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CHAPTER 7

General discussion

The overall aim of this thesis was to explore the possibilities for and effects of prevention of clinical urinary tract infections (UTI) in vulnerable very old persons.

The first part of this thesis investigates the effects of infections on functioning and examines which very old persons would benefit most from UTI prevention. Firstly, we focused on the most vulnerable very old persons, often with (advanced) dementia and with high and complex care dependency, in long-term care facilities (LTCF). For this, we studied changes in the natural course of care dependency in LTCF residents. The conclusions drawn from this prospective follow-up 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 risk of mortality (Chapter 2).

Secondly, within the Leiden 85-plus Study, we examined whether clinical UTI predict an increase in disability of the activities of daily living (ADL) among the oldest-old in the general population (Chapter 3). The general population was studied to unravel how infections and disability co-occur. This study showed that in 86-year-old persons without ADL disability, a clinical UTI is associated with a higher risk to develop ADL disability from age 86 years onwards. However, no such association was found for persons who already had disabilities related to ADL (Chapter 3).

Thirdly, we investigated which factors are predictive of clinical UTI among the oldest-old in the general population. This study showed that cognitive impairment, ADL disability, selfreported urine incontinence, and a one-year history of clinical UTI, are independent predictive factors of an increased incidence of clinical UTI from age 86 onwards (Chapter 4). These predictive factors can be used to target preventive measures to the oldest-old at high risk of clinical UTI.

In summary, the first three studies presented in this thesis show that the majority of LTCF residents remained stable in their care dependency status, that clinical UTI are frequently present in vulnerable very old persons, and that these clinical UTI have consequences for daily functioning. Furthermore, there are factors that 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. Therefore, we searched for preventive strategies which are suitable for the prevention of UTI in this specific population.

Until now, there are no evidence-based interventions that show a decrease in clinical UTI in institutionalized populations;¹ however, there is increasing evidence that cranberry products may lead to a decrease in the incidence of clinical UTI over a 12-month period, particularly in women with recurrent UTI.²⁻⁴ Although two studies reported that cranberry juice may be protective in older adults,^{5,6} the effectiveness of cranberry capsules in the protection against UTI in vulnerable older persons in LTCF had not yet been studied. Therefore, we designed the CRANBERRY study to assess the effectiveness and costs of cranberry capsule use to prevent

clinical UTI in LTCF residents, stratified for UTI risk at baseline. The results of the CRANBERRY study are described in the second part of this thesis.

The CRANBERRY study (Chapter 5) shows that taking cranberry capsules twice daily results in a 26% lower incidence of clinically defined UTI compared to placebo in residents at high risk of UTI, but that cranberry use is unlikely to be cost-effective in the investigated dosage, frequency and setting (Chapter 6). 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.

This chapter places the preventive care for vulnerable very old persons in a broader perspective and discusses the challenges and barriers of research in long-term care. The chapter ends by discussing the clinical impact of our findings for daily practice in long-term care and makes some recommendations for future research.

PREVENTIVE CARE IN VULNERABLE VERY OLD PERSONS

Within preventive care for vulnerable older persons, the traditional prevention goals (such as preventing diseases and mortality) should be extended by goals such as preventing loss of quality of life and self-reliance⁷, and the prevention of discomfort. This will enable older persons to be as independent and healthy as possible, in relation to their care needs and health problems.

The most vulnerable older persons generally live in LTCF. These older persons with multimorbidity, functional decline and a high prevalence of cognitive impairment, are dependent on care. In this population, preventive care focuses particularly on loss of quality of life, minimization of the impact of a disease, and reduction of the burden of this disease in the prevention of complications, comorbidity and disability. In addition, preventive measures to achieve a dignified end-of-life are part of the preventive tasks (e.g. mouth care, and prevention of pressure ulcers, urinary retention and constipation) of professional caregivers in long-term care.

