Elective Abdominal Aortic Aneurysm (AAA) repair: challenges remain

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PART III

Summary and future perspectives

Chapter 8

General discussion and future perspectives

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GENERAL DISCUSSION

Elective abdominal aortic aneurysm (AAA) repair is a prophylactic procedure with the goal to prolong patients' life-expectancy by preventing aneurysm rupture.[1,2] Over the past 25 years, the management of AAA disease has undergone profound developments. The gradual adaptation of endovascular aneurysm repair (EVAR) over traditional open repair resulted in a significant reduction of procedural mortality.[1,2] This, along with surgical ameliorations in general, resulted in an altered AAA patient population, including a broader spectrum of patients eligible for repair.[3] Patients of higher age, with more comorbidities and more women are now offered repair in the current era. Simultaneously, the recognition of AAA patients as high cardiovascular risk patients, has led to a progressive implementation of cardiovascular risk management (CVRM).[4] Although, AAA care has developed significantly over the past 25 years, several controversies and challenges remain.

The first part of this thesis focused on key questions regarding the 'EVAR-first strategy'. Taking into consideration the emerging concerns regarding its long-term durability that challenge EVAR as primary option for repair. It evaluated the presumed long-term survival differences of EVAR versus open repair. Thereby, it evaluated the impact of the developments in AAA management on the long-term life-expectancy. The second part of this thesis focused on other outcomes important in the evaluation of AAA care. It evaluated the presumed long-term cost difference of EVAR and open repair. In addition, it investigated how the patient perspective is currently embedded in AAA research. Hopefully, the data presented in this thesis can be used to further optimize (surgical) care for abdominal aortic aneurysm patients.

The five main conclusions of this thesis are that I) long-term (relative) survival between open versus endovascular aneurysm repair is equal; II) AAA patients remain a persistently high long-term (10-year) excess mortality after elective repair, with no change in mortality rates over the past 25 years; III) women have a notably higher short-and long-term mortality; IV) endovascular and open repair are considered cost equivalent; V) and the evaluation of the patient perspective/quality of life of AAA patients needs improvement.

PART I: AAA TREATMENT AND SURVIVAL

I: Long-term survival is similar for open and endovascular aneurysm repair

Although EVAR is now widely considered as primary option for repair, concerns exist regarding an impaired long-term survival in patients who underwent EVAR versus open repair.[5] In this context, it is important to note that these concerns are based on a small group of patients at risk and low generalizability of randomized controlled trials, as well as potential confounding by indication due to differences in patient characteristics between EVAR and open repair in retrospective cohorts.

In **Chapter 2** we therefore performed a systematic review and meta-analysis evaluating the survival of elective EVAR versus open repair, aiming to summarize the survival data and to minimize these impending factors. The analysis included 53 studies, which enrolled patients between 1980 – 2006.

Asymmetrical medical decision making, causing confounding by indication, was reflected in the age-difference between patients undergoing EVAR and open repair in the retrospective cohort studies, with the preference for EVAR in older patients. Although it is not possible to correct for all aspects of confounding by indication, any impact of age- and sex-dependent differences can be minimized by a relative survival analysis.[6,7] Furthermore a relative survival analysis allows to evaluate disease-specific excess mortality compared to the general population. Pooled results showed superior 30-day mortality of EVAR and demonstrated equivalent 3, 5, and 10 years relative survival rates of EVAR and open repair. Notably, the relative survival showed a steady decline from 3 to 10 years follow-up for both EVAR and open repair. This observation implicates that AAA patients have a high disease-specific excess mortality which persists after (successful) AAA repair.

II: Persistent high disease-specific excess mortality after elective AAA repair

To further evaluate the high disease-specific excess mortality after elective AAA repair observed in **Chapter 2**, we performed two time-trend analyses in **Chapter 3** and **Chapter 4**.

