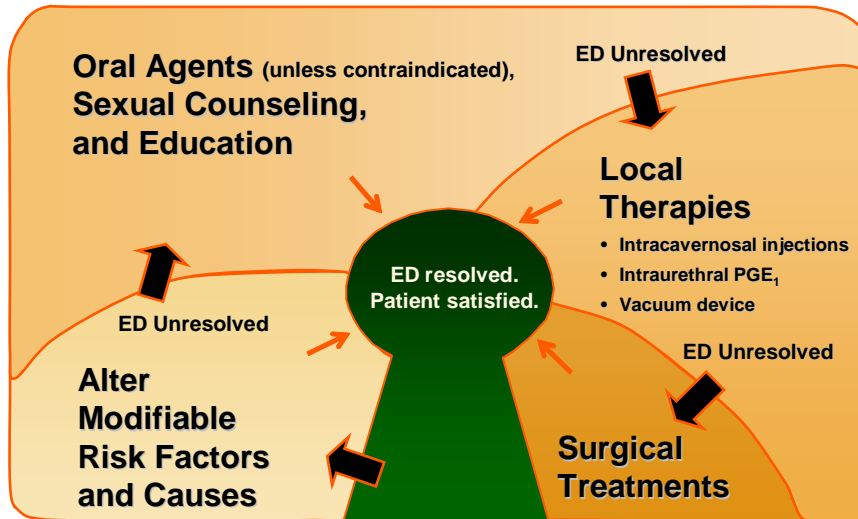
Managing ED involves to some degree almost all fields of human care (Figure 6). It naturally plays a major part in sexual medicine, but with present knowledge it has to be acknowledged, when assessing patients in most medical specialities.

This dissertation has focused on the extent to which some of the current knowledge regarding ED might impact on the clinical management of the patient.

In particular the aspect on how to approach a patient with ED, regarding the eventual correlation to certain co-morbidities (cardiovascular disease), correlation to other diseases (LUTS), the socio-economic influence on Sildenafil treatment and, finally, optimization of oral ED-treatment.

Figure 6.

Management of ED: World Health Organization Guidelines



Recommendations of the 1st International Consultation on Erectile Dysfunction. In: Jardin A et al, eds. *Erectile Dysfunction*. Plymouth, UK: Health Publication, Ltd; 2000:711-726.

AIMS OF THE STUDY

1. To investigate the association between erectile dysfunction (ED) and myocardial infarction (MI) and discuss its value in clinical practice (paper I).
2. To investigate the relationships between lower urinary tract symptoms (LUTS), the bother induced by LUTS, age and ED (paper II).
3. To discuss the value of the correlation between LUTS and ED in the clinical management of the individual (paper II).
4. To investigate treatment compliance for ED treatment with Sildenafil in clinical practice, with special focus on the association between cost and consumption (paper III).
5. To apply and evaluate outcomes and benefits, in clinical practice, of an ED treatment regime, including the opportunity to try three PDE-5 inhibitors (paper IV).

Patients and methods

Paper I.

The hospital files were searched for all male patients aged ≤ 70 years who had been hospitalized in the intensive care unit in 1999 due to a first MI. A total of 160 individuals were found with a mean age of 57.6 years. In October, 2001, a questionnaire, which had not been formally validated, was sent to the 138 men who were still alive; their mean age was 58.5 years (range 35 - 69 years). The questionnaire was returned by 100 (73%) of the men (mean age 59.5 years). In response to the question “How often is the erectile dysfunction a problem?”, the patients could choose from the following alternatives: “rarely”, “occasionally”, “every second time”, “mostly” or “always”. Information concerning CVD was collected from the hospital records. Smoking was defined as ≥ 10 cigarettes/day or equivalent tobacco consumption for ≥ 10 years. Diabetics included both patients treated with insulin and those using orally administered anti-diabetic drugs. Hypertension was considered to be present only if it was being pharmacologically treated. The same questionnaire was sent to 160 age matched men from the same geographical area who had not had an MI (control group). It was returned by 129 (81%), with a mean age of 57.9 years (range 35 - 70 years). ED was defined as in the study group. (Table VIII and IX).

Accordingly the results presented are based on the 100 patients with MI and the 129 in the control group who responded to the questionnaire.

Statistical methods.

The chi 2 test was used for statistical analysis.

Table VIII. *Characteristics of study and control group.*

Characteristics	Study group	Controls
N	100	129
Mean age (years)	59.5	57.5
Diabetes and/or CVD (%)	41	30
Diabetes (%)	11	8
Smoking (%)	82	45

Table IX. *ED and its severity in the study group before MI and in the control group.
Response = answer to the question: "How often is ED a problem?"*

Response	Study group	Controls
Rarely	2	2
Occasionally	20	9
Every second time	4	4
Mostly	7	11
Always	1	2
Total	34	30

Paper II

Men, 60-70 years old, living in Skövde and five surrounding counties, were randomly chosen from the population register. The men selected were sent a letter inviting them to participate and to fill in the 7-item International Prostate Symptom Score questionnaire (IPSS) as well as the IIEF-5 questionnaire (International Index of Erectile Function). Both are well established and frequently used questionnaires (34, 102). The sums of the first five questions in the IIEF-5 score reflect the erectile function and constitute the IIEF-5 score (range 0-25). Higher scores correlate with better sexual function. In the IPSS questionnaire, higher scores correlate with more severe urinary symptoms (range 0-35). The questionnaire includes an eighth question ("Om du skulle leva resten av livet med vattenkastningsbesvär precis som det nu är, hur skulle du känna dig inför detta?") concerning the bother induced by LUTS with bothersomeness as a score from 0 - 6 where 6 is maximal bother (102). The men were also given written instructions on how to perform the timed micturition measurements (the seconds required to void the first 100cc urine). The median of the measurements performed was registered. A reminder was not sent out to the patients who declined to participate.

In total, 2000 surveys were sent out, 1096 surveys were returned and after excluding those with incomplete answers in the IPSS and IIEF-5 questionnaires, 924 remained and were included in the study. Out of the 924 men, 199 (22%) were not sexually active (to be classified as sexually active, there had to be sexual activity including an attempt of intercourse during the last six months).

The results include only the 725 sexually active men (Table X).

Table X. *Demographics of the studied, sexually active, 725 men.*

Age	n	725
	Mean	65.0
	Median	65.0
	SD	3.2
IPSS	n	725
	Mean	7.9
	Median	6.0
	SD	6.4
IPSS \geq 8	%	45%
Bother	n	705
	Mean	1.6
	Median	1.0
	SD	1.4
Timed	n	494
Micturition	Mean	10.7
	Median	9.6
	SD	6.0

Statistical methods

All correlation coefficients presented are Spearman's rank correlations. Categorizations used are as follows: IPSS score was categorized as: none (IPSS=0), mild LUTS (IPSS<8), moderate LUTS (IPSS=8-19) and severe LUTS (IPSS>19) (83,102). IIEF-5 was dichotomized into ED (IIEF-5 \leq 20) or no ED (IIEF-5 >20); finally, the bother question was categorized as: Satisfied (bother score 0-2), Mixed (bother score 3) and Dissatisfied (bother score 4-6). To compare categorical variables, a chi-square test was used and pooling of categories was performed, if necessary, in a few cases. Finally, a multivariate logistic regression model was used. In this model, ED was the dependent variable and timed micturition, age, IPSS (categorized), bother score (categorized) were explanatory variables. In this analysis, timed micturition was log transformed due to its skewed distribution. All tests are two-sided. The statistical program SPSS 12.0.1 was used for all analyses.

Paper III

In February, 2003, a questionnaire was sent out to 92% (132/143) of all men with ED for whom oral treatment with Sildenafil was instituted at our clinic between 1998-2000. The mailed questionnaire covered issues regarding their current ED treatment, frequency of use, reasons for change of/or discontinuation of treatment, effect of treatment, partner relations and total income of the household before tax.