Depending on the goals, a well-considered choice has to be made in the selection of a preventive measure in LTCF. When considering preventive strategies to prevent clinical UTI in long-term care, several topics need to be addressed:

- 1. Care dependency and the resident's ADL status
- 2. Expected impact of clinical UTI prevention
- 3. Selection of residents at high risk for developing clinical UTI
- 4. Challenge of diagnosing clinical UTI
- 5. Selection of appropriate preventive treatment
- 6. Cost-effectiveness of clinical UTI prevention

These six points will be discussed in detail below.

1. Care dependency and the resident's ADL status

In this thesis, changes in the natural course of care dependency were examined to shed light on how to manage and provide better tailored care (including prevention) for individual LTCF residents (Chapter 2). Awareness of the natural course of care dependency is essential for residents, as well as for their formal and informal caregivers, when considering therapeutic and end-of-life care options, as well as preventive measures. With this in mind, research among the oldest-old needs to include an assessment of the impact of a disease on an individual's functional capacity and on maintaining their independence.⁸

Since aging is often accompanied by a higher incidence of infections and an increase in ADL disability, it is important to establish whether there is a relation between infections and ADL disability. In addition, prevention of infections may also prevent a decline in ADL. But how do infections and disability in ADL co-occur? It is known that disability in ADL is independently associated with the onset of nosocomial infections in hospitalized older persons,⁹ and is a risk factor for infections in LTCF.^{10,11} However, it is also known that, amongst the oldest-old in the general population, clinically diagnosed infections are predictive for the development of ADL disability in those without onset of ADL disability (Chapter 3). ADL disability can be considered as a risk factor for an infectious disease, but also as an outcome itself.^{8,9,11}

A decline in ADL in older persons has to be placed in a proper perspective. Other non-infectious illnesses and chronic diseases, such as cardiopulmonary, neurological and musculoskeletal diseases, can also lead to ADL disability. In addition, under-nutrition and incontinence can contribute to a decline in ADL.¹²⁻¹⁴ A severe decline in ADL can even lead to a higher mortality rate,¹⁰ more care dependency, and a higher risk of being admitted to a LTCF.¹⁵

2. Expected impact of clinical UTI prevention

In general, infections contribute to higher morbidity and mortality, infection outbreaks, increased antimicrobial medication use, and additional costs in LTCF.^{16,17} In addition, the frequent use of antibiotics contributes to more pathogens becoming multi-resistant to antibiotic treatment;¹⁸ moreover, prophylactic antibiotic use is controversial because of side-effects.

Clinical UTI are common and account for 25% to 40% of all bacterial infections in LTCF.¹⁹⁻²¹ They place a considerable burden on daily care and have serious consequences for vulnerable older persons living in LTCF. Clinical UTI not only cause several days of illness, but may have more severe consequences such as delirium, dehydration, urosepsis, hospitalization or even death^{22,23} and also lead to a deterioration in daily functioning, even when the infection is over (Chapter 3). Considering the impact of clinical UTI in LTCF residents, it seems important to prevent clinical UTI in these vulnerable older persons.

In this thesis, several studies illustrate the high incidence of clinical UTI. Although the study in Chapter 3 shows a decline in ADL in the oldest-old who are not yet disabled, in the CRAN-

BERRY study we were able to reduce the incidence of clinical UTI but were unable to show a reduction in functional decline or mortality. Because LTCF residents represent a vulnerable population, often with (advanced) dementia and high care dependency, the expected impact of clinical UTI in this population may be limited to mainly temporary discomfort, but can lead to higher care dependency, complications, and even mortality.

3. Selection of residents at high risk for developing clinical UTI

Since preventive strategies are best applied to those persons at risk for developing UTI, it is important to know which factors predict clinical UTI in older persons. Within the oldest-old in the general population, a history of UTI, cognitive impairment, ADL disability and urine incontinence, are independent predictive factors for developing UTI (Chapter 4). These predictive factors could be used to target preventive measures to the oldest-old at high risk of UTI. Despite that none of these predictive factors appear to be modifiable, they can be used to select individuals who will most benefit from preventive strategies. Selection of high-risk residents is a crucial first step in successful prevention of clinical UTI.