Over the past decades, the introduction of EVAR, ameliorations in surgical care, and the progressive implementation of CVRM lowered the procedural mortality, widened the spectrum of patients eligible for repair, and recognized AAA patients as (extremely) high cardiovascular risk patients. The question is to what extent these changes impacted the long-term survival of AAA patients, especially since results of **Chapter 2** showed a high excess mortality after repair. In **Chapter 3** we performed a time-trend analysis of the Swedish National Patient registry data. A time trend analysis was facilitated as both EVAR and the implementation of CVRM occurred in well-defined time frames. Three periods were compared, a period of predominantly open repair (2001 – 2004), a transition period (2005 – 2011), and a period with preferred EVAR (2012 – 2015). Over time, the proportion of patients with pharmaceutical CVRM gradually increased. Relative survival analyses were used 1) to address sex- age- and year- dependent differences in patient characteristics and life-expectancy over time, and 2) to evaluate possible changes in disease-specific excess mortality over time. This analysis showed that the changes in AAA management clearly improved short-term survival, but failed to improve long-term survival of AAA patients. In fact, AAA patients show an alarmingly high long-term excess mortality after AAA repair compared with the matched general population. Notably, women showed a profound survival deficit, with a doubled excess mortality rate of women compared to men.

This persistent high long-term excess mortality is an alarming result as it may imply that AAA patients are still sub-optimally treated for their long-term mortality risk. However, it could possibly be explained by an increased patient frailty over time, because EVAR has lowered the threshold for repair resulting in older and more comorbid patients being treated in the most recent period (chronological bias). [3,8,9,10] Thereby, the Swedish data was only available from 2001 onwards, a time when awareness for CVRM was already increasing, hence a potential benefit of CVRM could have been masked. At last, the results of the Swedish study could have reflected a national phenomenon. Therefore, in **Chapter 4** we validated and further elaborated the results of **Chapter 3** using another patient cohort with a more extensive

period of follow up including the period before CVRM had been implemented. **Chapter 4** described a time-trend analysis of Dutch National data, including all patients who underwent elective AAA repair between 1995 – 2017. Consequently, three periods were compared, a period dominated by open repair and rudimentary CVRM (1995 – 2000), a transition period (2001 – 2011) and a period with an EVAR-first strategy and full implementation of CVRM (2012 – 2017). All analyses were stratified by age and sex. Relative survival and corresponding excess mortality rates were used to adjust for changes in patient characteristics and life-expectancy over time and to evaluate disease-specific mortality. The study confirmed the persistent high long-term excess mortality of AAA patients, highlighting a clear sex- but no age-disparity, with a clear survival deficit in women. The potential interfering effect of chronological bias by an increase of patient age and comorbidity profile was addressed in sensitivity analyses. These showed that the persistent high excess mortality is largely independent of changes in patient selection.

In an attempt to gain insight in the cause for the persistent high excess mortality we evaluated the causes of death distribution. **Chapter 3** and **Chapter 4** showed a higher proportion of cardiovascular death in the AAA population compared to the general population. Consequently, in **Chapter 4** we performed a competing risk of death analysis to evaluate the risk of patients dying from cardiovascular versus non-cardiovascular causes over time. [11] Hypothetically, the implementation of CVRM could lead to a decrease of the cardiovascular mortality, thereby exposing the patient to other competing mortality risks and thus masking a potential beneficial effect of CVRM on overall mortality. The competing risk of death analysis showed that the risk of cardiovascular versus non-cardiovascular death did not change over time. This suggests that CVRM has a marginal effect on cardiovascular mortality in AAA patients. In this, women showed a higher risk for cardiovascular mortality, which persisted for a longer time after repair. No differences were found between age-groups.

The competing risk of death analysis indicates that the lack a of a survival benefit of CVRM could not be explained by the phenomenon of competitive deaths.[11] An alternative explanation for the limited impact of CVRM on cardiovascular mortality could be that AAA patients are relatively undertreated for their cardiovascular risk factors. Despite consensus endorsing maximal CVRM in AAA patients, studies show that approximately half of AAA patients do not receive optimal CVRM or fail to meet their target levels.[12] Thereby, it cannot be excluded that low therapy adherence biased the results leading to an underestimation of the possible beneficial effect of CVRM. Another hypothesis includes that CVRM has no effect on the long-term survival.[4] This could be due to the potential resistance of AAA patients to classical CVRM, as risk factors for AAA disease differ from traditional atherosclerotic risk factors.