At the time of the questionnaire 6 patients were dead and 5 lost in follow-up, of the 143, 132 could be identified (mean age 62 years range 22-89 years). The majority (91%) of the patients had not been treated for their ED prior to our evaluation. At the time when the treatment was initiated, all the patients had a clinical work-up with medical history, physical examination (including measurement of blood pressure, pulse, Body Mass Index (BMI), evaluation of cardiovascular, neurological, genital and rectal status) and a urine dipstick test for glucose. All patients answered the IIEF-5 (SHIM) questionnaire, and treatment for ED was prescribed when the IIEF-5 score was 21 or below. Assessment of cause of ED was made on clinical judgement. The treatment was started with a prescription of four 50 mg tablets of Sildenafil. The patients were recommended to start with one tablet and if not successful in receiving a satisfactory erection at two separate attempts with 50 mg to double the dose to 100 mg on their third attempt. The patients were followed up within 6-8 weeks with a phone call or an office visit if they not had reported the effects spontaneously and requested prescription. The results presented are based on the 91 (69%) patients that responded to the questionnaire.

Statistical methods.

The chi 2 test was used for statistical analysis.

Paper IV

Study population

Between June, 2003, and February, 2004, all patients, in our clinic, with ED and who were eligible for oral treatment with PDE-5 inhibitors, were offered the opportunity to try out 8 tablets with a shorter-acting potential (four 100 mg tablets of Sildenafil and four 20 mg tablets of Vardenafil) and 8 tablets with a long-acting potential (20 mg Tadalafil).

Their ED had been or was diagnosed with the help of the diagnostic tool IIEF-5. A score of 21 or lower was considered to be a diagnosis of ED (34).

The patient had to pay for the medication himself (none of the drugs were subsidized). The price difference between the cheapest (Tadalafil) and the most expensive (Sildenafil) was less than one EURO per tablet.

As many as 77% (**186/243**) eligible for the treatment procedure were willing to participate, and of these 78% (**145/186**) completed the program, trying out all three substances – 81% (52/64) of the naïve (never before treated) and 76% (93/122) of the previously treated patients.

Accordingly, the results presented in this paper are based on a population of 145 patients.

Study design

The patients were recommended to start with the “shorter-acting substances”. They were also asked to use all the tablets of one substance before trying the next one and not to try more than one tablet per 24 hours. A wash-out time recommendation before starting on a new drug was not given. Being a real life situation, the actual administration was up the patient’s own discretion and thus not recorded.

The patients were followed up every 3 months with a phone call or an office visit, if they had not spontaneously reported outcome of the treatment and requested renewal prescription for their preferred treatment within these time frames. Patients who had taken 8 doses or less after 9 months were excluded from further evaluation.

When the “programme” was completed, time to consume prescribed doses, preferred drug for renewal and reason for preference were recorded. Prescription renewal was regarded as treatment satisfaction and response. No further evaluation after each treatment or at the end of the treatment was performed.

A key issue in the design of the study was not to interfere with the routine management of these patients. An elaborate testing and validation of the patients ED, with extensive questionnaires, such as the IIEF, PAIRS, EDITS and GAQs (33-36) at the time of treatment initiation and follow-up as well as diaries during the treatment, are not everyday clinical standard procedures and was therefore not performed. Thus, the only difference from the daily clinical practice was that instead of being prescribed only one drug, the patient was prescribed the 3 drugs available, and asked to try out the best one in his opinion.

The assessment of the ED cause (organic, psychogenic or combined), was based on case history, medical examination, registration of ongoing medication and laboratory tests (serum lipids, blood glucose, HbA1C and serum testosterone).

At the time of prescription renewal, registration of preferred drug as well as the reason for preference was carried out by the physician.

Statistics

A professional statistician attached to Gothenburg University (M. Gellerstedt) was consulted and performed the statistic analyses on the preference choices, using chi-two test and cross tables two sided tests of significance.

Methodological considerations

A General

A.1 Selection bias

Paper I, II and III

The use of mailed surveys always raises a concern of selection bias. The two most important factors to consider are the percentage that responds and why they respond. In general a common and accepted response rate of mailed questionnaire is approximately 70%, but when issues of more intimate and personal character are enclosed it is not unusual for the response rate to drop down to 50% (103-105). With such a high number as half of the surveys unanswered, conclusions of collected data must be drawn with caution, particularly if the study population is small. With a large population, as in paper II, the data will be more reliable, even if the response rate drops (106,107).

This leads to the second issue, why does the subject answer or why does he neglect to do so? Several reasons have to be considered. The subject may have a special interest in the topic investigated and is thus eager to present his opinion or problem whereas in the case of the non-responder the opposite might be the case. Thus valuable data of the population studied could be lost and a bias established (108,109). This must be acknowledged as a possible cause of selection bias particularly in paper I and III. However, in both these papers the percentage of answered questionnaires in the study population is acceptable (almost 70%). In paper I there is a very high frequency of response (81%) from the control group.

Paper IV

Out of **243** patients eligible for the programme approximately one out of five did not enrol for various reasons that are explained in the paper. The remaining 77% (**186/243**) were willing to participate in the programme although their reasons for enrolment were not explored. There is a possibility that there was an overrepresentation among the previously treated patients, who were dissatisfied with treatment they previously had and were thus willing to try something better. The fact that 97% of the naïve patients volunteered to participate as compared to 70% among the previously treated is notable. There is also a possibility the naïve and previously treated are two different cohorts, since the preference choice in the one group is the opposite of that in the other. The naïve patients tended to prefer shorter-acting substances and the previously treated a long acting substance. Naïve and previously treated might value different aspects of the treatment. This was not explored in the study.

A.2 Questionnaires and scales

A.2.1 IIEF-5 (paper II, III and IV)

The short version of IIEF (International Index of Erectile Function) the IIEF-5 or SHIM (Sexual Health Inventory of Males) is a validated and frequently used scale to quantify a male's perception of his erectile function (110). It consists of 5 questions (appendix 1) regarding the male sexual function, with a scoring from 0-5 points on each question. Question number one addresses confidence in the erectile function, question 2-4 the actual erectile function capacity and question number five intercourse satisfaction. The scores of SHIM on disease severity are; 22-25 (inclusive) for no ED, 17-21 for mild, 12-16 for mild to moderate, 8-11 for moderate, and 1-7 for severe (34). The score range of 1-7 for severe ED is applicable to men who had the opportunity to engage in sexual activity and intercourse, but whose sexual functioning is so poor that they did not even bother to attempt sexual activity and intercourse (34). It is important to understand that the SHIM is not applicable to men who do not seek or have an opportunity to engage in sexual activity (34). A low score may be a consequence of a patient having no of opportunity or lack of interest in sex, rather than ED *per se*. Thus the scores have to be placed in the context of the individual patient's circumstances in interpreting the diagnostic significance of the overall score. The questionnaire does not address issues regarding partner relations, overall perception of sexual or life satisfaction. This is obviously a limitation when you are evaluating complexity of the male sexuality. Furthermore, if the individual has not engaged in sexual activity over a long period of time, there is a risk that the subjects self esteem and perception of his erectile function might be lower than the actual function, thus resulting in false low score. This scenario might be a concern (paper III), and explain why the average scores for the studied patients are lower than expected in this population.

A.2.2 IPSS score (paper II)

The International Prostate Symptom Score (IPSS) (102) is a validated eight-item scale for LUTS based on the evaluation of incomplete emptying, urinary frequency, intermittency, urgency, weak stream, straining, nocturia and bothersomeness (appendix 2). The first seven questions have an ordered categorical response frame that can be scored from 0 to 5 leading to an overall score of 0 to 35. Symptoms are classified as absent (IPSS = 0), mild (IPSS \leq 7),

moderate (IPSS 8–19), or severe (IPSS \geq 20). The fact that bothersomeness was studied using just one question could be debated. A more extensive evaluation of the actual discomfort caused, using the SF-36 questionnaire (111-113) might have been useful. Furthermore other validated scales for micturition problems like the Dan-PSS (114,115) could have been used. The IPSS is, however, much used and well validated and in previous studies, question eight has been used as a method to measure the bother induced by LUTS (83,102).

There appears to be a marked difference between how bothered patients with "clinical-LUTS" are in comparison to men with "questionnaire-LUTS". This rather marked difference between men seeking medical consultation due to LUTS and the results from a community-based study has some relevance. It must, for example, be born in mind when comparing and evaluating community based studies and studies performed among men seeking medical consultation due to voiding symptoms, as it is likely to be two different cohorts.

