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Optimising patient discharge and follow-up after surgical aortic valve replacement to reduce readmissions and improve patient-reported outcomes

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2 Abbreviations

AHA: American Heart Association

ANCOVA: Analysis of Covariance

AS: Aortic Stenosis

AVRre: Aortic Valve Replacement readmission

CABG: Coronary Artery Bypass Surgery

CONSORT: Consolidated Standards of Reporting Trials

COPD: chronic obstructive pulmonary disease

CPH: Cox Proportional Hazard

ESC: European Cardiology Society

EQ-5D-3L: EuroQol

GP: General Practitioner

HADS: Hospital Anxiety and Depression Scale

HF: Heart Failure

HRQoL: Health-Related Quality of Life

ICU: Intensive Care Unit

ITT: Intention-To-Treat analysis

LHL: Landsforeningen for Hjerte-og Lungesyke (Norwegian National Association for Heart and Lung Disease)

LMM: Linear Mixed Model

LOS: Length of stay

LVEF: Left ventricular ejection fraction

MI: Multiple Imputation

MRC: Medical Research Council

NOS: Newcastle-Ottawa Scale

OECD: Organization for Economic Co-operation and Development

OUH: Oslo University Hospital

PC: Project Coordinator

PP: Per-Protocol analysis

PREM: Patient-Reported Experiences Measures

PROM: Patient-Reported Outcome Measures

PROSPERO: International prospective register for systematic reviews

RCT: Randomised controlled trial

SAVR: Surgical Aortic Valve Replacement

SCG: Supra Coronary Graft

SCQ-16: Self-administered Comorbidity Questionnaire

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

StaRI: Standards for Reporting Implementation Studies

TAVR: Transcatheter Aortic Valve Replacement

TFU: Telephone follow-up

VHD: Valvular Heart Disease

WHO: World Health Organization

30-DACR: Thirty-day all-cause readmission

3 List of papers

This thesis is based on the following original publications, which are referred to by their Roman numerals (Papers I-V):

I. Lie I, Danielsen SO, Tønnessen T, Solheim S, Leegaard M, Sandvik L, Wisløff T, Vangen J, Røsstad TH, Moons P. Determining the impact of 24/7 phone support on hospital readmissions after aortic valve replacement surgery (the AVRre study): study protocol for a randomised controlled trial. *Trials* 2017; 18:246

II. Danielsen SO, Moons P, Sandven I, Leegaard M, Solheim S, Tønnessen T, Lie I. Thirty-day readmissions in surgical and transcatheter aortic valve replacement: A systematic review and meta-analysis. *International Journal of Cardiology* 2018; 268, 85-91

III. Danielsen SO, Moons P, Sandvik L, Leegaard M, Solheim S, Tønnessen T, Lie I. Impact of Telephone Follow-up and 24/7 Hotline on 30-day Readmission Rates Following Aortic Valve Replacement -A randomized controlled trial. *International Journal of Cardiology* 2019; Jul 30. pii: S0167-5273(18)36036-4. doi: 10.1016/j.ijcard.2019.07.087. (Published online: July 30, 2019; Article in Press)

IV. Danielsen SO, Moons P, Leegaard M, Solheim S, Tønnessen T, Lie I. Facilitators of and barriers to reducing thirty-day readmissions and improving patient-reported outcomes after surgical aortic valve replacement -a process evaluation of the AVRre Trial. Submitted to peer-review journal (October 2019)

4 Introduction

The main objective of this thesis research was to investigate and optimise hospital discharge and follow-up of patients after surgical aortic valve replacement (SAVR). This investigation was carried out in the context of the Aortic Valve Replacement Readmission (AVRre) trial (ClinicalTrials.gov Identifier: NCT02522663). The AVRre trial tested the efficacy of a post-discharge telephone support intervention designed to reduce readmissions after SAVR and improve patient-reported health and quality-of-life outcomes. In support of this randomised controlled trial (RCT), a systematic review and meta-analysis of the medical literature was conducted to uncover and assess the worldwide magnitude and variability of thirty-day all-cause readmission (30-DACR) rates after SAVR and transcatheter aortic valve replacement (TAVR). Finally, a process evaluation was conducted on the intervention implementation and the patients' and staff's reactions to the intervention to determine whether it was carried out as intended.

4.1 Overview of surgical aortic valve replacement (AVR)

Aortic stenosis (AS) is the most common type of valvular heart disease (VHD), leading to SAVR treatment in Europe. [1] Many conditions can cause the tissues comprising the valve leaflets to become stiffer. Functionally in AS, the valve opening is narrowed, reducing blood flow. If the valve becomes so narrow (stenotic) that overall heart function is reduced, blood flow will be inadequate to the rest of the body. Severe AS is mainly the product of a degenerative change (calcification of the valve) or a congenital condition (bicuspid valve), resulting in AS. [1]

The prevalence of AS increases with age, and due to growth of the ageing population in Europe, is projected to continue to increase in coming years. [2] This nexus of demographics and disease trajectory is a cause for great concern, because Europe's population of people older than 65 years is estimated to nearly double from 2008 to 2060. [3] Today in

2019, for patients younger than 75 years with severe AS, they are treated with SAVR. However, a heart team should consider what is the best treatment plan for patients >75 years, evaluating whether SAVR, TAVR, or medical therapy is the best possible treatment. Optimally, the heart team should comprise cardiologists, cardiac surgeons, imaging specialists, anaesthetists and, if needed, general practitioners, geriatricians, and heart-failure specialists, cardiac electrophysiologists, or intensive-care specialists. [4] The European Society of Cardiology (ESC) recommends using the following flowchart as a guideline for the management of severe AS (Fig. 1).

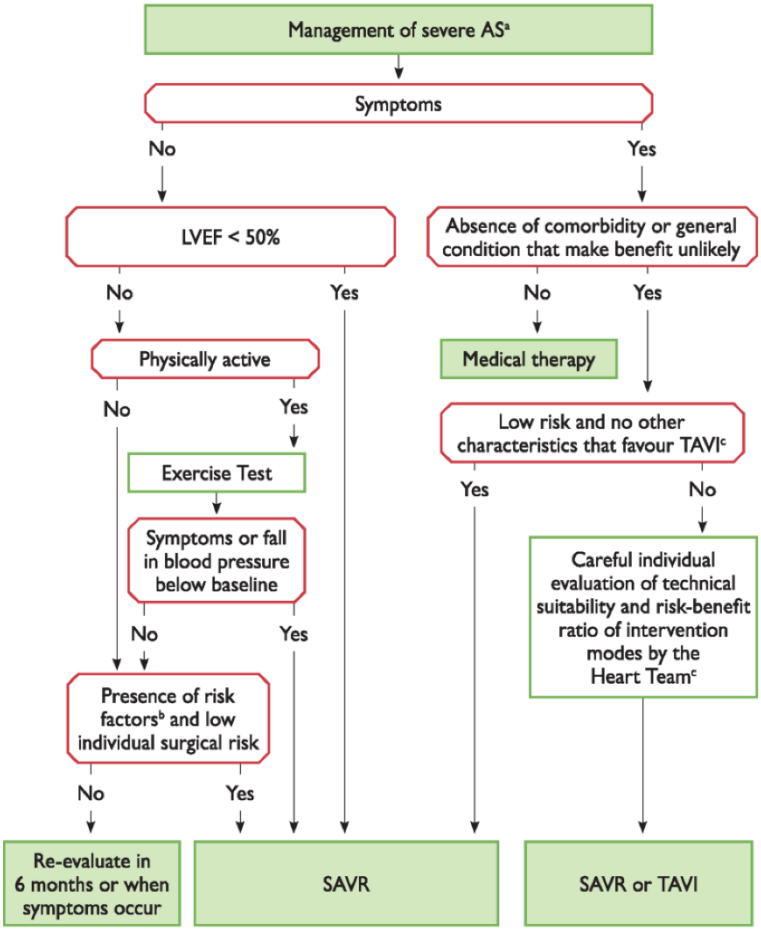


Fig. 1. Decision flow chart for the management of severe AS. (Reproduced with permission of the ESC, 2019. Original in [5]). Transcatheter aortic valve implantation (TAVI) is synonymous with TAVR. LVEF: Left ventricular ejection fraction

The 2016 annual report from the National Heart Registry in Norway reported that surgeons in 2015 conducted 1007 single-valve surgeries and 376 valve surgeries performed concomitantly with coronary artery bypass grafting (CABG) treatments. The proportions of females receiving the two kinds of valve surgeries were 46.2% and 26.6%, respectively. The surgical valve treatments of adults with valve diseases (including TAVR, starting from 2008) have increased annually from 645 in 1995 to 1736 in 2015. From 2004 to 2015, both SAVR and TAVR procedures have increased in Norway. [6]

In terms of treatment choices, the population of AS patients who are good candidates for invasive treatment has changed over time. TAVR has now emerged as the preferred choice of treatment — and the one superior to medical treatment — for patients who are not good candidates for surgery [7]. The nature of the SAVR procedure has also changed, originally comprising primarily mechanical valves to mostly comprising (> 80%) biological valves by 2010. [6, 8] The situation in Norway has followed the same trend from early 2000. [6, 8]

In-hospital clinical outcomes after cardiac surgery are well described. [9] However, patient-reported outcomes regarding perceptions of health and quality of life after hospital discharge for cardiac surgery are more sparsely reported. [10, 11] Heart failure (HF), cardiac rhythm disorders, and infections are common complications after discharge for SAVR, which often result in readmissions. [12, 13]

4.1.1 Transcatheter aortic valve replacement (TAVR)

The first TAVR procedure was performed in 2002 by Cribbier. [14] TAVR is widely believed to be superior to medical therapy for AS patients cleared for aortic valve replacement. [15] However, for moderate- to lower-surgical risk AS patients, sufficient evidence is lacking on whether replacing surgical treatment in favour of the minimally invasive TAVR is superior in terms of long-term survival and other clinical outcomes. [16] Robust evidence on the number of adverse events after TAVR, such as necessity of a permanent pacemaker, vascular

complications, and paravalvular regurgitations, ought to be clearly reduced before recommending that less symptomatic AS populations receive TAVR. Predictors of poor outcomes after TAVR include chronic lung and kidney disease (30-35% and 30-50% of the TAVR population, respectively), together with frailty [16] This lack of evidence for replacing surgery with TAVR is exemplified by the observation that the 30-day all-cause readmission (30-DACR) rate after TAVR was scarcely described before 2015. [17]

4.2 Hospital readmissions after AVR

In Norway, 30-day readmission is operationally defined as an unplanned and acute hospital admission for any cause to any hospital within 30 days after hospital discharge. [18] Thus, one can calculate over a population of patients and time period, what proportion is readmitted (i.e., percentage). The 30-DACR rate after SAVR is reported to be about 20%, based on a US population sampled between 1999 and 2011. [19] In Denmark, the 30-DACR rate in 2015 was reported to be up to 25% after valve surgery. [20] The 30-DACR rate after SAVR is unclear, reportedly ranging between 6.5-25.5%. [21, 22] In Norway, the risk-adjusted probability for 30-DACR reported in 2015 for elderly persons >67 years was 14.7%. [18] This value was determined on the basis of five diagnoses: asthma/COPD, heart failure, pneumonia, stroke, and bone fracture. Mean length of stay (LOS) in hospital for the first readmission in Norway within 30-days was 6.84 and mean days to the first readmission was 12.5. [18] The 30-DACR rates for SAVR populations, averaged over age (only patients > 18 years), are rarely described in the literature.

Hospital readmissions incur high costs. In the USA, for example, it is estimated that readmissions reached $17 billion, based on Medicare statistics (2005-2008) for patients >65 years) [23]. In Norway, the costs were 2 billion Norwegian Kroner (NOK) (reported in 2012). [24] In the USA since October 1, 2012, hospitals could be fined for excessive readmissions for certain kinds of diagnoses. [25] The Hospital Readmissions Reduction Program (HRRP) is

responsible for assigning economic penalisation and determining the threshold risk-standardised readmission ratio for certain conditions/procedures.

Increased efforts to prevent more readmissions have followed these financial disincentives, and research is well underway to monitor the patient health effects when readmission rates decline, especially how they affect mortality rate. [26] In Belgium, hospitals are penalised if a readmission occurs within 10 days after discharge. [27] Norway has no economic penalisation for readmissions. However, Norway offers positive economic incentives to hospitals for reducing hospital LOS. However, municipalities are penalised if they do not accept admitted hospital patients when the hospital has defined a patient as being discharge ready. [28] However, most SAVR patients in Norway are transferred to home from hospital. This could, in theory, represent a risk for early hospital discharge followed by readmission. [29] The Organization for Economic Co-operation and Development (OECD) reported for 2015 that the hospital discharge ratio (number of patients discharged from hospitals after at least one-night stay per 100,000 inhabitants[1]) was ~16% in Norway and Belgium. [28] Austria and Germany had the highest (~25% each), and Colombia, Mexico, Brazil, and Canada had the lowest (3-8%). [28] The mean hospital LOS reported by OECD in 2015 was 8 days across all OECD countries, ranging from 4 (Turkey) to 16 (Japan). [28]

Reports of the 30-DACR rate often come from registry studies. National- or hospital-level administrative or clinical databases are used to extract relevant readmission data. [30, 31] The National Patient Registry (Norsk pasientregister; NPR) in Norway is considered to be a high-quality patient registry, containing readmission data that are available to researchers. Researchers can gain access for minimal payment and with necessary ethical approval. [32] From 2009, hospitals in Norway have issued a unique NPR-identification number to every

[1] The hospital discharge ratio includes deaths in hospital following inpatient care. Same-day discharges are usually excluded (OECD (2019), Hospital discharge rates (indicator). doi: 10.1787/5880c955-en (Accessed on 26 October 2019).

admitted patient. [32] This number provides a way to record and track any new hospital stay a patient might have after discharge from the original treating hospital. This tracking procedure permits an accurate calculation of the 30-DACR rate. For the USA, any hospital readmission within 30-days of the initial discharge contributes to the 30-DACR rate. For Belgium, only readmissions to the same hospital where initial treatment was conducted contributes to the 30-DACR rate. [27] Examining medical charts and/or contacting patients (telephone interview, mail, survey) after discharge are ways of obtaining data for calculating the 30-DACR rate besides using registry data.

A 2015 annual report for Norway reported a readmission rate of 15% for adults > 67 years, [18] which is higher than Belgium's 2008 rate of 5.2% for adults > 17 years. [33] This means that 15% and 5.2%, respectively, of all discharged patients in these two scenarios get re-admitted to hospital within 30 days. This alternative way shows how different countries determine the 30-DACR rate. Within-country differences in the 30-DACR rate are also sometimes reported among hospitals after surgical treatment. For example, in US hospitals with high surgical volumes and lower mortality rates, fewer readmissions have been reported. [34] When interpreting and comparing readmission rates across different countries or hospitals with differing profiles, this diversity in procedures warrants caution. Thus, when publishing readmission rates, unequivocal and transparent reporting is paramount, especially with regard to how a readmission is defined, how admission data are collected and validated, and how they are analysed. Presently, there is no evidence-based guideline for consistently reporting 30-DACR rates.

The 30-DACR rate is often used as a quality indicator for hospital care performance [35], which might represent a valid proxy measurement for the quality of care after surgical treatment in a hospital. [34] Errors that interrupt the quality of healthcare delivery can be caused by structural or processual factors or be a natural consequence of the patient's co-

morbidity and clinical condition. [36] These could result in an adverse event like a hospital readmission. [36] Hence, in healthcare contexts, a readmission is often considered to be an adverse event. [36] Preventing readmissions are therefore an obvious goal for clinicians, as they are for administrators responsible for the readmission-related costs.

The number of preventable readmissions can be estimated, and the proportion of preventable readmissions can be as high as 79% (and as low as 5%). [37] We have found no reporting on the proportion of preventable readmissions after SAVR. Moreover, we do not know to what extent the 30-day interval is an appropriate period to assess when the objective is to optimise the discharge and follow-up after SAVR. Being readmitted to a hospital interrupts the expected care pathway and represents an extra burden for patients. Risk of iatrogenic errors are present in this situation, e.g., hospital-acquired infections or other complications affecting functional and/or cognitive status. [38]

4.3 Optimising discharge and follow-up after SAVR

Patient discharge is initiated at the hospital, and patient follow-up involves several steps before discharge results in a patient transferring to home, or more seldomly, to a healthcare facility having the appropriate level of care for SAVR patients (e.g., ordinarily a rehabilitation centre or a nursing resident home). Hospital discharge can be viewed as a journey in some ways, having multiple stops and transitions. It has been described this way:

> *'…hospital discharge is not an end point, but rather is one of multiple transitions occurring during the patient's care journey. The organisation and provision of this transitional care typically involves multiple health and social care actors, who need to co-ordinate their specialist activities so that patients receive integrated and, importantly, safe care.'* [39]

If a discharge increases patient satisfaction and quality of life and does not eventually lead to a hospital readmission due to prior hospital treatment within six weeks after discharge, it can be viewed as a successful discharge. [40]

The hospital discharge initiates the transition of care. In the health services, the transition of care is a concept having multiple definitions. Indeed, the World Health Organization (WHO) states that the concept incorporates more than just the act of clinical hand-over in healthcare, but should also comprise the views and values of the patients. [41] WHO refers to the American Geriatrics Society's definition of transition of care: *'a set of actions designed to ensure the coordination and continuity of health care as patients transfer between different locations or different levels of care within the same location'*. [41] As mentioned, the 30-DACR rate is considered to be a quality indicator of hospital service, and this rate, if too high, motivates investigations to improve discharge process and optimise follow-up after hospital stays. Providing necessary monitoring and management of patient symptoms after discharge are significant actions associated with the reduction of hospital readmissions. Promotion of self-management through patient education might also be a beneficial way to reduce hospital readmissions. [42]

Braet stated that if appropriate information is not provided, healthcare provider and management continuity can interrupt the transition of care and therefore disrupt the care continuum. [27] In Norway, the transition of care after SAVR is a primary concern of the university hospitals discharge management team, whose task includes transferring the patient to a local hospital. Then, the transition of care mostly ends with patients going home, with primary care being a responsibility of the general practitioner (GP). The GP is also responsible for patient follow-up. Some of the patients are directly transferred from hospital to a rehabilitation centre before going home. The transition of care for SAVR patients includes a prominent shift in roles in a rather short period, a shift from being a patient cared for by the

hospital to a private citizen being solely responsible for his own health. The 2014 national patient-reported survey of Norway on patients' experiences with hospital stays revealed that patients are often dissatisfied with the discharge process. [43]

Different discharge optimisation interventions have assessed how and whether they reduce the 30-DACR rate. Leppin et al. (2014) found that peri-interventions (around both in- and out-patient treatments) reduce the 30-DACR rate. [44] They also found that interventions conducted before 2002 were 1.6 times more effective than those conducted after 2002. [44] To explain this decline, it was hypothesised that improvements in care over time were either not recognised in the control group descriptions or simpler, fewer complex interventions were tested in years after 2002, such that they were inappropriate for the time period. More interventions measuring and reporting readmission rates differently, or more interventions with fewer human contacts also could have contributed to the finding of less effective interventions in reducing the 30-DACR rate after 2002. [44] There is also evidence that complex interventions with several components seem to be more effective than single-component interventions. [42, 44] Few surgical populations were included, and none were SAVR patients. Moreover, there was indication of publication bias. [44]

Hansen and colleagues defined interventions as either pre-, post-, or bridging interventions, and they found that no single intervention alone reduced the 30-DACR rate. [45] However, an RCT with a general medical adult population demonstrated that post-discharge telephone follow-up (TFU) had promising effects on reducing readmission rates. [45] Still, few RCTs on post-discharge TFU intervention RCTs of high methodological quality have been reported that show reduced 30-DACR rates. [45] To the best of our knowledge, no complex post-discharge TFU intervention with a bridging purpose (i.e., link between hospital and home by a 24/7 hotline) has been conducted that aimed to reduce the 30-DACR rate after SAVR.

According to the Donabedian model — the most cited and used framework for instituting quality improvement in healthcare — structural and processual factors of an intervention should also be analysed in order to improve healthcare quality. [46] Indeed, the intervention should not solely relate quality to the outcomes. [46] In this model, the structural factors include the hospital context where processual factors take place (e.g., the interactions among healthcare professionals and patients that occur during diagnosis and treatments), culminating in the outcomes of the intervention. The Donabedian model represents a logical approach to achieving quality improvement through which one also analyses the factors leading to the outcomes in order to establish excellent quality care. Using a mixed-methods approach, as in the AVRre trial, that includes sampling the participants and nurses' views on structural, processual and/or contextual factors, can deepen our understanding of the discharge process after SAVR. Hence, this rationale embodied in the Donabedian model motivated the research design for the AVRre telephone support intervention, allowing a broader and richer evaluation of its effects.

Patient-reported outcome measures (PROMs), metrics to explore how a patient experiences a disease or health condition, are now widely used. However, to be a scientifically valid measurement, PROM must be appropriate for the study context and aims, [47] and it must be transparently reported in the format recommended by the Consolidated Standards of Reporting Trials (CONSORT) extension of 2013. [48] Patient-reported experience measures (PREMs), metrics to explore how patients' experience healthcare services, are considered to be a valuable way to assess care quality. However, many PREM instruments still need more empirical evidence to overcome methodological issues related to its measurements and interpretations. [49] PREMs are considered to be useful for exploring patient perspectives when evaluating, for example, the applicability and usability of an intervention. [50] Therefore, both PROM and PREM instruments can produce valid results for evaluating the

effectiveness of an intervention. These kinds of measurements are also recommended for use in mixed-methods studies designed to evaluate a complex healthcare intervention, its implementation, and impact within an appropriate framework. [50]

4.4 Theoretical scheme: The Medical Research Council framework

The theoretical scheme used to frame and conduct this thesis research is described in the Medical Research Council (MRC) guidance on process evaluations of complex interventions in healthcare. [51] This highly cited framework recognises the value of process evaluation for RCTs, stating that it: *'…can be used to assess fidelity and quality of implementation, clarify causal mechanisms, and identify contextual factors associated with variation in outcomes.'* [52] We used the 2015 updated guidance, which elaborated and detailed the three themes for process evaluation described in the 2008 MRC guidance: implementation, mechanisms, and context. [51]

The logic flow in the process evaluation of an intervention as presented in the MRC framework has a similar structure to that described in the Donabedian model for quality assessment and improvement in healthcare. One key is recognising that it is imperative to analyse the processes prior to the care outcomes in order to construct a more complete picture of an intervention's relevance and potential. [46] The slightly modified MRC model (Fig. 2) used in this thesis research shows how the MRC framework was used to organise our investigation on how the TFU intervention impacts discharge after SAVR.

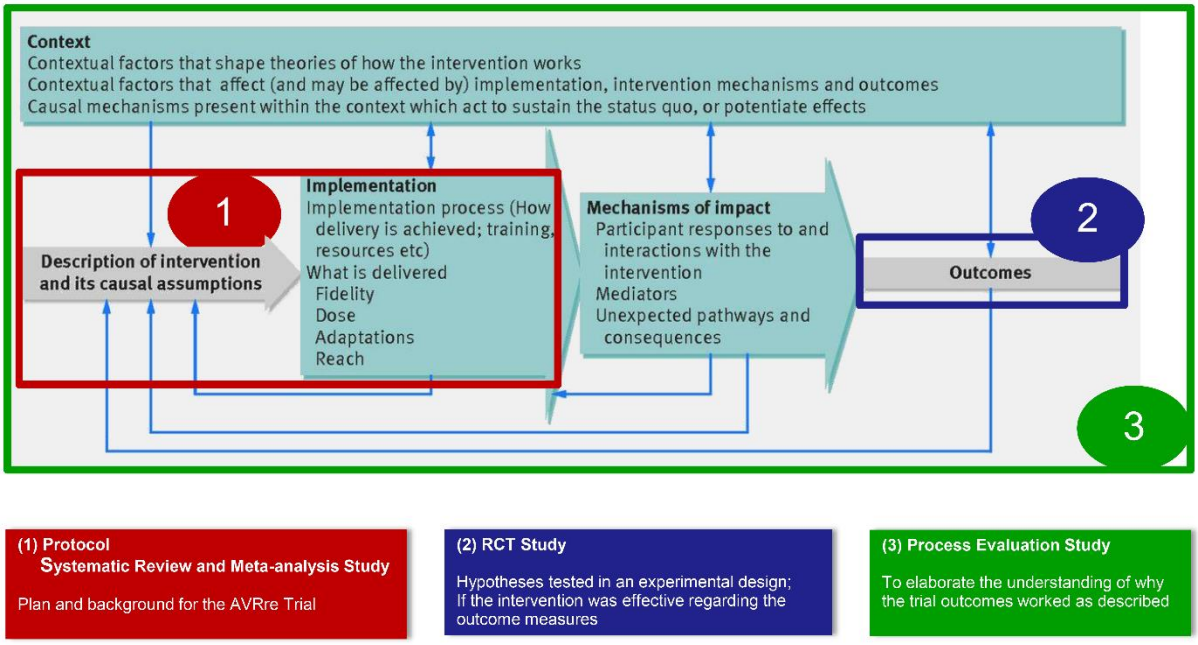


Fig. 2. Slightly modified MRC model used in organising, conducting, and evaluating this thesis research. (adapted from [51]; with permission from Graham F. Moore)

The MRC framework emphasises the need for a planned, prospective evaluation of RCT implementation; mechanisms of impact (patient reactions to the intervention); and contextual factors that influence the intervention. This approach is complemented by conducting a more traditional process outcome evaluation of the intervention in a RCT. The first step for the implementation aspect is to evaluate the development and piloting (including doing a feasibility check) phase of an intervention, which could reveal uncertainty related to procedural, clinical, or methodological issues. The outcome of this first step could highlight problems and lead to changes in implementation. [53] In the AVRre trial, we carried out the pilot and feasibility analysis together in an integrated approach, rather than conducting them separately as two unrelated steps. The second step for the implementation was to evaluate how the delivered intervention in the main trial was performed (i.e., its fidelity and dose). A planned evaluation strategy would allow tailored prospective and/or retrospective data collection for the process evaluation along with the outcome reporting, as the MRC

recommends. One reason for research waste in conducting RCTs can be traced to an inadequate development phase before the trials are fully tested in the main trials. [54, 55] Moreover, analysing qualitative findings related to quantitative results on interventions shows that such a mixed-methods approach can result in a deeper and broader understanding of an intervention. [56, 57] What is the 'gold standard' for evaluating a clinical intervention?

A RCT in healthcare science is often used to test the effectiveness of an intervention on selected outcomes. [58] Statistical analyses will provide answers as to whether the investigated intervention works or not on a targeted disease or an adverse medical event. Clinical trials producing nonsignificant results can lack sufficient statistical power to explore why results are negative. [59] Clinical trials are conducted in a real-world context, not a laboratory where one has more control over experimental variables to better pin down causal relationships between variables and outcomes. Applying a healthcare intervention in a clinical context is challenging. Why? Unlike in laboratory settings, in clinical settings it is difficult, even impossible, to control for potential confounding variables, to avoid experimenter or subject biases, to avoid random errors, or to choose the right outcomes. [59] Moreover, these experimental obstacles of RCTs are typically compounded by positive trial outcomes failing to be translated into clinical practice, [59] or if they are translated, by delays in getting the trial results into the hands of everyday practising clinicians. [60]

Modifying the pipeline to the clinic may be one way to get more positive clinical research results translated into clinical practice. That is, researchers might design clinical trials that integrate the participants'/patients' perspectives and views into the intervention and reported outcomes. [59] Providing trial participants an opportunity to express their experiences and feelings about their health and care during the RCT is not only appropriate within a mixed-methods design but might also go a long way towards achieving society's goals of making healthcare more patient-centred. [61] In short, greater participation of

healthcare consumers in the care system may improve overall healthcare. Analysis of Norwegian clinical medical guidelines developed between 2000 and 2009, for example, show that these were mostly developed without any patient involvement. Moreover, related literature searches show that they failed to include patient perspectives. [62]

Whether an intervention in an RCT design is complex or not, or even inherently complex, is an ongoing debate: '*We now think of a complex intervention as much more than the sum of its components parts. Its effects are likely to be modified by both the site and process of implementation.'* [53] According to Kernick, the issue of complexity in research emerged in the late 1980s, and many definitions of this concept have been proposed. [63] Briefly, one definition he provides captures the following essential elements:

> *'The [complex] system is different from the sum of the parts. In attempting to understand a system by reducing it into its component parts, the analytical method destroys what it seeks to understand. The corollary is that the parts cannot contain the whole and any one element cannot know what is happening in the system as a whole.'* [63]

Moreover, Kernick states that applying complexity theory in healthcare science might challenge the dominant positivistic view of science, in which there should be one correct answer to a problem, towards which all research will converge. However: *'Perhaps a more realistic perspective is to see complexity theory complementing existing approaches but alerting us to the importance of matching the research approach to the context and complexity of the environment to which it is applied.'* [63] Scriven characterises outcome research that is insulated from its 'how and why' as a kind of 'black box' evaluation. [64] By contrast, a 'clear box' evaluation provides a full explanation of how and why an intervention works. [64] However, the problem of a black box evaluation might not be overcome when considering that the increase in complexity can expand exponentially by adding a single

component to a complex intervention conducted within a health service that is a complex non-linear system. [65] All of these aforementioned considerations affected the design of the AVRre trial.

In the AVRre trial, after the initial design considerations, we reasoned that organising and conducting the study using the MRC framework could provide deeper and broader insight into the workings and potential clinical applications of the results. Using this scheme could also specifically inform the healthcare service about ways to optimise the discharge and follow-up care after SAVR. Prospective data collection using a mix of methods for evaluation purposes were integrated into the project from the beginning, especially with regard to including trial participants' perspectives into the new knowledge produced from the AVRre trial.

We reasoned that it would be appropriate and beneficial to use the MRC framework, which acknowledges the complexity of the intervention and the attendant problems that can emerge from conducting it within a complex non-linear health-services system. Using this organising scheme would also permit a better understanding of the AVRre trial outcomes and other potential important effects that might be translated quickly into clinical practice.

5 Aims of the study

5.1 Overall aim

The overall aim of this doctoral thesis research was to determine whether a remote post-discharge intervention could reduce hospital readmissions after aortic valve surgery and improve patient-reported health and quality of life. It included defining the current state of knowledge regarding 30-DACR rates after valve surgery and conducting specific process evaluations of AVRre trial reporting, implementation, and context. The AVRre trial was an RCT conducted in a university hospital in Norway.

5.2 Specific aims

I. To determine whether transparency was achieved in reporting the outcomes of the AVRre trial, according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.
II. To determine what the current reported proportion, causes, and risk factors of 30-DACR rate are after SAVR and TAVR through a systematic review and meta-analysis of relevant medical literature.
III. To determine the effectiveness of a post-discharge 24/7-telephone support intervention after SAVR on 30-DACR rate, patient symptoms of anxiety and depression, and perceived health state in the AVRre trial.
IV. To determine whether the AVRre trial programme activities were implemented as intended through a formal process evaluation of trial implementation, patient responses, and contextual factors.

6 Methods

This thesis comprises four published articles in peer-reviewed journals, in which the main objective was to investigate an aspect of hospital discharge and follow-up after SAVR. Table 1 presents an overview of the AVRre trial design and its relationship to this thesis.

Table 1. Overview of essential elements of the AVRre trial and its relationship to peer-reviewed thesis articles.

	Paper I	**Paper II**	**Paper III**	**Paper IV**[a]
Design	Protocol	Epidemiological	Randomised controlled trial (RCT)	Process evaluation of RCT
Methods	Qualitative and quantitative	Qualitative and quantitative	Quantitative	Qualitative and quantitative
Recruitment and sample	Literature	Systematic literature search N=141,102	Prospectively from a tertiary hospital, adult patients admitted for SAVR N=288	Prospectively from a tertiary hospital, adult patients admitted for SAVR, (N=288); Prospectively and retrospectively, nurses from a university hospital, (N=5); Retrospectively prior to study 1, former cardiac patients, (N=5)
Data collection	Literature review	Literature review	Self-report questionnaires Medical chart review	Self-report questionnaires Field notes Interviews Focus group interview

Analysis	Power calculation	Meta-analysis Meta-regression Qualitative review	Descriptive statistics Kaplan Meier Survival analysis Univariate GLM analysis Cox Proportional Hazards analysis Linear mixed-model analysis	Descriptive statistics Qualitative analyses

[a]Paper IV is submitted and is under review (see Section 3), as of 30 October 2019.