Following the results of the 85-plus Study (Chapter 4), the CRANBERRY study showed that through selection of residents at low and high risk of UTI, it is possible to distinguish groups of LTCF residents with varying risks of clinical UTI. For example, in the CRANBERRY study, residents with long-term catheterization, diabetes mellitus, or at least one UTI in the preceding year, were considered to be at high risk. Although our high-risk residents were selected using these criteria, it is possible that the use of other criteria might have selected a group at even higher risk or with even more preventable UTI. Prediction rules to select residents at risk for UTI need further study in order to make a more efficient and effective prediction of the UTI risk in this specific population. Improved identification of older persons at high risk of UTI may also improve cost-effectiveness.

Another point to be taken into consideration is that a UTI risk assessment should be evaluated regularly, because the risk for developing UTI can change over time. Moreover, a preventive measure should not necessarily be applied 'forever'. Additional research is required to develop rules related to 'stopping' because, for example, the preventive action of cranberry capsules can cease when a person has been one year free of UTI, and when no other risk factors are present.

4. Challenge of diagnosing clinical UTI

According to clinical guidelines (and also for many studies) the appropriate gold standard for diagnosing UTI is detection of the pathogen in the presence of inflammatory signs and clinical symptoms of micturition.^{24,25} A less rigorous definition can easily lead to over-diagnosis and false conclusions.²⁶ Although clinical UTI is a common bacterial infection in LTCF residents,^{1,27} diagnosing UTI in these vulnerable older persons remains a challenge. Factors such as impaired communication because of dementia, a high prevalence of incontinence, chronic

genitourinary symptoms, and a high frequency of positive urine cultures due to bacteriuria without complaints,²⁸⁻³⁰ make the diagnosis of UTI difficult. In addition, clinical symptoms of UTI are frequently absent³¹ and differentiating between asymptomatic and symptomatic UTI in this population is complicated.^{28,32} The use of the gold standard for diagnosing clinical UTI is not suitable for LTCF residents and would lead to substantial under-diagnosis. Thus, no unambiguous criterion standard for diagnosing UTI is available for LTCF populations and most of the clinical criteria applied to ascertain UTI in these vulnerable residents are based on consensus.³³⁻³⁶

Generally, these consensus 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 for evidence of the presence of nitrite and leukocyte esterase. A positive nitrite and leukocyte esterase test may indicate the presence of clinical UTI, and treatment with antibiotics may then start. Although UTI are often treated empirically,¹⁸ a urine culture may be necessary in LTCF residents with recurrent UTI to confirm the diagnosis and guide antibiotic treatment. In addition, the treatment of clinical UTI in LTCF residents is similar to that of older patients in the community, but with more emphasis on individualized and tailored antimicrobial therapy.^{24,36}

Because the confirmation of clinical UTI in LTCF residents remains difficult, in the CRAN-BERRY study two definitions for UTI were used, i.e. a clinical one and a 'strict' UTI definition (Chapter 5). The strict UTI definition is based on a scientific approach and includes the presence of micturition-related signs and symptoms, confirmed with a positive culture or dipslide. Using only this strict UTI definition probably leads to under-estimation of the true incidence of UTI in LTCF residents and could be less sensitive for our LTCF population.

To make research possible in a 'real world' LTCF population, besides the strict definition, a clinical UTI definition was used. This clinical definition is a broad and practical definition, follows the clinical practice guidelines for LTCF residents,^{25,37} and is based on the experience of elderly care physicians and nursing staff. Experienced staff can achieve an even higher diagnostic precision than that acquired with a urine culture.³⁸ There is also evidence that micturition-related signs and symptoms are predictive for UTI.²⁸ Although use of the clinical definition can lead to an over-estimation of UTI, it closely reflects clinical care in LTCF and adds knowledge to the practice guidelines to assist physicians in their decision-making. Because the beneficial effect of cranberry capsule use was only found when using our clinical UTI definition, the presence of false-positive clinical UTI is limited. Furthermore, the cost-effectiveness analysis described in this thesis (Chapter 6), also illustrates the relevance of the clinical definition, as clinical UTIs were followed by a significant deterioration in quality-of-life and survival, and an increase in care dependency and costs.

