CHAPTER 8

Summary

Urinary tract infections (UTI) are among the most frequently reported infections among older persons. Annually, 20% of all older persons visit their general practitioner for a UTI and about 50% of the residents in long-term care facilities (LTCF) get a UTI. This type of infection not only causes several days of illness but may have more severe consequences for older persons, such as a decline in functioning, as well as delirium, dehydration, urosepsis, hospitalization, or even death. It is generally assumed that infections also lead to a general decline in functioning, which is often irreversible and can cause a cascade of general deterioration, more care dependency, and a higher mortality risk. In addition, it is known that disability in activities of daily living (ADL) is independently associated with the development of infections. Considering this negative impact of UTI, we were particularly interested in how to prevent UTI in vulnerable very old persons.

To avoid the possible negative effects of UTI in vulnerable older persons, interventions are needed. To more efficiently prevent UTI and their subsequent negative consequences it is important to identify older persons at risk for UTI. Among vulnerable older persons, an increasing age, diabetes mellitus, stroke, urine incontinence, prior history of UTI, and impaired functional and cognitive status are predictive for the development of UTI. A first step towards effective prevention of UTI in older persons is to gain insight into whether these factors also play a role in the occurrence of UTI in the oldest old. If these factors are known, it should be easier to detect the group of oldest old with an increased risk of UTI.

The use of prophylactic antibiotics in older persons at risk remains controversial because of the associated side-effects as well as antibiotic resistance. In addition, no other evidence-based interventions are known to decrease UTI in institutionalized populations. However, prophylaxis with cranberry is a potential prevention strategy. Cranberries contain proanthocyanidins, which are stable compounds with anti-adhesion activity against, for example, *Escherichia coli*. Although two studies have reported that cranberry juice may be protective in older adults, the effectiveness of cranberry capsules in the protection against UTI in vulnerable very old persons in LTCF has not yet been studied.

The general aim of this thesis is to study the possibilities for and the effects of the prevention of UTI in vulnerable very old persons.

PART ONE: CORRELATES OF URINARY TRACT INFECTIONS

Chapter 2 focuses on the care dependency of the most vulnerable very old persons in LTCF, often with (advanced) dementia and with high and complex care dependency. In a prospective follow-up study in 21 Dutch LTCFs, changes in care dependency were examined over two 6-month periods, and the possible predictive factors of change and the effect of care dependency on mortality were explored. The changes in care dependency were examined to shed light on how to manage care and provide better tailored care for individual LTCF residents. A

total of 890 LTCF residents with a median age of 84 years participated. At baseline, and at 6 and 12 months, the care dependency status was assessed by the nursing staff using the Care Dependency Scale (CDS). The CDS comprises 15 items measuring basic care needs of LTCF residents.

The conclusions drawn from this study are that the majority of surviving LTCF residents were stable in their care dependency status over two subsequent 6-month periods, and that residents who are most highly dependent on care have an increased mortality risk. A 1-point decrease in CDS score between 0 and 6 months was related to an increased mortality risk of 4%. In addition, gender, age, urine incontinence, dementia, cancer and baseline care dependency status predict an increase in care dependency over time. The results of this study indicate that residents, and their formal and informal caregivers, need to be aware of the natural course of care dependency when considering therapeutic and end-of-life care options, as well as preventive measures, in long-term care.

Because infections are more common in vulnerable older persons and these infections may also have negative consequences for their (ADL), the study in Chapter 3 examined whether UTI or lower respiratory tract infections predict an increase in disability of ADL among the oldest old in the general population. This study used data from the Leiden 85-plus Study (a population-based prospective follow-up study) and was performed to establish whether infections at old age predict an increase in ADL disability, stratified for the presence of ADL disability. A total of 473 persons aged 86 years participated. ADL disability was determined at baseline and annually thereafter during 4 years of follow-up, using the 9 ADL items of the Groningen Activity Restriction Scale.