[b]Total N patients for all papers included in the review.

AVRre = Aortic Valve Replacement Readmission Study; SAVR = Surgical aortic valve replacement; RCT = Randomised controlled trial; GLM = General linear model.

6.1 Design and study sample

Patients scheduled for SAVR at Oslo University Hospital (OUH) were included in the AVRre trial. The trial was conducted in the OUH Department of Cardiothoracic Surgery at Ullevål and Rikshospitalet in Oslo, Norway. The first patient was enrolled in the trial on 24 August 2015. Inclusion of participants for the trial ended March 2017. The AVRre trial cohort was followed for one year after AVR surgery. The AVRre trial was registered at ClinicalTrials.gov (NCT02522663) on 11 August 2015.

Figure 3 presents a flowchart showing how participants were selected for, allocated, and followed up in the AVRre trial. To be included in the trial, a patient had to meet the following criteria: adult (> 18 years); elective surgery as a single SAVR (mechanical or biological), SAVR + coronary artery bypass surgery (CABG), SAVR + supra-coronary graft (SCG), or SAVR + CABG + SCG; understand and write the native language (Norwegian) well; and be able to be contacted by phone and use a phone after hospital discharge. Patients were excluded from the trial if they had a stay in the intensive care unit (ICU) for more than 24 hours or experienced any complications that would have prevented them from being assessed for any of the inclusion criteria. A total of 482patients were assessed for study eligibility (Fig. 3).

All patients were informed about the study before their SAVR surgery and given time to consider whether or not to participate. Recruitment was done with the knowledge that, before major surgery, a patient is vulnerable with regard to making decisions. [66] So, we were careful not to pressure patients to participate. The Declaration of Helsinki [67] informed our implementation of the ethical approval of the trial (see section 8.3 Ethical considerations). After patients gave their consent to participate, they were randomly allocated to the control or intervention group (Fig. 3). The control group was assigned to ordinary scheduled discharge management care before they were discharged to home. For the control group, a primary-care

GP was the ultimate healthcare professional responsible for their follow-up. We used block randomisation (size varied from 8-12) in a 1:1 ratio, produced using a web-based algorithm provided by the Unit of Applied Clinical Research, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway [68].

The pilot study (n=10) for the AVRre trial was conducted from April to May 2015. We conducted interviews with former cardiac patients recruited by the Norwegian National Association for Heart and Lung Disease (Landsforeningen for Hjerte-og Lungesyke; LHL) in February and March 2015. A focus group with the hotline staff was held retrospectively to explore their experiences with the hotline. The semi-structured interview-guide is provided as supplemental material in paper IV.

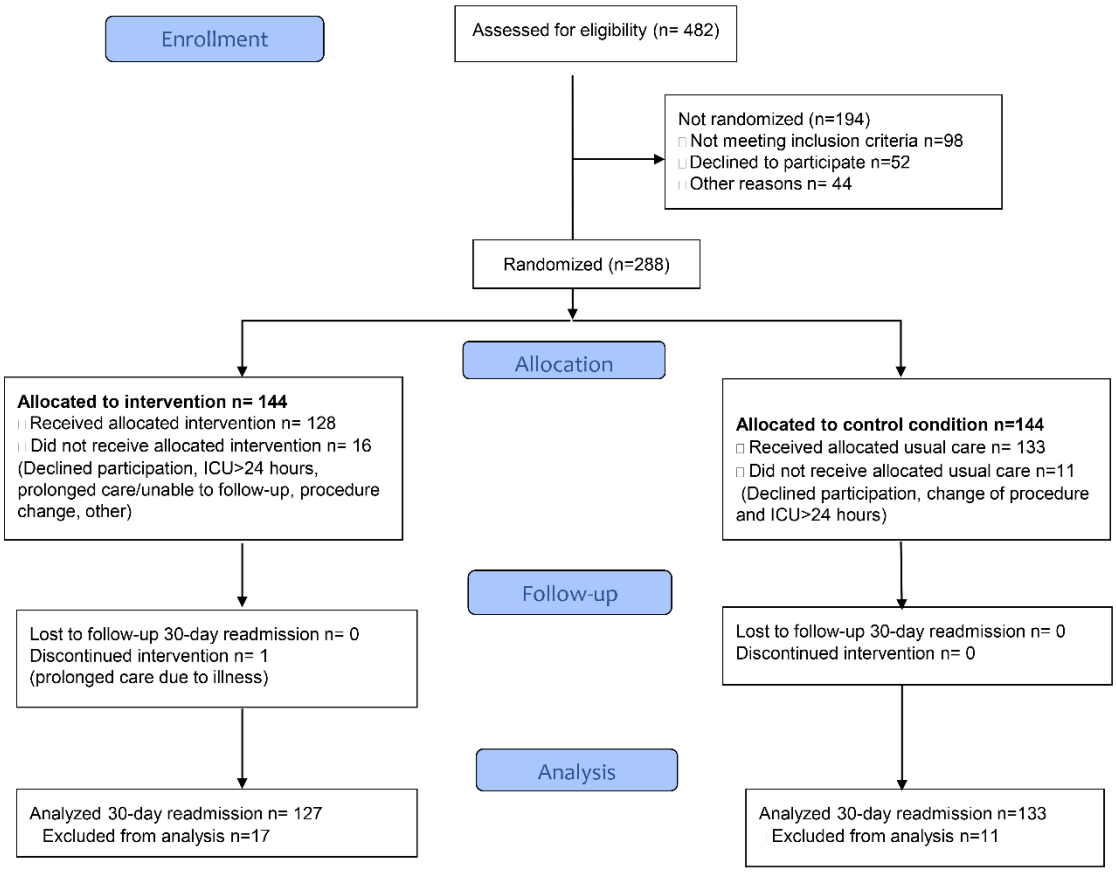


Figure 3. Flowchart for participant selection, treatment-type allocation, and follow-up in the AVRre trial

6.2 Telephone support intervention, training, and AVRre trial hotline manual

Participants in the AVRre intervention received post-discharge phone support in two ways: 1) they could freely call the 24/7 hotline staffed by experienced cardiac ICU nurses to access evidence-based health information when needed; and 2) they would receive a scheduled phone call on day 2 and day 9. The 24/7 hotline was available for the participants in the intervention group for 30 days after discharge from local hospital; they were explicitly told not to share the hotline number with other patients. The two scheduled phone calls could happen if the participant was discharged from the hospital to home or to a cardiac rehabilitation (CR) facility.

At the time of discharge from the university hospital where the participants received their SAVR, the project coordinator (PC) met the participants face-to-face and provided them verbal and written information about to which group they had been allocated (i.e., randomly). Only the PC and recruiting personnel knew the patients' group allocation before the day of discharge (or the day before). Participants allocated to the control group and hospital staff were not present when allocation information was given.

The information leaflet distributed to the participants reminded them of their participation in the AVRre trial. Only the intervention group received leaflets that contained necessary information like the hotline number. This leaflet also encouraged the intervention group participants to use the AVRre 24/7 hotline number, or a general medical emergency number, in case they were experiencing acute symptoms. The control group received information leaflets that reminded them about the importance of their follow-up (i.e., usual care; see questionnaires below) in the trial and that contained a note of gratitude for their participation. The PC followed the intervention patients' transition of care, was informed about discharge time from the local hospital, and then sent them an SMS to schedule the time of day for their first TFU call.

The TFU to the intervention group participants on day 2 and day 9 was a structured telephone call. That is, all intervention group participants were asked the same questions in the same order and were given the same information and reminders. The PC was prepared prior to the call with detailed information contained in the participant's medical and nurse charts about their health condition and in-hospital medical development after SAVR at the university hospital. The call also served as a reminder about their option to call the 24/7 hotline if they needed information or advice about managing their post-discharge self-care. The call also included advice about the positive effects of engaging in physical activity in the early CR phase. [69] Finally, the PC would answer any questions the patient might have about their present health condition. The hotline staff nurse was assigned to the phone service one week at the time. Concurrently, the PC had a paired phone to assist the hotline staff at any time. The participants were 'primed' to expect a possible short delay in the hotline response, if the nurse happened to be occupied with other tasks while on duty. An automatic recorded response would also state this possible delay, after which the participant could leave a recorded message. After a short time, the participant could expect to be called back if they had left a message; hotline staff and the PC gave these recorded messages priority.

Prior to the pilot and main AVRre trial implementation, to facilitate the implementation, we had meetings with key medical and nursing personnel that were involved in the care of SAVR patients in the hospital. In separate meetings, the cardiac surgeons and cardiologists were informed about their role in the AVRre trial, which was to be available for consultations with the hotline staff, if necessary. We conducted an orientation session in the emergency call centre to discuss experiences with listening, investigating, and responding to a phone call. We also studied and noted the way the emergency centre documented their work when carrying out their work by telephone. The local nurse and physician leaders were also informed about the trial, and we also met with the head of the Department of Patient Safety

and Quality at OUH to discuss and clarify hospital staff responsibilities related to the hotline service provided during the AVRre trial.

The hotline staff prepared for the intervention by attending one two-hour educational and training session before the pilot began. The PC discussed relevant background and outlined the rationale for the AVRre trial. A professional development nurse from the emergency call centre (113/911 quick-dial emergency numbers) also gave lectures on how to engage in active listening and shared experiences, gave useful advice, and answered questions from the attendees. In addition, at the end of this educational/training session, the hotline staff were given the opportunity to participate in role play, where they could practise answering and using the hotline manual under the guidance of the researcher conducting the session. After the session but before the pilot and the main study began, the hotline manual was made available to all staff involved in the AVRre trial for background reading and to prepare for the actual trial.

The evidence-based 24/7 hotline manual contained medical advice, elaborated information for the nurses related to the advice, and pertinent references. [29] The organisation of the themes in the manual was based on the experiences of former cardiac patients and on the universal convention of colour-coding red, yellow, and green in defining the emergency level of the calls. The manual was always available in the ICU ward, and the hotline staff also had a portable version with them when they were not present in the ward. More information about the manual can be found in paper I. [29]

Picture 1. Reproduction of the cover page of the portable 24/7 Hotline Manual used in the AVRre trial (Norwegian)

The PC was available to assist hotline staff on the paired phone whenever they needed relief from the hotline service for practical or other reasons. The paired phone also allowed the PC to monitor the number of hotline calls and the duration of the calls. The ICU nurses were accustomed to being on call for duty, as being on call was part of their ordinary work schedule. The PC was available for case consultations with the hotline staff at any time and held regular meetings during the main AVRre trial to discuss cases and how these were handled. We focussed on the most challenging calls and how they were perceived and interpreted by the staff.

Moreover, educational sessions with a specialist dealing with themes related to early rehabilitation were conducted in the main trial in order to support and empower the hotline staff. A cardiac surgeon conducted one educational session on handling dyspnoea issues; a cardiologist conducted one session on arrhythmias, especially focussing on atrial fibrillation; and a PhD cardiac rehabilitation physiotherapist conducted one session on post-SAVR patient physical activity and training.

6.3 Study procedures

The participants in the AVRre trial completed a baseline questionnaire before and up to one year after surgery (postal survey). The 30-DACR events were obtained by reviewing the medical charts. Table 2 shows the timeline for acquiring the data measurements in the AVRre trial.

Table 2. Timeline for data measurements in the AVRre trial.

Data type	Time after surgery					Time after trial
		Prospective				Retrospective
	Before surgery	1 month	3 months	6 months	1 year	
Demographic	X					
Clinical	X					
Co-morbidity	X					
HADS Questionnaire	X	X	X	X	X	
EQ-5D-3L Questionnaire	X	X	X	X	X	
30-DACR		X				
PROM and PREM survey			X			
Field notes	X	X	X	X	X	
Qualitative	X					X

AVRre = Aortic valve replacement readmission; 30-DACR = Thirty-day all-cause readmission from medical charts; HADS = Hospital Anxiety and Depression Scale; EQ-5D-3L = EuroQol-5D-3L; PROM = Patient-Reported Outcomes Measures; PREM = Patient-Reported Experience Measures; Qualitative interviews were conducted prior to surgery and after the main trial.

Paper I present the detailed study protocol that was ultimately used in the AVRre trial. The AVRre study sought to determine whether 24/7-phone support after discharge for SAVR reduces hospital readmissions within the 30 days after discharge from hospital (i.e., 30-DACR). For paper I, we followed the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) in reporting the details of the protocol paper [70]. The paper was submitted while recruitment was ongoing (November 2016). Using

the SPIRIT guidelines helps one to prevent selective reporting of study outcomes and offers transparency of the RCT for the benefit of the study population. [70]

The hotline manual described in paper I was based on thorough literature searches of relevant medical literature databases, including Medline, Cochrane, and Embase. We also acquired and studied the information leaflets of other cardiac surgery centres in Norway in order to enhance and refine our 24/7-telephone support manual used in the AVRre trial. Moreover, information about patient experiences after hospital discharge — especially during the first month — was obtained through focus group interviews with former cardiac patients (N=5) and through an interview with one participant organised through the Norwegian LHL.

A semi-structured interview guide [71] was developed and used during the interviews in order to consistently obtain data. Prior to the interviews, a mind map [72] was completed by the participants to enhance their recall during the interview. [73] Finally, the content of the hotline manual was appraised by two physicians and a nurse specialist with experience in early rehabilitation for cardiac surgery patients. Design of the manual was further informed by the Norwegian Medical Index for acute medical support. [74] Supporting material for paper I contains a translated excerpt from the hotline manual. Also included in the supporting material for paper I are the SPIRIT checklist we completed for the AVRre trial and examples of the informed written consent form used for the AVRre trial.

Paper II reported on the results of a systematic review and meta-analysis of papers in the medical literature to examine the overall incidence, causes, and risk factors of 30-DACR rate after SAVR and TAVR. On 30 March 2016, we prospectively entered the plan (PROSPERO no. 42016032670) (PROSPERO 2016 CRD42016032670; for conducting our systematic review and meta-analysis in PROSPERO, an international prospective register for systematic reviews in health and social care, welfare, public health, education, crime, justice, and international development, where there is a health-related outcome

(https://www.crd.york.ac.uk/PROSPERO/). We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in reporting the findings. [75]

We conducted a systematic search of the relevant medical literature databases after consultations with a senior research librarian at Oslo University Medical Library, whose supervision, professionalism, and experience ensured that we conducted an accurate systematic search in the selected databases. This rigour increased our chances that the search would capture relevant articles according to the aims of the study. The Patient/problem, Intervention, Comparison, Outcome (PICO) framework [76] was used to specify the search in relevant databases (details can be found in paper II). The systematic assessment led to the included papers and relevant numerical results for the analyses described in paper II (search strategy is shown as supporting material in paper II). The 30-DACR rates, study- and patient-level covariate data were collected and entered into a Microsoft Excel® spreadsheet. After identification of candidate papers from the literature search, two researchers with knowledge of the project independently assessed the full text of potential papers to be included in the review. Agreement for inclusion was reached through discussions between these two researchers. We used the Newcastle-Ottawa Scale (NOS) [77] for assessing the quality of the included papers. More details are provided in paper II.

Paper III reported on the outcomes of the AVRre trial. The CONSORT statement checklist from 2010 [78] was used and completed to ensure that we accurately reported the outcomes of the trial. Participants' demographic data, relevant clinical data, and data on their co-morbidities at baseline were collected from the medical charts and from the baseline questionnaire (Table 2). The baseline questionnaire used a self-report of co-morbidities, the Self-administered Comorbidity Questionnaire (SCQ-16). [79] Summaries of selected demographic, clinical, and co-morbidity data of the AVRre trial participants were presented in paper III.

The 30-DACR rate data were collected from the participants' medical charts for all hospital stays and from their responses in the questionnaire that was completed 3 months after the start of the intervention (Table 2). For the primary outcome variable, number and latency to readmission(s), we collected the following data: elapsed time to readmission; day of week for readmission; readmission at a university or local hospital; diagnoses (cause of readmission); and length of readmission stay. These data were additionally used in an ancillary analysis to estimate the proportion of avoidable and unavoidable readmissions in the study cohort. Two physicians and a nurse specialist (all members of the AVRre project group) independently estimated the proportions of avoidable and unavoidable readmissions for the study cohort (blinded for the participants' group allocation to intervention or usual care control).

PROMs, such as the Hospital Anxiety and Depression Scale (HADS) and the EuroQol (EQ-5D-3L) questionnaire, were used to assess the effects of the intervention on secondary outcomes. We used the Norwegian version of the HADS by obtaining a licence from the GL Assessment and the trusted translated version from Mapi Research Trust [80]. We also obtained permission to use the Norwegian version of the EQ-5D-3L. We measured the effect on health-related quality of life (HRQoL) [11] and on perceived health state. The latter is a measure equivalent to HRQoL and was used in this thesis when reporting results from the EQ-5D-3L questionnaire. EQ-5D-3L is a generic measurement of the respondents health states. It measures five dimensions of a respondent's perceived health state: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. [81] For each of the five dimensions, participants are scored on a 3-point scale (1, no problem; 2, some problems; 3, severe problems). Combining the dimension scores yields a 5-digit number, which equates to 1 of 243 possible combinations of health states. This score was converted to an index value using a value set derived by a time-trade-off (TTO)- and a VAS-based technique of a UK

population. [82] The EQ-5D-3L also uses a visual analogue scale (VAS) that ranges from 0 (absolute worst health state you could imagine) to 100 (perfect health state). Participants can select their overall current health condition on the VAS. Importantly, we assessed whether a ceiling or floor effect was present in the scores.

The HADS questionnaire was originally developed to assess whether patients in non-psychiatric hospitals might have anxiety and/or depression; it excludes questions about somatic symptoms associated with anxiety and depression in order to prevent interference with their somatic conditions. [83] The HADS questionnaire has seven items related to anxiety and depression. Each item is scored on a 4-point Likert scale (0-3 points), yielding a total item score of 0-21. [84] An item score of 8-21 points was considered to be indicative of symptoms of anxiety and/or depression. Using a cut-off score of 8 should give an acceptable balance between sensitivity and specificity (0.80). [83] Cronbach's alpha was used to measure the scale's internal consistency; a score > 0.7 is considered to be acceptable. [85]

The hotline staff always had easy access to a form used to register participant data relayed during the hotline calls: participant name, date and time of the call, elapsed time of the call, and an open form field where they could note keywords describing the content of the conversation. The form also included a section in which hotline staff could indicate (by tick mark) the caller's perceived symptoms or concerns and severity level of each symptom/concern (green, yellow, red) and the staff response to these concerns (i.e., whether or not they provided advice from the hotline manual). Picture 2 reproduces information on the call data registration form.

Set X for symptoms/clinical signs/questions from the patient. Additionally, log which red, yellow or green responses given:

		X	Codes (related to given advices)		
Symptoms/sign/question:			Red	Yellow	Green
Dyspnoea	1				
Heart rhythm	2				
Pain	3				
Prescribed medication	4				
Infection	5				
Psychological (anxiety, depression, cognitive)	6				
Activity	7				
Nutrition/Lifestyle	8				
Social network	9				
Sexuality	10				
Others	11				

Picture 2. Section in the call data registration form hotline staff used to register and assess participant information for each hotline call. This section allows staff to rate the caller's symptoms/concerns and symptom severity level (green, yellow, red); to note their response to the symptoms/concerns; and to describe advice they provided to the caller.

For paper IV, we used the MRC framework (see section 4.4) to guide the broader evaluation of the intervention. Moreover, the Standards for Reporting Implementation Studies (StaRI) guided the reporting of the process evaluation of the implementation, mechanisms of impact, and contextual influence of the intervention. [86] The qualitative design in the AVRre trial was informed by the methodological approaches described by Maxwell, [87] Malterud, [88] and Kvale and Brinkman. [71]

Three months after the start of the trial, the participants completed a follow-up questionnaire (i.e., the 3-month questionnaire). To get a better idea of the participants' experiences with the hotline and with their discharge, in general, we included three questions on how the intervention group participants used and experienced the hotline and questions on how all the participants experienced their hospital discharge. The questionnaire also contained an open-ended comment field in which participants could provide written feedback not captured in the direct questions. The first of the three questions for the intervention group was

a PROM question, which was to be answered by actual users of the hotline: ‘Were you satisfied or not with using the hotline?’ The second and third questions were PREM questions: ‘To what degree did having access to the hotline give you a sense of feeling safe?’ ‘To what degree did you think the hotline was a good offer?’ All three of these questions had six possible choices: not applicable, not at all, to a small extent, to some extent, largely, and to a very large extent. These questions were added to the questionnaire for evaluating purposes and were developed by the research group. The remaining questions were six PREM questions on the hospital discharge experiences of all participants; one question on whether a readmission had actually occurred (yes/no); and one question on whether it could have been prevented by the hospital (yes/no/don’t know), if indeed a readmission did occur. The six PREM questions had six possible choices, as indicated above. With the permission of the developers of these PREM questions (which were the same as those in a national survey reported in 2015), [43] we integrated them into the survey for evaluation purposes. The questionnaire was presented in Norwegian.

For the AVRre trial, all participants received a structured follow-up call from the project group PC on days 2 and 9 after hospital discharge to home. The PC collected the following data obtained during these calls: date and time, elapsed time of the calls, and contents of the conversations. These data were entered into a secure Excel® spreadsheet for later analysis. No personal identifiable data were recorded. In addition, the PC systematically took field notes from all the other encounters (regular meetings, educational sessions, and consultations) related to the hotline service in the prospective intervention, and these were preserved for clarification of what occurred during the encounters.

In the AVRre trial, research interviews were conducted prior to the pilot to inform and refine the content of the hotline manual. A convenience sampling of former SAVR patients was used in order to better understand their experiences with early rehabilitation after

hospital discharge. [71] Two small focus groups (2+2) and one single interview were conducted. The interviews were digitally recorded and transcribed verbatim. Details of this procedure are described above in the *paper I* paragraph of this section.

A small pilot study (N=10) was also conducted to evaluate the logistics, recruitment, randomisation, hotline and telephone follow-up, and method to inform patients of their group allocation in the actual AVRre trial. A visit to the medical emergency call centre and discussions with key medical and nurse leadership in the hospital were conducted to inform, facilitate the implementation, and determine factors that could potentially challenge or undermine the conduct of the intervention.

We also conducted a retrospective focus-group interview with hotline staff members (N=5). The participants were notified prior to the focus group through an email, which contained a reminder describing what they should try to recollect about their preparations and what was to take place during the intervention. A semi-structured interview guide was used to facilitate and guide the focus group interview, which was digitally recorded. This approach allowed us to collect information about the implementation and about the participants' reactions from the hotline staff's perspective, which also could provide important clues about potential mediators of an effect or unexpected outcomes related to the intervention. [89]

6.4 Data analysis

6.4.1 Quantitative analysis

In paper I, we presented the power calculation of the sample size we would need for the AVRre trial. The sample size was based on published data about hospital readmissions of patients > 65 years old in Norway. [90] We expected that the readmissions of participants in the intervention group would decrease by 10% compared to that in the control group, with a power of 80% and a risk of type I error of 5%. This yielded a sample size estimate of 143 in the two arms of the trial.

In paper II, we conducted a meta-analysis with sub-group analyses and a univariate meta-regression analysis of 30-DACR rates reported in the medical literature. For the meta-analysis, we used the DerSimonian-Laird method, [91] pooled the 30-DACR rates, and calculated the overall incidence of 30-DACR after SAVR and TAVR. These rates were presented in a Forest plot (Fig. 4). I^2 statistics were used to evaluate the heterogeneity between the studies. A sub-group analysis based on the collected participant covariates was conducted to evaluate heterogeneity. This was extended into a univariate meta-regression test using a random effects model to analyse whether the heterogeneity estimates were affected by the covariates. We conducted a sensitivity analysis to assess the robustness of the overall results. [92] All analyses were performed with STATA version 14.0 [93] and MedCalc version 16 [94] statistical software. NOS was used to assess the quality of the included studies. [77] Publication bias was assessed by visual inspection of Funnel plots and estimated using the Eggers test. [95]

In paper III, demographic and clinical data (i.e., categorical data) were presented as proportions (real numbers and percentages), whereas continuous data were presented as means or medians with standard deviations (SDs). Pearson chi-square tests and Fisher's exact tests were used to evaluate differences between the intervention and controls groups for the categorical data, whereas independent t-tests or Mann-Whitney U test were used to assess group differences for the continuous data. An intention-to-treat (ITT) analysis (N=282), along with a per-protocol (PP) analysis (N=260), were performed to evaluate the primary outcome (30-DACR). The Pearson chi-square test (between the groups) was used to evaluate the effect of the intervention on 30-DACR. To determine the time to readmission within the 30 days after hospital discharge, we conducted a Kaplan Meier Survival analysis, followed by log rank tests to evaluate any group difference. [96] A Kaplan Meier Survival plot was made to visualise the groups' time to readmission.

Analysis of covariance (ANCOVA) was performed to assess the intervention effect on the secondary outcomes at each of the assessment times (see Table 2), adjusting for the baseline scores using the covariates. This form of regression analysis is suitable for detecting an intervention effect with appropriate power. [97] A Linear Mixed Model (LMM) analysis was applied to measure the between-group differences in the secondary outcomes on repeated measures (up to one year after SAVR). The baseline score, time variable, and group were designated as fixed factors, whereas the intercept was designated as a random effect. LMM was an appropriate statistical analysis to use for our longitudinal data in the AVRre trial, because it allowed us to analyse both fixed and random effect factors in the modelling. [98]

Missing data are unavoidable in clinical and longitudinal studies and can cause analysis problems. Because most statistical tests assume that the dataset is complete [99], analysing incomplete datasets (e.g., leaving out entire cases with some missing data) can bias the results. [100] To address this issue, we analysed the missing value patterns of participants' data and performed multiple imputation (MI) with 20 iterations in each model for the secondary outcomes. [100]

A Cox Proportional Hazards (CPH) regression model was applied to explore predictors of 30-DACR after SAVR. The CPH model is often used to investigate the effect of multiple variables when a specific event will take place within a specific time span. [101] The chosen model was adjusted for other variables, using an appropriate number of covariates for the final model.

The assessment of the proportions of avoidable and unavoidable readmissions in the study population was assessed by two physicians and a nurse, who were blinded to the participants' group allocation, but they did have relevant clinical data available. This approach was deemed appropriate according to a recommendation for such assessments. [102] The readmissions were classified as either avoidable, unavoidable, or disagreement/questionable.

We chose not to resolve disagreements or readmissions deemed questionable due to an expected margin of error caused by individual physicians' preferences and different local healthcare systems.

In paper IV, we presented the descriptive statistics as numbers, percentages, and standard deviations. Fisher's exact test was used for comparative analyses of categorical variables with small numbers of cases.

6.4.2 Qualitative analysis

In paper II, we presented the results of the systematic literature review of the risk factors for and causes of 30-DACR after SAVR. The summaries of these factors and causes are presented as percentages in tables and in the corresponding text.

In paper IV, we qualitatively analysed the content of prospectively collected project staff field notes, memos, registration forms, and questionnaire narratives and the transcripts of a retrospectively conducted interview of participating staff. NVivo software, version 10 and 11 Pro, [103, 104] was used to organise the transcribed text from interviews, written questionnaire narratives, and field notes. Organising the text material and coding their content themes into meaningful text units are the two first steps in doing systematic text condensation, a qualitative analysis method described by Malterud. [88]

In the first step of this qualitative analysis, the texts were thoroughly read in order to gain an overview of the texts' content. In the second step, meaningful text units were retrieved and coded. NVivo was used in the second step to organise the codes and match them up with their associated text units. This is an important step, as it provided us with an overview of the data before proceeding to the third step of the analytical process. In the third step, we did text condensation, wherein the codes were abstracted into categories (meanings). In the final step, overarching themes were constructed; these represent the main findings (descriptions and/or concepts). [105] The technique of critical reflection was applied throughout all steps of the

analysis. [87] This involved maintaining close proximity with the relevant theory, by which the researcher moved back and forth between the analysis steps and the theory. This procedure was operationalised in that the researcher actively tried to challenge the validity of similarities between the codes and their categories. This analysis strategy requires time to achieve an appropriate level of critical reflection.

In our qualitative research study, the analytical process was not linear, in which data collection occurs entirely prior to the analysis phase. By contrast, in our study, analysis started and was conducted in parallel while the data were being collected. This enabled the researchers to carefully avoid, for example, confirmation bias and also to be open to various possible narratives, such as ones in which information tangentially related to the research questions could be considered. Such efforts were taken in order to prevent construction of one's own preconceptions and to simply prevent repeat acquisition of already-known information just to achieve appropriate scientific qualitative analysis. The critical reflection technique was supplemented through critical discussions of the preliminary and final findings with another researcher, who critiqued and challenged these findings. In our opinion, this procedure bolstered the trustworthiness of the findings obtained through qualitative analyses. It also lent support to the notion that qualitative approaches are essentially equivalent to statistical analytical approaches when it comes to validity assessments.

7 Brief summaries of the results

7.1 Paper I

Determining the impact of 24/7 phone support on hospital readmissions after aortic valve replacement surgery (the AVRre Trial): Study protocol for a randomised controlled trial

Paper I was a protocol paper that was timely published to ensure transparency in the reporting of the AVRre trial outcomes. Therein, we reported on the detailed protocol for the AVRre study (Table 1). We presented reasons why we believed that instituting a complex around-the-clock intervention within a university hospital-based setting would be an effective strategy for reducing the high readmission rates to hospital after SAVR. The paper presented the primary and secondary outcomes we would evaluate and presented the printed manual for conducting the telephone support.

In paper I, we also presented the power calculation for a reasonable sample size we would need to detect a 10% decrease of readmissions in the intervention group compared to the control group. We concluded that the knowledge gained from the AVRre trial would provide valuable insights for adjusting aspects of the healthcare system now and would likely highlight areas that could be improved in caring for SAVR patients after hospital discharge.

7.2 Paper II

Thirty-day readmissions in surgical and transcatheter aortic valve replacement: A systematic review and meta-analysis

In *paper II*, we reported on an investigation that determined the overall proportion of the 30-DACR rate and causes of and risk factors for 30-DACR after SAVR and TAVR (Table 1), as reported in the medical literature. The meta-analysis pooled the total numbers of patients. The proportion of 30-DACR following SAVR was 17% (95% CI: 16-18%), and for TAVR it was

16% (95% CI: 15-18%). Causes of 30-DACR after SAVR and TAVR were similar to those reported in the literature, with heart failure, arrhythmia, infection, and respiratory problems being the most frequently reported causes. A comprehensive list of risk factors for 30-DACR after SAVR has not been reported in the literature. The independent risk factors most frequently associated with 30-DACR after TAVR were diabetes, respiratory illness, atrial fibrillation, kidney illness, and using the transapical approach for inserting a new valve.

By examining subgroups in the reviewed papers, we found a higher proportion of readmissions in multicentre studies (SAVR, 20%; TAVR, 18%) versus single-centre studies (SAVR and TAVR, both 12%). Also, we found a higher proportion of readmissions in multicentre studies in the USA (18%) versus other countries (14%). Retrospective studies (17%) also had a higher incidence of readmissions compared to prospective studies (SAVR, 14%; TAVR, 11%). Only 6 prospective studies were included versus 26 retrospective studies.

Examining heterogeneity using meta-regression in univariate mode, we found that a higher proportion of readmissions in multicentre versus single-centre studies; both populations were significantly associated with the readmission rate (SAVR, *P*= 0.013; TAVR, *P*= 0.038). Furthermore, we found a weak association between a higher readmission rate in the TAVR population in the USA versus other countries (*P*= 0.091).

