Chapter 8

Summary, Discussion, and Future perspectives
This thesis presented the preparation, initiation, and interim results of the Heart-ROCQ PROBE study, with the overall aim of improving and understanding cardiac rehabilitation before and after cardiac surgery in order to prevent postoperative complications and improve functioning and postoperative health-related quality of life (HR-QoL). As such, this thesis demonstrated the feasibility of cardiac rehabilitation before and immediately after cardiac surgery and provides an important basis for continued research into the effectiveness and underlying working mechanisms of pre- and postoperative cardiac rehabilitation. The implementation of preoperative and postoperative cardiac rehabilitation could potentially be an effective intervention in response to increasing healthcare demands and economic costs. In this chapter, the main findings of the previous chapters are summarised and discussed in the context of methodology, clinical implications, and future perspectives.

**SUMMARY OF MAIN FINDINGS**

Physical fitness is key to rehabilitation in patients undergoing cardiac surgery. An important indicator of physical fitness is muscle strength. Despite the acknowledgement of a clear positive association between grip strength and HR-QoL in elderly people\(^1\), this association has yet to be confirmed in patients undergoing artery bypass grafting (CABG)\(^2\). However, it has been observed that poorer grip recovery (i.e., a larger decline in muscle strength after surgery) may be associated with a higher risk of post discharge complications within 30 days after discharge, independent of surgical risk\(^3\). Therefore, this thesis first evaluated the different trajectories of handgrip strength on postoperative HR-QoL (**chapter 2**). Our results showed that a relative improvement in weight-normalised hand grip strength (i.e., values at six months divided by baseline) was associated with improved postoperative HR-QoL at six months after CABG. Furthermore, as most muscle strength research is cross-sectional and conducted on a group level, we explored the presence of potentially clinically relevant subgroups among our study population on the individual pre- and postoperative muscle strength trajectories. Using these subgroup trajectories of muscle strength, we aimed to better understand the complex association between muscle strength and postoperative HR-QoL. Interestingly, two clinically relevant trajectories were identified: a) a “stable average” trajectory with a slight decline immediately after surgery and recovery to preoperative levels and b) a “high” trajectory with a sizeable decline immediately after surgery followed by a higher level of recovery compared to the preoperative level. As both groups differed with respect to preoperative risk factors and physiological responses to surgery, we expected that being a member of a particular group would be distinctive in relation to recovery in postoperative HR-QoL. Surprisingly, (multiple) regression analysis showed no association between muscle strength and HR-QoL. Hence, while change scores in grip strength predicted postoperative HR-QoL, trajectory subgroups did not predict postoperative HR-QoL. Thus, changes in the easy-to-measure handgrip muscle strength are clinically relevant for postoperative HR-QoL.

The muscle strength of the lower extremities is essential for daily activities,
mobility, and function. To better measure and understand the association between changes in lower extremity muscle strength and postoperative HR-QoL in future research, the Q-Force II, a custom-made, portable, isometric knee extensor strength testing device was developed (chapter 3). The Q-Force II demonstrated excellent test–retest reliability in middle-aged and older healthy adults. In addition, a low level of discomfort was experienced while performing the isometric knee contractions on the Q-Force II. For these reasons, we concluded that the portable Q-Force II is a comfortable, responsive, and relatively cheap device with excellent test–retest reliability. Evaluating the muscle strength of the patients’ lower extremities will be of additional value because it will provide further insights into overall muscle strength and its effects on, for example, hospital immobility, functioning, and general recovery.