At last, the finding of this thesis that there were no differences in excess mortality rates between age categories, implies that the existence of an AAA reflects overall vulnerability, resulting in an inevitable high mortality risk, regardless of whether a patient is 65 or 85 years old (**Chapter 4**). Therefore, future studies should focus on exploring the high sex-dependent excess mortality, and strategies to reduce accompanied comorbidity risks.

III: Women with an AAA have a profoundly impaired prognosis

AAA disease associates with a well-known sex-disparity, with higher short- and long-term mortality rates in women after elective repair.[13] The short-term mortality deficit of women is most pronounced after open repair, as mortality rates with EVAR are lower and more comparable to men. Given that women are at higher risk to undergo open repair, the high mortality rates have far-reaching consequences for medical decision-making. **Chapter 5** consisted of an in-dept exploration for the reason of this high procedural mortality of women after open repair. Results identified intestinal ischemia as the main contributor (44%) for procedural mortality after elective open repair in women. This observation aligns with other reports identifying female sex as independent risk factor for the development of intestinal ischemia after aneurysm repair. [14] The reason for this association, however, remains unclear. Possible hypotheses include selection bias (selection of more complex patients considered unsuitable for EVAR undergo open repair), anatomical differences (women have smaller vessel diameters, more angulation, less resilient mesenteric vascularization), and procedural aspects (women undergo more suprarenal clamping).[15,16,17]

In **Chapter 3** and **Chapter 4**, we aimed to evaluate the long-term excess mortality, with a specific emphasis on the outcomes of women. The data demonstrated an alarmingly poor long-term prognosis for women, with a doubled disease-specific excess mortality compared to men (Relative Excess Risk: 1.87 (95%CI 1.73–2.02). Direct explanations for this profound survival disadvantage of women are missing. A potential explanation includes a higher frailty profile of women. As women seem relatively protected against AAA development, eventual development of the disease may reflect a higher allostatic load.[15] However, **Chapter 4** indicated that the sex-disparity is not likely to be explained by a higher age in women at time of repair as there were no significant survival differences between age categories. Moreover, the comorbidity profile for men and women was equal, with an even lower effect size of comorbidity scores on survival in women. Therefore, the higher excess mortality of women probably does not solely relate to a higher comorbidity profile. These results are supported by a recent meta-analysis reporting fewer baseline comorbidities of women.[18] Note that this could also reflect an unawareness of (cardiovascular) comorbidities in the female population.[19] In **Chapter 4** the competing risk of death analysis of cardiovascular versus non-cardiovascular death showed that women have a higher cardiovascular risk of death, which persists for a longer time after repair compared to men. This finding suggests that women are sub-optimally treated for their cardiovascular risk, or that classical CVRM is not evenly effective in men and women.[12]

PART II: ASPECTS OF MEDICAL DECISION-MAKING

IV: Similar costs of open and endovascular aneurysm repair

Amid the concerns about the long-term durability of EVAR, the presumed higher costs after EVAR remain a matter of debate, challenging EVAR as primary option of repair.[20] However, these conclusions are interfered by time-related effects as confounding by indication, time-dependent effect modification, and asymmetrical evaluation of outcomes. The aim of **Chapter 6** was to settle the discussion with respect to excessive long-term costs for EVAR. To account for the interfering effects, we performed a

time-comparative analysis, which evaluated a period of exclusive open repair (1998-2000) with a period of established EVAR (2010-2012) while still allowing for a significant follow-up. Considering the broad spectrum of available endovascular devices and the fact that the device-costs are highly negotiable, a break-even approach was used. This point reflects the costs of an endovascular device at which EVAR and open repair reach cost equivalence. Asymmetrical evaluation of reinterventions was accounted by a systematic evaluation of all reinterventions related to the primary procedure. Although this evaluation showed clear differences in the type of reintervention, it was concluded that the number of procedure related reinterventions was similar for EVAR and open repair. Cost-equivalence for EVAR and open repair was reached at an endovascular device price of approximately 13.000, which reflects the current mean reported prices for an endovascular device.[21,22,23] Hence, for most routine repairs EVAR is not costlier than open repair until at least 5 years of follow-up.