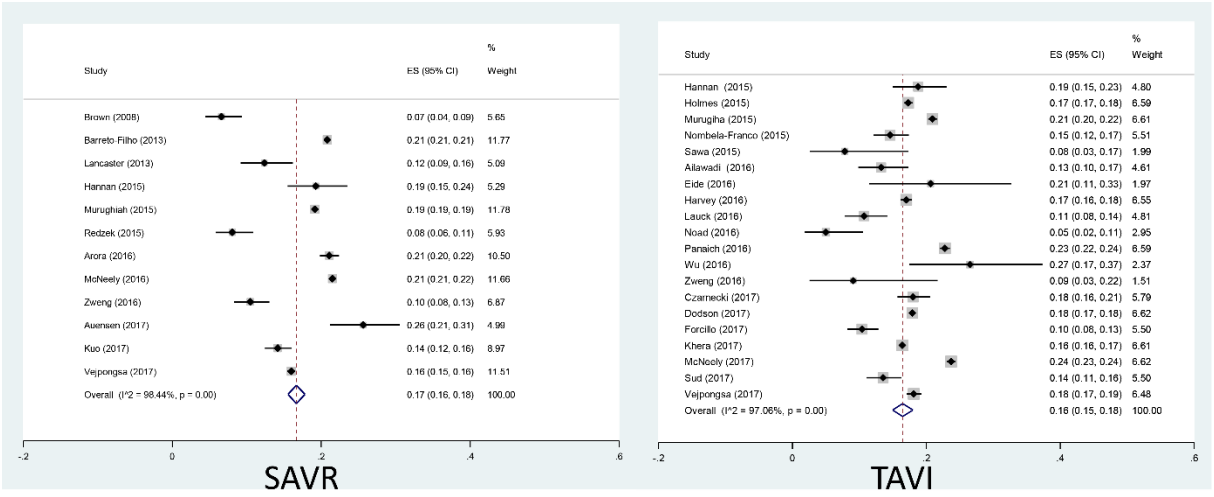


Figure 4. Forest plots summarising a meta-analysis of the proportion of 30-day all-cause readmission rate after surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR)

A quality assessment of the included papers revealed that most studies did not include a transparent validation statement of the readmission statistics.

7.3 Paper III

Impact of telephone follow-up and 24/7 hotline on 30-day readmission rates following aortic valve replacement – A randomised controlled trial

In *paper III*, we reported on an investigation (Table 1) that determined the effectiveness of the AVRre telephone support intervention in reducing the 30-DACR rate, symptoms of anxiety and depression, and improving the SAVR patients perceived health state. The results revealed that the intervention had no significant effect on the 30-DACR rate (P= 0.274). However, the intervention was effective in reducing symptoms of anxiety within one month after discharge (P= 0.031), but this reduction did not persist up to one year after SAVR surgery. The 24/7 telephone intervention also had no effect on reducing symptoms of depression (P= 0.758) or on improving the patients' perceived health state (EQ-5D-3L VAS, P= 0.636) up to one year after surgery.

Total unplanned 30-DACR rate was 22.3% in this cohort, and 83% of all readmissions occurred within 14 days after hospital discharge. The most frequent cause of readmission was cardiac rhythm disturbance (34%), in which atrial fibrillation was prominent. Interestingly, 14% of the readmissions were caused by pericardial effusion. Independent risk factors for 30-DACR after SAVR were symptoms of anxiety before surgery (P= 0.003) and pleural drainage after surgery but before hospital discharge (P= 0.027). We also observed that a high proportion of readmissions were unavoidable in this sample, estimated overall to be 75%.

The 24/7 hotline service in the trial was used by 46% of the participants, and women used the telephone service significantly more often than men (*P*= 0.046). Callers were more frequently readmitted than non-callers in the intervention group, a significant finding (*P*= 0.001).

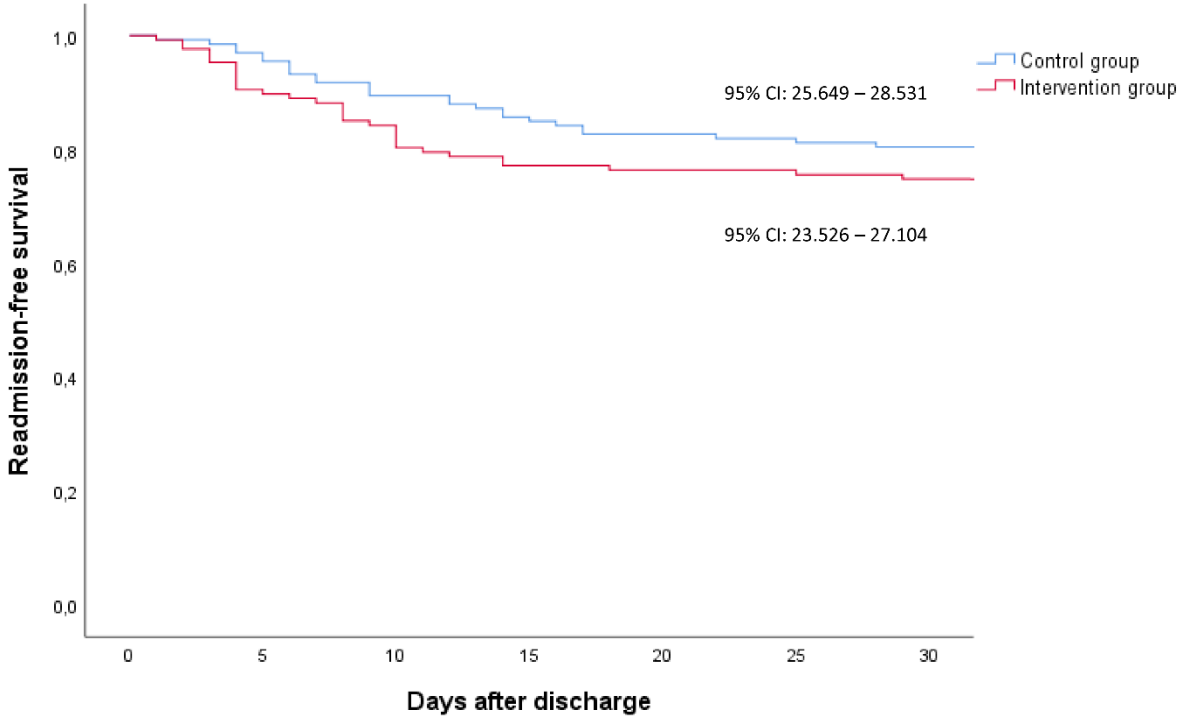


Figure 5. Kaplan-Meier survival curves demonstrating elapsed time to readmissions for the two groups in the AVRre trial.

7.4 Paper IV

Facilitators of and barriers to reducing thirty-day readmissions and improving patient-reported outcomes after surgical aortic valve replacement: A process evaluation of the AVRre trial

In *paper IV* [submitted], we extended the evaluation of the AVRre trial by conducting a process evaluation of the telephone intervention (Table 1). The findings revealed that SAVR participants were highly satisfied with the hotline service, and 91% perceived it as being a

trusted option. The TFU aspect of the intervention was also perceived as being trustworthy and valuable.

Our process evaluation found that a possible barrier to optimal implementation of the telephone support was that staff were insufficiently prepared in their training and education prior to the start of the trial. However, this is somewhat at odds with the prospective follow-up of the hotline staff conducted during the trial, in which the staff perceived it as being highly valuable and useful and that it facilitated the high-fidelity delivery of the intervention. Moreover, we found that the AVRre trial participants revealed that despite our efforts in conducting two telephone follow-up calls, they perceived a ‘gap in the care continuum’, ‘need for individualised care’, and ‘a need for easy access to health information’. We also found that discharge management of local hospitals had readmission rates from 0-50%, which affected the 30-DACR incidence.

The robust integration of user experiences into the AVRre trial produced a more complete picture of the impact of the intervention and the discharge and follow-up care after SAVR. This demonstrated the utility of a mixed-methods evaluation approach in a clinical trial with an RCT design, in addition to the direct outcome evaluation analyses.

8 Discussion

Hospital readmissions after SAVR incur high financial and emotional costs. Most SAVR patients in Norway are transferred to home from hospital soon after surgery, which could represent a risk for readmission. [29] A 2015 annual report for Norway reported that the hospital readmission rate was 15% for adults > 67 years. [18] The 30-DACR rate is often used as a quality indicator for hospital care performance [35], which might represent a valid proxy measurement for the quality of care after surgical treatment in a hospital. [34] Preventing readmissions is an obvious goal for clinicians, as it is for administrators managing readmission-related costs. Moreover, readmissions to hospital interrupt the expected care pathway and represent extra health and emotional burdens for patients. Thus, a primary aim of this doctoral thesis research was to test a post-discharge intervention that might reduce readmissions. Specifically, we sought to determine whether a remote intervention could reduce hospital readmissions after SAVR surgery and also improve patient-reported health and quality of life and symptoms that could affect them, such as anxiety. This aim was carried out in the context of the AVRre trial, an RCT conducted in a university hospital in Norway.

The AVRre trial used a mixed-method design to explore the discharge and follow-up of patients after SAVR treatments in the hospital to aid efforts in optimising the care. The aims were to provide a transparent protocol for the purposes of the AVRre trial and an answer to the overall incidence of the 30-DACR rate after SAVR and TAVR. Furthermore, we aimed to test whether a post-discharge telephone intervention would reduce the 30-DACR rate and improve patient-reported outcomes after SAVR. Finally, we aimed to provide a broader understanding of the clinical trial in the AVRre study in the context of the MRC process evaluation model.

An overview of the AVRre trial protocol was provided in paper I. In paper II, we reported through a systematic review of published studies that there is a high overall incidence

of 30-DACR after SAVR (17%) and TAVR (16%). To the best of our knowledge, the AVRre trial was the first to investigate the overall incidence of the 30-DACR rates after SAVR and TAVR using a systematic review and meta-analysis. The results of this review suggest that improvement is needed in most healthcare systems internationally to reduce the negative patient and financial impacts related to readmissions. Moreover, paper II revealed that new more rigorous prospective studies are needed that consistently report the 30-DACR rate.

In paper III, we reported results from the prospective AVRre trial, showing that the overall 30-DACR rate was 22.3%. Unfortunately, we found that the trial's telephone support intervention failed to significantly reduce the 30-DACR after SAVR. The intervention also failed to persistently improve patient-reported outcomes. Although symptoms of anxiety within one month after surgery did improve significantly, the improvement was not long-lasting, however, as the follow-up assessment one year after SAVR failed to show differences in anxiety symptoms. Symptoms of anxiety before surgery and pleural drainage before hospital discharge increase the risk of 30-DACR. We estimated the overall proportion of unavoidable readmissions to be 75%.

In paper IV, the SAVR participants reported being satisfied overall with the intervention, felt secure, and perceived the telephone support as being trustworthy. The intervention was implemented as planned, with the process evaluation providing evidence that the intervention was carried out with high fidelity. Although robust follow-up interviews with the AVRre staff during the trial favourably influenced implementation fidelity, more preparatory education and training might have further increased staff satisfaction with and fidelity to the intervention. The trial participants reported that the discharge was not optimal and could benefit if more follow-up was done during the transition of care for SAVR patients. The 30-DACR rate was found to be dependent on the context of local hospitals discharge management.

Overall, the research demonstrated that a mixed-methods approach is appropriate for this kind of clinical RCT. Moreover, it demonstrated that a process evaluation of the trial implementation and the impact of the intervention is useful for gaining a broader and deeper understanding of the results in this kind of clinical trial.

8.1 Methodological considerations

Although some positive results were observed, the AVRre trial had some limitations. Each paper will be considered in turn.

Study design and population

Paper I

The protocol for the AVRre trial was submitted for publication shortly before the trial was completed with no alterations, and outcome reporting was done according to the original plan (ClinicalTrials.gov Identifier: NCT02522663). There are several potential bias pitfalls regarding validity of the outcomes from clinical trials, in general, when the protocols are published in advance, such as unblinding biases, crossover biases, or bias related to the Hawthorne effect. [106] We considered these in the context of the AVRre trial.

Information on the internet and sharing of such information among trial participants is simple and fast through social media today. This situation presents challenges to the design of and interpretation of clinical trials, as more today than before, sharing information is so ubiquitous and easy. Concerns also might be raised because of the untimely publishing of the protocol paper. However, even though the 'protocol' manuscript was submitted while participant recruitment was still taking place, no data were entered to prevent ascertainment bias. [107] All research protocols for the AVRre study — available for scrutiny by readers of the 'protocol' paper — confirm that the outcome measures related to the efficacy of the intervention were not amended at any time. Protocol papers are intended to be prospectively

submitted to minimise scientific misconduct (e.g., reduce publication bias) and prevent selective publication and selective reporting of research outcomes. In other words, outcomes should only be a result of carrying out sound scientific practice.

We designed the AVRre trial in order to evaluate the telephone intervention. However, the trial could have been enhanced to focus data collection more specifically on other important factors (e.g., on local hospital discharge management systems). We may have underestimated the complexity of local hospitals' discharge practices in influencing the primary outcome, under-designing the trial with respect to confounding and/or interacting factors. However, there was limited theory on factors that affect the SAVR population and the 30-DACR outcome and on interventions that might reduce the 30-DACR rate. This lack might also have handicapped the refinement of our intervention according to the study population. Having highlighted these issues, present theory still provided a reasonable basis to attempt an intervention that might reduce the 30-DACR rate. Post-SAVR follow-up, including monitoring and managing symptoms early after discharge, reduces likely readmissions. [42]

Paper II

Conducting the systematic literature review and meta-analysis was the appropriate approach to accurately determine the overall proportion of the 30-DACR rate reported in the field after SAVR and TAVR. The review and analysis were performed in several steps to promote high-quality procedures and outcomes for the study. An early and vital step was performing a systematic review in which data collection was established by using a search strategy that efficiently searched the appropriate databases. Cooperation with a senior research librarian guaranteed that the strategy would systematically identify appropriate articles. Using this approach could be considered to be a validation step and a strength of this study. The number of published articles indexed by major literature databases has been increasing rapidly. [108] This fact motivated us to carefully consider which databases to search in order to do an

efficient, exhaustive, and accurate search. [109] We and others agree that a crucial initial step in a meta-analysis and systematic review, at least for less experienced researchers, is to cooperate with a senior research librarian. [110]

Another step in the review included the assessment of relevant candidate articles. This required spending sufficient time to ensure that all relevant articles were captured and systematically assessed. Since there is a risk of inadvertently overlooking relevant articles because of publication bias, [111] one cannot rule out the possibility that one or more articles were missed. However, we have no indication there was such bias in the present study, which is a strength of paper II.

Some reasons a relevant article may be overlooked is that there is no consensus on how an article should be titled in which the 30-DACR was the main objective of the study. This uncertainty can lead to identification mistakes (false negatives) when screening article titles and abstracts. However, our systematic procedure for scrutinising potential articles (two researchers involved was robust, helping us avoid duplicate inclusions. For example, by using the two-reviewer approach, we discovered that a candidate article's results were based on the same registry data recorded within the same time frame as data already included in another article. Therefore, this article was excluded from our analysis.

Another reason that the true 30-DACR reported in the literature might be underestimated is that completed studies that observed a higher proportion of readmissions in a single-centre observational cohort study or in an experimental study — one yielding a unfavourable statistical reduction in readmissions — are often less likely to be published in peer-reviewed journals. [112] In these cases, we would have had no opportunity to evaluate such articles for inclusion. Publication bias is present if the missing literature is systematically different from those we included. [111] However, we used several statistical tests (Funnel plot and Eggers test) for evaluation, and a sensitivity analysis confirmed that potential missing

publications were not systematically different from our sample. Therefore, we could conclude that the outcomes were less likely to be biased. As mentioned in paper II, we also did not assume a publication language bias was present due to the language limitations we used in the search strategy.

We also sent e-mails to researchers of publications asking if we could have a copy of the 30-DCAR rate data of the study population, and two authors failed to answer. We also considered whether overlooked 'grey literature' might also have introduced a publication bias leading to an inaccurate estimation of an effect size or a proportional size outcome. 'Grey literature' is defined as research *'that … is produced on all levels of government, academics, business and industry in print and electronic formats, but which is [sic] not controlled by commercial publishers'*. [113] Thus, these research results are produced but may not be published in the traditional commercial or academic publishing and distribution channels. There are several resources online for conducting a reasonable grey-literature search. [113] Even though we searched for relevant articles in the grey literature, and the tests for publication bias were negative, we cannot completely rule out the possibility that we might have missed relevant articles or data reports in the grey literature that could have pushed the true 30-DACR rate we observed in either direction (i.e., higher or lower).

An accurately conducted meta-analysis provides a cumulative analysis that can display patterns containing important insights for clinicians as well as for researchers. [111] The display or disclosure of patterns can generate new hypotheses and important clinical and methodological suggestions. The demonstration of patterns of proportions of readmission rates in a meta-analysis could therefore be viewed as a method to display more than a simple analysis. However, we used a meta-regression analysis in our study to investigate the relationship between readmission rate and study-level covariates. [111] Reporting the causes and risk factors for 30-DACR after SAVR and TAVR might provide a basis for tailoring new

interventions aimed at reducing the 30-DACR rate. It was interesting to note that in paper II, heart rhythm disturbances, heart failure, and infections are common complications after both kinds of treatments, a pattern that might suggest new clinical improvement projects to reduce readmissions after an invasive (conventional or mini-invasive valve replacement) heart valve procedure in the hospital. TAVR patients presently tend to be older and have higher number of co-morbidities. [12] This likely reflects a similar high proportion of early readmissions after TAVR, which is unexpected since the TAVR procedure is less invasive compared to conventional SAVR. [17]

Paper III

The experiment reported in paper III was an RCT, the 'gold standard' of experimental design when investigating the effects of a clinical intervention, in our case the post-discharge telephone support intervention. Using an RCT design is a strength of the AVRre trial. Why? One reason is that the randomisation of participant allocation to the treatment and control groups of an RCT generally prevents subject selection bias by distributing possible confounding variables fairly equally between the two experimental groups. Thus, statistical analyses of group performance can potentially detect a true intervention effect and not a spurious one that could be related to the presence of systematic confounders in one group or the other. [58]

In the AVRre trial, 96 candidate patients (20%) declined to participate or did not participate for other reasons. Potential participant self-selection might have led to selection bias in this study and, thus, threaten its internal validity. However, patients declined for different reasons, and we had no relevant data to analyse and compare this non-participating population with the participating ones on variables that may shed light on a potential self-selection bias. This was due mainly to the original approval conditions stipulated by the ethical committee regarding the scope of the AVRre trial; they did not give the AVRre trial

coordinators permission to obtain extra data without additional informed consent. The most common reasons for non-participation was that patients felt they would be too fatigued after surgery to participate in follow-up, or felt that for practical reasons, follow-up after discharge would be too burdensome (e.g., excessive traveling distance, inability to respond to the questionnaires in the required time frame). These kinds of factors increase the risk of selection bias being present. Having said this, however, we failed to find any systematic differences between the included study population and non-participants in terms of other kinds of self-reported treatments, age, or gender that would suggest our included study population was not representative of the general SAVR population. Thus, we can conclude, at least modestly, that we have some evidence that the AVRre trial was not harmed by selection bias.

The cumulative published research on interventions aimed at reducing the 30-DACR, in general (including a few mixed-cardiac surgery populations), have reported ambiguous positive effects of a reduction. It is noteworthy that results of intervention trials published after 2002 have reported less of an effect on reducing the 30-DACR rate than those published earlier. [44] Results from the AVRre trial, on the other hand, are the first to indicate which factors are predictors of 30-DACR after SAVR. Specifically, we reported in paper III that in-hospital pleural drainage and pre-surgery symptoms of anxiety are independent predictors of 30-DACR.

Based on the power calculation, we expected that the intervention would produce a 10% reduction in the 30-DACR rate between the two groups. It could be suggested that a 10% difference in a clinical trial might be too high and that the AVRre trial did not have sufficient statistical power to detect such a significant difference. Unfortunately, there were no previous studies on a SAVR population and 30-DACR rate after a TFU intervention that we could specifically use to inform us in calculating the sample size. However, studies using a TFU had reported a 10-30% reduction in the 30-DACR rates. [114, 115] If we had planned to conduct a

larger pilot study to guide our calculation of the needed sample size of the main trial, we might have been able to be more specific in our understanding on the trial's power to detect statistical significance between the groups. However, at the time, the main trial seemed to have sufficient power to detect a significant group difference for the primary outcome within the expected margin based on chi-square statistics. As discussed in paper III, the study lacked sufficient power to conduct a sub-group analysis on differences between the groups' proportions of unavoidable versus avoidable readmissions.

What other limitations and strengths can we note for the research reported in paper III? Blinding of group allocation can prevent bias in a RCT. [116] We did not design the AVRre trial to use 'true' blinding of group allocation in order to avoid performance bias. Having said that, the medical staff of the treating hospital and all participants were blinded until shortly before discharge from the university hospital. Participants were also encouraged to keep secret their group allocation and not openly display their information leaflet (section 6.2) until they were home. This request apparently was successful, since the hotline only received calls from intervention participants. Still, we cannot rule out the possibility that the group allocation was inadvertently revealed to discharging staff for some participants, which possibly could have influenced the standard discharge management (i.e., that was used for the control group). Also, the PC had updated knowledge about the context where the intervention was being conducted at the university hospital, but we detected no problem associated with the risk of information bias. However, the physicians and nurses involved in the discharge of the AVRre trial patients were aware of the study purpose and, thus, might have selectively increased their efforts to better inform the intervention group participants and caregivers at the time of discharge (i.e., Hawthorne effect). However, we have no direct evidence to support this speculation.

Are there other limitations and strengths that can be noted for the research reported in paper III? Performance bias can be introduced in a clinical trial in which several clinicians are determined to deliver one single intervention. [117] This can especially occur when the 'treatment' is based on the nurses' interpretation of the caller's message(s), or because of the communication skills of the caller or staff, previous professional experiences of the staff, and the actual skilled/unskilled use of the hotline manual. We cannot rule out the possibility that differences in how the individual AVRre-participating nurses delivered the hotline service might have impacted the fidelity of the intervention and the patients' expectations.

Another factor possibly affecting the delivery of the intervention was the presence of a learning effect over time manifest in the PC and the hotline staff. Thus, delivery of the intervention later in the trial might have improved, to some extent. In other words, intervention participants who took part earlier in the AVRre trial may have had a slightly different experience than those who took part later in the trial, because the staff would have gained mastery over the delivery over time and with practice. In the real-world clinical context, as our trial reflected, a certain level of individual differences in care performance are expected. However, we made efforts to minimise performance bias by ensuring information coherence in using a standardised manual for the delivered advice, conducting preparatory hotline staff training, recruiting a rather homogenous volunteer group of experienced ICU nurses in the field of cardiac surgery, and by providing robust and close support and supervision during the trial. We are confident that these precautions led to the delivery of the telephone intervention in as uniform a way as possible in a real-world context, minimising performance bias. We could have designed an intervention in which the participants received pre-recorded calls, although this approach poses its own problems. Still, the 'pre-recorded' approach might have given a more accurate understanding of whether performance bias related to intervention delivery was present.

In an effort to strengthen the AVRre trial, we chose not to severely constrain the age range requirement. Thus, we aimed to include adult patients electing SAVR who were > 18 years and not limit patient ages to > 65 years. This decision might have been even more appropriate with regards to statistical analyses due to the SAVR population's age composition (i.e., mean age 67, range 26-85 years). Prior trials with the 30-DACR rate as primary outcome have largely not included younger patients. [118] Not limiting participation in our intervention to patients older than 65 year enabled us to provide as complete a picture as possible about post-discharge care related to readmissions, without missing potentially clinically important knowledge on patients < 65 years. This is perceived as a strength. Combining the main sub-groups (see inclusion criteria, section 6.1) of SAVR patients into one group for analysis might have underestimated the intervention effect on the 30-DACR rate, if different sub-groups respond differently. More specifically, there was a risk of introducing selection bias due to potentially different clinical characteristics and mixes of co-morbidities across the sub-groups. Having said this, however, we did observe an equal distribution of important clinical variables between the sub-groups within each arm of the trial, and we observed a similar distribution of readmissions in the various sub-groups.

Paper IV

The MRC model was chosen to frame the AVRre trial, and it guided the extended process evaluation of the intervention reported in paper IV. This choice provided the opportunity to conduct a broader assessment of the outcomes and to identify other possible important findings related to the intervention and the participants' discharge experiences. Ideally, the process evaluation of the intervention should have been formally embedded from the start in the design using a defined model for its purpose. [53] Although the MRC-inspired process evaluation was not part of the original trial design, the evaluation was still mostly done prospectively, which strengthens this study.

The plan for data collection ensured that we had enough data to conduct the process evaluation in a valid manner. The retrospective interview with the hotline staff was conducted soon after trial completion. These interviews could also serve as a way to compare or check the field note results that were obtained during the intervention. On the other hand, by using a retrospective focus group, we might have inadvertently introduced confirmation bias, [119] in which prior interpretations from the field notes and the healthcare professional conversations during the entire trial possibly could have influenced the direction of the focus group. We were aware of this possible source of bias threat when planning the focus group, conducting it, and analysing the responses. However, employing two researchers to discuss emerging themes in the final stages of the qualitative analysis enhanced the trustworthiness of the results. Our research design using the planned broad data acquisition in a systematic and mostly prospective way robustly strengthens the study's validity and could also generate new hypotheses for further explorations and more tailored interventions. The design allowed us to conduct a thorough assessment of the strengths and limitations of the AVRre clinical trial enhanced by the transparency of the study (presented in paper I), together with the evaluations presented in paper III and IV.

The MRC framework emphasises the importance of doing a thorough developmental phase in planning for a clinical trial. [120] The developmental phase of the AVRre trial had several activities to facilitate the intervention definition and refinement, including conducting meetings with important personnel and presenting information within the university hospital, intensely developing the hotline manual, conducting pre-trial focus groups and interviews with former patients (user involvement in the planning phase), educating and training intervention staff, and conducting a pilot study. All these pre-main trial activities were recorded by the PC for evaluation purposes and strengthened the post-trial evaluation as informed by the MRC framework and presented in paper IV.

The main trial started with the hotline being served by the nurse staff in the cardiac ICU at the university hospital. However, after gaining experience within a few weeks, we recruited a group of volunteer nurses from the ICU to staff the hotline. The only change was that now fewer ICU nurses (8 in the group) would provide the same hotline service and give the planned intervention to the participants. We failed to analyse the ICU department's relationship with the intervention, which is a limitation. On the other hand, this trimming down of staff also strengthened the study in the sense that it facilitated achieving greater fidelity for the intervention by using a smaller, dedicated hotline staff. Some might perceive this change as a threat to the trial's validity, because we changed the logistics of intervention delivery. However, this staff change occurred early in the trial and in reality, did not affect the planned intervention in any way for the participants.

We conducted a one two-hour educational session and training opportunity for all the hotline staff to prepare for the intervention. Retrospectively, we concluded that this short session was a limitation of the study design. More education and training preparation might have improved the roll-out of the AVRre trial and ultimately might have improved the outcomes of the trial. In the follow-up of the hotline staff during the main trial, this suggestion is tempered by the fact that the follow-up led to a high-fidelity implementation of the intervention. Thus, we believe that the educational session and training was a true strength of the study. This is an important feature to consider when designing a similar future clinical trial. We also suggest that this aspect of the design likely saved time and effort prior to conducting the main trial. However, training must be carefully planned and evaluated to fit the actual study population and the healthcare system (context) in which the intervention unfolds.

The pilot study (N=10) was appropriate for its planned purpose and provided important information for refining the main trial and strengthened the overall study. One important input led to a change in how and when the participants were informed of their group

allocation. We found that a majority of the five pilot intervention participants had not opened the sealed envelope when calling them on day 2 after discharge from hospital. That led us to change how we informed the patients. Instead of giving them an envelope containing instructions, we directly relayed information face-to-face to the participant at the time of their discharge from the university hospital. This procedural change likely produced greater patient adherence in the follow-up of the study. Even though it was informative, conducting a larger pilot that would include testing, assessment, and refinement of the theoretical foundations of the intervention and how well the primary outcomes fit the intervention might have led to stronger positive outcomes. Information gained during a larger pilot study could also have contributed to a better sample-size calculation for the AVRre trial.

We might have underestimated the contextual influences on the intervention in the design, which limited our possibilities to analyse its impact on the outcomes. More attention on the influence of local hospitals, primary care (GPs), and caregivers could have been an area for even more elaborated explorations before and after the trial. However, we had already integrated validated questions related to some important features of contextual matters. These questions provided valuable knowledge about understanding the outcomes. The MRC model includes evaluation of contextual factors and has the potential to increase the value of clinical trials and reduce research waste. [53]

The value of integrating user experiences in the evaluation of the intervention was appropriate to achieve the aim of paper IV, a broader understanding of the ‘why’s’ in clinical trial outcomes, which is often warranted in medical research. [57] Applying a novel mixed-methods approach enhanced the extended evaluation purpose in this study, as presented in paper IV. Performing a longer longitudinal follow-up of the user experiences than what our study actually did might have bolstered the study.

Study outcomes

Paper II

In conducting our systematic review, we were guided by the considerations of Rao. [121] According to Rao, if researchers interpret that a set of papers to be reviewed contains too much clinical and methodological heterogeneity, then they might evaluate whether it is appropriate to conduct a meta-analysis. [121] Instead, they could consider doing only a systematic review. We determined that the pertinent studies we identified had little clinical and methodological heterogeneity; thus, we decided to perform a meta-analysis.

In paper II, we used I^2 statistics to determine the percentage of variance in a meta-analysis that is attributed to heterogeneity in the studies. [122] Our assessment using I^2 statistics revealed that there was a high degree of statistical heterogeneity (> 90%). Higgins and colleagues proposed using the following threshold I^2 values when quantifying the magnitude of heterogeneity: low, 25%; moderate, 50%; high, 75%. [123] We proceeded with sub-group and meta-regression analyses and were able to better understand potential causes of this heterogeneity; there was sufficient power (> 10 studies) to determine this. This in-depth analysis strengthened the study reported in paper II. Meta-regression was an appropriate analytical step for this purpose. If the I^2 ratio is large, then it is reasonable to analyse the heterogeneity further [111], which we did by using meta-regression in a random-effects model. Given that the I^2 is a measure of inconsistency across the findings of the included papers, the R^2 values from the regression analyses revealed how much of the heterogeneity could be explained by the study-level covariates. [111]

We used the NOS to evaluate the quality of the included articles. [77] A Scientific Statement From the American Heart Association (AHA) written by Rao and colleagues stated that there is no uniform agreement on how to evaluate the quality of different types of studies. [121] Since most cohort studies are observational, we chose NOS because it is widely used for

assessing cohort articles. [77] As we included different study types, we could have used other assessment tools in addition to NOS for assessing the observational cohort studies. Alternatively, we could have used the Grades of Recommendation, Assessment Development and Evaluation Working Group (GRADE), which is a promising tool for quality assessment of scientific evidence. [124] However, GRADE is an imperfect tool, and some write that it needs more empirical evidence to support using it for its intended purpose of making valid recommendations. [125] The AHA does not explicitly recommend specific tools to assess studies for meta-analyses. [121] However, one strategy that is acceptable to the AHA is using two researchers independently to carefully assess the weaknesses and strengths of the different included studies, instead of using NOS. [121] This approach revealed an interesting finding related to the quality of how validated hospital readmission statistics in individual studies are described. We were concerned about the lack of explicit/transparent statements in the included studies on how the readmission statistics were validated, which prompted us to assess the quality overall to be moderate to high. This finding mostly fits the retrospective cohort studies based on registry data that we included. This finding might also be considered to be a weakness of our meta-analysis, in addition to our warning about transparent descriptions on how thirty-day readmission data based on registry data are validated. This is also linked to our challenge of obtaining validated 30-DACR data from the NPR in Norway for analysing the primary outcomes of the AVRre trial reported in paper III.

Paper III

As described in paper I, we intended to extract readmission data from the NPR. In paper II, however, we found that very few studies done using registry data had transparent statements on how these data were validated. This lack changed our plans somewhat. Before paper III was published and prior to the AVRre main trial initiation, we purchased from the NPR,

anonymised historical data on the Norwegian 30-DACR rate after SAVR. Our goal was to verify that the primary outcome (30-DACR rate) data could be collected from the NPR with a high degree of validity. However, the NPR data was not considered to be a valid measurement of the 30-DACR after SAVR for our study population.

We measured the degree of co-morbidities by using medical diagnoses from participants' medical charts to calculate the Charlson Comorbidity Index (CCI) score, [126] an often used and valid method for pre-risk evaluation. [127-129] We decided not to include SCQ-16 scores, because many parts of the participants' questionnaire were incomplete or only partially completed and because its questions were answered inconsistently (i.e., there were many systematic errors). Indeed, participants reported that they were uncertain on how to fill out the SCQ-16. An informal comparison between the diagnoses in the medical charts and the answers on the self-reported SCQ-16 confirmed that including SCQ-16 scores likely would have introduced information bias. The risk of information bias via the SCQ has been reported previously. [130] Medical chart and other information collected at baseline provided an accurate description of baseline demographic and clinical variables for pre-risk scoring and other assessments; these data strengthen the AVRre study.