A.2.3 Timed micturition measurements (paper II)

A reduced urine flow is one of the LUTS symptoms (102) addressed in the IPSS questionnaire. Timed micturition correlates well with urine flow rate and also performed in a home situation it gives reliable result (116). However, incorrectly performed timed micturition and registration among the study population reduced the amount of subjects that could be analyzed and, consequently, data might have been lost.

A.3 Statistics

Paper I, II, III and IV

A professional statistician attached to Gothenburg University (M. Gellerstedt) was consulted and performed most of the statistic analyses, in the papers presented. In papers I, III and IV using chi-two test and cross tables two sided tests of significance. In paper II, all correlation coefficients presented are Spearman's rank correlations. All tests are two-sided. The statistical program SPSS 12.0.1 was used for all analyses.

B. Limitations in study design

Paper I

This is in part a retrospective study, based on data collected from medical files and on the patient's recollection of his erectile function prior to his myocardial infarction. Furthermore, the use of a questionnaire that had not been formally validated (although straight forward questions were used), is an aspect that has to be acknowledged. These might affect the

outcome of study. For example timing and degree of an ED prior to infarction might be difficult to recollect retrospectively, thus the severity and duration of ED presented might be somewhat inaccurate.

Paper II

That only 55% of the 2000 surveys were returned, could be due to limitations in the study design. Various explanations for the low response rate are possible. The fact that no reminder to answer the survey was sent out to the patients most likely affected the response rate (117). Furthermore, sexual function and dysfunction might have been considered to be of a too personal and sensitive topic for the subject to reveal in a survey. Finally the request to perform a timed micturition registration could have been too complicated or too time consuming for the individual to do, particularly if there was no benefit to be gained for the study subject.

After incomplete answered questionnaires had been excluded, 924 men remained. Out of these 199 (22%) were not sexually active (to be classified as sexually active, there had to be sexual activity including an attempt of intercourse during the last six months). The fact that the results include only the 725 sexually active men can be argued, but whether a sexually non-active person has an ED or not, is impossible to establish by the IIEF-5 questionnaire used in this study. Thus these patients had to be excluded from the evaluation in this paper.

Paper III

The analysis in this paper is based on a fairly small number of patients in each income group. This could have cause for concern regarding the results presented, however, the highly significant results ($p < 0,001$) strongly supports the conclusions drawn. The study was performed on a Swedish population and may not be applicable for other cultures and socio-economic structures. For example, in a society without a social welfare system, and where the patient normally pays for his treatment, the scenario might have been different, since no impact of a subsidization withdrawal would have been present.

Paper IV

There are several possible limitations that need to be addressed. It is important to understand that the purpose of this study was **not to** do a pure preference study between the three PDE-5 inhibitors. **Instead** the primary aim was to study if it is feasible in actual clinical practice to prescribe all three substances to a patient at the same time, and to evaluate whether the patient could benefit from such a treatment regime. Secondly preference and reason for choice was recorded. The high treatment response (89%) and the fact that as many as 77% completed the

treatment regime strongly support that patients will benefit of such a regime and the feasibility of prescribing all remedies at the same time. Prescription renewal as an indication for treatment response in clinical practice is also robust method (118). However, the results regarding the actual preference must be interpreted with caution because of limitations such as; the amount of each drug prescribed, the order in which they were taken, lack of washout time between each substance taken, time between first and last tablet taken, different cohorts studied (naïve and previously treated). Regular and frequent follow-up of ED treatment also improves treatment success (119). The regular contacts (every three months) in this study thus may have influenced the results.

Results

Paper I

Study group

Of the 100 men with MI, approximately one third (34%) reported that they had had ED before the MI. In three-quarters of the men the ED had lasted for > 3 years (Table XI). The incidence of ED among the men with CVD and/or diabetes was higher than among those without (37%, compared to 32%). After MI, another 19 patients developed ED. The incidence of ED post-MI was thus 53%. Only 10/53 (19%) of men with ED had consulted a physician due to their ED, but none of them before the MI.

Table XI. *Duration of ED in the study group before MI*

Duration of ED (years)	%
< 1	24
1-3	50
4-6	24
7-10	3
> 10	0

Controls

ED was reported by 30% (n=38) of the total control population, compared to 34% of the study population (Table IX). The relative risk was 1.189 (95% CI 0.680 - 2.079). The incidence of ED among the men without a history of CVD was 18%, compared to 32% for the study population. This difference was not found to be significant using the Chi 2 test, and the relative risk was 2.169 (95% CI 1.171 - 4.071). Of the men with CVD and/or diabetes, 56%

reported ED. Of the 38 patients with ED, 58% had CVD and/or diabetes. Of the 91 men without ED, only 19% had CVD and/or diabetes.

The proportion of smokers was rather similar among those with (50%) and without (40%) ED. Only 2/38 men (5%) with ED had contacted a physician for their ED.

Paper II

LUTS (IPSS)

The mean IPSS was 7.9 (SD 6.4) for the 725 sexually active men and the median IPSS was 6.0. The prevalence of moderate-to-severe LUTS, defined as an IPSS of ≥ 8 , was 45%. Only 6% had severe LUTS (IPSS >19). The mean timed micturition was 10.7 seconds (SD 6.0). There was a correlation between timed micturition and the IPSS, correlation coefficient (c.c.) 0.36, p-value <0.001. There was, suprisingly, no correlation between IPSS and age, c.c. 0.03, p-value >0.29 (Table I). Regarding LUTS induced bother (question eight in the IPPS), 74% were satisfied (score 0-2), 15% had mixed feelings (score 3) regarding their symptoms and 11% were dissatisfied (score 4-6). There was a significant relation between the IPSS score and the LUTS induced bother, c.c. 0.76, p-value <0.001 (Table XII). Patients with none-to-mild LUTS were very rarely dissatisfied (0-2%). Among men with moderate LUTS, 14% were dissatisfied, while men with severe LUTS had a noticeably higher degree of dissatisfaction, 62%. Timed micturition was weakly but significantly correlated with age, c.c. 0.14, p-value 0.002 and, as expected with IPSS, c.c. 0.36 p-value <0.001 (Table XII).

Table XII. Spearman's rank correlation between variables studied (bother = LUTS induced bothersomeness)

		Timed micturition	Age	Bother	IIEF-5
IPSS	c.c.	0.36**	0.03	0.76**	-0.29**
	p-value	<0.001	0.36	<0.001	<0.001
Timed micturition	c.c.		0.14**	0.28**	-0.11*
	p-value		0.002	<0.001	0.013
Age	c.c.			0.04	-0.16**
	p-value			p>0.20	<0.001
Bother	c.c.				-0.30**
	p-value				<0.001

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)

Erectile dysfunction (IIEF-5)

The mean IIEF-5 was 19.3 (SD 5.8) and the median IIEF-5 was 22.0. The prevalence of erectile dysfunction (ED), defined as an IIEF-5 score of <21, was 44%. There was a significant, but fairly weak, correlation between the IIEF-5 score and age, c.c. -0.16, p-value <0.001 (Table XII).

LUTS and erectile dysfunction (IIEF-5)

There was a significant correlation between IIEF-5 score and the IPSS score, c.c. -0.29, p-value <0.001 (Table XI). The IIEF-5 score was also correlated to the LUTS induced bother c.c. -0.30, p-value <0.001 (Table XII).

When IPSS is dichotomized into none-to-mild and moderate-to-severe LUTS, the bother category was related to ED (Table XIII). The trend was noticeable for those with moderate-to-severe LUTS where a high bother was associated with a higher ED incidence (p-value <0.001) (Table XIII). The pattern was not as distinct as among those with none-to-mild LUTS (p-value =0.071).

Table XIII. Distributions of ED (No/Yes) by bother category, controlling for LUTS (no/yes)

IPSS Category	Bother category	ED		Chi-square test
		No	Yes	
None-mild n=383	Satisfied n=362	67%	33%	p=0.071
	Mixed/dissatisfied n=21 (pooled due to few cases)	48%	52%	
Moderate-severe n=322	Satisfied n=159	56%	44%	p<0.001
	Mixed n=95	32%	68%	
	Dissatisfied n=68	28%	72%	

A multiple logistic regression model with ED (yes/no) as the dependent variable and with IPSS (4 categories), bother score (3 categories), timed micturition (log transformed) and age as explanatory variables was used (Table XIII). All explanatory variables except timed micturition were significant. The highest odds ratios were found for the IPSS categories (overall p-value<0.001). Men in the mixed group and dissatisfied men had an almost three times higher odds ratio than men in the satisfied group (p value<0.001). The odds ratio for age (p-value=0.042) was 1.07, which means that the odds ratio is nearly two times ($1.07^{10} = 1.96$) higher for a man who is one decade older than another man (Table XIV).