Currently, there is a lack of knowledge regarding the feasibility and effects of aerobic exercise and resistance training in patients awaiting cardiac surgery. This may be due to the expected increase in the risk of cardiac events attributed to these activities. Consequently, preoperative guidelines are currently limited to inspiratory muscle training only. However, studies indicate that patients awaiting CABG can remain physically active during the waiting period without an increase in adverse events. Therefore, this thesis evaluated, as preparation for a randomised controlled trial, the implementation of the Heart-ROCQ-pilot programme, a combined pre- and postoperative cardiac rehabilitation programme, in cardiac patients awaiting higher risk surgery (chapter 4). Our study showed that this group can safely follow a comprehensive cardiac rehabilitation programme, including aerobic exercise and resistance training during the waiting time (i.e., prehabilitation). It is extremely promising that patients with serious heart disease were able to improve their physical outcomes based on a personalised and closely monitored exercise programme before their heart problems were surgically treated. Our study included patients with limited oxygen supplies to the heart and limited blood circulation due to (stable) coronary artery disease, valve failure, and/or aortic dilatation. These cardiovascular limitations often lead to classic symptoms such as angina pectoris, shortness of breath, or fainting. In addition, there is an increased risk of cardiac events such as myocardial infarction, aortic disruption, and possible death. Despite these notions, in our study, patients awaiting cardiac surgery were highly compliant and able to safely follow an individualised comprehensive cardiac rehabilitation programme, in which, among other activities, supervised aerobic exercise training was provided along with ECG monitoring. Moreover, an increase in the workload–to–heart rate ratio (W/beat) was observed after both pre- and postoperative rehabilitation periods, suggesting training–based improvements in cardiac function and exercise tolerance. The Heart-ROCQ programme is a unique collaboration between the Heart and Rehabilitation Centres of the University Medical Center Groningen that encourages patients to be physically active before and immediately after surgery in a safe and effective manner.

Furthermore, we were interested in whether the Heart-ROCQ programme ensured enhanced recovery after surgery. Therefore, this thesis retrospectively explored the potentially short-term postoperative benefits and unintended consequences of the
Heart-ROCQ programme regarding in-hospital complications (chapter 5). Our study indicated a reduction occurred in the risk of postoperative atrial fibrillation (AF) by remaining physically active during the waiting period prior to surgery. This decline in postoperative AF is meaningful because AF is the most common postoperative complication after cardiac surgery and is associated with longer intensive care and hospital stays, higher readmission and operative mortality, along with higher medication use and healthcare costs in the first year after surgery\textsuperscript{13–15}.

In the literature, the lack of large, high-quality controlled studies on the effect of pre- and postoperative rehabilitation in cardiac surgery patients has been broadly emphasised\textsuperscript{16–20}. Therefore, this thesis presented a study design featuring a comparison between the final Heart-ROCQ programme and standard care: the Heart-ROCQ PROBE study (chapter 6). The Heart-ROCQ PROBE study is a powered, randomised, controlled, open trial with a blinded endpoint on pre- and postoperative cardiac rehabilitation and postoperative cardiac rehabilitation. For this study, a wide range of data are systematically collected during the waiting period and during (short- and long-term) postoperative recovery. These data provide a comprehensive and clinically relevant evaluation of possible changes in physical and psychological functioning, lifestyle risk factors, work participation, and HR-QoL following pre- and postoperative rehabilitation.

To conclude, an interim analysis of the ongoing Heart-ROCQ PROBE study was performed on the first 140 patients (chapter 7). We found no early evidence of any clear negative or positive effects of the Heart-ROCQ programme compared to the control group (i.e., a regular Dutch postoperative outpatient cardiac rehabilitation programme) in the interim analysis of the blinded primary endpoint. The blinded endpoint was a composite weighted score of functional status, surgical complications, readmissions, and major adverse cardiac events (MACE). Given these interim results, the Heart-ROCQ PROBE study will continue to include a full sample of 350 patients, thus, meeting the power requirements of the composite endpoint as the primary outcome. At the time of writing, more than 250 patients have been included in the Heart-ROCQ PROBE study, and the final patient is expected to be added by 2024. Therefore, the results of the one-year follow-up measurements are scheduled for 2025.

**METHODOLOGICAL CONSIDERATIONS**

The designs of the studies in this thesis included experimental, observational, and randomised studies. Data were collected retrospectively as well as prospectively. Several advantages and disadvantages of each design and the methodological considerations related to the interpretation of the results are discussed below.