Intention-to-treat analysis (ITT) analysis is a more conservative approach for analysing the effects of a clinical trial, but it can lead to an underestimate of the intervention effect and also yield a type II error. [131] By contrast, per-protocol (PP) analysis can lead to an overestimation of the effect and yield a type I error. [132] A type II error will, in the worst case, postpone an effective intervention, which is less harmful than exposing patients to an unnecessary and potentially harmful intervention by committing a type I error. In line with CONSORT recommendations, we performed both ITT and PP analyses, which yielded similar negative results on the primary outcome and confirmed that our intervention likely did not act to reduce readmissions after SAVR. For clinical purposes, we chose PP as the main way to

analyse the primary outcome and to determine the actual efficacy of the intervention. However, the preferred method is ITT, because with this method, losing statistical power due to reduced sample size is avoided and equal distribution of confounding variables is maintained between the groups. Thus, this approach avoided analysing a biased dataset. [132]

Not all randomly allocated participants (N=288) underwent SAVR. Thus, we chose PP to analyse data from participants who took part in the entire intervention (N=260) in order to estimate the effect of the 24/7 telephone hotline on 30-DACR rates. However, for sensitivity analyses, we conducted ITT analysis on the (N=282) participants in the cohort who underwent SAVR treatment. This enabled us to assess the effect of the assigned treatment, as the dataset for these participants was complete for the primary outcome. Performing both types of analyses is recommended, especially in cases where some data is missing due to lack of adherence to the protocol and/or due to loss to follow-up. [133] As the dataset related to the secondary outcomes had some missing data, we conducted MI for the PP and ITT analyses.

In the PP analysis, approximately 10% of the EQ-5D-3L scores and 6% of the HADS scores had missing data. For the secondary outcomes, total missing data was 12% (33/282) at T1; 15.5% (43/282) at T2; 13.5% (38/282) at T3; and 18% (51/282) at T4. In addition to the missing data that was > 10%, we found that at each measurement point, the control group had more missing data than the intervention group. We chose, therefore, to conduct MI to replace the missing data.

LMM analysis for the repeated measurements up to one year after surgery was chosen as the most appropriate method to measure the longitudinal results from the HADS and EQ-5D-3L questionnaires. Repeated measurements (in longitudinal studies) for each case are often dependent, but this can vary among cases. To mitigate this problem in statistical testing, without committing a type I error, we used a random intercept model in the LMM analysis to handle the heterogeneity in clusters of the data. [98] This approach avoids a

complete case analysis, in which single cases are deleted entirely if one or more of the measurements are missing. Of course, using this latter approach can threaten the needed sample size and statistical power, leading to a higher risk of having biased results. [98] LMM handles missing values better than analysis of variance (ANOVA) with repeated measurements, for example, which requires wholesale deletion of a case if any data in those cases are missing. [98] An often-used method for replacing missing values is to use the samples' grand mean value to perform single imputations, or to use the predictive distribution of each case having missing data. [100, 134] However, this method can lead to a flawed estimation of the variance and a biased result. [100] We, therefore, used MI with 20 iterations [100] to obtain a pooled estimate for missing data.

The total missing values (N=282) ranged from 12 to 18% from T1 to T4 assessment times. The missing value analysis suggested (produced by an SPSS 25.0 routine), together with our clinical evaluation, that we could validly conduct MI under the missing at random (MAR) assumption. For sensitivity purposes, we compared the MI results with those obtained by the single imputation method, in which we replaced the missing values of a given case with the samples' mean distribution value. This approach yielded similar *P* values but with larger standard errors, supporting our choice to use MI for our analyses.

The reliability of the scales (HADS and EQ-5D-3L) we used was acceptable, as determined statistically. The internal consistency of the HADS questionnaires was accessed by Cronbach's alpha and was good. [83] The Cronbach's alpha for HADS-A was 0.8 and that for HADS-D was 0.79. We chose to not use Cronbach's alpha to assess the internal consistency of the EQ-5D questionnaires, because of its inability to measure the scales' quality. [135] However, we measured the correlation between the EQ-5D-3L VAS scores and EQ-5D-3L index value (VAS UK set) scores, which yielded significant Pearson correlations ranging from 0.58 to 0.64. These values indicated a high degree of consistency between the

two health status scores within the questionnaire. A scale that measures PROMs might be less reliable, because it lacks the ability to fully capture extreme responses (i.e., those in the upper or lower part of the scale), yielding a ceiling effect. [136]

A ceiling effect was present in the EQ-5D-3L measurement of the UK index value score (VAS or TTO based); with this scale, a health state of 1 is the best imaginable health state. The ceiling effect was present three months after surgery (Table 4). Interestingly, EQ-VAS scores demonstrated no ceiling effect at any assessment during follow-up. One reason for these differences is that this scale might measure different qualities of the perceived health state (e.g., EQ-VAS might measure perceptions of 'overall health'), as suggested previously. [137] Therefore, EQ-5D VAS and EQ-5D index value cannot be compared as equal entities. The presence of a ceiling effect indicates that the index value scores of the scale (VAS based) scale might be less sensitive in capturing the full extent of any positive effect of our intervention longitudinally. Similar findings between EQ-5D VAS and EQ-5D index scores and ceiling effect have been observed previously. [138] The cut-off range for the highest scores was set to 97-100 for the EQ-5D VAS score and 1.000 for the index value score; a ceiling effect is present if more than 15% of the responses fall within that cut-off range. [139]

Table 4. Distribution of highest scores of the intervention group for the EQ-5D-3L VAS and EQ-5D-3L index values over time.

Elapsed time after surgery	EQ-5D-3L VAS	EQ-5D-3L UK index value (VAS based)	EQ-5D-3L UK index value (TTO based)
	Scale score from 0 to 100 mm	Scale score from 0.073 to 1	Scale score from 0.594 to 1
1 month (%)	2.1	9.5	9.2
3 months (%)	7.2	40.8	41.1
6 months (%)	8.2	40.5	40.5
1 year (%)	11.7	44.3	44.8

The ancillary analysis of the proportion of unavoidable and avoidable readmissions in the trial was conducted independently by three clinical researchers in the project group.

They were blinded to the individual case group allocation in the trial. Such analysis was subjective, even if only the diagnosis codes were used for assessing the proportions of unavoidable readmissions. Since the assessment was subjective, we chose not to discuss the cases that the evaluators disagreed and failed to reach consensus on. This kind of procedure can represent the real-world context in which local physicians and routine practices may or may not treat similar cases differently on readmission. The proportion of unavoidable readmissions in the AVRre trial reached at least 75% and might even be higher for this SAVR population. Such an analysis might have approached validity more closely if we had used external evaluators. However, we rationalised that this analysis needed to be carried out by those having knowledge of local healthcare systems, which we feel justified the use of internal evaluators.

Doing a CPH regression analysis was the most appropriate choice for our assessment of predictors of 30-DACR after SAVR, especially because of time. The first step was to assess the data population assumptions for conducting a CPH analysis; these were adequately met. The assumptions are as follows: independency of observations, no multicollinearity (low variance inflation factor), no interaction effects, and a constant hazard ratio (HR) across time for the individuals (the proportional hazards assumption). The latter can also be evaluated statistically with SPSS 25.0. The next step was to complete a univariate analysis of chosen covariates of interest. Covariates with a P value < 0.2 were selected for multivariate modeling of possible independent predictors of 30-DACR after SAVR. The chosen covariates were based on a clinical and theoretical assessment of the available data for the prediction model. We could have also used multivariate logistic regression analysis and odds ratios to identify the predictors of 30-DACR after SAVR instead of CPH with HRs, as both methods are measures that evaluate relative risk. [96] Because of proportionality in the CPH modelling, we could not determine whether the association with the covariates was real; rather, it was the

best approximation. [96] The final model in our CPH regression analysis did not overfit the number of predictors — i.e., describing the random error in the data rather than the relationships among variables — and the validation was accurate for the intermediate steps to reach the final model.

Paper IV

One strength of the present thesis work was the nature of the data collected and analysed. The amount and sources of data (i.e., from several different sources) enabled us to compare the various results of different aspects of the AVRre trial, which strengthened the validity of the process evaluation. Results from the focus group were corroborated the results from the field note analysis, even though they were different kinds of data; this nature of the data strengthened the validity of the interpretations of the analyses and findings presented in paper IV. The design of the study and parallel evaluation during the trial prevented confirmation bias. While the main trial was being conducted, the PC assessed in parallel probable interpretations of the field notes and observations during multiple conversations and discussions with the research group.

The parallel interplay between data collection, measurements, and theory-based interim analyses strengthened the trustworthiness of the final qualitative results, and these procedures were in line with recommended qualitative analysis approaches. [87, 88, 105] Although different tools are available for assessing the quality of the qualitative methodology used here, consensus is lacking on which tools are the most appropriate for each situation. [140] We mainly followed the recommendations of Malterud when we conducted the qualitative analyses for paper IV. [141] It is important to note that the PC was aware of the possibility for confirmation bias. This kind of bias can be introduced inadvertently early in a study and can potentially impact the remainder of the study. The presence of confirmation

bias can be challenging to rule out completely due to the subjective nature of qualitative analyses. However, from the beginning in the planning phase, we took precautions to prevent confirmation bias by being aware of it and taking appropriate action.

The risk of confirmation bias was mitigated, in part, by the high participant response rate. All participants who used the hotline phone service answered the questions about their experiences with the hotline, and 84% of the entire study population (same rate in both intervention and control groups) answered questions about their hospital discharge experiences. The high response rate increased our confidence in the validity of the AVRre trial.

For PREM questions related to the discharge, Cronbach's alpha was 0.74, which was an acceptable value for the scale's reliability. Since the results were similar to the findings of the Norwegian national survey of hospital discharge experiences, this increased the generalisability of our present results. While 58% of the hotline callers rated their use of the service to be highly satisfactory, another 20% of the hotline callers chose not to rate the service, instead answering the question as 'not applicable'. It is possible that some in this latter group of hotline callers might be participants who were dissatisfied with the service but declined to rate it negatively, because they viewed the intervention overall to be positive and have potential for being useful during the early rehabilitation phase. We found, however, no systematic associations between the participants and 'not applicable' responses. No other available data suggested reasons that might explain why 20% of the hotline callers chose not to rate the service. Another possible reason for declining to rate the service is simple negligence.

The PREM questions we used in the AVRre trial were based on similar questions used in a Norwegian national survey on patient experiences about hospital stay and discharge; this survey content was tested and found to be valid for its purpose. [142] The Norwegian

national survey was administered one month after hospital discharge in the sample population. By contrast, our questionnaire on discharge experiences was administered three months after surgery, a delay that potentially could have increased the risk of recall bias. [143] In our study, however, the mean hospital LOS was 10 days, with some participants being hospitalised for 2 or 3 weeks before being discharged. Because of these hospital stays, we are confident that the time when the questionnaire was administered (i.e., three months after surgery) was appropriate and was subject to minimal recall bias. Thus, we are confident that the results were valid.

The AVRre research group and PC continuously discussed intervention-related processes (case-related processes) among themselves and with the hotline staff. In addition, the hotline staff participated in educational sessions and consultations. This resulted in a robust setup for the follow-up of the intervention and greatly strengthened the evaluations. The PC essentially conducted active field work using a semi-structured approach, in which both deductive and inductive approaches were applied for evaluation purposes. This mixed-methods prospective approach enabled us to increase opportunities to observe, record, and interpret the outcomes, thereby ensuring valid results. However, applying methods that are highly structured and less inductive, as in this case, can inadvertently cause one to overlook potentially meaningful data, which can threaten the validity of the results. [87] To avoid this possibility, we took steps to ensure that the mixed-methods approach was balanced throughout the intervention, and we actively sought to prevent confirmation and performance bias, and the Hawthorne effect in the university hospital context. The novelty of the study design and outcome measurements were carefully handled and appropriately managed to yield valid and trustworthy results, which strengthened the interpretations of results presented in paper IV.

Study intervention

Paper III

In the AVRre intervention, we employed a novel approach for following up newly discharged SAVR patients by telephone. The telephone service in this intervention comprised two elements — standard TFU plus a 24/7 hotline — for a higher quality of follow-up in the early rehabilitation phase after hospital discharge. TFUs conducted in a timely fashion with educational and practical advice for using the TFU and for managing and monitoring symptoms have reduced readmissions in other clinical settings. [42] Making available the 24/7 hotline service during the initial month after hospital discharge after SAVR, in addition to the standard discharge care (TFU), empowered intervention participants to obtain advice whenever they wanted and thereby increased their level of self-care management. We hypothesised that this kind of follow-up system would reduce the 30-DACR rate after SAVR. However, our data indicated otherwise.

There are several possible reasons why an intervention effect was not observed. Firstly, the planned, and ultimately administered, TFU dose might have been too little (two calls). Perhaps we should have done more TFUs. More follow-up calls might have positively pushed participants at higher risk for readmission to solve simple health concerns. However, most readmissions took place within 14 days (83%), and nearly half of them occurred within one week of hospital discharge. This suggests that more calls should have been made within the first 14 days after discharge.

Secondly, as discussed in paper III, the increased attention to their health condition and symptoms after discharge could have contributed to the increased readmissions in the intervention group. We also noticed a quite high rate of readmissions among control group participants that was not significantly different from that of intervention group. A UK study found a paradoxical result: there were significantly more readmissions among intervention

participants who received home visits from a pharmacist who discussed with them several side effects of the patients' medication. [144] The authors suggested that more attention towards their problems, through the intervention, might have caused the paradox result.

We also performed ancillary analyses on the proportion of unavoidable readmissions and found that slightly more readmissions were deemed unavoidable for the intervention group (81% vs. 69%) compared to the control group. Even though the experienced clinicians in the research group assessed whether a readmission was unavoidable and even though they were blinded to group allocation, their decision to label a readmission as 'unavoidable' is subjective and not completely without bias. This could have contributed, in part, to these large unavoidable readmission percentages. With this in mind, these readmission numbers should be interpreted as rather crude numbers. We recognise that some of the readmissions the experts disagreed on could also have been labelled as 'unavoidable'. This means that the published statistics might represent a conservative estimate of unavoidable readmissions of patients after SAVR.

As alluded to above, the judgements of the clinicians are subjective, being moulded by their experience, professional views, and knowledge about the healthcare system. They are also sensitive to local differences in handling complications. For example, in one hospital a clinician may treat arrhythmias through out-patient consultations, whereas, in another hospital, a clinician would treat arrhythmias by hospitalising the patients. Nonetheless, we still conclude that a clear majority of the readmissions were unavoidable and that this likely affected the intervention's ability to reduce the total number of readmissions. Likely by chance there were slightly more readmissions in the intervention group than in the control group; this made it harder to detect an intervention effect. As we stated in paper III, this trial lacked sufficient statistical power to detect between-group differences in avoidable readmissions. We had no prior information about this possibility. So, this knowledge can now

be used to form new hypotheses and for power calculations in future studies aiming to reduce the 30-DACR rate after SAVR.

Paper IV

The nurses who staffed the intervention hotline had various skill levels of communication ability and styles of communication, and past experiences. This diversity of abilities increases the risk of performance bias when delivering the intervention. The risk of performance bias was reduced by close and continuous follow-up during the trial that included educational sessions, case discussions, and consultations provided together with the hotline staff.

Also, a learning effect for presenting trial-specific information to callers was likely present, and especially since the intervention had a longitudinal design. However, this was handled prospectively with planned follow-up during the trial. Thus, the response from the intervention participants, specifically, information in the questionnaire and the field notes, confirmed that the uptake of the intervention was good, which strengthens the study. Bolstering our evidence that a learning effect was minimised is seen in responses of participants in the control group. Several participants in the control group used the opportunity in the 3-month and the 1-year follow-up questionnaires to express their views (in written narratives) on the discharge care they received during the trial. Their narratives underlined the findings that we independently observed that there was a gap in the care continuum for the SAVR study population. They believed that the intervention was a reasonable offer to minimise the effects of a care gap, especially for the early rehabilitation phase after hospital discharge.

The intervention was delivered from the university hospital by experienced ICU nurses with several robust tools designed for the AVRre trial (the 24/7 hotline manual, the monitoring PC, experienced physicians on duty, own experiences with cardiac-surgery

patients) at their disposal when replying to participants' post-discharge calls. This collection of tools essentially provided the intervention-group participants with a fast and direct route to secure health advice. Approximately one of ten (9%) participants were transferred directly to a rehabilitation facility before transferring to home, and for these participants could have 'short circuited' their participation to some extent; this situation was one reason given by participants for why they chose not to use the hotline. However, the rehabilitation facilities did not have a physician present on duty at any time, and the nurse staffing at the rehabilitation facility is limited during evenings and nights. Having said this, some participants did call the hotline from the rehabilitation centre, as we instructed them to do freely, if needed.

Mostly, participants received the intervention in their specific home context, which could have differentially influenced their degree of adherence to the intervention and might have contributed to a lower external validity in the AVRre trial. We sent an alert SMS prior to doing the actual TFU calls, which allowed the participants to prepare for the call at a chosen time. This procedure might have facilitated the outcomes of the TFU for the participants and contributed to their high expressed satisfaction with the intervention. The field notes revealed that several participants had prepared questions that they were eager to ask when the PC called. The latter suggests, together with the present evidence from the study, that our intervention was truly clinically important for the participants, an important point that strengthens the rationale for conducting the intervention within our context.

External validity of the study

External validity in clinical research and experimental design refers to what degree the results from a clinical trial or experiment are generalizable to a given patient population in different contexts. [116] Are the results credible proxies for SAVR patients in the real world,

representing the true relationship between observations in a study and what the situation is in the real world for SAVR patients? Can we draw credible inferences from the results of the intervention to the observed effects? [116] These are important questions to answer in order to assess the external validity of a study, in our case, the AVRre trial.

We cannot rule out a possible patient selection bias in the AVRre trial, even though we accepted our study cohort as being representative of the elective SAVR patient population in Norway. Given our clinical experience and history at the university hospital, it seems reasonable that the study population was indeed representative. Having met this assumption, we felt justified in using comparative statistical testing.

Several factors increased the external validity in our study. Firstly, the study sampled a broad swath of the SAVR patient population in a university hospital, which is responsible for half of the national population. Secondly, the intervention was not too difficult for the participants to comply with. Thirdly, the gender distribution of participants in the study reflected the real-world gender composition of patients undergoing elective SAVR treatment. However, our statement of external validity should still be cautiously considered, knowing that even with an RCT design, it is challenging to draw true scientific inferences from the results of a study population sampled from the whole population. [145] This is especially the case if the theoretical basis of doing a study is not integrated into the study so that the 'why it worked' can be reached. In addition, it can be difficult with RCTs to determine statistical significance of the effectiveness of a "treatment". [145] As we discussed in paper III, the AVRre trial was a single-centre study in a specific context, which can decrease the generalizability of the study. To be able to make a reasonable critical appraisal of the external validity of a study, it is necessary to accurately describe the methodology used.

Several points strengthen the validity of the trial: the results from paper IV show that the intervention was conducted with high fidelity, the intervention dose that was delivered

occurred as planned, and participants were highly satisfied with the intervention. The high satisfaction of both components in the intervention also increase the external validity. However, as discussed, the lack of absolute adherence to the 'treatment' may be a threat to robust validity. One reason suggests that a slightly higher proportion of unavoidable readmissions occurred in the intervention arm, and another might have been that the usual care was not delivered as uniformly as we had assumed.

Usual care in the AVRre trial was conducted by several nurses and physicians, at different times and locations. We found that local discharge managements differentially affected the readmission proportions, which might also have impacted other factors related to increasing or decreasing readmission within 30 days after discharge. The AVRre trial might have underestimated the complexity of the usual care and might have been able to investigate the local influences more in-depth if we had planned for this aspect and obtained data accordingly. We cannot rule out the possibility of the Hawthorne effect due to the staff being aware of the interventions' intentions. However, we did not register any substantial changes during the intervention period. There was a raised awareness, though, towards the information process in the discharge at the university hospital, but no real changes were implemented that might have altered the discharge care. The participating hospitals are adhering to the ESC guidelines for the treatment of the heart valve patients. [5]

Transferability is an often used term in qualitative research, which can be regarded as the equivalent term of generalizability in quantitative research. [141] The appraisal of whether the sample was adequate and sufficiently varied can account for a higher or lower transferability of the qualitative results. We suggest that the qualitative findings are transferable from the study population to the SAVR population in general, given the same study context. Obviously however, the qualitative findings cannot be used to support generalizability based upon statistical evaluations, as often as it is with the use of quantitative

methodology. The research design, including a process evaluation guided by the MRC model, was able to generate knowledge and information to elaborate on the assessment of the external validity. This resulted in an increased external validity of the trial.

8.2 General discussion

8.2.1 Discussion of prospective protocol for the AVRre trial

We adhered to SPIRIT [70] and CONSORT guidelines, [78] specifications designed to prevent poor and/or irregular reporting of the methodology and the outcomes of clinical trials. A promising initiative to link and consolidate the outcome reporting of these two guidelines is the Planned Endpoints in Clinical Trials (InsPECT), [146] recommendations developed in accordance with the Enhancing the Quality and Transparency of Health Research Quality EQUATOR Network. [147] The reporting from clinical trials have improved over the years, but there are still quality differences between high- and low-impact factor journals, where lower-impact factor journals are more likely to publish trials that are less non-transparent and with a higher risk of bias. [146]

A review published in 2017 determined that 58% of the reported trials had unclear reporting of allocation concealment, which is a crucial aspect for being able to critically appraise an RCT. [148] Moreover, the so-called replication, or reproducibility, crisis in science [149] advocates more initiatives to achieve a higher standard of the reported outcomes. [150] Our protocol of the AVRre trial, together with the reporting in paper III and IV, produced a clear ‘picture’ of what we did, allowing for replication of at least the core elements of the intervention and facilitating a pragmatic replication of the intervention in another real-world context. That being said, we could have improved aspects of trial transparency (e.g., the descriptions of the contexts in which the intervention was conducted); doing this would have facilitated the replicability of the trial protocol reported in paper I.

Furthermore, we might have provided an even more detailed description of the theoretical background in paper I to meet the scientific critique of the problem basis of less commonly reporting of clinical trials. [150] However, the ambiguous and inconsistently reported evidence of readmission reduction effects of prior interventions justified doing the AVRre trial. Moreover, the novel and promising design of the effects of symptom monitoring and educational inputs after the discharge justified doing the trial. The participants' satisfaction and the documented burden within a month after surgery (e.g., symptoms of depression increased from baseline compared to one month after surgery) provided strong evidence of the scientific value of testing the intervention, as the protocol reported in paper I.

8.2.2 Discussion of overall incidence of 30-DACRs after SAVR and TAVR

We found a high and similar 30-DACR rate after SAVR and TAVR reported in paper II (17% and 16%, respectively). The 30-DACR rates were higher than the pooled results reported for the USA and Scandinavia (Denmark and Norway), and lower in other countries. Many of the large studies from the USA were retrospective, multicentre, and registry studies (mostly sourced from administrative databases). Registries might capture more readmissions if they can track patients across hospitals and ensure a high degree of data completeness compared to single-centre studies, which might register readmissions only to their own hospital. On the other hand, registry studies might have a larger error due to for example, incorrect coding, [151] which can lead to an overestimated incidence of the 30-DACR rate.

We found that when working with the readmission rate after SAVR in Norway, coding practice of hospitals and method of extracting the 30-DACRs are flawed for purposes of scientific analyses. In paper II, we concluded that studies using data from registries should begin to provide more transparent statements on how they arrive at their readmission statistics, a deficiency that has been highlighted before by van Walraven and Austin. [152]

However, using a prospective follow-up design and complete and clear definition of the 30-DACR rate, the AVRre trial revealed an overall rate of 22.3%.

Another issue surrounding discharge practices was reported in paper IV. Therein, we reported that local hospitals in Norway have different discharge management systems, which might lead to significant differences in calculated readmission rates. A recent study of Heggestad revealed that shorter hospital LOSs lead to an increase in readmissions. [29] Curtailing the LOS for financial reasons should not, for ethical reasons, be advocated if harm to patients is the result. However, in Norway, which does not penalise hospitals for readmissions and where hospitals' finances are partially driven by achieving diagnosis-related group points, a readmission will economically be positive if the patients are not hindering other patients' stays.

The United States healthcare system, in which economic penalties are enforced when the 30-DACR rate is above an expected risk-adjusted level, is probably less likely to be interested in funding more research on readmission outcomes. The recent literature suggests that 30-DACR rates are trending downward in surgical populations in the USA, with an accelerating decline after introducing the HRRP. [153] The findings of declining readmissions have also sparked a debate among researchers whether the HRRP has had the unintended consequence of producing higher mortality rates among heart failure patients. [154, 155] These considerations demonstrate the methodological challenges facing efforts to improve readmission outcomes and the use of 30-DACR rates as a quality indicator. Further, they may also speak to why there are differences among countries on readmission outcomes. It is known that readmission rates differ among countries, and it has been proposed that a search should begin for answers on how healthcare may be mismanaged, specifically, the hospital LOS or the aftercare by the GPs, for example. [156] Recent literature also reveals an interesting finding in which high-ranking hospitals in the USA have lower mortality rates and

higher patient satisfaction in cardiovascular care compared to lower-ranked hospitals. [157] However, the readmission rates are similar between the high- and low-ranked hospitals [157], which speaks to the critique of and challenges of using the readmission outcome as a quality indicator. [23, 158]

The accurate follow-up of the design and outcomes we analysed in the systematic review and meta-analysis yielded overall readmission-rate estimates, which are likely the best present evidence (within the confidence intervals) of the overall global 30-DACR rates after SAVR and TAVR. In paper III, we continued with a prospective RCT to test an intervention to reduce the 30-DACR rate after SAVR. The intervention failed to significantly reduce readmissions. However, at least it had no negative effect on mortality or other adverse side effects. Anecdotally, we observed some cases in which the telephone support intervention may have been lifesaving. [unpublished observations]

8.2.3 Discussion of 30-DACRs after SAVR and patient-reported outcomes

The meta-analysis of relevant studies reported in the literature demonstrated that the pooled 30-DACR rate for the SAVR population is 17%. In paper III, the AVRre trial yielded an overall 30-DACR rate of 22.3%. The few studies validly reporting the 30-DACR rate after SAVR demonstrate a similarly high rate, typically above 20%, in Scandinavia (Norway and Denmark), for example. [20, 21, 159] There are regional differences, as the meta-analysis demonstrated. Different economic drivers and healthcare systems across countries [156] might account for some of the difference between the AVRre trial's overall 30-DACR rate and the rates found in the meta-analysis.

An interesting finding in a meta-analysis reported in 2014 found that more recent interventions intended to reduce readmissions were significantly less effective than interventions conducted before 2002. [44] Recent research on TFU outcomes (led by nurses)

published after 2010 suggests that TFU does not reduce readmissions. [160] Our finding is in line with these results. However, it is important to discuss why later-tested interventions appear to be less effective in reducing readmissions. Leppin suggested some possible reasons, for example, a shift towards more technology-driven interventions in later years and less direct human contact. We suggest another possible reason: Increased quality of data collection across hospitals in capturing all relevant readmissions and improved data registration in recent years might lead to non-significant results. Thus, we speculate that in later attempts to reduce readmissions, more readmissions occurred in both usual-care and intervention cases, diluting any effect of the intervention.

Although we did not observe a significant reduction in 30-DACR rates as a result of the intervention, we did observe a significant reduction of anxiety symptoms up to one month after surgery and discharge in the intervention group (P= 0.031). Was this statistically significant difference clinically meaningful as well? Really, it needs to be considered from the patients' perspective.

The minimal clinical important difference (MCID) can be achieved by using distribution-based or anchor-based methods. [161] The partial Eta-squared score (a distribution-based score) in the General Linear Model (GLM) univariate (ANCOVA) analysis can be viewed as a correlation between an effect and the dependent variable. Eta and partial Eta describe the association related to the sample, while the Omega squared score estimates the association with the population and might be a stronger measure of the effect size. [162] However, distribution-based methods do not account for patients' perspectives of a meaningful difference. [161] The statistically significant difference we observed between the groups made clinical sense when analysing the findings of the survey on the hotline and the qualitative analyses as reported in paper IV. These findings must be preconditioned in order to state a clinically meaningful difference regarding symptoms of anxiety experienced by the

two groups. The conclusion would have been stronger if inclusion of the participants' perspectives had been designed to function as an anchor-based method together with the distribution-based methods, as recommended. [161] Thus, a cautious interpretation is required, and as we have reported in paper III, due to a small effect size (partial-eta square = 0.019) in the ANCOVA analysis.

Ancillary analyses provided several interesting findings. We found an interesting trend in which the youngest participants, those < 50 years old, had twice as many readmissions compared to patients > 50 years old. Recent research shows that patients < 65 years with concomitant chronic conditions might have more readmissions. [118] This finding warrants more research and clinical attention to be focussed across the age span of SAVR patients in order to determine the optimisation of the hospital discharge and follow-up needs to be titrated according to age. [118] It has already been demonstrated that advancing age increases the incidence of 30-DACR after SAVR. [163]. However, this is different from the findings of the AVRre trial, but is likely related to the observation that much of the research in this area of hospital readmissions has been conducted largely on older populations (> 65 years), at least in the USA. [118] This is appropriate in terms of research methodology and for statistical purposes when comparing different groups within the older segment of the patient population. However, we might not capture important information that is clinically important for the younger segment of the patient population to improve efforts to increase care quality.

Ancillary analyses provided other interesting findings. Firstly, we found that most of the readmissions in the intervention group could be considered unavoidable in the study context. More readmissions were cardiac related, which underlines the higher proportion of unavoidable readmissions we observed. This outcome hurt the likelihood of the telephone intervention reducing readmissions. Secondly, there was slightly more unavoidable

readmissions in the intervention versus the control group; however, this difference was not statistically significant.

We found in the study reported in paper II that there was little evidence about which risk factors specifically lead to 30-DACR after SAVAR. Therefore, we conducted a CPH analysis in that study. We found that patients who had symptoms of anxiety before surgery and/or were undergoing pleural drainage in hospital before discharge independently predicted 30-DACR after SAVR. This new and important finding implies that clinicians and researchers should attempt to improve the discharge and follow-up care of SAVR patients. This new knowledge can be used to individually tailor the discharge to take into account these factors, with the goal of preventing more readmissions.

Preoperative risk assessment, including testing for symptoms of anxiety, can be easily conducted. For patients undergoing pleural drainage, it might be determined that before discharge, they should be scheduled to get an outpatient consultation within one week of being discharged to home. With systematic cooperation of local hospitals, this simple change could reduce the 30-DACR rate. However, cost-benefit analyses need to be carefully undertaken to assess whether this will be cost-effective compared with the actual current discharge care procedures, since CPH modeling is a simplification of the real-world where the strengths of the statistical associations must be critically appraised.

Also, we found that the intervention reduced symptoms of anxiety within a month after the discharge, and combined with the knowledge that preoperative symptoms of anxiety predicts readmissions, indicates that the patients' anxiety state might be an important factor to address for healthcare professionals involved in SAVR discharge and follow-up care.

The monitoring and managing of participants' symptoms after hospital discharge during the AVRre trial prompted us to request two acute referrals to the university hospital because of a life-threatening cardiac tamponade. Both participants were < 60 years old, had

been treated with a mechanical valve, and were being treated with warfarin. A 1986 study conducted in Sweden found that surgical valve replacement (likely mechanical valves at that time) in combination with warfarin treatment was a common factor among patients diagnosed with late tamponade (median elapsed time to occurrence, day 8 after surgery; mean age, 53 years old, and total incidence of 1%). [164] A more recent study found that median day for occurrence of cardiac tamponade was day 17 after surgery. [165] In this study, the mean age was 58.5 years old; the total incidence was 4.3%. Furthermore, having a mechanical valve was an independent risk factor for tamponade. When the tamponade condition is drained in a timely fashion, the problem is solved and very few recurrences occur after the first drainage is completed. [165]

Solem and colleagues demonstrated that nausea and impaired well-being are early symptoms after SAVR, [164] and You and colleagues reported that the symptoms *'can be easily missed'* after discharge. [165] We found a total incidence rate of tamponade of 2.8% (8/282) within 30-days after discharge in the AVRre trial, whereas the incidence of in-hospital tamponade we observed was 4.3% (12/282). Moreover, the mean age for the population experiencing tamponade (N=8) within 30 days after discharge was 54 years, and 7 were males (88%). The symptom descriptions contained more common symptoms like reduced feelings of well-being, generalised chest pain, increasing dyspnoea, and coughing. In line with You et al., [165] specific knowledge and experience is required to interpret this condition as a possible pericardial effusion or tamponade.