Among the men with moderate LUTS 9% without ED were dissatisfied, compared to 19% of the men with ED. This difference was found for men with severe LUTS where 53% without ED and 67% with ED were dissatisfied (bother score 4-6). Men with ED were thus more bothered by their LUTS than men without ED.

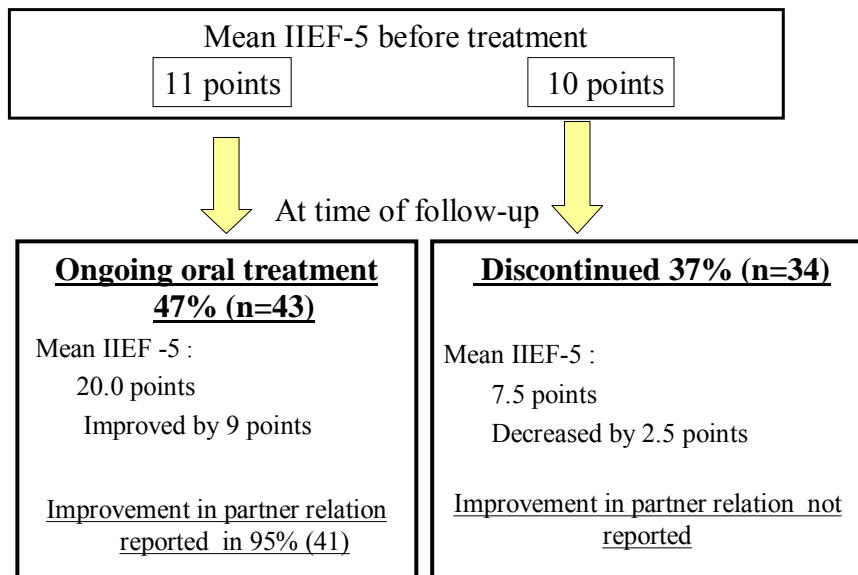
Table XIV: Odds ratio for ED, by explanatory variables

	p-value	Odds ratio	95.0% CI	
			Lower	Upper
IPSS	0.001			
None		1		
Mild	0.046	4.55	1.03	20.11
Moderate	0.003	9.74	2.15	44.20
Severe	0.021	7.93	1.36	46.10
Bother question	<0.001			
Satisfied		1		
Mixed	<0.001	2.92	1.63	5.25
Dissatisfied	0.006	2.72	1.34	5.51
Ln tim mic	0.396	0.84	0.55	1.26
Age	0.042	1.07	1.00	1.14

Paper III

The majority (87%) of the 91 patients had a stable partner relation (married or regular partner). The mean IIEF-5 before treatment was 11 points (median 15 SD \pm 5). More than half of the patients (53%) were undergoing treatment for ED at the time of the questionnaire. Forty-three (47%) patients still used Sildenafil. Five men used other means to achieve an erection, 2 (2%) had penile implants and 3 (3%) intracavernous injections. The remaining 43 patients (47%) reported that they had discontinued Sildenafil. The reason for abortion in the case of nine patients (10%) was a return of normal satisfactory erections. The remaining 34 (37%) reported the following reasons for discontinuation, either alone or in combination: could not afford the treatment (n=19), medical reasons (n=12, myocardial infarction, angina, stroke and cancer), loss of efficacy (n=6), side effects (n=4), partner disease (n=1), loss of partner (n=1) and unspecified reasons (n=3). The 43 patients who still used Sildenafil showed an improvement of 81% in the mean IIEF-5 from 11 to 20 (range -2 to 15) and 95% (41/43) also reported an improvement in the partner relationship. In the case of the patients who had discontinued treatment and still had an erectile dysfunction, the mean IIEF-5 had fallen by 25%, from 10 to 7.5 (range -9 to 2). No improvement in the partner relation was recorded in this group (Figure 7).

Figure 7. Change in mean IIEF-5 before treatment and at time of follow-up

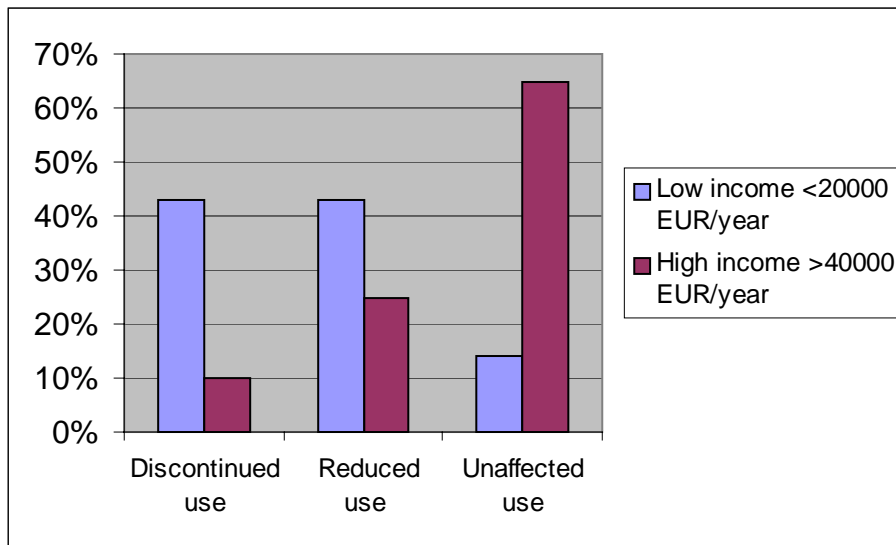


There was a significant ($p < 0,001$) difference in Sildenafil consumption between high and low-income households after the withdrawal of subsidization.

Twenty-one of 91 patients (23%) had a total household income before tax of EUR 20000 or less per year. In this group, 43% (9/21) had stopped ED treatment due to the cost and 43% (9/21) rationed their treatment for the same reason. The withdrawal of the subsidization of the treatment played a major role in their abortion. If the medication were subsidised again, 81% (17) said that they would resume or increase their use of the medication.

In the group ($n=20$) with an income of more than EUR 40000 per year, only 10% (2/20) stopped and 25% (5/20) had rationed their treatment due to the cost. For 65% (13/20), the cost of the treatment had no impact on their consumption (Figure 8). However, 50% (10/20) would increase or resume their use if the cost of medication was reduced.

Figure 8. Discontinuation of or reduction in treatment with Sildenafil after withdrawal of the subsidization in relation to income



Paper IV

As many as 78% (**145/186**) completed the program, trying out all three substances, 81% (52/64) of the naïve and 76% (93/122) of the previously treated patients. The median time to complete the programme and consume all the tablets was 18 weeks (range 6-34 weeks).