V: Need for improved patient involvement in AAA

The developments in AAA management led to a considerable reduction in procedural morbidity and mortality.[24] As result, traditional outcome parameters as mortality- and complication rates become less discriminatory to evaluate care, and patient-derived outcomes gain importance. Thereby, as an AAA is mostly asymptomatic any intervention is likely to highly impact patients' quality of life. Considering this, to further improve care for AAA patients, it is essential to thoroughly understand the patient perspective in order to be able to adequately involve patient priorities in the evaluation of care. In an effort to systematically include the patient perspective in AAA research, there is a call for the development of Core Outcome Sets (COS).[25] COS are collections of key-outcomes, including the patient perspective, that are recommended to be reported in future research.[26] Today, studies addressing the patient perspective generally rely on quality of life (QoL) as its quantitative equivalent. **Chapter 7** consisted of a scoping review, which aimed to provide an overview the currently used quality of life (QoL) tools in AAA repair and to evaluate whether these tools adequately reflect the patient perspective and could therefore be incorporated in COS.[27,28] It is concluded that the patient perspective of AAA patients is mainly evaluated by general quantitative QoL scales (88%), such as the SF-36 (48%) and EQ-5D (24%). It was shown that these scales poorly align with the patient perspective. Efforts are made for disease-specific QoL tools (AneurysmDQol, AneurysmSRQ, AneurysmTSQ), which better align with the patient perspective, but still lack some important aspects. Hence, it was concluded that there is currently no established tool that fully captures all aspects of the patient perspective on QoL. To fulfill the need for COS a more comprehensive understanding and overview of the patient perspective is warranted.

FUTURE PERSPECTIVES

This thesis showed that over the past 25 years the management of AAA care has clearly improved from a surgical perspective. This is evident through lower procedural mortality rates and a broader spectrum of patients eligible for elective repair. However, despite these advancements, challenges remain concerning the severely impaired long-term mortality of AAA patients after elective repair, the profound survival disadvantage of female AAA patients, and inclusion of the patient perspective in the evaluation of care.

How to answer future research questions. The role for alternative study designs.

This thesis revealed that, despite several developments in AAA management, long-term survival of AAA patients has not changed over the past 25-years. In fact, the long-term life-expectancy of AAA patients remains severely impaired after elective repair. Since the main goal of elective AAA repair is to prolong life-expectancy by preventing aneurysm rupture, the persistent high long-term excess mortality questions the overall benefit of elective repair when weighted against the possible risk of rupture. Furthermore, the reason for the persistently low long-term excess survival remains unknown, particularly regarding the role of cardiovascular risk management (CVRM).

To address these issues new research strategies are required. Currently, randomized controlled trials (RCTs) are considered to provide the highest quality of evidence.[29] However, RCTs are limited, as they do not represent the real-world patient population due to strict inclusion criteria, are timely with a limited follow-up, are costly, and are considered unethical for a variety of research questions. For example, it is considered unethical to randomize between elective repair and no repair, making it impossible to evaluate the true survival benefit of elective repair. On the same note, current CVRM practice does not allow to randomize between optimal CVRM and no CVRM. Moreover, due to the low number of events, sufficient patient enrollment is impractical. Due to limited patients at risk, RCTs are underpowered to identify optimal treatment strategies for specific subgroups, such as women. Hence, new research strategies are eagerly anticipated.[30]

In the recent years, several alternative RCT designs have been introduced, such as stepped-wedged randomized controlled trials, registry based randomized controlled trials and trials-within-cohorts.[31] The use of these innovative trials designs shows promising results in overcoming the limitations of RCTs in surgical research.[32,33,34,35] Consequently, large (population-based) datasets will play an important role in the future when correctly handled and interpretated. Thereby, these datasets can also contribute to reflect towards one's own clinical abilities. Currently, quality audits serve as the basis for clinical reflection. By linking quality audits with large databases, not only the registration burden can be reduced, but also insight can be gained into variables not captured in current quality registries or variables with a low event rate. For example, in the Netherlands, the Dutch Surgical Aneurysm Audit provides valuable (pre) operative information, but lacks long-term survival data and detailed patient characteristics.[36] Linking multiple registries with a correct handling of them will provide meaningful information for evaluating care in the future.