The occurrence of more general symptoms in early stages of this complication after discharge requires experienced cardiovascular personnel to detect and diagnose the condition. The work of the experienced nurses staffing the hotline in the AVRre trial confirmed that they had the necessary requirements we needed for reliably delivering the hotline service. Two participants were acutely referred and readmitted with tamponade, requiring immediate

invasive drainage, which demonstrated a potential lifesaving benefit of the intervention. To illustrate one important challenge in the early rehabilitation phase, one patient in the AVRre trial was disallowed admission to a local hospital the evening before he was transferred to the university hospital for acute treatment of his tamponade. No fatalities resulted from the occurrence of the tamponade in the study population, which suggests that the present healthcare system works in favour of the patients experiencing tamponade. However, these patients need a final invasive solution sooner rather than later, which suggests that putting in place a bridge (hospital-home) intervention might be useful to potentially save lives. We noticed that men expressed more symptoms of dyspnoea in hotline calls after discharge compared to women

The theoretical foundation of how the intervention might reduce readmissions after SAVR needs further thought. Managing and monitoring symptoms after the discharge combined with educational input produce fewer readmissions after hospital discharge. [42] However, the expected self-preserving actions of the participants (hotline calls) are also based on the notion that patients will change their behaviour appropriately according to health advice given. In the AVRre trial, we could have emphasised important elements related to behavioural changes more in addition to the medical information provided by the intervention. For example, what strategies related to the discharge are best suited for promoting behavioural changes leading to enhanced self-efficacy and that prevent adverse medical events after SAVR? We might have underestimated the value of making clearer the connections between the components yielding increased self-efficacy and how this might unfold in the specific intervention we offered the SAVR patients. Medical personnel are trained to effectively provide information that promotes knowledge about healthy patient behaviour. However, they are often not trained in the use of specific strategies that might increase the likelihood that patients adhere optimally to a certain treatment or rehabilitation they are offered. [166]

We found that participants' symptoms of depression increased between baseline assessment (before surgery) and one month after surgery (supplemental material in paper III). The perceived health state, as measured by the EQ-5D UK index value score, decreased over the same assessment period (Figs. 6 and 7; supplemental material in paper III). This indicates that, for many of the participants in this study, they struggle to maintain a reasonable level of self-efficacy to achieve good health in the early rehabilitation period. This result has been reported earlier in other studies also. [167]

Fig. 6. Average participant total EQ-5D-3L index value score (UK VAS-based) over time in the AVRre trial

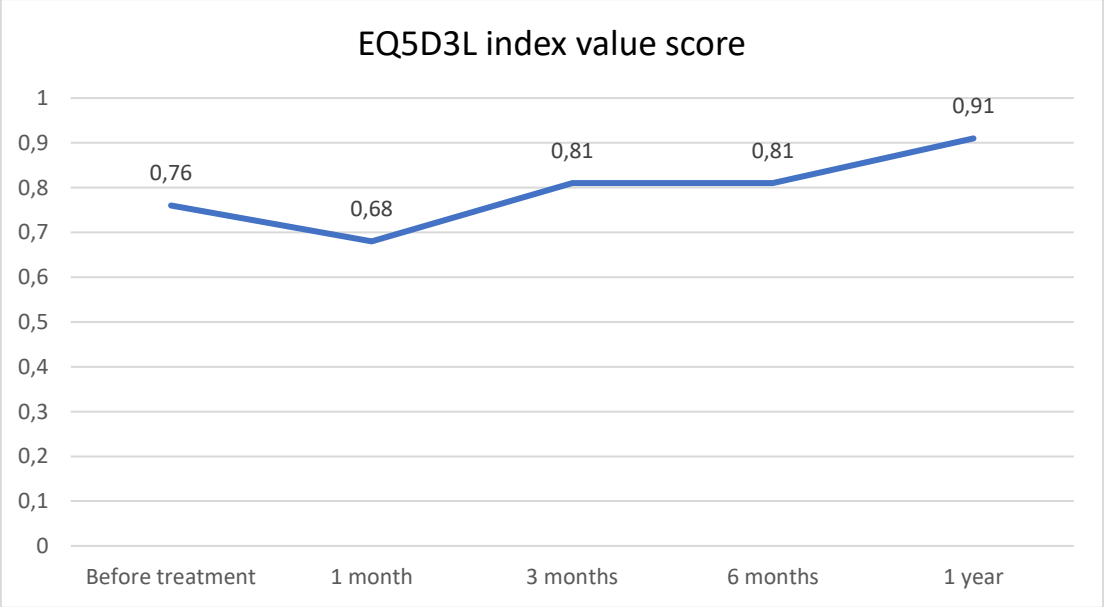
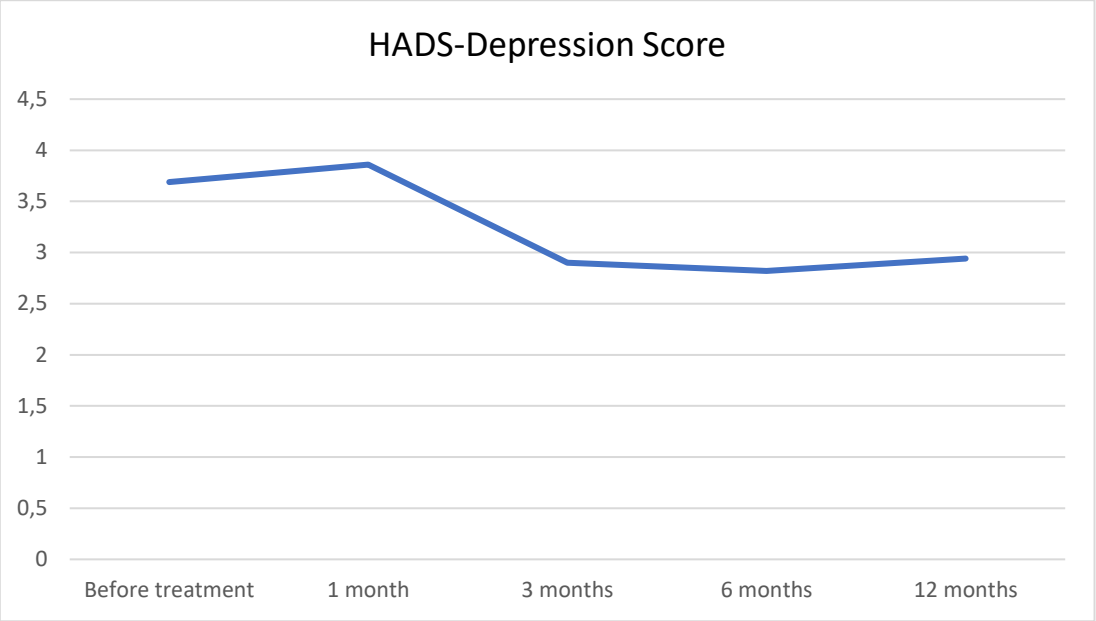


Fig. 7. Average participant total HADS score for depression over time in the AVRre trial



The findings presented in Figures 6 and 7 also suggest that our expectations regarding the outcomes were not adequately realised for several participants in the early rehabilitation phase; the qualitative findings reported in paper IV also support this idea. This result suggests that enhancing patient self-efficacy is both an important goal and a challenge for the SAVR population. Moreover, it suggests that a greater emphasis should be placed on using relevant strategies to encourage behavioural change. This, in turn, might increase adherence to the given treatment and aid reaching a health condition that could prevent new adverse medical events. On the other hand, participants of a RCT need to have a certain level of engagement and understanding in order to change their behaviour and reach healthier decisions. [168] This might have been difficult for many participants in the AVRre trial if they rehabilitated more slowly than they expected in the early phases after surgery.

Self-monitoring of behaviour, risk communication, and use of social support might be effective strategies for promoting behavioural changes by health care personnel. [169] Important determinants to produce behavioural change that promote health and prevent disease are, for example, increasing *knowledge* about health risks and benefits of healthy behaviour, possessing perceived capacity for *self-efficacy*, and *outcome expectations*. [170]

The latter determinant is based on Banduras' work on social cognitive theory, [171, 172] also commonly known as the theory of self-efficacy and its role in changing behaviour, as discussed by Sheer. [171, 172] The telephone intervention in the AVRre trial had elements designed to improve the participants' knowledge, their understanding of symptoms and risk assessments, and support their outcome expectations according to their individual needs. However, the trial might have benefitted more from a design that enhanced these core elements even more. Hence, we specifically emphasised how the elements could increase the participants' level of self-efficacy to positively influence the outcomes in the AVRre trial.

We targeted several aspects of what constitutes the participants' self-efficacy in order to support their healthy choices, which presumably would aid in reducing adverse medical events, including lowering readmissions. Participants received TFUs on two occasions within the first 14 days after discharge. These calls systematically related knowledge to the participants about the importance of engaging in physical activity to lower the probability of experiencing adverse events. Increased physical activity is associated with lower number of readmissions [173], and even reduces the risk of mortality after valve surgery. [174] To realise this aim, the hotline staff participated in an educational session with a specialist physiotherapist during the main trial that covered how to do this. They were also well prepared to always be aware of giving this important advice to intervention-group participants during the early rehabilitation phase after hospital discharge. Increased physical activity after cardiac surgery might also be associated with lower amounts of pleural effusion. [175]

We found that pleural drainage before discharge was a risk factor for readmission. The relationship between physical activity and incidence of pleural effusion in SAVR patients needs more attention from clinicians and needs to be studied more by researchers, especially in terms of optimising discharge and avoiding new medical adverse events. Moreover,

engaging in and adhering to CR should be emphasised more. [176] Our study participants, as reported in paper IV, stated that they often dismissed opportunities to take advantage of CR, because of excessive travel distances to a CR centre; this reason has also been reported to be a barrier to participating in CR. [177] We believe that the AVRre trial intervention provided the participants with sufficient knowledge about the importance of engaging in physical activity. However, we might have underestimated the extent to which we should have emphasised other components necessary for changing behaviour in both the short- and long-term: the risk part of imparted knowledge, the individuals' specific capacity for self-efficacy, and promotion of realistic expectations regarding outcomes.

According to Bandura, one's own beliefs in one's capacity to behave appropriately in prospective situations is crucial for producing outcomes of targeted behaviour [178]: *'Perceived self-efficacy refers to beliefs in one's capabilities to organize and execute the courses of action required to produce given attainments.'* [178] Promoting healthy behaviour requires appropriate communication, an aspect of post-discharge care that the ESC guidelines on secondary prevention and lifestyle modification highly recommend. [179] Actually producing more behavioural changes is still challenging to do (e.g. getting cardiac patients to adhere to CR). [179] One reason might be that healthcare interventions might not fully or effectively use knowledge from the social cognitive theory espoused by Bandura. It is surprising, given there is a range of instruments (disease-specific and generic tools) to measure self-efficacy in a healthcare context. [172] It might be useful in the future to develop a risk-assessment tool specifically for cardiac patients undergoing an invasive valve procedure, which would measure their self-efficacy before a treatment. Having results from such a tool for SAVR patients in early CR might allow researchers to further explore ways to modify behaviour to promote a healthier lifestyle that would avoid readmissions.

8.2.4 Discussion of the process evaluation of the implementation and impact of the intervention

The AVRre trial participants who actively used the hotline support service rated it as satisfactory and much needed, because they felt safe and secure, as reported in the 3-month questionnaire. The results from the qualitatively analysed interview data supported these findings. Although the 30-DACR rate was not reduced in the intervention group, it was likely not because the intervention, as it was carried out, was lacking in fidelity. Monitoring and managing symptoms and giving educational advice to the participants was hypothesised to be the core intervention elements that might lead to fewer readmissions. The high proportion of unavoidable readmissions is part of the explanation (paper III) as to why the 30-DACR rate was not reduced as a result of the telephone support intervention. Ten intervention participants were readmitted due to medical complications, and two of them had acute cardiac tamponade; the latter of which was invasively treated with a favourable outcome. The qualitative findings confirmed that the monitoring and managing assistance for symptoms offered through the intervention was valuable for the participants. The patients appreciated the educational advice given, and the hotline staff evaluated it as being useful, mostly because of the participants' reactions. Analysis of the participating staff's field notes also showed that the participants were satisfied with the 'link' to the university hospital. Therefore, the study's theoretical foundation was justified clinically, as measured by how the participants reacted to the intervention. However, the theoretical basis that would support patient behavioural change according to evidence-based healthcare advice aimed at avoiding readmissions after SAVR needs more investigation to tailor new interventions aimed to reduce readmissions.

An important finding in paper IV was that participants reported experiencing a gap in the care continuum from hospital to discharge to follow-up care. A perceived gap in the care continuum can be caused by several factors. [27] Lack of information as perceived by the

patients and between healthcare institutions and professionals is reported to be a common cause for gaps in the care continuum, often resulting in readmissions. [27] Physicians and nurses inform patients according to their individual needs; Norwegian national legislation mandates this approach. [180] Healthcare professionals target mostly the knowledge part of the delivery of post-discharge patient information. [169] Moreover, the SAVR patients are transferred only when considered physically stable and evaluated to be able to care for themselves after discharge.

Why, then, did the SAVR participants of the AVRre trial still experience a gap in the care continuum? The PROM data in paper III demonstrated that the first month after surgery was demanding for the participants (Figs. 6, 7). However, the intervention participants reported that the telephone support system 'bridged' the care continuum, because they received and had access to trusted healthcare advice. The intervention was conducted at the hospital where the surgery was done, which helped the participants to feel safe and secure, an outcome highly appreciated by them. This outcome might point towards another reason for the participants' perception of a gap in the care continuum after discharge, such as low socio-economic status and health literacy. [181, 182] Being independent and self-caring at home after surgery and discharge might come too early for some patients, as their statements suggested that they needed that kind of support.

In addition to supporting and securing the participants' physical condition after surgery, a more systematic approach was needed to enhance their socio-psychological support too; assistance in reorienting themselves after discharge also seemed warranted. Patients are vulnerable during transition of care. [183] We found that symptoms of anxiety before treatment predicted readmissions, as reported in paper III. Being aware of this possibility can help identify patients with anxiety, who can be followed up after discharge, hopefully to prevent readmissions.

Eight of 10 participants in the intervention group reported feeling more safe and secure because of the hotline availability, an observation that was corroborated by the contents of the field notes. This underlines the interventions' effect on reducing symptoms of anxiety and can be understood in terms of the qualitative finding that participants experienced a gap in the care continuum. The national surveys in Norway of patients reporting less satisfaction with the discharge supports the participants' statements, and challenges the idea that the transition of care between hospital to home and primary care is known. [43] The main objective of the Norwegian Healthcare Coordination Reform initiated in 2012 was to construct a more efficient healthcare system for patients moving from hospital to primary care, all the while without compromising the quality of care. [184] Our finding in which the participants indicated that the transition of care related to the discharge and follow-up needed to improve suggests that the objective of the coordination reform has not yet reached SAVR patients. There is no evidence to suggest that the coordination reform has led to more readmissions. [185] A recent governmental initiative in Norway designed to enhance patient satisfaction with hospital discharge (named 'Safe discharge') became part of the national Patient Safety Program in 2017. [186]

Half of the AVRre intervention participants did not use the hotline service for various reasons, as reported in paper IV. However, these participants stated that they recognised the value of the intervention for more vulnerable patients and also said that they appreciated the availability of it if they needed it themselves. The non-users underlined the potential positive effects of the intervention in the early rehabilitation phase. Therefore, we cannot conclude that the TFU somehow limited the effect of the hotline could have had on the outcomes. The hotline was perceived as an attractive and necessary service if the non-callers should need any advice on their health condition in addition to the two scheduled TFU phone calls.

The TFU phone calls on day 2 and 9 after discharge were administered as planned and were greatly appreciated by the participants. The PC experienced a learning curve as the TFU service unfolded, a phenomenon that could have introduced performance bias, in which the later participants received more tailored information than earlier ones. However, the PC was prepared for the possibility of a learning effect issue and had expert physicians for consulting purposes standby. Moreover, all intervention participants received at least two follow-up calls. In retrospect, the hotline staff said they wished they had more education and training in the pre-trial phase. This feeling of the staff not being at the asymptote of the learning curve before the main trial began might have impaired the fidelity of the delivery of the intervention early on in the main trial. However, the results were convincing enough for us to conclude that the intervention was delivered with high fidelity. The robust follow-up of staff during the main trial was one important factor contributing to the high fidelity.

More research attention needs to be focussed on how contextual factors and the diversity and complexity of local hospitals discharge practices affect the readmission rates following SAVR. We found significant statistical differences among comparable local hospitals and the 30-DACR rates. Unfortunately, we did not have the relevant data to analyse this difference. This lack could be seen as a limit of the study. What local factors impact the 30-DACR rate is a future question to be investigated, one that requires a different design for data collection. Our results from the AVRre trial, however, can provide a foundation for developing hypotheses. Clues derived from the evaluation suggest possibilities.

We observed challenges related to patient transfer to local hospitals, the admission process at local hospitals, competence levels dealing with the SAVR patients' condition at local hospitals, and local hospital discharge management practices. One recent study demonstrated that top-ranked hospitals in the US do not have fewer readmissions but still have lower mortality rates and more satisfied patients compared to lower-ranked hospitals.

[157] When considering the SAVR treatment and the risk of readmission within 30-days after the discharge, it might be reasonable to expect a higher number of readmissions related to ensuring patient safety. Previous studies have demonstrated that cardiac valve surgery yields higher readmission rates than CABG, for example. [187] In the AVRre trial, monitoring and managing of symptoms during the intervention resulted in admissions of participants to local hospitals due to complications requiring hospital care as presented. The university hospital where the intervention was performed is the largest in Norway. However, most readmissions in the AVRre trial were locally initiated. This aspect is a limitation, as we cannot evaluate more deeply the local contexts' influences. With our mixed-methods design, we were able to at least broaden the understanding of the intervention's outcomes and reduce problems associated with a potential 'black box' evaluation. [64] Moreover, the World Health Organization states that because of the diversity of results in attempts to reduce adverse events during transition of care across different settings, it is very important to thoroughly describe the intervention implementation so the healthcare providers can understand what is most effective for improving the quality of care. [183]

To optimise the discharge and follow-up after SAVR in the AVRre trial, we found it appropriate and useful to use a mixed-methods approach. Thus, we integrated user experiences into the overall trial evaluation right from the start with the development of the hotline manual to the process evaluation of the completed trial. Having easy access to a direct phone line to secure health advice from trained project staff who were attuned to their specific health condition and individual needs, together with their self-management behaviour, was an important sign of the 'good' healthcare according to the participants' perspectives in this study. Thus, we were able to understand more of the complexity concerning the discharge and follow-up of SAVR patients, other than just understanding the effectiveness of the tested intervention on primary outcomes.

In a real-world context, where science unfolds quickly and stakeholders strive to understand the core elements of a specific topic, one cannot fully describe all aspects of a RCT in one or two papers. However, those studies can accumulate certain pieces of evidence that can contribute to theory and then bring the clinical problem towards a relevant solution to apply in the clinic. This notion is in line with traditions spanning Donabedian ideas [46] to the MRC organising framework [51] and others that attempt to expand our scientific knowledge through the integration of different methodologies to profile human subjects and their behaviour in the healthcare context and the society where behaviour takes place. A valid scientific description can be accurate at the time of its birth; however, it evolves over time, pushing the science to change accordingly. With the new technology revolution of today and political disputes about science, it seems *à propos* to mention these issues, as it affects the context where research is taking place. We can appeal to the science communities to increase their flexibility of scientific thinking and to adapt to the evolution of an issue in order to overcome contextual challenges. This shift in thinking will, I believe, preserve knowledge as the most valuable human asset, one that can be used to guide development when applied wisely.

8.3 Ethical considerations

The AVRre trial was approved by the Regionale komiteer for medisinsk og helsefaglig forskningsetikk sør-øst (REK) (Norwegian Regional Committees for Medical Research Ethics; REK South-East B; approval no. 2013/2031B) that oversees human subjects' research at the University of Oslo. The OUH Data Protection Officer approved the focus group interviews with the nurses staffing the hotline. To ensure anonymity, all digital data were stored on a secure server within the OUH system, and all patients paper documents were stored in a closed safe at the Center for Patient-centered Heart and Lung Research,

Department of Cardiothoracic Surgery, Division of Cardiovascular and Pulmonary Diseases, OUH, Ullevål, Oslo, Norway. Finally, all participants gave their written informed consent to participate in the AVRre trial, per the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. [67]

We observed that some participants were not content with being assigned to the control group during randomisation. The PC spent time reasoning with these patients, informing them about the important role that control-group participants play in clinical trials and how valuable their answers are in follow-up questionnaires. Still, some control-group participants stated that the 24/7 hotline should obviously be provided to all patients. We paid attention to these concerns by taking additional time to make sure that they understood information about the trial, and most importantly, the control-group concept, that comparing treated and untreated groups is necessary in order to determine the true effects of an intervention. We seriously considered their explicit disappointment of being randomly allocated to the control group by discussing their concerns with them, emphasising the critical contribution of control patients, that without them, we cannot determine whether the intervention is indeed effective or useful.

For researchers conducting the trial, the concerns of control-group patients were an important topic worthy of consideration and notice. It led to discussions to determine, or at least to arrive at some hypotheses as to, what their concerns might mean. Also, we discussed ways on how to inform control patients in cases when we perceive that all of the participants greatly desire to receive the intervention. The researchers discussed *a priori* whether the control group should be offered a lighter version of the intervention, an offer we know, in retrospect, would have likely led control-group participants to be more satisfied after discharge. However, due to the risk of introducing additional 'noise' into the analysis of the intervention effects, we chose not to do so and not to construct a 'black box problem' larger

than necessary for understanding the experimental outcomes. However, the control participants did receive the standard care at the time, which the ethical committee took into consideration when assessing our study protocol for approval.

In 2000, Emanuel and colleagues proposed an ethical framework for conducting ethical clinical research using an RCT design. [188] Value is one of seven requirements in the proposed framework, which highlights the necessary aims of producing potentially positive effects for the participants and society, and the responsibility of publishing both negative and positive results. [188] The participants in the AVRre trial evaluated the intervention as a service that promotes a feeling of safety and trust in patients, and as a satisfactory early rehabilitation intervention after SAVR surgery.

8.4 Surplus data and future research considerations

The AVRre trial collected ancillary data that was not analysed as part of this thesis work due to time and economic constraints. Firstly, we did not conduct a cost-utility analysis. This will be part of future research, which will address the main research question: Is the intervention in the AVRre trial more cost-effective than usual care? Secondly, an investigation of the one-year readmissions data from the AVRre trial will be conducted. This planned study will address the following research questions: What is the one-year incidence of readmissions after SAVR? What causes readmissions in the first year after SAVR? What predicts one-year readmissions after SAVR? What is the incidence of planned and unplanned out-patient consultations in the first year after SAVR? Are there any differences between the trial groups with regard to the incidence of readmissions in the first year after surgery? Thirdly, we will analyse the content of research interviews with physicians, patients, and caregivers regarding their experiences with the transition of care after SAVR. The following possible research questions will be addressed: How do stakeholders perceive the discharge and care after

SAVR? What do the qualitative perspectives of trial participants reveal in terms of what can improve the discharge and follow-up of SAVR patients? Fourthly, I wish to continue the work with the NPR to gain valid thirty-day readmission data on SAVR, which also would be useful for TAVR populations with a similar care trajectory after the discharge. Fifthly, a Master's thesis in Nursing Science was completed in 2019 at the University of Oslo. The Master's thesis analysed data obtained from the registration forms used to log information about the hotline calls of the AVRre trial; the goal was to identify the various themes participants talked about in the calls. [189] This topic will be a similar objective for a planned peer-reviewed paper reporting on what concerns participants had during the intervention period.

9 Conclusions

The thesis work discussed here, and reported in the four published papers, provides new and important knowledge for optimising the discharge and follow-up care of SAVR patients. Firstly, this work found a high proportion of 30-DACRs following SAVR surgery, providing clinicians and researchers vital knowledge on to what extent readmissions burden not only patients and by extension their informal caregivers, but also the healthcare professionals charged with their care and the healthcare system, in general. These findings, therefore, serve as an impetus to improve healthcare related to discharge and readmissions after SAVR. Secondly, the AVRre trial found that the telephone intervention reduced patient symptoms of anxiety within the first 30 days after surgery but failed to reduce the 30-DACR rate. Attempts to reduce symptoms of anxiety is warranted, because less anxiety is associated with a lower risk of mortality and other adverse events. [190] Thirdly, the trial also found a high proportion of unavoidable readmissions associated with the SAVR treatment. This finding is important and provides clues to tailoring new interventions to improve discharge and follow-up of these patients. Fourthly, patient participants experienced the intervention as being useful, bolstering their trust in the intervention and giving them an overall sense of security. The 24/7 hotline also increased their satisfaction with the discharge process and follow-up after SAVR.

Taken together, these findings demonstrate that the novel scientific mixed-methods approach employed in the AVRre trial was useful, as was having users participate from the trial design stages to formal evaluation of this clinical trial, for gaining the knowledge needed to optimise the discharge and follow-up of SAVR patients.

Conclusions as they relate to the aims of the AVRre study[2]:

I.

[2] Roman numerals identify the published papers.

- **A protocol paper was published in a timely manner to ensure transparency in the reporting of the AVRre trial outcomes.**

II.

- **The overall worldwide incidence of 30-DACRs after SAVR is relatively high at 17% (95% CI: 16-18%), which is similar to the incidence after TAVR, which was 16% (95% CI: 15-18%).**
- Multi-centre studies yielded statistically significantly higher 30-DACR rates than single-centre studies after SAVR and TAVR.
- There is a lack of prospective studies on 30-DACR rate after SAVR.
- There is lack of evidence on independent risk factors for 30-DACR after SAVR, and there is lack of transparent reporting on the validation of readmission data used in clinical research.

III.

- **The intervention did not significantly reduce the 30-DACR rate after SAVR nor did it, in general, improve patient-reported outcomes, except for symptoms of anxiety (which did significantly decrease up to 30 days after surgery).**
- Total incidence of unplanned 30-DACR after SAVR was 22.3%, and of these, most (83%) occurred within 14 days after SAVR, providing an impetus to tailor future readmission-reduction interventions to target the first 30 days after hospital discharge.
- Independent risk factors for readmission within 30 days after SAVR are the presence of symptoms of anxiety before surgery and pleural drainage before hospital discharge.
- Unavoidable readmissions after SAVR were estimated to be as high as 75%.

IV.

- **Participating SAVR patients were generally satisfied with the intervention and perceived it as valuable in bolstering their trust in their care and providing them with a sense of security. These findings underline the value of an additional process evaluation that involves investigating the implementation of and patient reactions to an intervention in a clinical trial.**
- Some lack of hotline staff preparedness might have been a barrier to the fidelity of carrying out the intervention; however, robust support given to the staff during the main trial enabled the trial to be performed safely.
- Context influences the 30-DACR rate after SAVR, and local hospitals should focus more attention on determining and analysing the causes of the significant differences in discharge practices among hospitals in order to identify factors that might be targets for reducing the overall readmission rate after SAVR.

10 Future perspectives

A large amount of data was collected in the AVRre trial through its mixed-methods design. As described in section 8.4, a Master's thesis based on data from the AVRre study has been completed, and more research data will be finalised in order to further analyse other discharge-related outcomes for this SAVR patient population. However, due to similarities with the present TAVR population and for future benchmarking of various treatment choices available today, physicians may choose to apply the less invasive TAVR technique to other at-risk AS patient populations. In that case, the kinds of analyses done in this thesis work will have to be replicated in these other kinds of TAVR populations.

Knowledge gained from this PhD dissertation work will guide future research on discharge-related outcomes of those AVR patients. To fully capture an intervention's effect on a patient population, more clinical research will have to be predicated upon obtaining intervention-user knowledge and perspectives, and these must be sampled and considered at all phases of healthcare intervention development and conduct. Furthermore, user knowledge and perspectives should be included in a timely fashion, as should careful ethical considerations, scientific assessment of clinical relevance, and validation of results in terms of the user's perspectives. Systematic implementation of these aspects will help future researchers and clinicians better grasp the validity and efficacy of a clinical trial, enabling them to reach appropriate and more robust conclusions on the effectiveness of the healthcare intervention they are assessing. For future interventions aimed at optimising patient discharge and follow-up after surgical aortic valve replacement, faithfully implementing such a research programme will likely reduce hospital readmissions, improve patient-reported outcomes, and improve healthcare in general.

11 References

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Trials

STUDY PROTOCOL Open Access

Determining the impact of 24/7 phone support on hospital readmissions after aortic valve replacement surgery (the AVRre study): study protocol for a randomised controlled trial

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Abstract

Background: Patients undergoing surgical aortic valve replacement (sAVR) have high rates of 30-day readmissions. They also report a low health-related quality of life (HRQOL) and elevated anxiety and depression. The aim of the AVRre study is to determine the efficacy and cost of a 24/7 phone-support intervention in reducing post-discharge readmissions after sAVR. The nature of the support is to help patients better understand and self-manage non-urgent symptoms at home.

Methods/design: AVRre is a prospective, randomised controlled study comprising 30 days of continuous phone-support intervention and then intermittent follow-up for the first 12 months. Phone call data from and to patients are evaluated qualitatively; thus, the study has a mixed-method design. Two hundred and eighty-six patients, aged >18 years, scheduled for a sAVR — singly or in combination with another procedure — are recruited from locations in southeast Norway. Patients are randomly assigned to the intervention group, who are purposively phone-called individually 2 and 9 days after discharge and offered on-demand 24/7 (around-the-clock) telephone support for 30 days post-discharge. The primary outcome variable is the number of 30-day hospital readmissions. Secondary outcomes are anxiety and depression symptoms, as measured by the Hospital Anxiety and Depression Scale, HRQOL and quality-adjusted life years, measured by the EuroQol (EQ-5D). Intervention and hospital readmission (diagnosis-related groups (DRGs)/length of stay) for the first year after initial discharge from hospital are used for a cost-utility analysis. Standard parametric and non-parametric tests are used for evaluations over time. Analysis of covariance is used to control for possible differences at baseline. Narratives from phone calls are transcribed verbatim and analysed using systematic text condensation.

Discussion: A complex 'around-the-clock' intervention within a university hospital-based setting could be an effective strategy to reduce the high readmission rates to hospital after sAVR. Furthermore, the AVRre 24/7 phone-support manual can be adapted to other high-risk surgery populations with high readmission rates.

Trial registration: ClinicalTrials.gov, NCT02522663. Registered on 11 August 2015.

Keywords: Thoracic surgery, Patient readmission, Clinical trial

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Background

Severe aortic stenosis that demands surgical aortic valve replacement (sAVR) due to considerable morbidity and mortality is increasing in prevalence as the elderly population increases globally [1]. sAVR remains the definitive treatment for aortic stenosis (AS), and sAVR has an estimated annual incidence of 85,000 cases [1] in the USA and 1500 cases in Norway (unpublished data from Norwegian Heart Surgery). Irrespective of good immediate surgical outcomes, sAVR patients are characterised by high rates of 30-day readmissions to hospital after discharge. For example, the rates are 19.6% in a US population [2] and 26% in a Danish population [3], and from unpublished register data in Norway (Norwegian Patient Registry, AVR patients' readmission to hospital, 2011–2014, the Norwegian Directorate of Health 2016), it is estimated to be 22.4% in Norway. Reasons for 30-day readmissions after sAVR are available in two studies. In an American study, heart failure, cardiac rhythm disorders, stroke or transient ischaemic attack, pneumonia, pneumothorax/pleural effusion and gastrointestinal bleeding were reported [4]. In a Danish study, atrial fibrillation, pericardial effusion, congestive heart failure and pneumonia were the most dominant reasons for 30-day readmissions; these conditions occurred acutely in 25% of cases [3]. One in five patients in a study after major surgery was readmitted to a non-index hospital. The use of an index hospital with specialised competence, versus non-index re-hospitalisation, resulted in significantly lower in-hospital mortality [5].