The study showed that in persons without disability in ADL between age 85 and 86 years, infections are associated with a 1.6 times higher risk to develop ADL disability from age 86 years onwards compared with older persons without infections. However, no such association was found for persons who already had disabilities related to ADL. In addition to treatment, active functional rehabilitation may be important to restore independence in ADL.

In order to take effective preventive measures against UTI, especially older persons who are at increased risk to develop UTI should be selected. Therefore, the study in Chapter 4 determined which predictive factors of UTI among the oldest old in the general population were predictive for UTI. This population-based prospective follow-up study (also based on data from the Leiden 85-plus Study) showed that cognitive impairment, ADL disability, self-reported urine incontinence and a one-year history of UTI, are independent predictive factors of an increased incidence of UTI from age 86 onwards. These predictive factors can be used for the development of a clinical prediction rule to select the most appropriate persons for preventive strategies.

PART TWO: THE CRANBERRY STUDY

Until now, apart from general hygienic precautions, adequate hydration, regularly toilet visits and sufficient urination (bladder emptying), there are no evidence-based non-antibiotic interventions that show a decrease in clinical UTI in institutionalized populations. However, there is increasing evidence that cranberry products may lead to a decrease in the incidence of clinical UTI over a 12-month period. Although two studies have reported that cranberry juice may be protective in older adults, the effectiveness of cranberry capsules to protect against UTI in vulnerable older persons in LTCF had not yet been studied; therefore, we designed the CRANBERRY study.

The CRANBERRY study is a double-blind randomized placebo-controlled multi-center trial, in which a total of 21 LTCF from the University Network for the Care sector in South-Holland (UNC-ZH) participated. The CRANBERRY study assesses the effectiveness and costs of cranberry capsule use to prevent clinical UTI in vulnerable older persons living in LTCF, stratified for UTI risk at baseline. Participants were stratified according to UTI risk at the start of the study. Participants with long-term catheterization, diabetes mellitus, and at least one UTI in the preceding year, were considered to be at high risk for UTI. In total, 928 residents (225 men and 703 women) aged over 65 years of age were randomized in two groups: one group received cranberry capsules and the other group a placebo. Cranberry and placebo capsules were provided twice daily for 12 months.

The primary outcome was the incidence of UTI. However, because diagnosing UTI in vulnerable older persons is difficult, the CRANBERRY study not only used the prevailing scientific gold standard (strict definition), but also used the clinical diagnosis made for each individual resident (clinical definition). The strict definition is based on a scientific approach, which always involves the presence of clinical symptoms and the presence of bacteria in the urine. In contrast, the clinical definition varies between residents and is therefore a broad and practical definition, following current clinical practice guidelines and based on clinical agreement of 'elderly care' physicians and the nursing staff.

The study in Chapter 5 investigates the effectiveness of cranberry capsule use in the prevention of UTI in vulnerable older persons living in LTCF. The CRANBERRY study shows that the use of cranberry capsules reduced the number of clinical UTI by 26% in LTCF residents with a high UTI risk; this treatment effect occurs after 2 months of capsule use. Also, more than 20% of the residents no longer developed any UTI at all. No difference in incidence was found in residents with low UTI risk. For UTI defined according to the strict definition, no difference was found in UTI incidence between residents who used cranberry or placebo capsules.

The use of cranberry capsules requires not only evaluation of its clinical effectiveness but also an examination of its cost-effectiveness. Therefore, the economic evaluation presented in Chapter 6 investigated the effect of clinical UTI on health and costs and examined whether the preventive use of cranberry capsules in LTCFs is cost-effective. This study concluded that,

in high UTI risk residents, taking cranberry capsules is unlikely to be cost-effective in the investigated dosage, frequency and setting. In other words, although cranberry capsules reduce the number of clinical UTI in vulnerable very old persons living in LTCF, the capsules cost more than they save in relation to the costs of regular treatment of clinical UTI.

Finally, Chapter 7 presents a general discussion on the main findings of the work presented in this thesis. The chapter also reflects on the difficulties in diagnosing UTI in vulnerable older persons with dementia, considers the clinical implications of our findings for daily practice in long-term care, and makes some recommendations for future research. The preventive care for vulnerable very old persons is placed in a broader perspective and the challenges and barriers of research in long-term care are discussed.