Patient frailty: daily practice vs. research. The need for an unified frailty measurement.

One aspect highlighted in this thesis is the importance of adequately characterizing and evaluating the impact of patient frailty on outcome measures in AAA research (**Chapter 3** + **Chapter 4**). This is particularly important in AAA disease, given that the patient population consists of primarily older adults with multiple (chronic) comorbidities. Additionally, with the introduction of EVAR more patients whom were previously deemed at too high risk for open repair are now being considered for repair. From a clinical perspective, the assessment of patient frailty will enhance pre-operative risk stratification

and empower clinicians to make informed decisions regarding the appropriate type of procedure or to determine when a procedure is likely to be futile.

Although the importance of patient frailty is widely acknowledged; the challenge lies in the fact that there is currently no consensus on how to best assess it. Interestingly, while decisions on patient frailty are made on a daily basis in the clinic, frailty assessment in research is heterogenous and inconsistent with clinical results.[37,38,39] The absence of a standardized definition and measurement tool for frailty poses a significant challenge to ongoing research and clinical practice. To establish a unified frailty assessment further research is needed. Firstly, a scoping review should be conducted to provide an overview of the currently employed frailty tools in AAA research, examine their correlation to clinical outcomes, and asses their predictive value. Secondly, it would be particularly interesting to investigate how vascular surgeons determine patient frailty (eyeball test) and identify differences between the surgeon's eye and currently employed research tools.[40] This could be accomplished by a Delphi study. With the information obtained, a prospective study can evaluate which variables are suitable for frailty assessment in AAA research. By addressing these challenges, we can take significant steps to establish new, unified frailty measurements that are universally applicable, clinically relevant, and associate with clinical outcomes.

Female patients: disadvantaged every step of the way.

The severely impaired long-term life-expectancy of women after elective AAA repair is perhaps the most alarming finding of this thesis. In AAA disease, a clear sex-disparity exists at all stages of disease. While women have a lower prevalence of disease, they develop an AAA at older age, experience higher rupture rates at lower diameters, and exhibit profoundly higher short- and long-term mortality compared to men.[41,42] Furthermore, women are banned from screening programs, which probably lead to an accumulation of risk factors before AAA presentation. Giving the higher prevalence of AAA in men, it is not surprising that most evidence is derived from studies that underrepresent women. In fact, less than 5% of trial population is female.[43] As result, current guidelines and care strategies clearly leave women at a disadvantage. To optimize AAA care for women, a better understanding of the sex-disparity in AAA disease is warranted. This necessitates the establishment of sufficiently powered cohorts of women, which can be achieved through international collaboration among clinical centers, databases, and vascular registries along with standardized monitoring and outcome reporting.

These efforts will enable us to address several ongoing challenges related to female AAA patients. One primary challenge is to evaluate the reason behind the sex-dependent long-term mortality deficit in women. While this is generally attributed to women's pre-operative condition, this thesis demonstrates that the sex disparity cannot be solely explained by women's higher age or comorbidity profile at time of repair (**Chapter 4**). However, based on the (cardiovascular) literature, the recognition of comorbidities in women may be less straight forward and currently overlooked.[44] This is supported by the observation that women tend to have a more extensive vascular disease with a higher prevalence of concomitant thoracic aortic aneurysms.[45] This may call for a different approach of pre-operative screening for women. Moreover, it would be of interest to assess women with AAA in conjunction with other cardiovascular