Readmission to hospital in Norway is defined as an unplanned, emergency admittance 8 hours to 30 days after discharge from hospital, accompanied by at least one overnight stay with the readmittance [6]. The majority of patients (96%) discharged approximately 1 week after complex sAVR return home intending to be responsible for their own physical and mental health and for arranging follow-up by their general practitioner (GP) when needed. However, following discharge, patients/inhabitants and partners experience insecurity and the psychological and physical burdens associated with potential readmissions. Moreover, the estimated cost of readmissions is 2 billion Norwegian kroner (NOK) each year, with an estimated readmission rate of approximately 20% [6].

The clinical experience of specialists and municipal healthcare services reveals that standard care at discharge does not typically include patient education. Two systematic reviews and meta-analyses of randomised controlled trials (RCTs) that sought to reduce 30-day hospital readmissions for different diseases concluded that no single intervention (e.g. education, telephone follow-up) was associated with reduced risk for 30-day re-hospitalisation [7, 8]. For example, Melton et al. (2012) suggested a two-time telephone follow-up after discharge during office time [9]. More complex, high-methodological quality interventions, ones in which patients are educated and receive support for self-care, are recommended for preventing hospital readmission and increasing health-related quality of life (HRQOL) status, which otherwise is poorly self-reported [3].

Research on readmission after heart surgery highlights a great need for interventions to be implemented during the first 30 days after discharge to ensure that patients receive quality healthcare and engage in safe practices [3, 5, 10–13]. In a Norwegian home-based intervention the first month after cardiac surgery ($n = 185$), patients and relatives pointed to several negative factors, including lack of information at discharge, insecurity and lack of a 'connection' to the index hospital. This was especially true in the first month after surgery, if complications such as pleural effusion and arrhythmias appeared post-discharge [14].

Furthermore, the Norwegian patient experience surveys (2016) report that almost 50% of patients received incomplete information related to discharge preparation, especially regarding what symptoms to expect after discharge, and how and whom to contact if complications occur [15]. These experiences may contribute to feelings of anxiety in patients. Indeed, approximately 29–61% of all patients experience moderate to severe levels of anxiety and depression during the first month after cardiac surgery, with symptoms remaining elevated up to 6 months following surgery [16, 17]. These factors deserve our attention, because anxiety and depression are predictors of morbidity and mortality after heart surgery [18–21]. Therefore, one can hypothesised that interventions that target patients' and relatives' need for information and follow-up during the first month after cardiac surgery and the provision of these interventions around the clock could avoid unnecessary hospital readmissions. Indeed, a 24/7 follow-up service by phone goes beyond the results of regular telephone follow-up during office time. No study has tested the effect of an around-the-clock follow-up intervention, where the patients' needs and symptoms are the base for the intervention. Expert healthcare professionals will be able to assess worsening of symptoms on the phone before a critical stage, and patients can be advised to contact a GP. Telephone follow-up also allows for inclusion of patients who live a long distance from both index and non-index hospitals.

This paper presents the detailed protocol for the AVRre study, in which we aim to determine the efficacy and cost utility of 30-day around-the-clock, 24/7 phone-support intervention after discharge for sAVR. The study's design and protocol are in accordance with the current Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [22]. A SPIRIT checklist is available online for this manuscript (see

Additional file 1). Results will be reported following the CONsolidated Standards Of Reporting Trials (CONSORT) guidelines for non-pharmacological interventions [23, 24].

Study objectives

Primary objective

The primary objective of this study is to determine whether a 30-day, around-the-clock, 24/7 phone-support intervention reduces the number of hospital readmissions 30 days after discharge from hospital. The intervention begins immediately after initial discharge, and the outcomes of patients in the intervention are compared to a control group, which receives usual care.

Secondary objectives

The secondary objectives of the study are as follows:

- To determine whether an around-the-clock, 24/7 phone-support intervention implemented within 30 days after discharge reduces objectively measured symptoms of anxiety and depression compared to a control group in the first year after discharge from hospital
- To determine whether the around-the-clock, 24/7 phone-support intervention implemented within 30 days after discharge improves HRQOL and quality-adjusted life years (QALYs) compared to the control group in the first year after discharge from hospital
- To perform an economic evaluation specifically to (1) determine the cost utility of the intervention compared to usual care in the study population and (2) assess the cost of readmission to hospital and the cost of GP consultations during the first year after discharge for the intervention and the control groups

Methods/design

Study design

AVRre is a prospective, randomised controlled trial (RCT), comprising 30 days of intervention and 12 months of follow-up. The main study began in August 2015. As the intervention consists of phone calls from patients to hospital and vice versa, the design of the study includes an explorative, qualitative component. Thus, this study employs a mixed-method study design. Supporting material for the AVRre study is provided in Additional file 2.

Study population, recruitment, randomisation and follow-up

Patients eligible for study participation are 18 years or older and are referred for sAVR surgery for the first time at Oslo University Hospital, at either the Ullevål or Rikshospitalet locations, the largest hospitals in southeast Norway. Consecutively admitted sAVR patients are asked by project nurses to participate, and they are included if they meet the following criteria: (1) the surgery is an elective treatment with a single AVR (biological (b) or mechanical (m), an AVR (b or m) + aortocoronary bypass or an AVR (b or m) + supracoronary tube graft; (2) the patient can understand, speak and write the Norwegian language and (3) can be contacted by phone after discharge from hospital. Exclusion criteria are the following: (1) the patient has been admitted to an intensive care unit (ICU) for more than 24 hours; and/or (2) has complications related to surgery (e.g. surgery caused cerebral insult with significant impact on cognitive functions).

One to three days before the planned sAVR, patients arrive at hospital for preoperative preparations. During this time, the project nurse informs the patients about the aim and process of the study. The patients are then given the informed consent form and the baseline questionnaires for review and are given time to consider participation in the study. Patients are contacted a second time before surgery to answer any questions about the study and to deliver further information about the study.

After the patient has provided written informed consent, patient assignment to either usual care (control) or intervention is accomplished by a web-based randomisation system developed and administered by the Unit of Applied Clinical Research, Institute of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway. This system has been approved by the Data Protection Officer at Oslo University Hospital as complying with human experimental subject protections. Randomisation (1:1 ratio) is performed consecutively with block randomisation and varying size of the blocks to make it impossible to predict to which group the patients are likely to be allocated. Randomisation is done without stratification to the two cardiothoracic sites of the study hospital (i.e. Ullevål or Rikshospitalet).

Before standard discharge from the university hospital to the patient's local hospital on the fourth day post-sAVR, the project coordinator (SOD) informs the patient verbally and in writing (with a leaflet) to which group he/she has been allocated. For both the control and the intervention groups, the follow-up assessment takes place 1 month (T1), 3 months (T2), 6 months (T3) and 12 months (T4) after discharge from hospital. Follow-up consists of mailing by postal questionnaires with prepaid stamps for return post after completion (see the patient flow and data collection chart of Fig. 1).

Usual care

Preoperatively, all patients recommended by a thoracic surgeon to have aortic valve replacement surgery receive information on expected HRQOL improvement, longer life expectancy and possible complications of surgery.

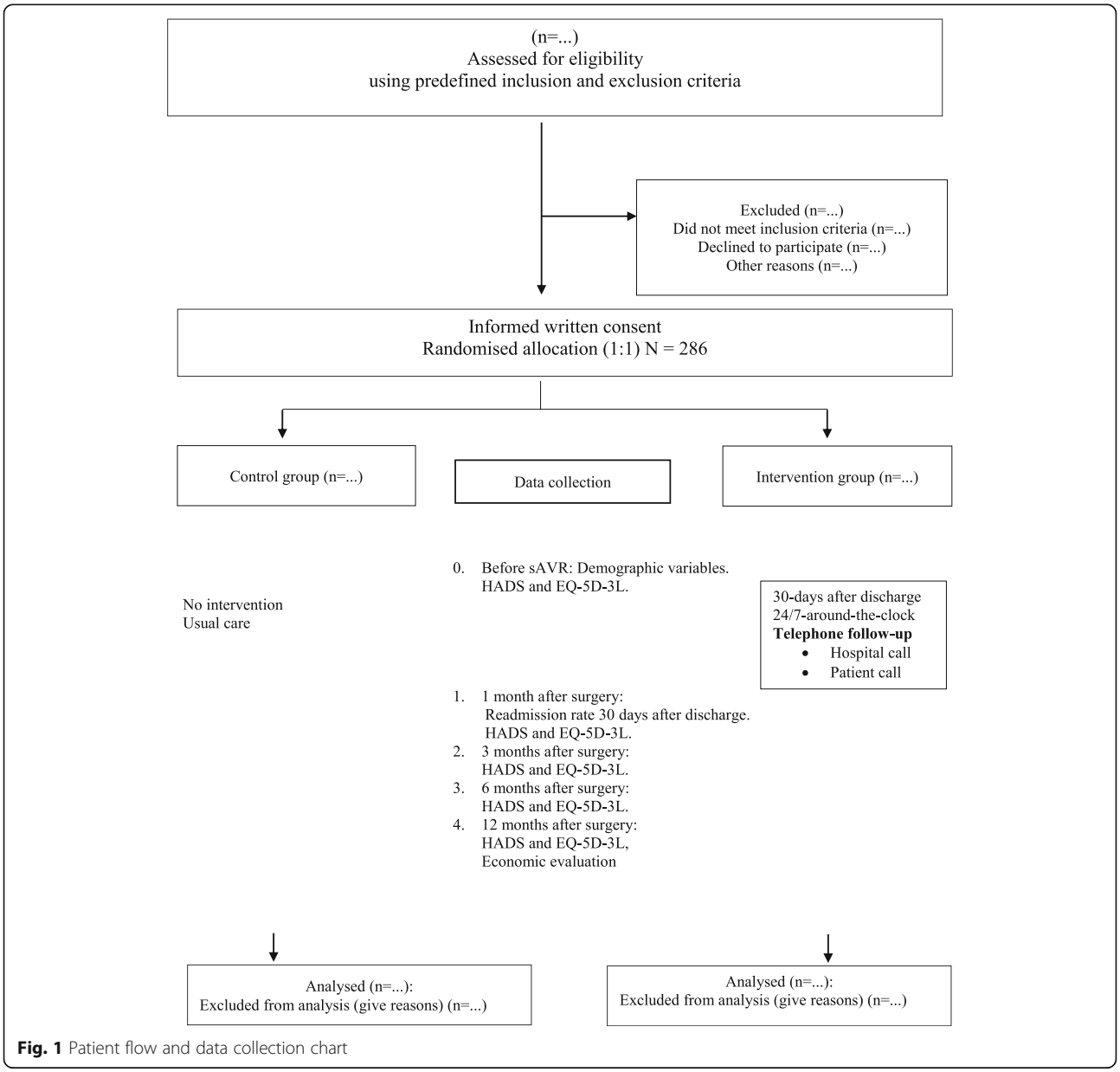

Fig. 1 Patient flow and data collection chart

Currently in Norway, at discharge, there is no standard information or post-discharge telephone support in usual care, not from nurses, doctors, university hospitals or local hospitals. There is no blinding in the study.

Intervention: two components

A brief description of the development of the 24/7 phone-support manual and an example section of it is available online (Additional file 1). The intervention consists of two components.

Component 1

Patients in the intervention group are purposely called on days 2 and 9 after discharge by the project coordinator to proactively assess the patient's present condition and to determine if the patient has questions or if problems have emerged. Details in the patient's medical history are compiled in advance and reviewed prior to the phone calls, and each structured call relays reminder information to the patient about the availability of the 24/7 phone-call service as part of the intervention. The project coordinator emphasises the importance of daily physical activity [3] and how it has a positive effect on rehabilitation, morbidity and mortality after sAVR. When the patient receives a Short Message Service (SMS) one day ahead of the phone call, he/she has the opportunity to respond if the scheduled day or time is inconvenient for them. Data from the phone calls will be collected in a written, standard

format. Also, patients will be encouraged to relate their individual responses/experiences/narratives, for example, when they experience anxiety symptoms.

Component 2

The intervention group is also offered 24/7 around-the-clock telephone availability during the entire first month post-discharge. Volunteer, expert intensive care nurses on duty in a cardiac ICU have been trained by an interdisciplinary team to answer the calls from sAVR patients during the first month after discharge. One aspect that the ICU nurses make extremely clear is that this 30-day 24/7 phone-support provision is not a replacement for emergency calls to 113 (911 in some countries). For ethical reasons and because of hospital responsibility to the patients, we include some 'red' responses (i.e. acute or emergency) in the manual. However, we expect that the sAVR patients will call the intervention phone line mostly for non-urgent health information. If a patient's problems demand advanced expertise, the project nurse will consult the thoracic surgeon or cardiologist on call in hospital to ensure that accurate diagnostics are completed and suggestions for treatment are made. The project coordinator is always available for the ICU nurses to consult, and will take initiative to arrange regular follow-up meetings and interdisciplinary discussion of challenging phone calls.

Variables, sources and measurement

Patients will be longitudinally assessed five times during the course of the project: before sAVR and 1, 3, 6 and 12 months after discharge for sAVR. Additional file 1 includes a SPIRIT checklist for the schedule of enrolment, intervention and assessments as presented in Fig. 2. The written informed consent form for the AVRre study is included as Additional file 3.

Primary outcome

Readmission

Data from the Norwegian Patient Registry (NPR), the Norwegian Directorate of Health and patients' medical records will be used to gather the numbers of readmissions within 30 days after sAVR discharge. Moreover, data on causes of readmissions (ICD-10 codes), time and location (index and non-index hospital) will be collected.

Secondary outcomes

Anxiety and depression symptoms are measured using the Hospital Anxiety and Depression Scale (HADS) [25, 26], a

	Enrolment	Allocation	Close-out					
TIMEPOINT	$-t_1$ *Before surgery*	0 *At discharge*	*30 days 24/7 phone support*	t_1 *1 month*	t_2 *3 months*	t_3 *6 months*	t_4 *12 months*	t_x
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
24/7 phone support			⟷					
Control group			X					
ASSESSMENTS								
Baseline variable:								
HADS	X							
EQ-5D	X							
Comorbidity	X							
Outcome variable:								
Readmissions			X				X	X
HADS				X	X	X	X	X
EQ-5D				X	X	X	X	X

Fig. 2 SPIRIT schedule of enrolment, interventions and assessments for the AVRre study

standardised, self-report instrument consisting of 14 items in two subscales. The 14 items include seven items for anxiety (HADS-A) assessment and seven for depression (HADS-D). Patients rate themselves on each item from 0 (not present) to 3 (maximum), yielding a total possible score of 21 for each subscale. The psychometric properties of the HADS are well documented in research conducted in many different countries; this includes valid use in heart patients [26].

HRQOL and QALY are assessed using the internationally recognised EQ-5D instrument [27]. EQ-5D is a standardised instrument comprising five dimensions of self-reported health status for clinical and economic appraisal. These dimensions are mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The respondent rates himself on each dimension for the degree (no problem, some problem, extreme problem) that best describes his/her present health status.

Economic evaluation

Economic analyses are performed for two reasons. (1) The time it takes to proactively call the patients, as well as the time needed to answer the patient on the intervention phone and the time needed for calling back if consulting the physician at hospital, will be measured and valued. (2) Register data on the cost of readmission to hospital (diagnosis-related groups (DRGs)/length of stay) and the number of GP consultations during 30 days and the first year after discharge will be used for the cost-utility analysis and will be reported as an incremental cost-effectiveness ratio (ICER). Sensitivity analyses will be conducted to measure uncertainty in the estimates. In addition, data from the patients' medical records are gathered, e.g. comorbidities.

Data management and statistical analysis

The first and second author have the daily responsibility for overseeing patient safety, study design, database integrity and study conduct and have access to the final study dataset. No data will be entered before the intervention is finalised, to make sure that the baseline data will not influence the intervention. A random check of at least 20% of entered data will be performed to ensure data quality before starting the full data analysis. Data are presented as means ± standard deviations for continuous variables and percentages for nominal variables. The primary outcome variable is measured using the chi-square test to evaluate group differences. The secondary outcome variables are measured longitudinally to assess changes over time. Symptoms of anxiety and depression (HADS) will be analysed in continuous-form variables before being transformed to a cut-off score ≥8 for anxiety and depression respectively. We will apply a multilevel logistic model with the time nested within the patient, and Hosmer's step-down procedure [28] to establish a final model. Analyses will be conducted in R version 3.3.2 (2016-05-03, R Core Team, 2016) (https://www.r-project.org/). Mixed model analyses will be applied for repeated measurement of anxiety (yes/no) or depression (yes/no) using HADS and EQ-5D [29]. Analysis of covariance (ANCOVA) is used to test mean changes between groups, controlling for possible differences at baseline [30, 31]. A paired sampled t test is used to analyse mean changes within groups. A statistic will be considered significant when the corresponding P value is <0.05. The Statistical Package for Social Sciences (SPSS), version 21 (released 2012, IBM Corp., Armonk, NY, USA) is used for statistical analysis.

Missing data

The amount of missing data in the study and the methods used to handle missing data in the analysis will be reported [32]. Complete registry data will be available on primary outcome readmission 30 days after discharge for sAVR. If a patient dies within 30 days, it will be counted as readmission. Out of a total sample of 286 sAVR patients, we estimate 0–2 deaths. These numbers will not influence the power of the study. Regarding secondary outcomes, the guidelines in the article of Little et al. [32] will be followed; hence, we will perform multiple imputation analyses in analyses where missing data are not handled properly otherwise. In addition, sensitivity analyses will be performed to assess the robustness of assumptions made.

Narrative data analysis

Data/narratives from patients' phone calls to hospital and project coordinator phone calls to patients

All qualitative data are transcribed verbatim and analysed in several steps using systematic text condensation in accordance with the approach of Malterud [33]. Experts in qualitative analysis in the research group responsible for the AVRre study will re-read the narratives independently before the subsequent data reduction into meaning units, condensed meaning units, subthemes and themes guided by the study's aim.

Mixed methods

Qualitative data as narratives from the patients are intended to complement and enrich the quantitative data from study measures. Using narratives from patients' phone calls will focus on the spontaneous needs and symptoms from the patients' perspective, thus avoiding recall bias that may occur during interviews at a later time. The two approaches are planned to be used in tandem to answer the research questions in this study [34]. One challenge that needs to be figured out is how to interpret conflicting results.

Sample size and power calculation

In 2013, a total of 503 patients had aortic valve replacement surgery at Oslo University Hospital. To estimate the sample size required to make confident conclusions about the primary outcome — the number of readmissions 30 days after discharge from hospital — we used published data on readmissions in Norway for patients >65 years old. Seventeen percent of the patients are readmitted to hospital within 30 days from discharge [6]. A sample size of 286 patients with 143 patients in each group will achieve at least 80% power to detect an expected difference of 15% in the control group and 5% in the intervention group at the 5% significance level using the chi-square test.

Ethical considerations: ethics and disseminations

The study is conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Regional Committees for Medical and Health Research Ethics (approval 2013/2031-3). All patients receive both verbal and written information about the aim of the study and are informed that they are free to withdraw from the study at any time. Patients sign an informed consent document prior to inclusion. The codebook with study numbers and person-sensitive information and data from phone calls is kept in a locked, firewall-secured cabinet. To be able to perform the cost-utility analysis, we included in the written, informed consent form the patients' permission to collect person-identifiable sensitive data from the medical record and from the Patient Registry Department at the Norwegian Directorate of Health. The results are presented so that the identity of the subjects cannot be identified, either directly or from derived information. Results from this study will be published in peer-reviewed journals.

Discussion

This randomised controlled study, which we call AVRre, is the first programme to offer and test the effectiveness of a complex 24/7, around-the-clock intervention to optimise sAVR patients' safety and healthcare in the vulnerable readmission phase 30 days after discharge. The intervention is complex, because phone calls are made proactively to the patient 2 and 9 days after discharge, and because telephone support from expert healthcare professionals is made available day, evening and night during the first 30 days after hospital discharge. Combining experimental and explorative approaches results in mixed-method data, which will strengthen the conclusions we can draw and produce more solid information about sAVR patients' experiences at home.

Analyses of patient narratives about the symptoms they experience and their needs during early rehabilitation will produce new insights for developing effective patient information systems and education programmes relevant for sAVR patients in the future. Moreover, symptom monitoring combined with evidence-based and clinical expertise advice can accommodate patients' desires to feel secure and to submit their requests for information after discharge from hospital [14]. Moreover, as we have hypothesised, this should reduce the number of 30-day hospital readmissions and reduce symptoms of anxiety and depression. Readmissions after sAVR are sparsely documented in the research literature, and reports of readmissions in RCTs, except for a few registry studies/observational studies, are almost unknown [8].

Mixing both quantitative and qualitative methods in this RCT increases the probability of obtaining valuable empirical knowledge from sAVR patients in addition to evidence of treatment effect [34]. First, triangulation generated by different data sources is possible; e.g. suppose a patient in the intervention group has a high score for anxiety on HADS, and that patient calls the AVR 24/7 phone to elaborate on and get advice for a case he felt anxious about after sAVR. This would validate information that stems from the instrument.

Prevention of missing data to increase the representativeness of the sample in this trial is related to both designing and conducting the trial [32]. In designing the intervention, former patients and interdisciplinary specialists in the cardiac field revealed the themes for the intervention manual and 24/7 follow-up after discharge, in accordance with evidence-based literature. Moreover, the intervention is flexible, as it is based on when the patients need support. The patients in the control group receive information at discharge about group allocation and the importance of comparing the intervention and the control group in order to offer future sAVR patients a solid follow-up based on patients' needs. When conducting the study, the participants' burden and inconvenience of data collection is limited to only two questionnaires with a few items, to avoid missing values and drop-out. The project coordinator is dedicated to follow up the participants and the expert nurses responsible for the 24/7 intervention to limit missing data in the conduct of the study. It is time-consuming to carry out a 24/7 phone support service, and it requires expert healthcare professionals to be deeply and continuously motivated to seriously carry out the study. This is an ongoing challenge, and it is necessary to safeguard the strength of the study. The intervention is bolstered by experiencing and discussing patient cases and by the teaching of relevant themes during the intervention period. Moreover, assessment of the intervention's cost utility will provide valuable information for the healthcare system to develop ways to improve the transition of patient care to reduce readmissions [35]. Furthermore,

knowledge from this study may add valuable information to optimize healthcare for future comparison to the emerging transcatheter aortic valve implantation (TAVI) patient population.

Insight into an individual patient's pathway through the readmission process is made possible for the first time by patients' agreeing to allow researchers to gain access to register data. A normal pathway for a patient undergoing sAVR is to be transferred from an index, specialised hospital to a non-index hospital with a lower level of care at the fourth day after surgery. Fragmented care, which can occur when patients are transferred between hospitals at different levels in healthcare systems, increases the risk of mortality [5] and is a present challenge for patients and the healthcare system. This study is limited in that it includes patients only at one university hospital with two departments.

Before surgery, the patients are informed about the expected increase in health status after surgery. Adding the QALY analysis takes into account both the quantity and quality of life generated by healthcare intervention and may add valuable preoperative information for future patients undergoing sAVR.

The lack of masking in this study related to patients may have a potential influence on outcomes [24]. Patients are informed about group allocation 1–2 days before discharge from the University Hospital. If a patient from the control group and one from the intervention group by coincidence are in the same room, the project nurse has organised separate information about further follow-up in the study. The patient in the intervention group is encouraged not to share information about the intervention. The general information of the ongoing AVRre study at the Department might influence the patient in the control group and the caregivers, e.g. to offer more information than usual care and possibly threaten internal validity (the Hawthorne effect).

In conclusion, the knowledge gained from this study will provide valuable insights for adjusting aspects of the healthcare system now to improve care for patients undergoing sAVR and will inform future studies on sAVR. The 24/7 phone-support manual has the potential to be modified and adopted for use by other surgical populations with high readmission rates.

Trial status at the time of initial manuscript submission

Recruitment for this trial is ongoing.

Additional files

Additional file 1: SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol. (DOC 122 kb)

Additional file 2: Supporting material for the AVRre study. (DOCX 82 kb)

Additional file 3: Written informed consent form. (DOC 49 kb)

Abbreviations

DRG: Diagnosis-related group; EQ-5D: EuroQol-5 dimensions; HADS: Hospital Anxiety and Depression Scale; HRQOL: Health-related quality of life; QALY: Quality-adjusted life year (QALY); sAVR: Surgical aortic valve replacement

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available for three reasons: this request was not included in the ethical application or in the written informed consent form and also due to restrictions from the hospitals' Data Protection Officer. However, the datasets are available from the corresponding author on reasonable request.

Authors' contributions

TT, SS, ML, THR and JV in collaboration with IL, SOD and PM designed the study and developed the protocol. LS and TW provided methodological and statistical expertise. SOD and IL performed the analyses of the pilot study data. IL and SOD drafted the manuscript. All authors read and gave their final approval of this version of the paper to be published.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Ethics approval was obtained from the Regional Committees for Medical and Health Research Ethics, Health East South, Norway (approval 2013/2031-3). All participants give written informed consent.

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Thirty-day readmissions in surgical and transcatheter aortic valve replacement: A systematic review and meta-analysis

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ABSTRACT

Background: The 30-day all-cause readmission rate after surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR) vary substantially. We conducted a systematic review and meta-analysis to examine the overall incidence, causes, and risk factors of 30-day all-cause readmission rate after SAVR and TAVR.
Methods: Eight medical research databases were searched; Cochrane, Medline, Embase, UpToDate, PROSPERO, National Guideline Clearinghouse, SweMed and Oria. We followed The Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) for this study.
Results: Thirty-three articles were included in the systematic review, 32 of which were appropriate for the meta-analysis. Overall, 17% (95% CI: 16–18%) of patients in the SAVR group, and 16% (95% CI: 15–18%) in the TAVR groups were readmitted within 30 days. Heart failure, arrhythmia, infection, and respiratory problems were the most frequent causes of all-cause readmission after SAVR and TAVR. Most frequent reported prior risk factors for all-cause readmission following TAVR were diabetes, chronic lung disease/chronic obstructive pulmonary disease, atrial fibrillation, kidney problems, and transapical approach/nonfemoral access. For SAVR, no risk factors for 30-day all-cause readmission were reported in the literature to date.
Conclusion: In conclusion, the overall proportion of 30-day all-cause readmission after SAVR and TAVR are high. Interventions to prevent avoidable readmissions ought to be developed and implemented.

1. Introduction

Today, surgical aortic valve replacement (SAVR) is the standard treatment for patients with operable severe aortic stenosis (AS) [1,2]. Surgical treatment for AS improves survival and enhances patients' quality of life [3–5]. In older patients (>75 years) with symptomatic severe AS and who are at high surgical risk, transcatheter aortic valve replacement (TAVR) is the established alternative to SAVR [1,6,7]. TAVR yields favorable outcomes compared to medical treatment [8].

Arrhythmias, infections, or other complications after SAVR and TAVR are relatively frequent [9] and often require readmission to the hospital. Unplanned readmissions are costly for individuals and the public and negatively affect patients' quality of life and rehabilitation [10]. Furthermore, it increases the risk for hospital-acquired complications [10]. In the literature, it is reported that the incidence of 30-day all-cause readmissions after SAVR and TAVR is about one out of every four discharges results in a readmission [9,11,12]. However, reported readmission rates vary substantially. Hence, the precise estimation of the magnitude of the problem remains unaddressed. Moreover, risk factors for and causes of readmissions following SAVR and TAVR have not yet been systematically scrutinized. This information is important, because it can guide clinicians, hospital administrators, and policy-makers in developing and implementing programs to improve the quality of care for SAVR and TAVR patients following hospital discharge. This will be even more important in the coming years, as the increasing trend in

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life expectancy translates to more SAVR and TAVR procedures [5,13–15]. An accurate estimation of readmission rates and risk factors leading up to them is also relevant for researchers in the area of valve replacement, because resulting data could be used for benchmarking and would enable researchers to calculate the sample sizes needed for future trials that assess interventions to reduce readmissions.

These issues prompted us to conduct a systematic literature review and meta-analysis. Our aims were (i) to estimate the overall 30-day all-cause readmission rate in patients following SAVR and TAVR, and (ii) to identify risk factors for and causes of 30-day all-cause readmissions after discharge of these patients.

2. Methods

The protocol for this systematic literature review and meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; no. 42016032670). The Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines were used. [16].

2.1. Literature search

The first author (SOD) developed the search strategy in collaboration with an experienced research librarian. The following databases were consulted: Cochrane (Cochrane database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, NHS Economic Evaluation Database, Health Technology Assessment Database and Other Reviews); Medline (accessed through PubMed; http://www.ncbi.nlm.nih.gov/pubmed); Embase; UpToDate; PROSPERO; National Guideline Clearinghouse; SveMed; and Oria.no. In addition, reference lists of candidate articles were screened to find additional references missed by our search strings (i.e., snowball method). Details on the search terms and the search strings can be found in online Table 2. Publication date limits were set from database inception to October 8, 2017. Language search was limited to English, and the Scandinavian languages. If necessary information was missing, we emailed the authors to obtain additional information.

Articles were eligible for inclusion if they reported study results on 30-day all-cause readmission following SAVR and TAVR procedures. For the present review, we defined 30-day all-cause readmission as an unplanned readmission for any reason within 30 days after discharge [17]. We excluded articles that reported results from studies dealing with multiple valves or specific diseases/conditions related to the SAVR and TAVR treatment. We also excluded articles that reported results from studies dealing with procedural or cardiac-related causes or other specific causes for readmissions, because they did not address all-cause readmissions. One researcher (SOD) screened all the records identified by title, and two researchers (SOD/IL) assessed the full-text candidate articles of the first screening using the inclusion criteria listed above. Before our review was completed, we consulted the databases several more times to check whether we had missed any eligible articles (Online Table 2).

2.2. Data abstraction

Data from included articles were extracted onto a standard form according to an a priori protocol. Extracted data included information on study-related characteristics, patient-related characteristics, and main findings. The study-related variables included the article's year of publication; country where the study took place; representativeness of the cohort (single-center, multicenter, or nationwide data); whether the cohort was prospectively or retrospectively studied; and whether 30-day all-cause readmission was reported as a primary or secondary endpoint. Patient-related variables included mean age and proportion of the study population that were males. The results we were interested in, and what we extracted, pertained to the total sample size reported in the article and the number of events (30-day all-cause readmission).

2.3. Quality of the studies

Two researchers independently assessed the quality of the studies (SOD/IL) using the Newcastle-Ottawa Scale (NOS). NOS is an established scale for assessment of cohort studies [18]. For studies with no relevant data accordingly to NOS items for appraisal, we noted them as "not relevant" (NR). Consensus by discourse resolved disagreements.

2.4. Statistical analysis

To calculate an overall incidence of 30-day all-cause readmission, we used a random effects meta-analysis of single proportions according to the DerSimonian-Laird method [19]. We used the Freeman-Turkey double arcsine transformation to stabilize the variance [20]. Heterogeneity between studies was assessed with the Cochran's Q test, and its magnitude was evaluated by the I^2 statistic. This describes the proportion of total variation due to heterogeneity rather than chance [21]. To investigate possible sources of heterogeneity, we performed analyses stratified by the study characteristic, prospective versus retrospective timing of the study, representativeness of the cohort (single- versus multi-center), country where the study took place (USA versus others), and whether or not 30-day all-cause readmission was reported as the primary endpoint. Further univariable random effects meta-regression analyses were used to examine whether estimates were affected by the study-level covariates. Source of heterogeneity was considered to be important if the covariate decreased between-study variance. The estimate of $\tau 2$ in the presence of a covariate versus its omission allows the proportion of the heterogeneity variance explained by the covariate to be calculated. For power consideration, we determined that a minimum of 10 studies per covariate was required in a single model of meta-regression [22]. An additional sensitivity analysis was conducted by iteratively omitting one study at a time from the meta-analysis and assessing its influence on the overall results [23]. Publication bias was evaluated visually by funnel plots and further assessed using a test of asymmetry (Egger's test of the intercept) applied to funnel plots [24].