5. Selection of appropriate preventive treatment

As very old people can differ considerably from one another with respect to their health, and functional and cognitive status, instead of a 'one size fits all' approach a personalized preventive care approach is needed. In addition, it is recommended to incorporate 'lag time to benefit' in the preventive care decisions for older populations.³⁹ Lag time to benefit is defined as the period between an intervention and the moment that improved health outcome is observed.⁴⁰ Incorporating lag time estimates into preventive care for vulnerable older persons will encourage a more explicit consideration of the risks and benefits of prevention.⁴¹

In this thesis, cranberry use for the prevention of clinical UTI showed a positive treatment effect from 2 months of follow-up onward, with a risk reduction of 22% in high UTI-risk residents during the 12-month follow-up (Chapter 5). This level of risk reduction seems to be meaningful in this specific population in which clinical UTI are frequently present.

The CRANBERRY study showed positive effects of cranberry capsule use for UTI in LTCF residents; other benefits of cranberry capsules may also be considered. For example, in daily practice, cranberry use may also reduce antibiotic prescription, including inappropriate prescriptions. In other words prevention with cranberry may lead to even less antibiotic resistance in long-term care. Also, less clincial UTI will lead to a reduction in the burden of UTI symptoms and to less discomfort.

It is important to realize that many preventive measures have not yet been tested in LTCF populations. More research is needed in this specific population to achieve an optimal, personalized and tailored prevention strategy, in which prevention is focused on increased quality of life, minimization of the impact of disease, reduction of the burden of disease in the prevention of complications, comorbidity and disability, and a dignified end-of-life.

Thus, prevention in LTCF needs to be examined in contexts other than the traditional prevention approach which has the prevention of disease and mortality as its ultimate goal. A new framework for preventive care in LTCF needs to be developed which involves both the older person and their informal caregiver(s). Within the individualized preventive care for vulnerable very old persons, the practical feasibility of interventions needs to be taken into account, as well as an effective implementation in daily care which includes education, knowledge and professional development, regulations, and financial considerations.

6. Cost-effectiveness of clinical UTI prevention

Justifying the implementation of new prevention strategies not only requires evaluation of its effectiveness, but also requires economic evaluation. For an economic evaluation in long-term care the impact of clinical UTI on the resident's health is relevant, and the resident's quality of life plays an important role in the societal valuation. The ultimate goal in long-term care is not simply adding 'years to life' but adding 'quality of life to years'. Therefore, the costs and benefits of interventions to prevent clinical UTI in LTCF populations need to be carefully weighed.

The CRANBERRY study shows that it is unlikely that cranberry capsule use will be costeffective in the investigated dosage, frequency and setting (Chapter 6). However, cranberry capsules can be 'efficient' from the perspective of the individual resident with a high risk of UTI, resulting in a lower incidence of clinical UTI, less impact of UTI on the resident's health (e.g. less disability in ADL, care dependency and less discomfort), and a better quality of life. Also, less antibiotic use and (probably) less antibiotic resistance is likely to lower the costs. The costs attributed to antibiotic resistance were not discounted in the CRANBERRY study.

Economic evaluations usually express the effects of the intervention in the number of lifeyears gained and in health-related quality of life.⁴² Preferably, a cost-utility analysis is performed for economic evaluations, whereby the effectiveness of the intervention in terms of quality-adjusted life years (QALYs) is expressed in a cost-utility ratio per QALY. This ratio is defined as the amount of money the society is willing to pay to gain one QALY.^{43;44} The CRAN-BERRY study shows that the health gain in terms of QALYs was small in comparison with the costs. Most of this gain was due to the prevented clinical UTI mortality, i.e. a QALY gain in life expectancy of two weeks (Chapter 6). Although two weeks seems relatively small, in a vulnerable LTCF population with a life expectancy of around 1.5 years after admission to a LTCF, this is relatively large. The six-month mortality rate in LTCF residents with advanced dementia ranges from 18% to 37%,^{45,46} and the overall 2-year mortality rate after institutionalization is 57%.⁴⁷