The first consideration is the representativeness of the included study participants. The advantage of our retrospective analysis of the prevalence of in-hospital postoperative complications (chapter 5) was that it provided an overview of all the patients rather than just those who wanted to or could participate. This overview of all the patients resulted in a higher level of generalisability concerning the results. However, the representativeness was possibly lower in our prospective study on time
courses of muscle strength (chapter 2) and in our study on the feasibility of the Heart-ROCQ-pilot programme (chapter 4). A lower representativeness was possible because, generally, patients who are less physically fit or less ill are more likely to participate in clinical studies or cardiac rehabilitation programmes than those who are fitter or more seriously ill21. According to the overload principle of training, a minimum intensity or threshold is required to challenge the body sufficiently to improve physical fitness22. If more patients who were less physically fit or more ill were included in the study in chapter 4, then the physical improvements shown in chapter 4 may have been higher because the training threshold required to improve physiologically is generally lower in these patients22. In our prospective study on the time courses of muscle strength (chapter 2), the study group showed higher levels of grip strength as well as HR-QoL at baseline and at six months compared to the literature23–26. Moreover, the tendency for lower preoperative grip strength values and HR-QoL in the dropouts than in the included patients suggests some selection bias. It is possible that an analysis with dropouts would have a wider spread (owing to an increase in the lower values). This subsequent increase in variance could lead to more distinct trajectory groups, which may better predict the postoperative HR-QoL. Conversely, the group consisted mainly of male patients of an older age with higher BMIs, which are typical characteristics of patients undergoing CABG, indicating a representative population in our study. To better understand the generalisability of our results and account for selection bias, a registry was added to the Heart-ROCQ study design (chapter 6). In this registry, data on routine care were collected from patients who were not willing to participate but provided written consent for the use of their medical data. In this way, potential differences between patients who participated in the Heart-ROCQ PROBE study and those who did not can be further explored.

The second consideration is that, throughout this thesis, we used various adequate and advanced statistical techniques to explore the data at a deep level. First, we used latent class growth mixture modelling (LCGMM) to identify clinically relevant subgroups based on grip strength changes (chapter 2). In this way we obtained valuable insights into how grip strength developed over time within clinically relevant subgroups. Applying this type of advanced statistical technique more frequently in future research will expand our knowledge, which will help to better adapt interventions to individual patients. Second, we monitored training characteristics during bicycle and strength training sessions that provided insights into patients’ physical fitness or exercise tolerance, without determining oxygen consumption (chapter 4). In addition, data of the training characteristics reflected the actual executed exercise protocol, which is paramount for improvements in physical fitness. Third, as previously mentioned, we conducted a propensity score analysis to improve the balance between the prehabilitation group and the control group (chapter 5). Improving the balance between the prehabilitation group and control group resulted in a reduction in bias27.

The third consideration is that as a powered, randomised, controlled, open trial with a blinded endpoint, the Heart-ROCQ PROBE study has several strengths. First, to our knowledge, the Heart-ROCQ PROBE study is the largest randomised, con-
trolled trial focusing on the effects of pre- and postoperative cardiac rehabilitation in patients awaiting cardiac surgery. Hence, this study contributes to the need for large, high-quality controlled trials. This need has been emphasised in many reviews evaluating the effects of prehabilitation in major surgeries, including open-heart surgery16–20. Second, the Heart-ROCQ PROBE study has broad inclusion and exclusion criteria, thereby examining the effect of cardiac rehabilitation on the entire cardiac surgical group. Most studies on cardiac rehabilitation have focused patients with coronary artery disease28, 29. The majority of these patients underwent a percutaneous intervention (PCI) or suffered from a myocardial infarction (MI). In addition, prehabilitation studies focusing on cardiac surgical patients have mainly included CABG patients7–10. Third, the primary and secondary outcomes selected in the Heart-ROCQ PROBE study were in line with the trends observed in cardio-thoracic clinical care. For example, postoperative complications, serious adverse events, and HR-QoL have been selected as the primary outcomes since major declines in postoperative mortality have been noted in recent decades. Moreover, an economic evaluation will be conducted since cardio-thoracic clinical care is challenged by increasing health care costs. If the Heart-ROCQ programme is proven to be effective in reducing atrial fibrillation or other postoperative complications and serious adverse events, it is expected to be cost-effective in the long term and thus of interest to policymakers and healthcare providers. Fourth, in contrast to other cardiac (p)rehabilitation studies8–10, 18, detailed information about the training load (i.e., for bicycle training: external workload, heart rate response, and rate of perceived exertion using the Borg Scale; and for strength training: sets and repetitions) of the Heart-ROCQ programme and regular cardiac rehabilitation programme were collected in the Heart-ROCQ PROBE study. These data, together with the assessed and potential moderators, enable in-depth analyses, such as multilevel analyses and latent class modelling, which have been proven to identify meaningful subgroups of individuals over time24 and will provide new insights into physical training and recovery patterns before and after cardiac surgery. In this way, responders and non-responders to pre- and postoperative cardiac rehabilitation can be identified, and factors associated with better outcomes can be further explored. The development of treatment guidelines for clinical practice, especially regarding (p)rehabilitation programmes as part of routine surgical treatment, is listed as an important aim in the government agreement ‘Integraal zorgakkoord: Samen werken aan gezonde zorg’30. The Heart-ROCQ PROBE study has a robust design and will provide additional knowledge about optimisation before and optimal recovery after elective cardiac surgery. This knowledge will contribute to the development of (p)rehabilitation guidelines as part of routine surgical treatment.