All statistical analyses were performed with STATA 14.0 (STATA Data Analysis and Statistical Software; StataCorp LP, College Station, TX, USA.)

3. Results

3.1. Included articles

One article was excluded because it reported results from another article we had already included. Another article was excluded because the mean age of participants in the study was >80 years. We identified a total of 6867 candidate articles (Fig. 1). After duplicates were removed, we reviewed the title and abstract of 6848 articles, 6588 of which were not relevant for our purposes. The remaining 260 articles were assessed for eligibility based on full-text review; 227 were deemed ineligible. We included 33 articles in the systematic review and 32 in the meta-analysis, 12 on the SAVR population and 20 on the TAVR population.

3.2. Study characteristics in included articles

The characteristics of the studies included are presented in Online Table 1. We identified 12 cohort studies [14,25–35] on SAVR, all of which were published from 2008 to 2017. Ten studies used a retrospective design, 8 studies were conducted in the USA, and 7 designated 30-day all-cause readmission as the primary endpoint. Overall, 558,396 patients were included in our review of SAVR studies, yielding 111,909 readmissions. Mean age of the included patients ranged from 61 to 81 years; the proportion of males ranged from 48% to 71%.

For articles reporting TAVR results, we identified 20 cohort studies [6,7,11–13,28,34–47], which were published from 2015 to2017. Sixteen studies employed a retrospective design; 11 studies were performed in the USA; and 11 studies had 30-day all-cause readmission as a primary endpoint. In these 20 studies, 109,730 patients were included, yielding 21,192 readmissions. Mean age ranged from 80.7 to 84.3 years; the proportion of males ranged from 34% to 57%.

3.3. Quality assessment and publication bias

The overall quality of studies in the included articles was moderate on the NOS. Many of these retrospective studies failed to provide descriptions of how the outcome was derived and how it was validated. Thus, this produced an overall assessment of moderate quality (online Table 3). We found no publication bias, neither in SAVR studies (Egger test, $p = 0.255$) nor in TAVR studies (Egger test, $p = 0.140$). Funnel plots are presented in online material (Online Fig. 1).

3.4. Incidence of 30-day all-cause readmission rate following SAVR or TAVR

The incidence of 30-day all-cause readmission rate for SAVR ranged from 7 to 23%, and for TAVR, from 5 to 27%. The pooled estimated proportion of the 30-day all-cause readmission after SAVR was 17% (95% CI: 16–18), with substantial heterogeneity ($I^2 = 98.44\%$) (Fig. 2). Subgroup analysis of heterogeneity in the SAVR population revealed a significantly higher readmission rate in multicenter studies (20%) compared to single-center studies (12%) (Table 1). Regional differences were also observed, with higher readmission rates in the USA (18%) compared to other countries (14%). A lower incidence of readmissions

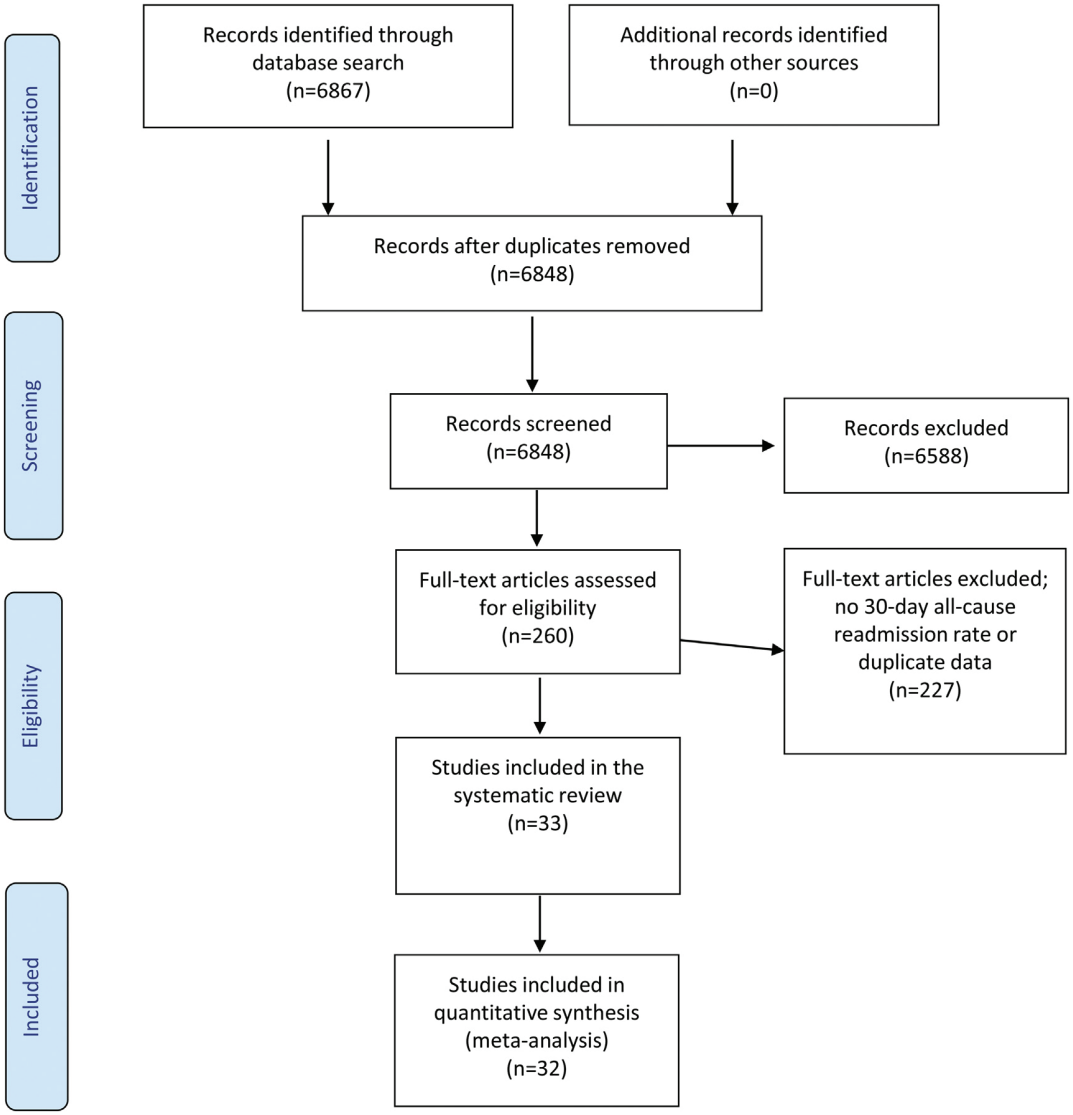

Fig. 1. PRISMA flowchart describing literature search and article selection.

was found in prospective (14%) compared to retrospective (17%) studies. We also found a difference in studies reporting on readmission as a primary (17%) versus secondary (15%) endpoint (Table 1).

The pooled estimated proportion of the 30-day all-cause readmission after TAVR was 16% (95% CI: 15–18), also with substantial heterogeneity ($I^2 = 97.06\%$) (Fig. 2). Subgroup analysis revealed more readmissions in multicenter studies (18%) compared to single-center studies (12%) (Table 1). Regional differences were observed, with a higher incidence in the USA (18%) compared to other countries (14%). A lower incidence was found in prospective (11%) studies compared to retrospective (17%) studies.

We also extended the analyses by using a random effect meta-regression model in the univariable mode. With this approach, we found that the only study-level variable significantly associated with readmission rate was single-center studies versus multicenter studies (Table 2). Sixty-nine percent of between-study heterogeneity was accounted for by this study-level variable in the SAVR population ($p = 0.013$), and 24% in the TAVR population ($p = 0.038$). Furthermore, USA versus other countries was marginally associated with readmission in the TAVR population ($p = 0.091$).

In the meta-analysis, the results from the sensitivity analyses appeared to be robust against the influence of individual studies.

3.5. Cause of 30-day all-cause readmissions after SAVR and TAVR

We found three articles reporting on causes of 30-day all-cause readmissions for SAVR patients [28,31,34]. Heart failure (15–19%) and cardiac rhythm disorder (10–14%) were the most frequently reported causes of 30-day all-cause readmission after SAVR. Infections, lung complications/respiratory problems, and bleedings ranged from 3 to 14%, as causes of readmissions after SAVR (Online Table 4).

We found nine articles reporting on causes of 30-day all-cause readmissions after TAVR. Heart failure (up to 30%), respiratory problems (up to 14%), infections (up to 13%), and arrhythmia (up to 10%) were the most frequently reported causes of 30-day all-cause readmission after TAVR (Online Table 5).

3.6. Risk factors for 30-day all-cause readmissions after SAVR and TAVR

We identified six articles reporting data on risk factors for 30-day all-cause readmission after TAVR [7,11,37,39,40,48]. Independent risk factors of diabetes (OR: 1.13–1.18); chronic lung disease/chronic obstructive pulmonary disease (COPD) (OR: 1.18–1.32, HR: 1.16); atrial fibrillation (OR: 1.26–1.70); kidney-related access (OR: 1.33–1.62, HR:

Table 1
Pooled estimate of total incidence of readmission with stratification on study-level characteristics using the random effect model.

	SAVR[a]			TAVR[b]		
Subdivision	N	Incidence (95% CI)	I^2 (%)	N	Incidence (95%CI)	I^2(%)
All studies	12	0.17 (0.16–0.18)	98.44	20	0.16 (0.15–0.18)	97.06
Single center	6	0.12 (0.08–0.17)	93.31	6	0.12 (0.08–0.13)	80.00
Multi center	6	0.20 (0.18–0.21)	98.95	14	0.18 (0.16–0.19)	97.64
Country						
USA	8	0.18 (0.17–0.19)	98.75	11	0.18 (0.16–0.20)	98.21
Other	4	0.14 (0.09–0.20)	94.53	9	0.14 (0.11–0.17)	79.80
Primary endpoint						
Yes	7	0.17 (0.16–0.19)	98.43	11	0.17 (0.16–0.19)	96.82
No	5	0.15 (0.10–0.20)	97.14	9	0.15 (0.12–0.18)	97.11
Timing of study						
Prospective	2	0.14 (0.12–0.17)	99.80	4	0.11 (0.06–0.18)	97.53
Retrospective	10	0.17 (0.16–0.18)	98.59	16	0.17 (0.16–0.19)	79.69

[a] SAVR = surgical aortic valve replacement.
[b] TAVR = transcatheter aortic valve replacement.

1.20–1.23); and transapical approach/nonfemoral access (OR: 1.21–1.43) were among the most frequently reported risk factors. Risk factors with an OR value of >2.0 were major/life threatening bleeding (2.41), length of stay of 7–10 days during primary admission (2.32), length of stay of >10 days during primary admission (3.06), and second prior admission in the year before TAVR (2.33). Details are included in online Table 6.

We found no articles that comprehensively reported on risk factors for 30-day all-cause readmission after SAVR.

4. Discussion

Reported hospital readmission rates vary substantially following SAVR and TAVR, obscuring rational guidance for clinicians, hospital administrators, and policy-makers. An accurate estimation of readmission rates and risk factors is also relevant for researchers, because reliable estimates are needed for benchmarking new valve replacement prototypes and to calculate study population sample sizes.

The meta-analysis we report here estimated a pooled 30-day all-cause readmission rate of 17% for SAVR and 16% for TAVR. The readmission rates are high, which we know are an additional burden for patients and caregivers, costly for society, and increase the risk of hospital-acquired infections and other errors [10]. Poor quality of care and transitional care contributes to high numbers of readmissions, but some readmissions are not necessarily attributable to the quality of care [49]. Some are unavoidable and occur due to expected complications after the treatments [49]. We don't know the proportion of avoidable readmissions after SAVR and TAVR, and this makes the interpretation of readmissions as a quality indicator difficult. Greater age and higher comorbidity, and major surgery, suggest a need to examine the proportions of avoidable and unavoidable readmissions after SAVR and TAVR. Having firm data on avoidable and unavoidable readmissions would help healthcare professionals to tailor new interventions to prevent readmissions, especially avoidable ones, and to improve transitional care in order to reduce burdens associated with readmissions.

Studies on 30-day all-cause readmission rates in SAVR and TAVR populations, support the notion that the proportion of readmissions in these two groups of patients are not significantly different [28,34], and are approximately similar to the estimates of the meta-analysis. However, because the populations differ (e.g., in age and comorbidity), one cannot obtain generalizable data by directly comparing the 30-day all-cause readmission rates between SAVR and TAVR patients [28]. When the two groups of patients were matched, though, the 30-day all-cause readmission rates seem to be similar [28]. Interestingly, studies have shown that TAVR done with a transapical approach (TAVR-TA) seems to produce a higher proportion of readmissions than TAVR done with a transfemoral approach (TAVR-TF) and SAVR [43], possibly due to a higher risk profile [34].

In the SAVR and TAVR studies we analyzed, we found a significant increase in the proportion of 30-day all-cause readmissions in multicenter studies compared to single-center studies. Cohort studies with 30-day all-cause readmission numbers retrieved from large administrative databases might capture more readmissions than single-center studies. Single-center studies might not capture all readmissions if patients are admitted to other hospitals outside their area [33]. Moreover, registry data can also be biased/corrupt [50]. Indeed, studies depending on administrative data from a registry rarely contain detailed descriptions of how the data were validated [50]. When evaluating the methodological quality of the included studies, we found that none of them provided a detailed transparent statement on the validity of the 30-day all-cause readmission numbers.

We observed regional differences among studies in the meta-analysis, with more 30-day all-cause readmissions in the USA versus other countries. In October 2012, the USA began to penalize hospitals (Medicare) as part of the Hospital Readmission Reduction Program (HRRP) under the Patient Protection and Affordable Care Act. HRRP has led to increased interest and research into the field of readmissions

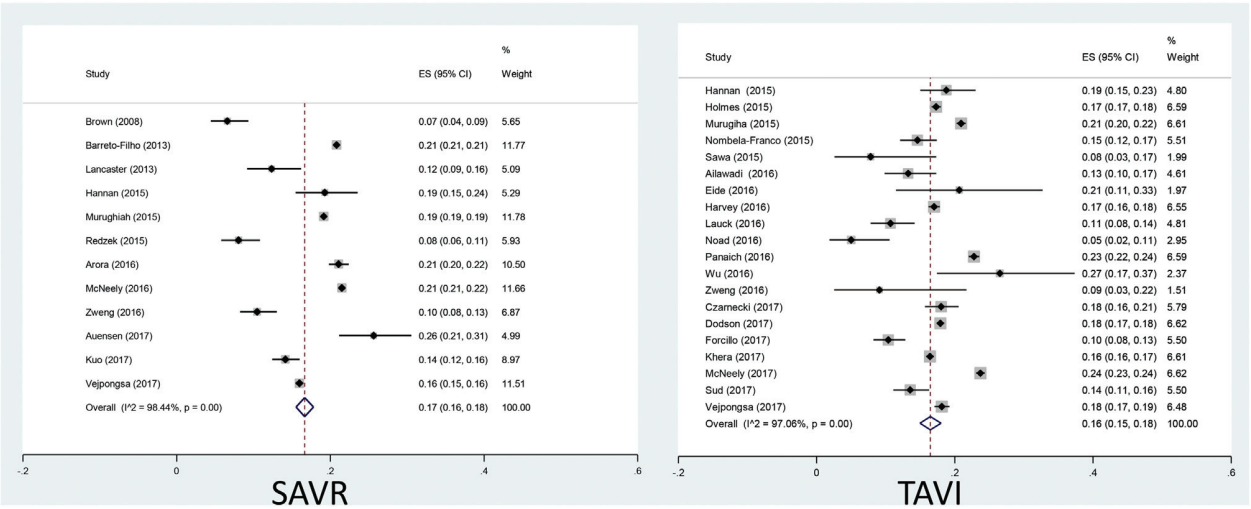

Fig. 2. Forest plots summarizing the proportions of 30-day all-cause readmission after surgical and transcatheter aortic valve replacement (SAVR and TAVR).

Table 2
Estimate of the random effect meta-regression model between incidence of readmission and the study-level variables.

Covariates	N	Level	β-Coefficient	Std. error (β)	t	*p*-Value	τ^2	Adj R^2 (%)[a]
SAVR[b]								
None	12	–	0.1723	0.0149	11.54	<0.001	0.00157	–
Single center	12	Yes/no	−0.0698	0.0231	−3.01	0.013	0.0004	69.20
Prospective	12	Yes/no	−0.0129	0.0523	−0.25	0.810	0.0016	−8.48
Primary endpoint	12	Yes/no	0.0270	0.0311	0.87	0.406	0.0014	1.16
USA	12	Yes/no	0.0488	0.0321	4.82	0.160	0.0008	46.48
TAVR[c]								
None	20	–	0.1793	0.0093	19.18	<0.001	0.0008	–
Single center	20	Yes/no	−0.0529	0.0315	−2.24	0.038	0.0006	23.78
Prospective	20	Yes/no	0.0209	0.0393	−1.35	0.195	0.0008	5.53
Primary endpoint	20	Yes/no	−0.0014	0.0209	−0.07	0.946	0.0009	−10.71
USA	20	Yes/no	0.0420	0.0235	1.79	0.091	0.0009	14.87

[a] Heterogeneity accounted by the covariate.
[b] SAVR = surgical aortic valve replacement.
[c] TAVR = transcatheter aortic valve replacement.

in the USA, and this might explain a difference between the USA and other countries. Even though readmissions have declined since 2012 for certain diagnoses for Medicare fee-for-service patients [51], more readmissions after 30 days and 1 year are reported for the USA compared to other countries in, for example, the TAVR population [52].

Causes of 30-day all-cause readmissions after SAVR are poorly described. In this systematic review, we found that heart failure and heart rhythm disturbances are prominent causes. This is similar to the reported causes for readmissions after cardiac surgery, in general, in addition to infections and bleeding [53]. In the TAVR population, heart failure is the most frequently reported cause of 30-day all-cause readmission. However, heart blocks are also common [35], requiring postoperative implantations of permanent pacemakers in 10–30% of the patients [54,55].

Examining the risk factors for 30-day all-cause readmission after TAVR showed that these patients harbor high comorbidity and an underlying frailty [11,34]. COPD, diabetes, heart failure, greater age, and being female have been reported to be predictors for 30-day all-cause readmission after cardiac surgery [9,33,53,56–59]. Many of these predictors for readmissions are also described in the general cardiac surgery population. Risk factors for 30-day all-cause readmission after SAVR are not comprehensively described, at least for articles included in our exhaustive search.

4.1. Clinical implications

Recent evidence suggests a slight increase in mortality among heart-failure patients, simultaneously with the reduction of readmissions due to the implementation of HRRP in the USA [60]. Knowing that heart failure is a prominent cause and risk factor of readmissions after invasive cardiac procedures, such as SAVR and TAVR, this gives rise to concern for the care of these populations in the discharge and early rehabilitation phase.

Given that the population of older ones continues to increase, we expect that SAVR and TAVRs procedures also will increase in the coming years. If most readmissions after SAVR and TAVR are unavoidable, then we should tolerate a higher number of readmissions to avoid unintended consequences of focusing exclusively on avoiding readmissions. One meta-analysis showed that 27% of readmissions are considered to have been avoidable [61]. Increasing the quality of symptom monitoring in the early phase after discharge might prevent avoidable readmissions and maintain patient safety for those who must be readmitted [62].

4.2. Research implications

The overall numbers of 30-day all-cause readmissions after SAVR and TAVR can be used to achieve more robustly powered studies. Indeed, the present meta-analysis provides reliable figures for calculating sample sizes for future intervention studies (e.g., aiming to reduce readmissions) [63] or for improving the transition of care. Furthermore, the high number of readmissions underscores a greater need for research aimed at determining the proportion of avoidable readmissions, because that type of readmission is auspicious for quality-enhancing interventions. Completing more prospective studies will ensure higher data quality and detailed follow-up. Finally, to understand and to be able to appraise the readmission statistics, transparency on how the readmission numbers are validated in research should be comprehensively reported in the publications.

4.3. Methodological considerations

The present systematic review and meta-analysis has methodological strengths. In both the SAVR and TAVR groups, there were >10 appropriate articles evaluated, which enabled us to perform a random effects meta-regression on study-level variables. Furthermore, none of the included articles reported on studies that were of poor quality. The extensive search we conducted implies that we likely missed few or no relevant studies. In addition, we found no publication bias, and the sensitivity analysis shows that the results are robust and strengthens validity of the results from the meta-analysis.

However, there were also some methodological limitations of our review and analysis that warrant discussion. First, there was great heterogeneity between the studies reported on which could be caused by differences in competence among surgeons, cardiologists, intervention radiologists, etc. There were also differences in patient volumes among the hospitals, device usage, and follow-up strategies after discharge. This heterogeneity limits to some degree what can be interpreted from the results. Second, the reporting of clinical data was inconsistent. This inconsistency prevented us from doing a random meta-regression analysis on patient-level variables. Third, none of the included articles provided a detailed, transparent validation of the readmission data presented in the articles. In large retrospective trials, administrative databases are often used to obtain the readmissions figures. It is well known that, with these databases, there are errors in coding practice and methodological problems regarding extraction of exact, relevant data [50,64]. Fourth, English-language bias can have been introduced due to our language limitations, but likely with less effect [65]. Fifth, the proportions of avoidable and unavoidable readmissions are not described, making it difficult to evaluate to what degree the readmissions after SAVR and TAVR are a matter of quality of care or an anticipated clinical outcome due to the natural course of the condition after treatment. Because of this issue, some believe that readmission is not a reliable quality measurement of hospital care for cardiac surgery patients [66].

5. Conclusions

Our findings demonstrate a high proportion of 30-day all-cause readmissions after SAVR (17%) and TAVR (16%). In the SAVR group, higher readmission rates were reported in multicenter studies, the USA, retrospective studies, and studies with readmission as the primary outcome. In the TAVR group, higher readmission rates were reported in multicenter studies, the USA, and in retrospective studies. Heart failure and hearth rhythm disturbances are common causes of readmission in patients with heart valve problems. The results of the present systematic review and meta-analysis provide new impetus for conducting quality-enhancing projects and provide the necessary data for accurately calculating sample sizes for future trials.

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Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.05.026.

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Impact of telephone follow-up and 24/7 hotline on 30-day readmission rates following aortic valve replacement -A randomized controlled trial

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ABSTRACT

Background: Thirty-day all-cause readmissions are high after aortic valve replacement (AVR). We aimed to assess the effectiveness of a structured telephone follow-up (TFU) and a 24/7 hotline on reducing 30-day all-cause readmission (30-DACR) after AVR, on reducing symptoms of anxiety and depression and on improving perceived health state.

Methods: A prospective randomized controlled trial was conducted. Patients (n = 288) were randomly allocated to either post-discharge usual care or to care that provided TFU and access to a 24/7 hotline after AVR. Ancillary endpoints were time-to-event (readmission), proportion of avoidable versus unavoidable readmissions after AVR, and predictors of 30-DACR after AVR.

Results: 30-DACR was 22.3%. The structured TFU and 24/7 hotline intervention failed to reduce 30-DACR rates after AVR ($P = 0.274$). Symptoms of anxiety were significantly reduced 30 days after surgery ($P = 0.031$), an effect that did not persist one year after surgery ($P = 0.108$). Most readmissions occurred before 15 days post-discharge, and 75% of them were deemed to be unavoidable. Pleural drainage before hospital discharge ($P = 0.027$) and symptoms of anxiety before surgery ($P = 0.003$) were predictors of 30-DACR after AVR.

Conclusion: The TFU and 24/7 hotline had no effect on reducing 30-DACR after AVR. However, we did measure reduced symptoms of anxiety the first month after AVR. Anxiety reduction appeared to be an important target for intervention, because we found it to be a risk factor for readmission. Future research should focus on the effectiveness of interventions to prevent avoidable unplanned readmissions.

Trial registration: ClinicalTrial.gov, NCT02522663.

1. Introduction

Severe aortic stenosis (AS) caused by calcification of the aortic valve is the prominent reason for aortic valve replacement (AVR) treatment [1]. The prevalence of AS increases with age [2], and is estimated to reach about 10% in 80–89 year old's [3]. In developed countries, a growing older population will expectedly increase the prevalence of AS and the number of invasive treatments [1]. Untreated symptomatic AS has a high mortality rate (up to 85%) within 5 years after onset of symptoms [4]. However, when AVR is done early in the disease course, patients have approximately the same life expectancy as their non-AS counterparts from the general population [3]. In-hospital mortality after AVR is 2–5% [5,6], and increases up to 6–7% for patients >85 years [5]. Postoperative atrial fibrillation and heart failure are common cardiac complications after AVR and causes of readmissions [7].

A recent meta-analysis showed that hospital readmissions following AVR occur in 17% of patients (range 7–23%) [8], and AVR have higher readmissions than coronary-artery-bypass-surgery [9]. Because of the economic impact of readmissions and its increased burden on the

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quality of life of patients and their caregivers [10], preventing hospital readmissions are of paramount importance.

Interventions to reduce readmissions after discharge can be divided into mainly pre-and post-discharge types, and "bridge" interventions (both pre- and post-discharge targets) [11]. Pre-discharge interventions typically include discharge planning and patient education. Interventions done in the post-discharge phase are often telephone follow-ups (TFUs), home visits, or telephone "hotlines" for patients. Few interventions have proven successful in reducing hospital readmissions [11]. TFU and monitoring and managing symptoms after discharge (e.g., home visits) are suggested to have favorable effects in reducing readmission rates [11]. However, such follow-up and support are seldom offered "off-hours," triggering avoidable readmissions when AVR-related symptoms occur in the evenings, at night, or during the weekend. Therefore, a 24/7 hotline in combination with structured TFU is hypothesized to provide a critical resource of support in the immediate post-discharge period [12]. However, to the best of our knowledge, the effectiveness of a 24/7 hotline staffed with specialized professionals and combined with TFU to reduce readmissions has not been investigated to date. Therefore, we conducted a randomized controlled trial to examine the efficacy of such a telephone support system for patients following AVR. The primary objective of the present study was to test the effectiveness of the 24/7 hotline and structured TFU on the 30-day all-cause readmission (30-DACR) rate after discharge for AVR. The secondary objectives were to determine whether this kind of support system would reduce symptoms of anxiety and depression and improve perceived health state. As ancillary objectives, we examined the proportion of avoidable and unavoidable readmissions and predictors of 30-DACR after AVR.

2. Methods

2.1. Participants

We conducted a prospective, randomized controlled trial with parallel groups, following the CONSORT guidelines for reporting [13]. Patients aged 18 and older assigned to the following AVR treatments were eligible for inclusion: First-time isolated AVR, AVR with concomitant coronary artery bypass grafting (CABG), or AVR with concomitant supra-coronary tube graft (SCG). Further, patients had to be available by telephone after discharge, and had mastered the Norwegian language verbally and in written form. We excluded patients who were admitted to the intensive care unit >24 h postoperatively, or patients who experienced physical and/or cognitive impairment following complications after AVR treatment [12]. Patients were operated in two cardiac surgery locations within Oslo University Hospital in Norway. After initial treatment at the tertiary hospital, most patients were transferred to a local hospital (as part of the elective stay and treatment) for medical follow-up until discharge to home. Participants gave written informed consent.

2.2. Intervention

The telephone-support intervention consisted of two parts. First, the project coordinator actively called each intervention patient on day 2 and day 9 after hospital discharge to home (telephone follow-up). Structured telephone calls, comprising advice on the importance of physical activity in the early rehabilitation phase after AVR, were made to remind the participant about the availability of 24/7-telephone support and to answer questions they might have had about their present health condition (patient-centered instructions and/or reassurance). Second, the patients could call a dedicated phone number to receive information whenever they wanted during the first 30 days after discharge (patient-activated hotline). The 24/7-phone hotline was staffed by a group of dedicated and experienced advanced nurse practitioners trained for this service. Participants assigned to the intervention are the experimental group.

Both groups received standard discharge care, which included a scheduled consultation with the treating surgeon before discharge from the tertiary hospital. Individual information was given to each patient about the treatment and the present health condition. The nurses coordinated the transport to local hospital and ensured that necessary documentation followed. A cardiologist in charge at the local hospital, in cooperation with nurses, discharged the patient after a planned final consultation to ensure follow-up and a safe return to home. The patients' general practitioners got notified by email from the tertiary hospital to inform them about the given treatment before the patient was returning home. As part of the discharge care, a short pamphlet about the treatment and early rehabilitation was given all patients before surgery.

2.3. Outcomes

The primary outcome was 30-DACR rate after discharge for AVR treatment, which was defined as an unplanned readmission for any cause to any hospital at least 8 h, and up to 30 days, after discharge from the local hospital. Readmission data were obtained through the patients' medical records from all hospital stays.

Secondary outcomes were symptoms of anxiety, depression, and self-perceived health status. We used the Hospital Anxiety and Depression Scale (HADS) to measure symptoms of anxiety and depression [14].

We used the EuroQol (5D-3L) to assess participants' self-perceived health status [15,16]. EQ-5D-3L assesses five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The descriptive health state was converted to a single index value using the time-trade-off (TTO) technique, which was based on the UK population [17]. The EQ-5D-3L additionally has a visual analogue scale (EQ-VAS), ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). EQ-5D-3L is validated for the use of assessing patients' self-perceived health after heart valve surgery [18].

Assessments of HADS and EQ-5D-3L were conducted before surgery, and at 1, 3, 6, and 12 months after the surgical treatment.

The assessment of avoidable versus unavoidable readmissions was performed by a cardiac surgeon (T.T.), a cardiologist (S.S.), and a nurse with expertise in the field of discharge management (I.L.). They had available for evaluation the relevant clinical pre-, per- and postoperative information of each patient in addition to readmission data. They were blinded with regard to group assignment (i.e., experimental vs. control).

2.4. Study overview

The AVRre Study was approved by the Regional Committees for Medical and Health Research Ethics, Health East South, Norway (approval 2013/2031-3), and complied with the Declaration of Helsinki principles.

2.5. Randomization

Randomization was performed by using a web-based randomization system developed and administered by the Norwegian University of Science and Technology, Trondheim, Norway.[15] Patients were randomly assigned in a 1:1 ratio, block-randomized with block-size randomly varied between 8 and 12 [12].

2.6. Statistical analysis

Sample size and power calculation was published in a protocol [12]. Categorical values are presented as numbers and percentages, and continuous data are presented as means or medians with the standard deviation (SD). To characterize the sample and evaluate differences between the intervention and control groups, we used Pearson Chi-

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square or Fisher's exact tests for categorical variables. Independent *t*-tests or Mann-Whitney *U* tests were used to test for significant differences between groups on continuous variables.

Assessment of the primary objective was conducted by comparing the 30-DACR rates of the intervention and control groups, using a Chi-square test (per protocol analysis, N = 260). Intention-to-treat (ITT) analysis (N = 282) was performed as part of the sensitivity analysis. For analyses of secondary outcomes at the first month post-discharge, we first performed analysis of covariance (ANCOVA) as per protocol, adjusting for baseline scores as a covariate. Assumptions for ANCOVA were checked and were adequately met. Furthermore, a linear mixed model (LMM) was used to evaluate the difference in HADS-A and HADS-D and in EQ-5D-3L VAS and EQ-5D-3L index value (TTO) scores between the groups on repeated measures, up to one year after surgery (N = 260). In each model, the baseline score, time variable, and group were specified as fixed factors, while the intercept was specified as a random effect. The percentage of missing values in HADS-A and HADS-D index scores was 6.5% and 6.4%, respectively. For the EQ-5D-3L VAS and TTO index scores, the percentages of missing index values were 10.31% and 8.23%, respectively. Missing index values in HADS and EQ-5D-3L were substituted by means of multiple imputation with 20 iterations and analyzed under the missing-at-random assumption [19]. The assumptions underlying mixed-model analysis were checked and were adequately met.

We conducted ancillary analyses. First, we described the use of the 24/7 hotline within the intervention and the readmission cohort. Second, we analyzed whether the readmissions were avoidable or unavoidable. Third, we performed a time-to-event analysis using Kaplan-Meier survival curves. The survival analysis was stratified by group to quantify the time to readmission within 30 days after discharge, censored at day 31 and tested for significance by the log-rank test. Finally, we performed a Cox proportional hazards regression analysis to examine the predictors associated with 30-DACR after AVR (complete analysis without imputation). The assumptions underlying the Cox regression analysis were checked and were adequately met. We examined first predictors in a univariate analysis. Variables with *P* values <0.2 were included in a multivariate model, using a stepwise approach. The multivariate model contained the following variables: women, age, group assignment, pleural drainage before discharge, and anxiety at baseline.