Usually the QALYs are based on health-related quality of life, measured using the European Quality of Life utility measure (EQ-5D); this is a generic preference-based measure using a health state classification system with five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).48 Although use of the EQ-5D allows to compare economic evaluations internationally, it is less suitable for use in the LTCF setting.⁴⁹⁻⁵¹ Normally, quality of life measurements require the resident's self-assesment of their fulfilment and impairment in daily life;⁵⁰ however, because the most vulnerable people, often with (advanced) dementia, live in LTCF, the proxy (e.g. the responsible nurse, or relative) generally provides the utility measure. However, there is evidence that the rating of quality of life by proxy is influenced by the personal and/or professional characteristics of the proxy, the nature of the relationship, the time spent with the resident, the stage of dementia, and also the caregiver burden.^{49,50} Thus, there is often a discrepancy between the quality of life rating acquired from the residents themselves and that of their proxy, although the viewpoint of the proxy appears to be important when rating the EQ-5D.⁵² Despite that, the responsible nurse is well acquainted with the residents, it is difficult to rate the resident's pain/discomfort and anxiety/depression, especially in residents suffering from dementia. The EQ-5D is too narrowly focused and does not cover the domains relevant to the quality of life of persons with dementia. In the CRANBERRY study the EQ-5D had to be filled in by a professional proxy because 76% of the participants had dementia. A recently developed prototype of the Dementia Quality of life Instrument (DQI) seems more suitable, but has not yet been tested in a large LTCF population.⁴⁹

Another aspect related to economic evaluations in LTCF needs to be adressed, i.e. how do we measure the additional nursing care for LTCF residents who already have continous care? Until now, there is no standard for measuring the costs of additional nursing care in LTCF residents who are already highly care dependent. Therefore, we calculated the additional nursing costs during the two weeks following a clinical UTI, by estimating the proportion of change on the Care Dependency Scale (Chapter 6).⁵³ Although this method was suitable for our study, additional research is required to validate this method.

In the light of all these difficulties related to economic evaluations in long-term care, there is an urgent need for a more suitable instrument to conduct economic evaluations, because the present methods may never demonstrate cost-effectiveness.

RESEARCH IN LONG-TERM CARE FACILITIES: CHALLENGES AND BARRIERS

The above mentioned substantive and methodological points show that research in LTCF populations is challenging and needs specific knowledge and a specific infrastructure. This section discusses the challenges and barriers to research in LTCF populations.

The proportion of older people is steadily rising worldwide; moreover, they live longer and manage their daily activities for longer than ever before.⁵⁴ However, these people also have a higher risk of higher care dependency, institutionalization and mortality.^{55,56} Admission to a LTCF is usually the result of a complex interaction of problems in many domains, in which care and treatment are insufficient to handle all the needs that the individual resident has. Especially behavioral problems (e.g. wandering, aggression, delusions), as well as depression and anxiety, apathy, resistance to care, functional impairment, incontinence, and informal caregiver burden, are reasons for institutionalization.^{57,58} Therefore, in the future, LTCF will probably admit only the most problematic and vulnerable persons, often with (advanced) dementia. Prevention of loss of quality of life and self-reliance is challenging in this vulnerable population. However, an even greater challenge is to minimize the impact of a disease, and reduce the burden of this disease in the prevention of complications, comorbidity and disability; all this requires specific insight and solid evidence. Therefore, research is needed in LTCF populations to generate specific knowledge that also takes into account implementation of this new knowledge into daily practice.