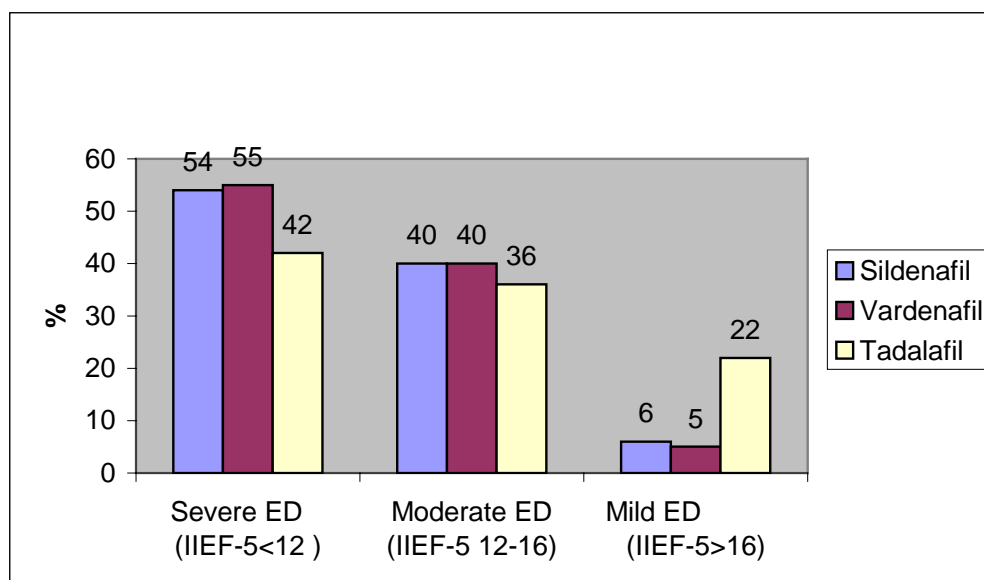
Five percent (**7/145**) were non-responders. Of the 138 patients who responded to the treatment, 76 (55%) had a primary preference for a drug with long-acting effect duration (Tadalafil) and 61 (44%) for a drug with shorter effect duration (for Sildenafil 27% and for Vardenafil 17%). The difference was not statistically significant ($p < 0.3$). One patient had no preference (1%). Although having initially stated a primary preference, as many as 19% (28/138) requested a combination of both a shorter and long-acting medication to accommodate their needs. Of those who had a prior shorter-acting medication, 56% ($n=46$) switched to long-acting treatment and 10% ($n=3$) on long-acting medication switched to a shorter-acting drug. At the end of the programme, one of four, 26% ($n=31$) preferred the treatment they had had before the programme started. Three out five (60%) of the naïve patients who completed the regime preferred a shorter-acting drug and 38% a long acting drug ($p < 0.01$). Among the previously treated patients who completed the regime the opposite was found, thus 68% preferred a long acting drug ($p < 0.01$). Relatively more patients with mild ED tended to prefer a long-acting substance, but there was no obvious difference between age or cause of the ED (Table XV and Figure 9).

Table XV. Patient preference of responders* who completed the programme

	Sildenafil 100mg Mean IIEF-5 = 10,5	Vardenafil 20 mg Mean IIEF-5 = 11	Tadalafil 20 mg Mean IIEF-5 = 13	Total number of patients
All patients	28%	17%	55%	137*
Age 55 or below	22%	17%	61%	49
Age 56-and above	31%	17%	52%	58
Organic ED	23%	12%	65%	43
Psychogenic ED	25%	21%	54%	24
Mixed ED	31%	19%	50%	70
IIEF-5 11 or below	32%	21%	47%	64
IIEF-5 12-16	30%	20%	50%	50
IIEF-5 17 or above	29%	5%	66%	23

- One of 138 could not give any preference and found all the drugs to be equal

Figure 9. Distribution in % of each drug in relation to preference and severity



For responders preferring a shorter-acting drug (Sildenafil, Vardenafil), the primary reason was efficacy (better erection quality, harder erections, better reliability and better overall perception of the erection rendered) 82% (n=50), few side effects 15% (n=9) and short time to onset 3%, (n=2). For responders preferring a long-acting drug (Tadalafil), the primary reason was long duration 96% (n=73) and few side effects 4% (n=3) (Table VI). Only 37% (=51) of the responders gave a secondary reason for their preference. The most important secondary reason was fewer side effects 52% (n=27).

Over all **89% (165/187)** patients had a positive treatment response although not all patients tested all the three substances.

Discussion

General

The studies presented in this thesis have confirmed the correlations between CVD and ED and between ED and LUTS and shown that most men with ED do not seek consultation for this predicament. The most commonly used remedy the PDE-5 inhibitors were shown to have a high discontinuation rate. One of the major causes of this low compliance was the cost of the drug, a factor with the highest impact in households with a low income. A way to increase the use of drug is to allow the individual to try both shorter-acting and more long-acting drugs at the highest equipotent doses.

Despite the very high prevalence of ED among middle aged and older men (paper I), only a minority seek consultation or have been consulted regarding their erectile function (2,3,43). This is particularly notable since many of the men at this age often are under regular medical supervision for chronic ailments (hypertension, diabetes, depression CVD etc) and that there is safe, simple and effective ED-treatment available (44-49). Naturally the low number of treatment seekers is a concern (and will be) in all discussions regarding ED as clinically useful predictor regardless of the ailment to be predicted. Thus, if the vast majority of males with ED for various reasons do not seek consultation, nor are consulted regarding their erectile capability, the overall clinical value of ED as a useful tool as a predictor or marker for the onset of a severe disease or as an indicator of more severe form of an already established ailment, is low. Better information to healthcare professionals and to the general public regarding the increased risk to the general health, which might be associated with ED, could possibly persuade more men to seek medical attention. However, experience from other health campaigns, such as informing of the health risks associated with smoking, have shown their limitations. Today, it is more or less common knowledge that smoking will increase the risk for a severe cardiovascular event and lung cancer, still people continue to smoke and start smoking. It is unlikely that a widespread information campaign of ED and its eventual associated health risks would venture any significant change in treatment seeking behaviors. However, an increased awareness among healthcare professionals managing patients with chronic diseases, where an ED might be an indication of a more severe form of their primary disease, would probably be a better alternative to identify patients at risk (120,121).

Another reason for the low number of patients seeking ED treatment is apparently the cost (53). If there was a remedy that resulted in a permanent cure of the ED, this would most probably have a positive effect on the treatment-seeking patterns as well as on the willingness

to pay for the treatment. However today, the therapy is goal and on-demand orientated, restoring the function for a limited amount of time. When cure is not an option other factors are of importance such as safety, degree of response, efficacy and cost. Optimizing and individualizing the treatment to achieve the best response in each case is fundamental (119,122). If this is neglected, the risk for treatment abortion will increase (119). Letting the patient and his partner try more than one of the available remedies and designing the treatment according to their needs is one way of addressing the issue of treatment optimization and increasing treatment response (paper IV). Whether this will lead to fewer patients discontinuing their treatment in the long run is not known. Standardized mono therapies with PDE-5 inhibitors reported in the literature do have a lower response rate (60-80%) and a high drop-out rate in a 2-3 year perspective (22, 53, 100, 123).

ED and CVD

The correlation between ED and CVD is well established, but it is debatable whether ED is a clinically useful predictor of more severe manifestations of CVD, such as MI. ED does not appear, as a single symptom, to justify the view that ED should be a reason to instigate an investigation of risk factors for coronary artery disease. The prognostic value of such investigations (stress test i.e. treadmill exercise) of the severity of underlying coronary disease and the patient's prognosis is not proven in otherwise symptomfree men (124-127). For example, exercise testing cannot predict angiographic findings or a poor prognosis of a CVD with certainty (124,128). Although exercise testing is more sensitive and specific for high-grade coronary stenosis, the test procedure is considered to be too time-consuming and expensive for routine use with asymptomatic persons (129). Finally, neither resting nor exercise ECG reliably detects the mild to moderate atherosclerotic lesions that are often responsible for acute coronary events (124,130). Another important issue with screening for asymptomatic CAD is the lack of solid evidence of earlier detection leading to better outcomes (124,131,132). The only interventions proven to reduce coronary events in asymptomatic persons are addressing risk factors such as smoking, high cholesterol, and elevated blood pressure. Naturally, these factors have to be explored in the medical history. There are also high costs associated with widespread screening which have to be taken into account. The fact that ED is so common in elderly men (up to 50%), also indicates that ED is less useful as a predictor for MI in this cohort!!

In addition to CVD, there are several other common causes of ED, ageing and psychological factors being among the more common. In up to 25% of cases, ED has a psychological rather than a somatic aetiology (2). This further lowers the predictive value of ED for CVD. Among men without known CVD and/ or diabetes, the incidence of ED was higher in the MI group (32%) than in the control group (18%) (paper I). The difference was neither large nor statistically significant and two-thirds of the MIs were not preceded by ED. The observation thus does not support the idea that ED is a clinically useful predictor, nor does it support the notion that ED in an apparently healthy man should prompt a cardiovascular workup. This, however, does not contradict the idea that ED in combination with other risk factors, such as obesity, hypertension, hyperlipidaemia and diabetes, might be a sign of the presence of a more severe CVD (99). In this population a reason to instigate an investigation could be beneficial for the patient (133).