The first three studies presented in this thesis show that clinical UTI are frequently present in vulnerable very old persons and that these clinical UTI can have consequences for the daily functioning of the oldest old who are not yet disabled. In addition, the majority of LTCF residents remained relatively stable in their care dependency status. Furthermore, it was established that some factors can be used to identify older persons at risk for developing clinical UTI. Thus, prevention of clinical UTI is important and it is possible to identify vulnerable very old persons at risk for developing clinical UTI.

The results of the CRANBERRY study allow to conclude that the use of cranberry capsules (twice daily) is effective in the prevention of clinical UTI in LTCF residents at high risk of UTI. The capsules reduce the incidence of clinical UTI and thereby reduce the days of illness and the negative consequences of UTI, e.g. reducing the burden of the symptoms of UTI and less discomfort. Although the use of the capsules was not cost-effective, for reasons of effectiveness it is still recommended to give residents at high risk of UTI preventive treatment with cranberry capsules.

Because the confirmation of clinical UTI in LTCF residents remains difficult, in the CRANBERRY study two definitions for UTI were used, i.e. a clinical one and a strict UTI definition. The appropriate scientific 'gold standard' for diagnosing UTI is detection of the pathogen in the presence of inflammatory signs and clinical symptoms of micturition. However, factors such as impaired communication due to dementia, high prevalence of incontinence, chronic genitourinary symptoms and a high frequency of positive urine cultures due to bacteriuria, without being clear whether these bacteria are from the urine bladder or from the environment after urination, makes the diagnosis of UTI even more difficult. The use of the 'gold standard' for diagnosing clinical UTI is not suitable for LTCF residents and will probably lead to substantial underdiagnosis. As a result, no unambiguous criterion standard is available for diagnosing UTI in LTCF populations; most clinical criteria to ascertain UTI in these vulnerable residents are based on consensus about grouped clinical manifestations, as presented in clinical guidelines. Currently, these guidelines define a clinical UTI as the presence of specific and non-specific symptoms and signs of UTI, such as dysuria, change in the character of urine, and change in mental status, confirmed with a urinalysis to evaluate the evidence of the presence of nitrite

and leukocyte esterase. UTI are often treated empirically, but a urine culture may be necessary in LTCF residents with recurrent UTI to confirm the diagnosis and guide antibiotic treatment.

Although several guidelines are available to assist physicians in the diagnosis of clinical UTI in this population, no unambiguous definition of clinical UTI is available. The current guidelines are not optimal for clinical decision-making or for a 100% confirmation of clinical UTI. Additional studies are required to further refine these consensus guidelines and to establish how to optimally diagnose clinical UTI in vulnerable very old persons.

Within the preventive care for vulnerable older persons, the traditional prevention goals (such as preventing diseases and mortality) could be extended by goals such as preventing loss of quality-of-life and self-reliance, and the prevention of discomfort. Because the most vulnerable older persons generally live in LTCF a well-considered choice has to be made in the selection of a preventive measure in this population. Additional studies are required to investigate whether prevention is effective in providing improvement in care from the perspective of the resident. Care improvement in LTCF needs to focus mainly on quality-of-life, minimization of the impact of a disease, and a reduction in the burden of this disease in the prevention of complications, comorbidity and disability. All this requires specific insight and solid evidence. Therefore, research in LTCF populations needs specific knowledge that also takes into account the implementation of this new knowledge into daily practice and a specific infrastructure.

Future research in LTCF can best be performed within an academic nursing home research network, such as the UNC-ZH. An academic nursing home network has expertise related to performing studies in complex care among vulnerable older persons living in LTCF. Within this network, care professionals collaborate with scientists of a university medical center to develop, implement, and test initiatives to improve quality of care. Within this structure, university and practice are closely linked and research outcomes can be directly implemented in the daily practice and education of care professionals.