LTCF residents are often excluded from participation in research, sometimes due to the high prevalence of cognitive impairments (e.g. dementia) and sometimes due to medicoethical considerations.⁵⁹ Also, difficulty in acquiring informed consent for study participation from representatives is often a reason for not conducting research in this population. In addition, various methodological issues may form a barrier to research in an LTCF population: for example, difficulties in formulating clear research outcomes or clinical endpoints, problems in defining a clear and unambiguous diagnosis of the disease, the high mortality rate in this population, and the related high level of drop-out during a study. Moreover, some logistic challenges in performing research in LTCF are present, such as obtaining permission from the directors for their organization(s) to participate in the research project and the geographical distance between the participating organizations; often, this distance makes data collection and monitoring of the research project both difficult and costly.

Most research in LTCF is pragmatic and will take place in a 'real world' LTCF population. Therefore, research in LTCF requires a specific infrastructure as well as a considerable effort to enable research in this population. In 2003 the formation of academic nursing home research networks was started in the Netherlands. Currently, in 2014, there are five networks (located in Amsterdam, Groningen, Leiden, Maastricht, and Nijmegen) that have expertise related to performing research in complex care among vulnerable persons living in LTCF. The mission of an academic nursing home research network includes the development of an infrastructure for research.^{60,61} Care professionals collaborate with scientists of a university medical center to develop, implement, and test initiatives to improve quality of care.⁶⁰ Within this structure, university and practice are closely linked. Research outcomes will be directly implemented in daily practice and in the education/training of care professionals; hopefully, all this will serve to improve directly patient care.

CLINICAL IMPACT AND RECOMMENDATIONS FOR FUTURE RESEARCH

Based on the work presented in this thesis, the following conclusions can be drawn:

1. The natural course of care dependency is a dynamic process. LTCF residents can either improve or deteriorate in their care dependency status during their stay in a LTCF. Regular and simple assessment of the care dependency status is important, since this allows nursing staff to become more aware of the variability in the care dependency status of their residents, manage care, anticipate residents' care needs, and provide better tailored care for individual residents. Awareness of the course of care dependency is essential for residents, as well as for their formal and informal caregivers, when considering therapeutic, palliative, and end-of-life care options. Although care dependency can be influenced by individually-tailored interventions, these types of interventions need additional research.

2. In older persons without ADL disability at 86 year of age, clinical infections predict the development of disability in ADL from age 86 years onwards. These infections may be used as a predictor for ADL disability in the oldest-old who are not yet disabled. General practitioners and elderly care physicians should be vigilant when older persons without ADL disability have an infection. Besides treatment, they may start active functional rehabilitation to maintain independence in ADL. Future studies need to address whether the prevention of infections, a quick recovery after infections, and functional rehabilitation, are beneficial in the oldest-

old in the general population to maintain independence in ADL and to avoid adverse health outcomes.

3. Diagnosing clinical UTI is challenging in vulnerable very old persons. Although several guidelines are available to assist physicians in the diagnosis of clinical UTI in this population, there is no unambigous definition of clinical UTI. 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.

4. It is possible to select vulnerable very old persons at high risk for developing UTI. LTCF residents with long-term catheterization, diabetes mellitus, or at least one UTI in the preceding year, are considered to be at high risk of UTI. It is possible that the use of other criteria would have selected a group with even higher risks or even more preventable UTI. Therefore, prediction rules to select residents at risk for UTI need to be studied to enable a more efficient prediction of the UTI risk in this specific population. In addition, it is recommended to evaluate UTI risk on a regular basis, because the risk for developing UTI can change over time.

5. 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. a reduction of the burden of the symptoms of UTI and less discomfort. The use of the capsules was shown not to be cost-effective; nevertheless, for reasons of effectiveness, it is still recommended to give residents at high risk of UTI preventive treatment with cranberry capsules.

Finally, additional studies are required to investigate whether, for example, clinical UTI prevention with cranberry capsules is effective in providing improvement in care from the perspective of the resident. In this case, the care improvement should 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. To stratify residents and to make a well-considered choice for the indicated preventive interventions, assessment of the impact of the disease on an individual's functional capacity and their ability to maintain independence, is recommended.

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