If ED is to be a clinically useful predictor, it must also be a reason for a man to seek medical attention, which was rarely the case in the population presented. The incidence of ED was, as expected, much lower among the healthy controls (18%) than among the members of the control group with CVD and/or diabetes (56%) and this difference was statistically significant ($p < 0.01$). This was, however, not the case among the men who subsequently suffered an MI. The incidence of ED among the men without CVD and/or diabetes was 32%, i.e. similar to that (37%) among the men with CVD and/or diabetes. This may have been because the apparently “healthy individuals” had an undetected CVD, which later would result in an MI. The high incidence of ED after MI is probably multi-factorial. The causes may be somatic (including a reduced cardiac output), psychological, the result of medication or a combination of these factors (134). The incidence of ED after a MI is so high that it would be relevant to ask every man who has had his first MI about his subsequent erectile function. If it is impaired, he should not only be given counselling about treatment, but also evaluated to discover whether the ED is a possible manifestation of a more severe form of CVD that needs additional monitoring. Based on the results presented, a relevant study from a clinical perspective is to prospectively observe patients after MI to see if patients with ED have a poorer prognosis than those with a satisfactory erectile function.

ED and LUTS

Lower urinary tract symptoms (LUTS) are common among middle-aged and older men (78). It increases with 7% per decade from the age of 20 (135). Age-associated structural and

functional changes in the lower urinary tract including benign prostatic enlargement are the causative factors behind the LUTS (136). It is also a well-established fact that the erectile function becomes less satisfactory with increasing age (2). As many as 34% of men aged 60-70 years have an ED (Figure 4).

The results from recent studies (79,80,82,83) have suggested an association between LUTS and ED. LUTS has thus been described as an independent risk factor for sexual dysfunction (79). The initial results presented (83) are not based on direct clinical observations and studies to investigate the association more in depth are lacking. The results are instead a product of statistical multivariate analysis of data obtained from large epidemiological studies. Although the association is statistically significant (83), it is not impressive. This is probably the reason why it has not been clinically observed previously. Even though scientifically interesting, the weak association raises the question of its clinical relevance and importance. Although based on the correlation between ED and LUTS a clinically intriguing aspect is to treat one of the disorders and have beneficial effect on the other, however there are no solid scientific data regarding such an approach (137). Instead, the physician currently has to be able to manage both these symptoms (LUTS and ED) simultaneously (137) when they are present in a patient. The physician has to be aware that medical therapies for either one of these conditions may affect the other one. This is, however, not a new concept in the managed care of patients with BPH, who in the past have been counselled regarding sexual side effects of BPH/LUTS treatment (138-142). For example 5alpha-reductase inhibitors such as finasteride and dutasteride are associated with a greater risk of ED, ejaculatory disorders (EjD) and decreased libido, than is placebo treatment (139,143). Among alpha (1)-adrenergic blockers, tamsulosin is associated with an increased risk of EjD (137,144). However, some alpha (1)-adrenergic blockers (alfuzosin) can have a positive impact on erection, at least in animal models (137).

PDE-5 inhibitors are commonly used to treat ED. There is increasing evidence that they also might have a beneficial effect on LUTS, probably through the nitric-oxide pathway (137,145). An association (paper II) between LUTS (as reflected in the IPSS) and ED (as reflected in the IIEF- 5score) was verified. However, the correlation in this study as well as in other studies (79,80,84-86) was rather weak, telling us that only 9% ($0.32^2 = 0.09$) of the variation in IIEF-5 is explained by LUTS or the LUTS induced bother. LUTS is thus only one among many other etiological factors behind ED. Cardiovascular disease, diabetes, depression, physical inactivity and age are among the more important factors (2).

There was, as expected, a correlation between IPSS and the bother it induces. The fact that the bother associated with LUTS is correlated to the erectile function is not surprising. It has even

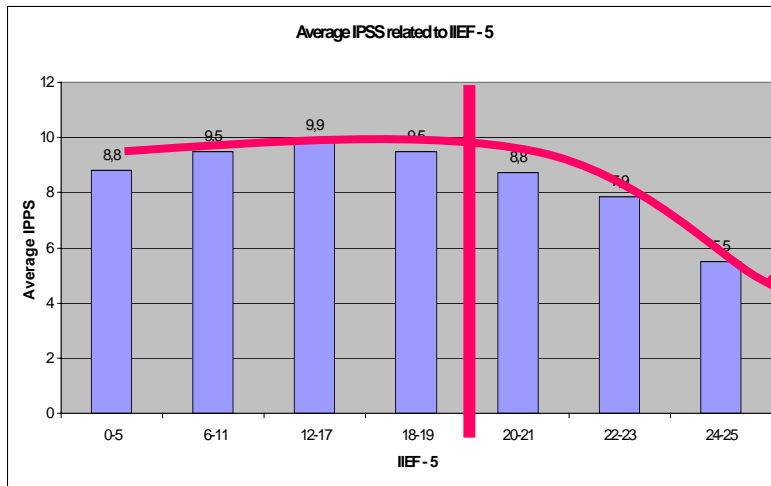
been suggested that it is not the severity of the urinary symptoms but the bother they cause that lies behind the correlation between LUTS and ED (84). To further support this, there was a correlation, between IPSS score among men without ED (IIEF-5 \geq 20), but no correlation between IIEF-5 and IPSS among men with ED (IIEF-5 < 20) (Figure 10). One explanation of this might be that the symptoms (reported in the IPSS) caused by LUTS have an impact on the sexual performance in a sexually well-functioning man, but once ED was present it did not play any significant role. Another interesting observation was that the proportion of dissatisfied men due to LUTS was higher among men with ED. Men with a concomitant ED were thus more bothered by their LUTS. This is a relationship that has not previously been described. It suggests that the correlation between LUTS and ED has a psychogenic component.

The weak correlation between LUTS and ED, consequently appears to be less useful in the management of the individual patient receiving medical attention due to LUTS (apart from what is already done in the management and counselling of patients whom are about to receive treatment for their LUTS). It is, however, of considerable scientific interest and studies attempting to further evaluate the mechanisms behind it are warranted.

The LUTS induced bother was also found to correlate with ED, independent of the severity of LUTS as reflected by the IPSS.

This finding is also worth further exploration. Acquiring a more profound understanding of the underlying psychological factors, for instance, the mental (social) discomfort caused by LUTS in a sexual situation would be worthwhile (146).

Figure 10 Average IPSS related to IIEF - 5



For men with IIEF-5 >20
c.c. -0.165 ($p > 0.01$) between IPSS and IIEF-5
For men with IIEF-5 <20
c.c. -0.006 (n.s.) between IPSS and IIEF-5

ED and treatment cost

There was a high abortion rate in the case of oral ED treatment (paper III), as has been shown in other studies (100,123). Only every second man continued to use Sildenafil after 2 years. Surprisingly the cost of the drug was the most common cause, especially so since it is not very high for the average user (less than EURO 30 per month) and a good sexual life is considered to be important for the individual (53,147).

The cost of the treatment is one issue that has not been particularly well explored, although some knowledge is available. There is a substantial group of patients who will never initiate the treatment at all due to the cost (101). Few patients, who aware of the treatment when they initiate their treatment, will, however, eventually discontinue due to the cost. In Sweden prior to 1 April, 2002, when ED treatment was subsidized, the cost was not a major issue, but when the subsidization was withdrawn, it became an important factor for treatment discontinuation, especially in low-income households (paper III). Cost thus exerts on different levels a great influence on the use of PDE-5 inhibitors. The common practice of tablet splitting, a clinically well known observation, however not confirmed in studies, strongly supports the contention that cost plays a significant role in the oral treatment of ED (53).

There are obvious absolute reasons for discontinuation such as severe illness, lack of efficacy, and severe side effects, causes that need no further exploration (100,123,148,149). However, they do not represent the majority of reasons for discontinuation (100,123,148,149). The

situation is more complex, and the decision to cut back on the use is instead due to several concomitant reasons, the impact of which varies. Increasing age, decreasing libido, disharmony in partner relationships, declining health, co-morbidity and social and cultural aspects all contribute. (100,123,148-150). It is in this group of concomitant reasons that the treatment cost seems to play an important role.