CLINICAL IMPLICATIONS

All the studies in this thesis are motivated by the aim of improving the clinical care of patients undergoing cardiac surgery. Several implications for clinical care can be deduced from our studies, as discussed below.

First, changes in grip strength can serve as an indicator of physical fitness and
functioning to help stratify risk or determine the need for necessary interventions, such as cardiac (p)rehabilitation, in cardio–thoracic clinical care. Our results confirm, in line with the study of Fu and colleagues (2019)\(^3\) that assessments of changes in grip strength are predictive of surgery outcomes (chapter 2). The stratification of risks and tailoring of interventions are increasing in importance since more elderly patients and patients with comorbidities are listed on the waitlists for cardiac surgery\(^31\). Possibly for logistical reasons, measurements of physical fitness or muscle strength are currently not standard practice in surgical clinical care. In contrast to measuring maximum oxygen consumption (i.e., the gold standard for physical fitness), grip strength can easily be measured with an inexpensive, hand-held dynamometer, which requires little training or space. Therefore, in principle, it could be administered by any member of the (para–) medical staff and introduced into every outpatient clinic and hospital department. Moreover, handgrip strength is an important marker of frailty and has high prognostic value for declines in cognition, mobility, functional status, and mortality in the elderly, as well as in patients with heart failure\(^32, 33\). Determining grip strength, pre- and postoperatively (short and long-term), will thus provide more insights into the pre- or postoperative physical status of the patient, which will help practitioners with risk stratification and treatment choices regarding cardiac rehabilitation and surgery.

Second, the findings of this thesis contribute to the shift from curative care following cardiac surgery to (secondary) prevention before cardiac surgery. By implementing cardiac rehabilitation before (i.e., prehabilitation) and soon after cardiac surgery, earlier attention is paid to physical, psychological, social, and behavioural statuses. Preoperative risks and recovery risks soon after surgery can be recognised and treated earlier, thereby possibly preventing (further) poor recovery. An early focus on these multi-disciplinary aspects might thus help to regulate the increase in patients with higher numbers of comorbidities registered on the waitlist for cardiac surgery\(^31\). Within the Heart–ROCQ programme, cardio–thoracic care is organised in such a way that the patient, both before and after surgery, is treated in one multi-disciplinary team specialised in cardiac rehabilitation. The advantage of this is that although the treatment is provided by practitioners from different disciplines (e.g., physical therapists, dieticians, psychologists), it is nonetheless coherent. In addition, patients do not experience separate waiting times per discipline. It also has the advantage of the practitioners knowing the preoperative status of the patient. Knowledge of the preoperative status will enable faster recognition of delays in (e.g., cognitive or physical) recovery after surgery. This knowledge allows treatment to be better tailored to the individual patient, for whom a relative recovery compared to their preoperative status is more important than a recovery relative to a group average.

Third, the findings of this thesis support the advice to measure workload to heart rate ratio during the bicycle rehabilitation sessions. External workload is an important measure for daily functioning. A decline in the workload to heart rate ratio features an enhanced efficient of the physiological system as fewer heartbeats are required to perform a given external workload. Although, the exact association with
measures as cardiac function and exercise tolerance require further investigation, the
workload to heart rate ratio is a practical measure because insight into an individual's
progression is obtained without conducting additional physical tests.