diseases to determine whether the significant sex-disparity is specific to AAA or extends to the broader female cardiovascular population in general.
Another challenge is the ongoing scientific uncertainty regarding the surgical threshold for women. It is hypothesized that a lower surgical threshold for women would prevent accumulation of risk factors, broaden the eligibility for EVAR, and reduce the risk of rupture.[46,47] However, the finding that women face a high procedural mortality risk, particularly after open repair (30-day mortality of 12%) (**Chapter 5**) challenges a lower surgical threshold, which potentially put women at risk of death by performing a prophylactic procedure. Furthermore, the result that women have a severely impaired life-expectancy after repair (**Chapter 3** + **Chapter 4**) questions the overall survival benefit of a lower threshold. Consequently, a randomized trial seems inevitable at this point.[46]

Cardiovascular death and events. Consider it a dynamic process.
This thesis showed that the progressive implementation of CVRM did not alter the cardiovascular mortality risk, nor impacted overall long-term life-expectancy of AAA patients over the past 25 years (**Chapter 3** + **Chapter 4**). A clear univocal explanation for this apparent limited impact of CVRM on long-term mortality is missing.[48,49] Not surprisingly, future studies are needed to evaluate the prevalence, therapeutic effect, and therapy adherence of CVRM in the AAA population.

As mentioned before, adaptive trials designs can be employed to evaluate the therapeutic effect of CVRM. One important aspect to consider is that studies conducted in the general cardiovascular population indicate that while CVRM clearly reduces or postpones cardiovascular events, its impact on overall (cardiovascular) survival is marginal.[50] In this thesis, the primary focus was on long-term survival. Thus, although an effect of CVRM on cardiovascular survival could not be demonstrated, there may still be an effect on cardiovascular events. Therefore, future studies should include both the effect of CVRM on cardiovascular mortality and events. In this, it is crucial to acknowledge that cardiovascular mortality and events are competitive and thereby a dynamic process. To be more specific, a patient might experience numerous events before dying (e.g. non-fatal myocardial infarction), whereas a patient who primarily dies is no longer at risk for events. As a result, a statistical model that simultaneously considers events and mortality is required. Multistate models represent stochastic processes in which patients can occupy different intermediate states (disease conditions) before reaching the final outcome. Thereby correcting for competing risks (e.g. malignant death over cardiovascular death).[51,52] Therefore, the application of multistate models is essential to simultaneously evaluate the effect of CVRM on cardiovascular events and mortality.

Patient perspective. The need for qualitative research.
A critical component in improving care for AAA patients is to involve the patient itself. **Chapter 7** shows that the patient's perspective is not yet adequately captured in the research of AAA care and that to adequately involve the patient in AAA research, a more thorough understanding of the patient perspective is needed. Qualitative research provides the opportunity to explore the patient perspective in-depth.[53] This will allow clinicians to appraise patient preconceptions, treatment experience, quality of

life, illness understanding, and subsequent need or desire for information.[54] Therefore, moving forward qualitative research must be the cornerstone in AAA research.

To illustrate: a noteworthy aspect that has emerged from this thesis is that a most important facet for patients in their care is their perceived need for information (**Chapter 7**). While this may appear obvious, studies show a clear discrepancy between the information that clinicians consider important and subsequently provide, and what patients truly find important.[55] By employing qualitative research to explore the information needs of patients, we can better align the perspectives of patient and clinician and deliver information that is both clinically relevant and relevant for patients.[56]

Figure 1. Future perspectives in AAA research

- We must critically appraise the reason for the high sex-specific long-term excess mortality.
- There is a need for alternative study designs to answer future research questions.
- Large population-based datasets are essential not only to evaluate real-world patient practice but also to reflect towards one own's clinical performance.
- We need a unified patient frailty tool which is clinically relevant but also practical for (retrospective) research.
- To improve outcomes for female AAA patients, a more women centered approach is necessary.
- The prevalence, adherence and therapeutic effect of CVRM on cardiovascular mortality and events must be evaluated for the AAA population.
- Cardiovascular mortality and events should (statistically) be considered a dynamic process.
- The patient perspective must be better understood and incorporated in AAA care.
- Qualitative research must be a cornerstone in AAA research.

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