There are several studies showing that effectively treated ED improves quality of life and self-esteem (32,151-153). Restored sexual function can improve partner relations and motivate continued ED treatment (paper III). The majority (95%) of those who continued their oral treatment reported an improvement in partner relations. No individual in the group, which had discontinued their treatment, reported any similar improvement. If the treatment only restored erectile function but did not improve quality of life, this could be a reason for dropping out. Another reason might be that there is a group of men for whom erectile function is less important, but with a new simple treatment, like a PDE-5 inhibitor, they might just “give it a try” to see if it is worth it. If not, leave it at that. In this scenario, the cost of the treatment would be an important co-factor.

Cost appears to be, not solely a co-factor for treatment abortion, but to have an intrinsic value of its own (paper III). Supporting this is the marked difference between the patients with a high income and those with a low income. As many as 47% of the patients with a low income stated that they benefited from the treatment but could not afford to take the treatment as often as they wished. The same situation was not present in the high-income group where the cost played a minor role in drug consumption (10%). Furthermore, the fact that a majority of the patients with a low income (81%), would resume their treatment if subsidization were reintroduced, supports the independent role of cost as a factor in treatment abortion. In other words regardless of whether the availability of treatment is regulated or restricted by what the patient can or is willing to afford, cost ultimately influences the patient’s treatment compliance.

ED and optimizing treatment

There is considerable variation in what patients and couples expect and demand from ED treatment (31,53). This naturally has to be taken into consideration when the optimal treatment for an individual is sought (53). Determinants of preference can be broken down into three factor groups; *medication, patient and partner* (87). The exact weighting of the three groups and the factors within each group varies between patients and between couples.

For example, the factors that may be important to a 65-year-old couple may be quite different to those that are important to a 45-year-old patient who has a 30-year-old partner.

The *medication factors* that impacts upon patient satisfaction include efficacy, quality of erection, consistency of response, speed of onset of the erection, duration of action, adverse event profile, route of administration, and cost (87). Consistency of response is essential for the prevention of dropout (87).

Patient factors that may impact upon the preference for an ED drug include factors such as age, the desired frequency of sexual relations, the duration of ED, and the dynamics of his sexual relationship (87,88, 154).

Partner factors include age, menopausal status of female partners, partner interest level in sexual activity, and the period of abstinence from sex (53,87).

Treatment optimization is an essential tool for the physician to reduce dropout frequency and increase patient satisfaction. McCullough and co-workers (119) presented 6 different aspects to optimize treatment with Sildenafil (Table XVI).

With the addition of two more PDE-5 inhibitors on the market (Vardenafil and Tadalafil) these drugs also have to be taken into consideration when considering treatment optimization in clinical practice.

Table XVI. *Six aspects to optimize treatment with Sildenafil*

1) Assessment of intercourse success rate	<ul style="list-style-type: none"> • Intercourse success reaches a plateau after approximately 8 attempts • ≤ 8 doses should be considered when initiating treatment
2) Disease management approach	<ul style="list-style-type: none"> • medical history, physical examination • modification of lifestyle factors • counselling and educational material about ED
3) Improvement of practice patterns among primary care physicians (PCP) in erectile dysfunction management	<ul style="list-style-type: none"> • PCPs play increasingly important role in the primary management of ED
4) Re-education and counselling patients and partners who were initially non responders	<ul style="list-style-type: none"> • Will result in up 50% success among non responders
5) Control of associated risk factors	<ul style="list-style-type: none"> • Medication and lifestyle modification. • Hormonal assessment
6) Assessment of treatment satisfaction	<ul style="list-style-type: none"> • Follow-up visits at regular intervals to assess treatment progress are essential for the best possible treatment outcome

Applying the aspects of treatment optimization presented by McCullough and co-workers, in a simple treatment regime in clinical practice, where the patient and his partner are given the opportunity to try out all available PDE-5 inhibitors, resulted in a very high overall response rate (paper IV). A majority of patients with ED are also willing to try out all the drugs to find their optimal treatment. This is regardless of whether they were naïve (never treated before) or on previous mono therapy.

Interestingly, even though there was no large difference in patient preference between the three drugs, **one out of five** patients requested two different drugs to meet their needs. This indicates that the treatment of ED is not a static entity, but needs to be adjusted for several different occasions. Some patients will thus require more than one drug. **Three out of four** patients on prior ED treatment had changed their initial treatment at the end of the regime. It is thus highly possible that a patient already undergoing treatment will find a medication that suits him better if given the opportunity to try out all the available, even though the drug given from the beginning is effective.

The high frequency of responders (89%) is notable; well over what has been reported in other studies 60-80% (45-50). One reason might be that the alternative of trying out all the drugs could result in a better optimization of the treatment for the individual couple and thus result in a higher response rate. The fact that the patients were followed-up and assessed every three months may also have influenced the high response rate. Another factor in the study design that is important to observe is that all patients started on the highest dose available. This might be, although not often stressed, of pivotal importance in order to achieve the best initial treatment success. Many men with ED do have low self-esteem, particularly regarding their performance capability, at the initiation of treatment (153). Thus starting on a low dose may not produce satisfactory results and could further aggravate their low self-esteem. A down titration instead of up titration of dose might have the opposite effect. There are few, if any, safety issues with such an approach based current data on the three PDE-5 inhibitors (155).

With the treatment regime presented, regardless of whether previously treated or naïve, approximately 50% chose a drug with a shorter duration (Sildenafil or Vardenafil) and 50% a drug with long-acting potential (Tadalafil). The observation that treatment preference for previously treated patients was the nearly the exact opposite to treatment of naïve patients is intriguing. An explanation might be that two different cohorts are studied. Thus among those who continue their treatment for a couple of years might value other aspects of a treatment, than those who had not previously received treatment. Although no obvious difference between age or cause of ED and preference was found, there was a tendency that patients with

mild ED preferred Tadalafil and patients with more severe ED seemed to prefer Sildenafil or Vardenafil (Tables IV, VI and Figure 2). Similar results have been reported from other studies (97,156,157).

Two factors are apparently of major importance for the preference, long duration and efficacy. Short time to onset seems to play a minor roll. A fair assumption is that the medication must have the desired effect before any choice of preference is made (53). It seems unlikely that anyone would prefer a medication with long duration or rapid onset if it did not produce a satisfactory erectile response. From this standpoint, the responders who preferred the long-acting potential must have experienced an additional benefit from this pharmaco-kinetic potential.

Conclusions

1. There is undoubtedly an association between CVD and ED, but ED, as a single symptom does not seem to justify an investigation of risk factors for coronary artery disease.
2. If ED is to be a clinically useful predictor, it must also be a reason for a man to seek medical attention, which at the moment, rarely seems to be the case. Thus at present the value of ED as a predictor of CVD is limited.
3. There is a correlation between LUTS, the bother induced by LUTS, age and ED.
4. The relationships are however rather weak. Thus the correlation appears to be of less importance in the management of the individual patient seeking medical attention due to LUTS and/or ED.
5. The treatment compliance for Sildenafil in clinical practice is just under 50% two years after treatment initiation. Cost appears to be an important factor for both treatment abortion and rationing.
6. A treatment regime that allows the patients to try out the three available PDE-5 inhibitors, at the highest recommended dose, is a feasible option in clinical practice and will lead to a very high response rate (89%) in both previously treated and previously untreated patients.

Conclusion in Swedish

Populärvetenskaplig sammanfattning på svenska

Introduktion

Erektionssvikt eller Erekttil Dysfunktion (ED) definieras som ”oförmåga att få och bibehålla en erektion tillräcklig för sexuell aktivitet”.