Fourth, the findings of this thesis suggest that the current postoperative reha-
bilità guidelines regarding resistance training of the upper extremities might be
too restrictive (chapter 4). Our study patients commenced strength training exer-
cises approximately two weeks after surgery. These also included arm exercises that
involved the exertion of pressure on the chest (e.g., rowing, triceps dips, and chest
presses performed at low intensity, starting with median weights ranging from 4 to 7
kg). This rehabilitation strategy diverge from the current Dutch cardiac rehabilitation
guidelines in which patients are advised not to engage in strength training of the
upper extremity during the first six to eight weeks after surgery. Thus, patients who
participated in the Heart-ROCQ programme commenced strength training approx-
imately four to six weeks earlier than the current cardiac rehabilitation guidelines
suggest. Our results are consistent with previous research showing that no direct
evidence exists linking upper limb activities and sternal complications. Moreover,
the current Dutch cardiac rehabilitation guidelines regarding strength training are
inconsistent with the guidelines of the American College of Sports Medicine (ACSM),
which state that patients should be as physically active as their abilities and condi-
tions allow. Cardiac rehabilitation guidelines regarding early postoperative resis-
tance training need to be less restrictive because prohibiting movement can induce fear
of movement in patients, which will result in patients being less physically active.

Nonetheless, implementing less restrictive clinical guidelines regarding early
postoperative resistance training is possible challenging because resistance train-
ing includes a wide variety of exercises. Therefore, patient-specific and professional
guidance is required to ensure the patient's safety during the early postoperative
phase. Adams and colleagues (2006) developed a tool that classified 13 standard
weightlifting activities for cardiac rehabilitation after CABG based on safety and
effectiveness. Additionally, for each activity, the tool indicated how long after CABG
the specific exercise could be performed. This classification was based on a compre-
hsive kinesiologic analysis (i.e., analysis of the anatomy, physiology, and movement
patterns of the exercise). Such tools can be helpful in implementing strength training
in a safe and effective manner immediately after surgery. This tool was developed for
patients undergoing CABG with median sternotomy. As the safety and efficacy scores
would be different for patients undergoing valve or aortic surgery, and especially
those undergoing new surgical approaches such as the lateral approach and mini
sternotomy, research is needed to expand the tool to a wider array of cardiac surgical
treatments. Moreover, the tool is currently limited to 13 exercises. Thus, the tool
should be expanded to include more exercises in future research, such as seated leg
press or rowing. Using such tools could thus be helpful in making pre- and postoper-
ative rehabilitation guidelines regarding resistance training of the upper extremities
less restrictive in a safe manner.

Fifth, we observed the disadvantage of care being organised far from home, even
in the Netherlands. Approximately 6% of the eligible patients could not participate in the Heart-ROCQ-pilot programme and Heart-ROCQ PROBE study because of travel limitations (chapters 4 and 7). In most patient groups, rehabilitation can be organised closer to home when implemented in second-line hospitals, primary healthcare, or as a home-based/remote programme. However, to organise preoperative rehabilitation in an individualised, safely monitored, and standardised way, a number of criteria must be met. First, prehabilitation should be provided without a waiting period, which is necessary to avoid unnecessary postponement of the surgery. Second, physiotherapists may not have experience in training patients scheduled for cardiac surgery and may require additional training or specialisation to provide aerobic and strength training for these patients. Furthermore, there should be access to well-instrumented practice using bicycle ergometers with cardiac surveillance (e.g., ECG and blood pressure monitoring), power output information, and accurate dose characteristic monitoring. Third, safety must be ensured when providing remote aerobic exercise or strength training before and immediately after surgery. To date, there is little published data to confirm the safety of such training. Research on the effects of home-based cardiac rehabilitation programmes was mainly focused on younger patients who underwent percutaneous intervention with low residual cardiovascular risk. Recently, a pilot study showed that a home-based prehabilitation programme, which consisted of balance exercises and some strength training exercises, was feasible in patients undergoing CABG or valve surgery. Hence, more well-powered randomised controlled trials are needed to confirm the feasibility and safety of home-based or remote programmes before and immediately after cardiac surgery.

Moreover, future research should consider the role of barriers to physical activity when implementing home-based or remote programmes. Next to psychosocial factors, such as fear, uncertainty, and lack of motivation, perceived support (from fellow patients or care givers) might also be important. The adherence of the patients who participated in the Heart-ROCQ programme was remarkably high (> 83%, chapter 3). Patients even returned immediately to the prehabilitation group when their operation was postponed at the last moment. This may have been because they felt supported by their fellow patients and/or care givers. Moreover, patients awaiting surgery and patients who had just undergone surgery trained together. This may have given patients a better idea about their recovery after the operation and facilitated them to be more physically active. In summary, there are still many questions to answer in future research in order to provide a cardiac-specialised, comprehensive, multi-disciplinary pre- and postoperative rehabilitation programme, such as the Heart-ROCQ programme, that can be provided closer to home.

Sixth, a disadvantage we noticed was that patients participating in the Heart-ROCQ programme received clinical and preventive support only up to eight weeks after surgery. The Heart-ROCQ programme could be improved by prolonging it with a remote or home-based cardiac rehabilitation programme, with the aim of maintaining long-term physical activity. A remote or home-based programme is a low-threshold method (e.g., no transport problems, less costs for the patient) for when the patient
has resumed daily, work, and/or social activities. Therefore, a remote or home-based rehabilitation programme could be an affordable way to encourage patients to remain physically active. Moreover, activity trackers and wearable technology could be used to understand patients’ objective physical activity and help physiotherapists and cardiologists provide adequate feedback to support a physically active lifestyle.

**FUTURE PERSPECTIVES**

As previously mentioned, the Heart-ROCQ PROBE study will provide new insights into the effects and mechanisms of pre- and postoperative cardiac (p)rehabilitation. The results of this study will not only provide answers, but also new questions for future research. In anticipation of the results of the Heart-ROCQ study, I would like to share the following suggestions for future research in advance.

**Prehabilitation: what works for whom and when?**

As the evidence supporting prehabilitation is still growing\(^\text{10,43–45}\), future research is expected to gradually focus less on whether prehabilitation works and more on what prehabilitation works best for whom. It has been suggested that prehabilitation should only be provided to patients with poor preoperative status because these patients are at higher risk for poor postoperative recovery and might therefore benefit more from prehabilitation\(^\text{6,46,47}\). However, the results obtained in a prehabilitation study in CABG patients with broad inclusion criteria showed that patients accepted for CABG generally have a lower physical fitness than healthy age-matched references, thus, implying a lower level of preoperative physiological reserve\(^\text{10,48,49}\). Furthermore, declines in functional status during an unsupported waiting time were shown in low-risk CABG patients, whom the author indicated to be relatively healthy\(^7\). Other studies that showed the harmful effects of the waiting period had broad inclusion criteria\(^\text{50,51}\).

These results suggest that the entire cardiac surgery population could benefit from prehabilitation, but the optimal timing, duration, frequency, intensity, and form (e.g., type of prehabilitation or exercise) are likely to differ among individuals. Consequently, providing the right type of prehabilitation to this heterogeneous population will be challenging and require systematic observational monitoring and, hence, research on the effectiveness of distinct types and strategies of prehabilitation. Focusing on the physical component of prehabilitation, various training modalities of strength and aerobic exercise training with different intensity strategies could be explored. Identifying responders and non-responders will also be an important aspect of future research in this context. In the Heart-ROCQ programme, we provided low intensity training for all patients, as not much was known about the safety of aerobic exercise training during prehabilitation in this higher risk group. Given the feasibility of the Heart-ROCQ programme, it will be interesting to explore the feasibility of more efficient training methods. High intensity interval training (HIIT) can induce physiological improvements similar to traditional endurance training in the short term with a lower total exercise volume and training time commitment and would thus be attractive for prehabilitation\(^{52}\). Indeed, HIIT has been shown to
be effective in patients undergoing lung cancer surgery\textsuperscript{53}. HIIT also seems safe and resulted in greater improvements in peak oxygen uptake in older patients with stable coronary disease and heart failure\textsuperscript{54}. HIIT protocols have been modified for clinical populations to include less strenuous exercise intensities compared to those used for athletes\textsuperscript{54}. The standard intensity of 85\% of HR peak is the same intensity used in a pilot prehabilitation study in patients awaiting CABG\textsuperscript{9}. This intensity may also be feasible for patients awaiting cardiac surgery who are better at tolerating physical training, such as patients with mitral valve impairments.