Introduktionen av Sildenafil (VIAGRA[®]) i slutet av 1990 talet och möjligheten att erbjuda en tablett för behandling av ED, medförde stora förändringar. Allt flera män med ED sökte sjukvården för att få hjälp och allt fler läkare började nu också ge patienter med ED behandling. Under 1990 talet genomfördes också en mängd olika vetenskapliga studier rörande olika aspekter på erektionen och dess dysfunktion (ED). Epidemiologiska studier klarade den höga frekvensen och sambandet med tilltagande ålder. Sambandet till andra sjukdomar, orsakerna till varför män sökte eller avstod från att söka behandling och varför man avbröt en påbörjad behandling studerades också. Man påvisade ett tydligt samband mellan hjärt-kärlsjukdomar, diabetes och ED, och att det även föreligger ett samband, om än inte alls så starkt, mellan ED och vattenkastningsproblem (LUTS). Andra studier visade att många (upptill 60%) efter 1-2 år avbryter sin ED-medicinering trots att behandlingen fungerade. Oftast var det inte en enskild orsak utan flera i kombination som ledde till detta. Biverkningar, spontan förbättring eller otillfredsställande effekt var självklara skäl att avbryta, men också faktorer som tillkomst av allvarlig sjukdom, förlust av partner, minskat intresse för sexuell aktivitet, störningar i partner relation, kulturella aspekter, och socioekonomiska spelade roll.

I början av 2000 talet kom två snarlika tabletter till Sildenafil ut på marknaden, Vardenafil (LEVITRA[®]) och Tadalafil (CIALIS[®]). Frågan om vilket av dessa preparat som var bäst för patienten rönste stort intresse. Flera så kallade preferensstudier genomfördes för att klarlägga frågan. Tyvärr var resultaten motstridiga och gav inte den kliniskt verksamme läkaren ett tillfredsställande stöd.

Denna avhandling

Målsättningen med avhandlingen var att studera:

1. Sambandet mellan ED och hjärtinfarkt och vilket värde detta kan ha i klinisk verksamhet.
2. Sambandet mellan vattenkastningsproblem (LUTS), besvär av LUTS, ålder och ED, samt diskutera värdet av detta samband i handläggningen av den enskilde patienten.
3. Hur ofta avbrott sker vid Sildenafil behandling och speciellt vilken betydelse kostnaden har för användningen av preparatet.
4. Om, i rutin verksamhet, en enkel behandlingsmodell där patienterna får möjlighet att pröva samtliga tre tillgängliga PDE-5 hämmare (Sildenafil, Vardenafil, Tadalafil) leder till bättre behandlingsresultat.

Avhandlingens delarbeten

Delarbete I: Sambandet mellan ED och hjärtkärlsjukdom (CVD) i en av dess allvarligare former, hjärtinfarkt (MI) och om ED kan användas om en tidig markör för en kommande hjärtinfarkt studerades. Förekomsten av ED hos 100 män med MI jämfördes med förekomsten av ED i en åldersmatchad kontrollgrupp utan MI. ED visade sig vara överrepresenterat hos patienter med hjärtkärlsjukdom och diabetes i båda grupperna. Få av de patienter som hade ED hade sökt sjukvården för detta. Ingen av de patienter som hade en ED före de drabbades av sin MI hade sökt för sin ED.

Delarbete II: Sambandet mellan vattenkastningsproblem (LUTS), besvären orsakade av LUTS, ålder och ED studerades. Ett frågeformulär utsändes till 2000 slumpvis utvalda män mellan 60-70 år. Frågeformuläret bestod av två självskattningsskalor en för LUTS (IPSS) och en för erektionsförmågan (IIEF-5). Frågeformuläret besvarades av 1096 män, varav svaren från 924 män var möjliga att utvärdera. Både LUTS och hur de besvär som vattenkastningsproblemen ger visade sig ha ett oberoende statistiskt samband till ED. Sambandet var emellertid ganska svagt och den kliniska relevansen av sambandet, i handläggningen av den enskilde patienten kan ifrågasättas.

Delarbete III: Orsaker till avbrott i ED behandling studerades med speciell tonvikt på sambandet mellan behandlingkostnad och användning. Ett frågeformulär utskickades efter det att läkemedelsförmånen avskaffats för behandling av ED till 132 patienter som minst två år tidigare påbörjat behandling med Sildenafil (VIAGRA®). Formuläret, som innehöll frågor rörande; aktuell behandling för ED, användningsfrekvens, orsaker till förändringar eller av-

brott i behandlingen, behandlingens resultat, uppgifter relationen till partnern, inkomsten för hushållet före skatt, besvarades av 69%. Knappt hälften av dessa patienter använde vid enkät-tillfället fortfarande Sildenafil. Kostnaden för behandlingen visade sig spela en stor roll för fortsatt behandling. Speciellt i de hushåll som hade en låg inkomst, där majoriteten (86%) hade slutat eller minskat sin behandling till följd av kostnaden. I hushåll med hög inkomst hade bara 35% påverkats på samma sätt.

Delarbete IV: En behandlingsregim, där patienterna med ED fick möjligheten att pröva samtliga tre tillgängliga PDE-5 hämmarna (Sildenafil, Vardenafil, Tadalafil), utvärderades. I undersökningen deltog 186 patienter. Av dessa hade 34% aldrig tidigare behandlats för ED och 66% hade en pågående ED behandling. Studien visade att en sådan regim är genomförbar i klinisk rutinverksamhet och ger oftare en mycket hög frekvens av tillfredställande behandlingsresultat. Ungefär hälften av patienterna valde ett preparat där effekten varade under en kortare tid (Sildenafil, Vardenafil) hälften ett där effekten varade längre tid (Tadalafil). Valet av preparat styrdes främst av hur effektiv medicinen upplevdes vara och hur lång tid den var verksam, mindre av om den var snabbt insättande eller inte.

Sammanfattande slutsatser

- Det finns ett samband mellan CVD och ED, men ED som enda symptom tycks inte vara tillräckligt för att påbörja omfattande utredningar av hjärtkärlsjukdom hos i övrigt friska män. Om ED skall bli en klinisk användbar markör för hjärtkärlsjukdom krävs också att fler söker för sin ED problem. Något som för närvarande inte är fallet.
- Det finns ett samband mellan LUTS, hur LUTS upplevs, ålder och ED. Sambandet är emellertid ganska svagt, och tycks därför ha begränsat värde i den kliniska vardagen vid bedömning av patienter som söker för LUTS och/eller ED.
- Nästan 50% av de som börjat behandling med Sildenafil har slutat använda medicinen inom 2 år. Kostnaden för behandling spelar en stor roll för användningen speciellt i hushåll med låg inkomst.
- En behandlingsregim där patienter med ED får pröva de tre PDE-5 hämmarna i den högsta rekommenderade dosen, är genomförbar i kliniskt rutin och leder till en mycket hög respons (89%) på behandlingen.

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Appendix 1

Patient Instructions	Subject Initials: _____				Date Completed: __/__/__ - DD/MM/YR	
Sexual health is an important part of an individual's overall physical and emotional well-being. Erectile dysfunction, also known as impotence, is one type of very common medical condition affecting sexual health. Fortunately, there are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your doctor identify if you may be experiencing erectile dysfunction. If you are, you may choose to discuss treatment options with your doctor.						
Each question has several possible responses. Circle the number of the response that best describes your own situation. Please be sure that you select one and only one response for each question .						
OVER THE PAST 6 MONTHS:						
1. How do you rate your confidence that you could get and keep an erection?						
Very Low	Low	Moderate	High	Very High		
1	2	3	4	5		
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?						
No sexual activity	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always	
0	1	2	3	4	5	
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) you partner?						
Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always	
0	1	2	3	4	5	
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?						
Did not attempt intercourse	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult	
0	1	2	3	4	5	
5. When you attempted sexual intercourse, how often was it satisfactory for you?						
Did not attempt intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always	
0	1	2	3	4	5	

SCORE: Add the numbers corresponding to questions 1-5. If your score is 21 or less, you may want to speak with your doctor.

Appendix 2

1. The International Prostate Symptom Score (IPSS)

Please answer the following questions about your urinary symptoms.
Write your score for each question at the end of each row.

Over the past month, how often have you...	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
1. ...had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. ...had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. ...stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. ...found it difficult to postpone urination?	0	1	2	3	4	5	
5. ...had a weak urinary stream?	0	1	2	3	4	5	
6. ...had to push or strain to begin urination?	0	1	2	3	4	5	
And finally							
	None	Once	Twice	3 times	4 times	5 times or more	
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
Add up your total score and write it in the box.							Total

Supplementary question - Quality of life due to urinary symptoms.

If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that? (Please tick which best describes how you would feel).

0. Delighted
1. Pleased
2. Mostly satisfied
3. Mixed - about equally satisfied and dissatisfied
4. Mostly dissatisfied
5. Unhappy
6. Terrible

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