In addition, it would be interesting to examine whether optimal distribution of the training intensity could optimise the physical component of prehabilitation. Training-intensity distribution is generally recognised as an important factor in training progression in elite athletes\textsuperscript{55}. Training models, such as the polarised training model (a large volume, \~75\%, of training below the first lactate or ventilatory threshold combined with significant doses of training with loads eliciting 90\%--100\% of maximal oxygen uptake), could be modified (i.e., lower maximal loads) for patients awaiting cardiac surgery\textsuperscript{55}. As elite athletes time their optimal performance for competition, whether such a pacing strategy is beneficial when patients time their optimal performance for the surgery could also be explored.

Another important question for future research is how to optimally estimate exercise capacity prior to prehabilitation. Estimating exercise capacity is necessary to determine the optimal and safe training intensity for a patient starting with exercise. A direct measurement of the maximal oxygen can be conducted, but is often not advisable in older patients with heart disease\textsuperscript{56,57}. In addition, such tests may due to practical reasons such as time or no resources to measure oxygen not always be feasible in everyday clinical settings. Another way to determine maximal exercise capacity is using a submaximal test. The maximal exercise capacity is then calculated using a formula, which is based on the assumption of a simultaneously, linear increase in heart rate, workload, and oxygen uptake\textsuperscript{57,58}. However, such formulas or nomograms are often developed based on healthy adults and it is not investigated whether those directly can be applied to clinical populations, such as patient awaiting cardiac surgery\textsuperscript{57}. The ergometry test protocols used in previous prehabilitation studies differ from each other\textsuperscript{9,10,59}. It would be interesting for further research to explore which protocol is optimal with regard to practicality, determining optimal training intensity, and safety (of the stress test and subsequent prehabilitation sessions).

It would also be interesting for future research to investigate the optimal time to initiate prehabilitation. Figure 8.1 visualises the general timeline from the moment an elective patient seeks care until surgery. While in most studies the waiting time is defined as the period between the date of acceptance for surgery (final decision) and the day of surgery (Phase C in Figure 8.1\textsuperscript{59}), a patient experiences the waiting time from the moment of seeking care\textsuperscript{59}. The period between the patient seeking care and being accepted for surgery (Phase A and B in Figure 8.1) is thus understudied. It would therefore be interesting to explore when patients begin to experience the first negative signs of the waiting time (defined from the patients’ perspective). For
this patient group, it would then be particularly important to ascertain whether and when patients experience barriers to being physically active. Such barriers are, to my knowledge, only explored after cardiac surgery. Furthermore, it would be interesting to explore when patients’ feelings of stress and anxiety increase. Additionally, factors causing these negative effects as well as patients’ readiness and need for prehabilitation could be further explored.

Another point of interest would be to explore the benefits of initiating prehabilitation before the date of acceptance for surgery. As visualised in Figure 8.1, the decision to operate requires careful consideration (phase B in Figure 8.1). To make an adequate decision, further examinations, such as echocardiography, a CT scan, an MRI, coronary angiogram, or consultations (for example, with a surgeon, lung specialist, or geriatrician) are often required, which also take time to schedule. For example, patients with an indication for valve surgery often have to undergo coronary angiography before...
the final decision regarding surgery is made (i.e., valve or valve combined with CABG). In addition, for patients with high-risk profiles, more information is often needed to determine whether the patient’s condition is operable. Commencing prehabilitation from the time of diagnosis or surgical indication, rather than the time of the final treatment decision, will prolong prehabilitation and thus give patients more time to optimise their mental and physical health before surgery. Perhaps more importantly, beginning prehabilitation earlier may better prevent the deterioration of mental and physical health. Another advantage is that the characteristics of a high preoperative risk profile can be recognised earlier and in more detail during the guidance of the (para-) medical staff of the prehabilitation programme. It would therefore be interesting in some cases to explore the benefits of involving the (para-) medical staff of the prehabilitation programme in the decision-making process regarding the surgical treatment. A future prospect might even be to provide prehabilitation to inoperable patients (e.g., patients with severe obesity or are deconditioned), who may become more resilient through a more extensive period of prehabilitation, possibly allowing them to undergo surgery. A consequence of commencing prehabilitation earlier may be that some patients participate who are ultimately not accepted for surgery. If this is the case, prehabilitation may well function as a good conservative treatment. Implementing prehabilitation at an earlier stage might therefore be a step forward in cardio-thoracic clinical care by immediately addressing physical, psychological, social, and behavioural treatment in addition to medical care.

Another important aspect with respect to the timing of prehabilitation for future research is whether in some cases it would be beneficial to prolong prehabilitation and thus ‘postpone’ the surgery. This is a complex decision that must consider multiple factors. However, this type of decision is more common in cardio-thoracic treatment. For example, in patients with aortic stenosis, the risks of conservative management (e.g., sudden cardiac death, progressive left ventricle remodelling, and fibrosis) are weighed against the risks of valve replacement and the finite lifespan of a bioprosthetic valve or the disadvantages of mechanical valves (i.e., anticoagulation with increased risks of bleeding)\textsuperscript{61}. In these situations, the best timing of surgery is

\textbf{Figure B.2} A surgery can be postponed when it is proven that the benefits of prehabilitation exceeds the risks related to delaying the surgery.
the point in the disease course when the benefits of valve replacement exceed the risks related to native valve disease. This principle can also be applied in planning prehabilitation and surgery. A surgery can be postponed when it is proven that the benefits of prehabilitation exceed the risks related to delaying the surgery (Figure 8.2). In order to support evidence-based decision making on this aspect, future research should investigate the dose–response for different durations and types of prehabilitation. Additionally, how such response is related to better recovery should be investigated. To gain more knowledge on this, it is required that, in parallel to measuring outcome measures, the dose of the prehabilitation programme (type, frequency, duration, and intensity) and change in modifiable risk factors, are measured consistently in future research.

To ascertain which (p)rehabilitation programme works best for whom, powered observational and randomised trials are required to compare the previously mentioned aspects. The Heart-ROCQ PROBE study was limited by its single-centre design, thus, requiring more time to reach the desired sample size of 350 and potentially making the results less generalisable. The advantage of a multi-centre study is that the data can be collected more rapidly. In addition, the use of a multicentre study would also facilitate targeted research into the differences in the benefits of prehabilitation by diagnosis group (e.g., coronary artery disease, aortic stenosis, mitral valve insufficiency) or in smaller populations within cardiac surgery, such as females. It should be noted, however, that such multicentre studies are logistically much more complex to set up, and special consideration should be given to the standardisation of the intervention management and data collection, since these would be conducted by more people. However, these aspects can be managed through effective cooperation between the hospitals.

**Prehabilitation to target postoperative cognitive decline and preoperative inflammatory status**

In the Heart-ROCQ PROBE study, we were unable to include all the relevant outcomes that can be targeted with prehabilitation and rehabilitation soon after surgery. Future research could focus on whether such rehabilitation is beneficial in preventing postoperative cognitive decline (POCD). Depending on the timing and measurement of POCD, an incidence rate of 21–34% has been reported after CABG or valve replacement. In the previous decade, more evidence has been collected regarding the association between exercise and cognition. In addition, some evidence suggests that cognitive impairment can be improved with cardiac rehabilitation after surgery. In line with this, it would be interesting to investigate the possible anti-inflammatory effects of prehabilitation on the pre- and postoperative inflammatory state. Inflammation is a common etiological factor for postoperative complications such as POCD and AF in patients undergoing cardiac surgery.
Conclusion

This thesis has shown that implementing aerobic exercise and resistance training in a pre- and postoperative cardiac rehabilitation programme in patients undergoing elective cardiac surgery is feasible and that such a programme could contribute to the prevention of postoperative complications and major adverse events by improving patients' preoperative status and reducing the burden of physical inactivity in clinical care before and after cardiac surgery. However, the results of this thesis should be interpreted as preliminary outcomes and need to be confirmed by the final results of the Heart-ROCQ PROBE study. This study will provide new evidence regarding the effectiveness of pre- and postoperative cardiac rehabilitation in patients awaiting cardiac surgery, which will help counteract the adverse effects of physical inactivity before and after cardiac surgery. In the future, cardiac rehabilitation guidelines should not only focus on restrictions and precautions regarding exercise-based cardiac rehabilitation but should also mention the possibility of being physically active. In addition, future research should provide standardised research on the effectiveness of distinct types and strategies of prehabilitation to better tailor prehabilitation to the individuals within this heterogeneous population.
References


SUMMARY, DISCUSSION, AND FUTURE PERSPECTIVES