Statistical significance was evaluated using a two-sided *P* value of <0.05. Analyses were performed with the Statistical Package for Social Sciences (SPSS), version 25.

3. Results

3.1. Study population

Overall, 482 patients were screened for participation from late August 2015 to mid-February 2017, 288 of which were randomly assigned to either usual care (control group) or to the 24/7-phone support group (intervention group) (Suppl Fig. 1). A total of 27 of these allocated patients were excluded before they were discharged, 16 in the intervention group and 11 in the control group. In the intervention group, 9 were excluded because they were admitted to the ICU >24 h postoperatively, 4 were receiving prolonged care, 2 underwent a non-AVR procedure instead, and 1 moved to another hospital. In the control group, 5 patients were excluded because they were admitted to the ICU > 24 h postoperatively, 3 underwent a non-AVR-procedure, and 3 withdrew from the trial. Table 1 shows the distribution of baseline characteristics of participants, stratified by group assignments. In-hospital outcomes are shown in Table 2. In this sample, 30-day mortality was 0, and 1-year mortality was 0.7% (2/282).

3.2. Use of the 24/7 hotline

During the trial, 58 of the 127 (46%) participants in the intervention group used the 24/7-phone support hotline (including two caregivers calling for their spouses). More women than men ($P = 0.046$) used the 24/7 hotline, and callers were more often readmitted compared with non-callers ($P = 0.001$). Supplement Table 1 shows the characteristics of the intervention participants before the trial and outcomes related to the use of the 24/7 hotline.

3.3. Primary outcome: 30-DACR

A total number of 58 participants (22.3%) experienced an unplanned 30-DACR. In the intervention group, 32 participants (25.2%) were readmitted compared to 26 participants (19.5%) in the control group. This difference, however, was not statistically significant (χ^2 [1, $N = 260$] = 1.196, $P = 0.274$). The ITT analysis on 30-DACR yielded a non-significant result also ($N = 282$, $P = 0.317$). Readmissions to local hospitals accounted for 86.2% of the total numbers of readmissions and 13.8% to the tertiary hospital. A few patients were discharged direct to rehabilitation ward (9%). The characteristics of participants with and

Table 1
Baseline characteristics of participants in the AVRre study (N = 282).

Variables	Intervention group[a]	N	Control group	N
Demography				
Age, y, mean (SD)	65.8 (11.1)	141	67.3 (9.8)	141
Male gender, n (%)	101 (71.6)	141	100 (70.9)	141
Married or partner, n (%)	105 (75.5)	139	96 (76.8)	125
Medical history		141		141
Non-rheumatic aortic stenosis, n (%)	118 (83.7)	–	111 (78.7)	–
Hypertension, n (%)	61 (43.3)	–	52 (39.6)	–
Atrial fibrillation, n (%)	13 (9.2)	–	25 (17.7)	–
Diabetes, type I and II, n (%)	23 (16.3)	–	16 (11.3)	–
Coronary artery disease, n (%)	55 (39)	–	55 (39)	–
Heart failure, n (%)	13 (9.2)	–	8 (5.7)	–
Pulmonary disease, n (%)	8 (5.7)	–	5 (3.5)	–
Thoracic aortic aneurysm, n (%)	16 (11.3)	–	20 (14.2)	–
Medications at baseline		141		141
Anticoagulants/antiplatelets, n (%)	88 (62.4)	–	85 (60.2)	–
Statins, n (%)	89 (53.1)	–	79 (56)	–
Beta-blockers, n (%)	59 (41.8)	–	53 (37.6)	–
Diuretics, n (%)	19 (13.5)	–	15 (10.6)	–
Risk factors				
Charlson Comorbidity Index, n (%)		138		138
0, n (%)	53 (38.4)	–	53 (37.6)	–
1–2, n (%)	69 (50)	–	72 (52.2)	–
≥ 3, n (%)	16 (11.6)	–	13 (9.4)	–
EuroScore, mean (SD)	5.40 (2.1)	130	5.5 (2.2)	127
NYHA classification		131		129
Class I, n (%)	2 (1.5)	–	2 (1.6)	–
Class II, n (%)	59 (45)	–	54 (41.9)	–
Class III, n (%)	65 (49.6)	–	72 (55.8)	–
Class IV, n (%)	5 (3.8)	–	1 (0.8)	–
Ejection fraction		126		128
Normal >50%, n (%)	101 (80.2)	–	109 (85.2)	–
Moderate ≥30–50%, n (%)	22 (17.5)	–	15 (11.7)	–
Low <30%, n (%)	3 (2.4)	–	4 (3.1)	–
Echocardiographic measures at baseline				
Aortic valve area, cm^2, mean (SD)	0.9 (0.5)	123	0.9 (0.6)	127
Aortic peak velocity, m/s, mean (SD)	4.30 (0.9)	131	4.32 (1)	132
Aortic mean gradient, mmHg, mean (SD)	49.62 (16.7)	125	50.96 (18.6)	118
End diastolic diameter of left ventricle, cm, mean (SD)	5.3 (0.9)	125	5.27 (0.9)	130

NYHA, New York Heart Association; SD, standard deviation.
[a] 24/7-telephone support hotline (control group received usual care).

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Table 2
In-hospital outcomes of participants in the AVRre study.

Variables	N	Intervention group	N	Control group	N	*P*
Surgery	279		141		138	
Mechanical single valve, n (%)		22 (15.6)		26 (18.4)		0.641
Biological single valve, n (%)		61 (43.3)		56 (39.7)		0.741
Valve with concomitant surgery, n (%)	279	58 (41.1)	141	56 (40.6)	138	0.925
Total surgery time, min, mean (SD)	272	182.5 (43.7)	137	179.1 (45.2)	135	0.302
Ischemic time, min, mean (SD); range (34–166 min)	275	87.3 (23.6)	137	83.7 (23.7)	138	0.381
Total time on heart-lung machine, min, mean (SD)	275	117 (32.4)	138	114.8 (33.7)	137	0.254
Maximum troponin, ng/L, mean (SD)	240	630 (409)	117	670 (362)	123	0.828
Maximum CK-MB, μg/L, mean (SD)	274	27.4 (16.5)	137	27.4 (16.9)	137	0.363
Complications						
Reoperation, n (%)	279	5 (3.5)	141	7 (5.1)	138	0.530
Atrial fibrillation, n (%)	282	79 (56.8)	139	77 (56.6)	136	0.971
Heart blocks, n (%)	258	12 (9.4)	127	11 (8.5)	131	0.767
Pleural drainage, n (%)	282	32 (22.7)	141	37 (26.2)	141	0.489
Pericardial drainage, n (%)	282	6 (2.1)	141	6 (2.1)	141	1.000
Infection treatment, n (%)	281	19 (13.6)	140	32 (22.7)	141	**0.047***
Permanent pacemaker implantation, n (%)	268	12 (8.9)	135	6 (4.3)	133	0.152
Postoperative delirium, n (%)	260	11 (8.7)	127	11 (8.3)	133	0.705
Stroke/TIA, n (%)	282	5 (3.5)	141	2 (1.4)	141	0.447
Echocardiographic measures at discharge						
Aortic valve area, cm^2, mean (SD)	205	1.95 (0.6)	100	1.9 (0.6)	105	0.879
Aortic peak velocity, m/s, mean (SD)	258	2.45 (0.6)	129	2.42 (0.5)	129	0.195
Aortic mean gradient, mmHg, mean (SD)	196	15 (7.1)	99	14.5 (5.7)	97	0.284
Length of elective stay						
In university hospital, da, mean (SD)	277	5.2 (3.2)	139	4.91 (2.7)	138	0.148
Total elective hospital stay, da, including local hospital, mean (SD)	275	11 (6.6)	137	10 (4.1)	138	**0.006***

SD, standard deviation; TIA, transient ischemic attack.
* Statistically significant.

without a readmission are summarized in Supplement Table 2. In Supplemental Table 3 are the causes of 30-DACR given.

3.4. Secondary outcomes

3.4.1. Symptoms of anxiety and depression

The intervention group experienced significantly fewer symptoms of anxiety compared to the control group one month after surgery (N = 260, $P = 0.031$; adjusted for baseline score). The partial eta-squared score was 0.019, indicating a small effect size. There was no statistically significant difference between the groups on symptoms of anxiety at the one-year assessment (N = 260, $P = 0.108$). The LMM analysis done without multiple imputations also showed no effect of the intervention on anxiety at the one-year assessment (N = 260, $P = 0.096$). The time course of all participants' HADS-Anxiety scores is presented in Suppl Fig. 2A of the online-only Data Supplement.

Participants in the control group had more symptoms of depression before surgery compared to those in the intervention group; however, this difference was not statistically significant different (N = 260, $P = 0.213$). Up to one year after surgery, there was no statistical difference between the groups on symptoms of depression (N = 260, $P = 0.758$). The progression of the HADS-Depression scores over time is presented in Suppl Fig. 2B of the online-only Data Supplement.

3.4.2. Perceived health state

There were no statistically significant differences between the groups on perceived health state, as measured by EQ-5D-3L VAS (N = 260, $P = 0.636$). There was also no significant difference between the groups on perceived health state, as measured by EQ-5D-3L index value TTO up to one year after surgery (N = 260, $P = 0.485$). The time course of EQ-5D-3L VAS and index value (TTO) scores are presented in Suppl Fig. 3A, B of the online-only Data Supplement.

3.5. Ancillary analyses

3.5.1. Avoidable vs. unavoidable readmissions after AVR

Overall, the proportion of unavoidable readmissions was 75%. In the intervention group, 26 out of 32 readmissions (81%) were unavoidable. In the control group, 18 out of 26 readmissions (69%) were considered unavoidable. Non-adherence to medication (33%) and chest discomfort or pain (67%) were the reasons for the readmissions assessed avoidable.

3.5.2. Time-to-event analysis of readmissions

Construction of Kaplan-Meier survival curves showed that 45% and 83% of all 30-DACR occurred within 7 days and 14 days after discharge, respectively (Fig. 1). The calculated readmission-free survival of the intervention and control groups was not significantly different (log rank χ^2 (1) = 1.439, $P = 0.230$).

3.5.3. Predictors of 30-DACR after AVR

The Cox proportional hazards multivariate analysis demonstrated that participants' symptoms of anxiety before surgery (95% CI: 1.333–4.022, $P = 0.003$) and pleural drainage before hospital discharge (95% CI: 1.072–3.213, $P = 0.027$) were independent predictors of 30-DACR after AVR, when adjusted for other variables (Fig. 2). Participants' age was borderline statistically significant (HR = 0.979, $P = 0.067$). Moreover, 30-DACR showed a downward trend in risk with increasing age; that is, as age increased in our sample, risk of readmission decreased.

4. Discussion

To reduce 30-DACRs after AVR, we developed and evaluated an intervention that used a structured TFU accompanied by a 24/7 hotline. We hypothesized that a 24/7 hotline would strengthen the promising effects of TFU in reducing readmissions. However, with this study population, our study results failed to find this hypothesis. Our findings did not show a significant difference in readmission rates between the intervention group and control group after discharge for AVR. The intervention was effective, however, in reducing symptoms of anxiety within the first month after surgery. This reduction did not persist. One year after discharge there were no differences in anxiety between the intervention and control group. The intervention also did not affect symptoms of depression or perceived health status. Symptoms of anxiety before surgery and pleural drainage before discharge predicted well 30-DACR. Three quarters of the readmissions were evaluated to be unavoidable.

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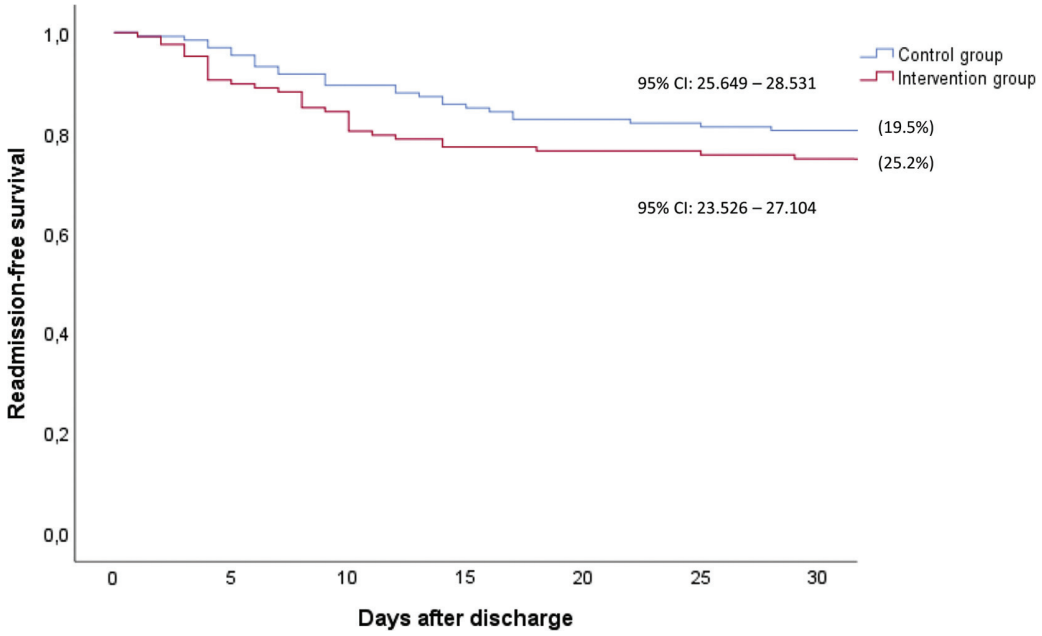

Fig. 1. Kaplan-Meier curves illustrating the results of the time-to-event analysis on the thirty-day all-cause readmission rate between the groups in the AVRre study.

In this trial, the 30-DACR rate was 22.3%. This readmission rate is higher than the pooled 30-DACR rate of 17%, as found in a recent meta-analysis [8]. However, the readmission rate in the present study is somewhat lower than that of an earlier study in our hospital (26%) [20]. Hospitals within and between countries vary on readmissions rates, and this is often attributed to differences in healthcare systems, policies, or hospital volumes, which evolve over time [21–23]. Achieving the lowest readmission rate is not necessarily an indicator of good-quality care. Indeed, in the USA, implementation of the Hospital Readmission Reduction Program is associated with fewer readmissions but with higher mortality [24]. Therefore, it would be more useful to focus on appropriate versus inappropriate readmissions, or avoidable and unavoidable readmissions.

This study is the first to report on the proportion of avoidable versus unavoidable readmissions after AVR. Three quarters of the readmissions in our trial were unavoidable. The most common reasons for readmission were atrial fibrillation, pericardial and pleural effusions, and infections, which is in line with prior studies [25–27]. Obviously, such complications cannot be managed or averted using a 24/7 hotline or TFU. Conversely, TFU can act as an appropriate gateway to needed readmissions. Indeed, participants in the intervention group who called the 24/7 hotline were more often readmitted than those who did not call. We observed that our intervention referred 10 patients to readmission, and only 3 of these might have been avoidable. Furthermore, two of the referred patients had tamponade and were invasively treated acutely. This suggests that our intervention might have the potential for enhancing patient safety post-discharge. It would be useful to investigate the effectiveness of our intervention specifically on the prevention of avoidable readmissions. Unfortunately, our trial was not powered to do this analysis. Greater emphasize on the causes for the avoidable readmissions might have prevented the avoidable readmissions.

Our intervention succeeded in reducing symptoms of anxiety in the first month after AVR. This effect did not last up to one year after surgery. Interventions (including TFU) delivered post-discharge have been shown to reduce anxiety after cardiac surgery [28]. Personal

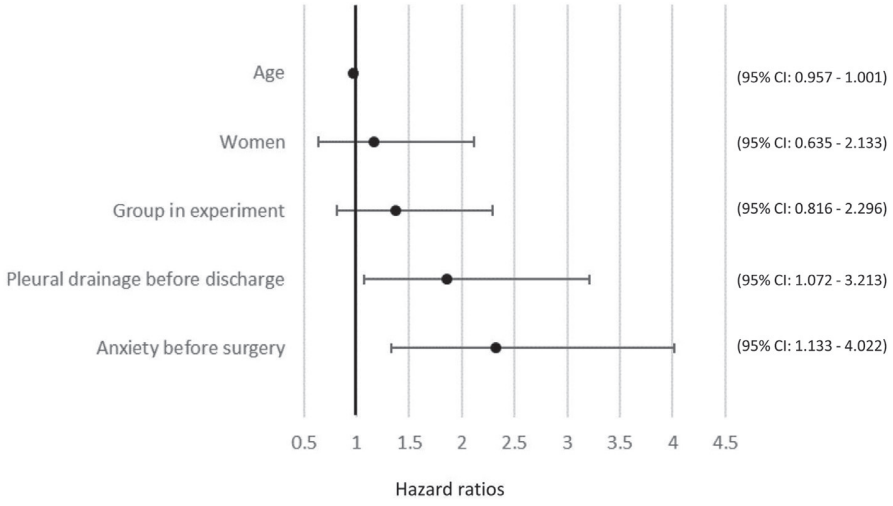

Fig. 2. Hazard ratios from Cox regression analyses. The analyses were adjusted for the following variables: Living alone, Charlson Comorbidity Index, hypertension, atrial fibrillation, and diabetes before surgery, length of stay in tertiary hospital, and depression score before surgery.

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contact with patients before discharge from the tertiary hospital, opportunities to directly contact at any time post-discharge professionals at the tertiary hospital (24/7 hotline), and satisfaction with the structured TFU may be responsible for the lower level of symptoms of anxiety after surgery. However, with a small effect size present the result must be interpreted with caution. Targeting anxiety is important, because anxiety is as an independent risk factor for mortality and major morbidity after cardiac surgery [29]. In the present trial, anxiety levels before surgery predicted readmissions. Hence, in order to improve other outcomes, anxiety would be an appropriate target for an intervention.

Another risk factor for readmission that emerged from the present trial was pleural drainage before discharge. Knowing the impact of pleural drainage before discharge on readmissions after AVR should lead to heightened attention toward these patients in the discharge planning. Enhanced cooperation with local hospitals and primary care, including effective communication and systematically pre-scheduled outpatient consultations, could enhance the follow-up of AVR patients whose pleural cavities are drained before discharge [30].

4.1. Methodological considerations

The AVRre study has several strengths. First, it is the first study that aimed to use a 24/7 hotline to reduce readmissions after AVR. The methods and statistical approaches are transparently reported in order to be replicable. Second, we accessed and tabulated necessary medical information and had complete data on the primary outcome. Third, we used well-established, valid, and reliable instruments to assess changes in the secondary outcomes over time. Forth, we had high response rates on the questionnaires, which were a result of the planned logistics and our conscious choice to use only two small self-report questionnaires to assess these patients. Fifth, we perceive this as a low-cost intervention because no extra personnel needed to be hired for the intervention, and it can be implemented as a part of the 24/7 patient care provided by experienced nurses of cardiovascular wards.

Nevertheless, the interpretations of the findings in our study must be used cautiously because of some limitations. First, the study was conducted at a single center, which could limit the external validity of the results. Second, there was likely some heterogeneity in the way the intervention was delivered; e.g., a learning effect of TFU over time and possible differences in the way different nurses staffed the hotline. Third, the heterogeneity of multiple local hospitals (some were rural requiring >4-hour drive time from the tertiary hospital), with different discharge procedures and rehabilitation offers, must be considered when interpreting the findings. Fourth, different quality of services among primary care providers might have contributed to differences in the post-discharge phase and readmission rates of the AVR patients. Fifth, the intervention might have introduced a bias effect, in which more attention was paid toward a patient's health condition during a sensitive phase of his early rehabilitation. This might have led to slightly more readmissions in the intervention group compared to the control group. Sixth, our trial was powered on the reduction of 30-DACRs with 10 percentage points. Given our finding that only 10%–25% are avoidable, the study was insufficiently powered to carry out analyses on the effect of the intervention on avoidable readmissions. Future studies should target avoidable readmissions and evaluate whether our intervention is capable of reducing this type of readmission. Seventh, we cannot provide evidence on the costs of the intervention, yet. However, we are preparing a cost-utility study to investigate the benefit-burden ratio of the intervention.

5. Conclusions

Our findings did not support the hypothesis that a structured TFU and a 24/7-patient-support hotline intervention would reduce post-discharge readmissions after AVR. The intervention was effective, however, in reducing symptoms of anxiety within the first month after AVR surgery. We found that a three-quarter of the readmissions were unavoidable. Therefore, our results indicate that it could be promising to shift our focus from reducing all-cause readmissions to reducing avoidable readmissions and test the effect of interventions on such avoidable readmissions. Such future studies would, at the very least, preclude the possibility that unavoidable readmissions are reduced at the cost of increased mortality.

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Declaration of competing interest

None of the authors have any connections with industry or financial associations that pose a conflict of interest in relation with this study. Conflict of interest: none declared. The authors report no relationships that could be construed as a conflict of interest.

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IV

Facilitators of and barriers to reducing thirty-day readmissions and improving patient-reported outcomes after surgical aortic valve replacement: a process evaluation of the AVRre trial

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ABSTRACT

BACKGROUND

The Aortic Valve Replacement Readmission (AVRre) randomized control trial tested whether a telephone intervention would reduce hospital readmissions following surgical aortic valve replacement (SAVR). The telephone support provided 30 days of continuous phone-support (hotline) and two scheduled phone-calls from the hospital after discharge. The intervention had no effect on reducing 30-day all-cause readmission rate (30-DACR) but did reduce participants' anxiety compared to a control group receiving usual care. Depression and participant-reported health state were unaffected by the intervention. To better understand these outcomes, we conducted a process evaluation of the AVRre trial to gain insight into the (1) the dose and fidelity of the intervention, (2) mechanism of impacts, and (3) contextual factors that may have influenced the outcomes.

METHODS

The process evaluation was informed by the Medical Research Council framework, a widely used set of guidelines for evaluating complex interventions. A mix of quantitative (questionnaire and journal records) and qualitative data (field notes, memos, registration forms, questionnaire) was prospectively collected, and retrospective interviews were conducted. We performed descriptive analyses of the quantitative data. Content analyses, assisted by NVivo, were performed to evaluate qualitative data.

RESULTS

Telephone intervention nurses desired to receive more preparation before intervention implementation. SAVR patient participants were highly satisfied with the telephone intervention (58%), felt safe (86%), and trusted having the option of calling in for support

(91%). The support for the telephone hotline staff was perceived as a facilitator of the intervention implementation. Content analyses revealed themes: “gap in the care continuum,” “need for individualized care,” and “need for easy access to health information” after SAVR as themes as. Differences in local hospital discharge management practices influenced the 30-DACR incidence.

CONCLUSIONS

The prospective follow-up of the hotline service during the trial facilitated implementation of the intervention and contributed to high participant satisfaction and likely reduced their anxiety after SAVR. Perceived less-than-optimal preparations for the hotline could be a barrier to AVRre trial implementation. Integrating user experiences into a mixed-methods evaluation of clinical trials is important for broadening understanding of trial outcomes, the mechanism of impact, and contextual factors that influence clinical trials.

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KEYWORDS

Surgical aortic valve replacement, 30-day readmission, post-discharge telephone intervention, process evaluation, implementation

Background

Severe aortic stenosis (AS) is the most common reason for surgical aortic valve replacement (SAVR) [1]. Calcification of the heart valve leaflets is a prominent cause of altered cardiac blood flow, a pathology that leads to AS [1]. Non-rheumatic aortic stenosis, or valve degeneration associated with aging, requires intervention, leading to more invasive surgeries like SAVR and less-invasive ones like transcatheter aortic valve implantation (TAVI). The frequency of these two treatments is accelerating in Western countries because of growing aging populations [2]. The prevalence of AS in the US has risen from less than 1% for people <44 years old to 13.3% for people >75 years old [3]. For patients >65 years, long-term mortality after SAVR surgery is very low, with a median survival of 11-13 years [4, 5]. However, hospital readmissions after SAVR are common. A recent meta-analysis of 30-day all-cause readmission (30-DACR) rates after SAVR showed an average rate of 17%, with substantial variability across countries and different assessment methods [6].

Hospital readmissions have a high societal and economic burden and significant impact on healthcare systems. Readmissions during the rehabilitation phase also affect the quality of life of patients and their caregivers [7, 8]. Frequent causes for readmissions after SAVR are atrial fibrillation, infections, and heart failure [6, 9]. For these reasons and the institutional and personal burdens mentioned, healthcare providers aim to reduce readmissions. Also, governments enact legislation that provides incentives to reduce hospital readmissions. Research results on the efficacy of interventions aimed at preventing readmissions is ambiguous to date [10-13]. Hence, more rigorous research is needed that uses robust experimental designs. One such study is the Aortic Valve Replacement Readmission (AVRre) trial [14]. This intervention involved the following.

From August 2015 to April 2017, we conducted the AVRre trial [14]. This randomized controlled trial (RCT) tested the effectiveness of a post-SAVR discharge telephone service from which participants could get healthcare information. It tested specifically whether a 24/7 patient-activated telephone hotline and intermittent, scheduled telephone follow-ups (TFUs) would reduce the 30-DACR rate, alleviate symptoms of anxiety and depression, and improve patients' self-perceived health state. A control group received usual post-discharge care [14]. The AVRre RCT was ineffective in reducing the 30-DACR rate [15]. However, the 24/7 hotline and TFU were effective in reducing symptoms of anxiety during the first month after surgery. Symptoms of depression and the patients' self-perceived health state remained unchanged after SAVR surgery for up to one year [15].

In order to understand why the intervention failed in some aspects and succeeded in others, we conducted a process evaluation that was informed by the Medical Research Council (MRC) guidelines [16]. Our process evaluation aimed to gain insight into (1) the appropriateness of the AVRre intervention dose (i.e., number of days and calls administered) and fidelity of the intervention (i.e., delivered as designed); (2) the mechanism of positive/negative impacts; and (3) the contextual factors that may have influenced the intervention in unanticipated ways. The aim of the present study was to report the process evaluation of the AVRre trial.

Methods

Overview of completed AVRre intervention

To better understand our process evaluation goals and results, we first describe the original AVRre RCT. Before implementing the AVRre trial, we developed an evidence-based manual for use with a 24/7-hotline telephone service and completed a pilot study of its use. To refine

the intervention, we considered users' experiences obtained from research interviews with former cardiac surgery patients (Supplement 3). The hotline staff nurses and the project coordinator were educated on the purpose of the intervention and were trained to administer it effectively. During the AVRre trial, the hotline was staffed by experienced nurses [14]. The nurses were closely assisted and monitored through consultations with the project coordinator. These consultations included regular case discussions. Nurses also participated in educational sessions with expert physicians and a physiotherapist.

As part of the AVRre trial, AVR patients received a structured telephone follow-up that was conducted by the project coordinator on days 2 and 9 after discharge. The patients' answers from the two follow-ups were recorded in a form and later analyzed. Patients also completed questionnaires 1, 3, 6, and 12 months after surgery [14].

Framework for and design of process evaluation of AVRre trial

While outcome evaluations assess the effectiveness of an intervention in producing change (in this case, reduction in 30-DACR), process evaluations help researchers see ***how*** an intervention outcome or impact was achieved and if it was implemented as intended [16]. To carry out the process evaluation of the AVRre trial, we used the updated MRC framework for developing and evaluating complex interventions [17]. This version guided the process evaluation of relevant aspects of the AVRre trial. Ideally, a process evaluation should start at the feasibility and pilot phases of a proposed intervention and be followed by periodic prospective evaluation during the AVRre trial implementation phase [16]. Done in parallel with the outcome evaluation, the process evaluation provides additional important insight about whether the intervention activities of the RCT were implemented as intended and why or why not they were effective.

We used quantitative and qualitative methods to carry out the process evaluation. Mixed-methods research is rigorous and uses multiple types of data to leverage the strengths and offset the weaknesses of each data type. This approach aids in real-life contextual understanding of a clinical intervention from multi-level perspectives [18]. Our MRC-informed process evaluation (Fig. 1) first evaluated aspects of the intervention implementation. We assessed design and implementation aspects prior to and during the AVRre trial. We aimed to determine whether preparation and execution of the hotline manual was adequate, and whether the pilot study and education and training program influenced the fidelity of intervention delivery. We also aimed to determine whether the dose (i.e., number of days and calls administered) of the intervention was given as planned, and whether the follow-up calls done by the project coordinator influenced the fidelity. Secondly, we sought to determine the mechanism of impact by analyzing AVRre trial participants' responses to the intervention using several data sources, like field notes, questionnaires, and the nurses' feedback from individual consultations, team case discussions/consultations, and a focus group interview of the nurse staff experiences. Lastly, we analyzed patient-reported data (questionnaire and narratives) and medical records' data to local hospitals' discharge patterns of the SAVR patients, for example, readmission length of stay. Table 1 gives the overview of the process evaluation of the AVRre trial hotline intervention.

Study population

Patients included in the trial were initially treated and had SAVR surgery at a tertiary hospital in southeast Norway. After surgery, patients in the RCT were transferred to a local hospital before discharge to their home. RCT participant inclusion and exclusion criteria are described in the published AVRre RCT protocol. [14]

Data collection and procedure

AVRre trial participants were 1:1 block (8-12) randomized to reduce the risk of selection and allocation bias [14]. There were two groups: the intervention group and a control group, the latter received only the usual follow-up care for SAVR surgery [14]. All data used for the process evaluation were collected prospectively during the AVRre trial, except for data obtained in the prior and post-intervention focus interviews. We used a semi-structured interview guide (Supplemental files 2 and 3) to collect information during the interviews regarding former cardiac patients' experiences prior to the study, the nurses' experiences during preparations for the intervention and their performance and how they perceived patient reactions to the 24/7 telephone hotline service during the intervention. We also used a mind map prior to the interview with former cardiac patients to cue and enhance their memories [19]. The mind map was constructed by the researcher and filled in by the respondent prior to the interview (a tool to frame past experiences) (Supplemental file 4). The follow-up questionnaire given 3 months after surgery comprised questions related to the use of the hotline and questions on patient-report experiences measures (PREM) from a national survey on patient experiences with discharge from hospitals; this questionnaire also had an open-ended comment field so participants could elaborate [20, 21].

The AVRre trial obtained institutional ethical approvals [14], and all participants and nurses gave written informed consent. Consolidated Standards of Reporting Trials (CONSORT) guidelines [22] were followed in the reporting of the effectiveness of the intervention [15]. Standards for Reporting Implementation Studies (StaRI) informed the reporting of the process evaluation reported in this article [23] together with the CONSORT.

Data analysis

Using SPSS [24], we calculated frequencies and did crosstab analyses of quantitative data from the self-report questionnaire completed 3 months after surgery. Data are presented as

numbers and percentages. Fisher Exact tests were used to evaluate differences between the intervention and control groups and between other variables. Qualitative data collected prior to the AVRre trial was organized using QSR International's NVivo 10 qualitative data analysis software [25]. Team member field notes taken during the follow-up of the AVRre trial were analyzed. Planning of the qualitative analysis approach was informed by Maxwell [26] and by Kvale and Brinkmann for the interviews [27]. Content from the TFU field notes, open-ended participant comments from the questionnaire, and the focus group were analyzed by systematic text condensation, as described by Malterud [28] and NVivo 11 Pro software [29]. All assessments and analyses were periodically discussed with one of the co-authors.

Results

In the AVRre trial, 288 patients were included as participants. Of the 127 participants in the intervention group [15], 46% used the hotline service. Ancillary analyses estimated that 81% of the readmissions in the intervention group were unavoidable (vs. 69% in the control group) [15]. These findings were relevant for the process evaluation. In the intervention group, 62.5% of the readmissions were due to a cardiac-related cause, compared to 50% for the control group (ns, P>0.05; Suppl Table 1). There was a non-significant trend toward more readmissions in the control group compared to the intervention group.

Implementation

Dose: All 127 of the intervention participants received the planned structured TFUs on days 2 and 9 after discharge from the local hospitals (Suppl. Table 2). In very few cases (N=4), the TFU dose deviated from the planned dose, mainly due to unexpected events. These deviations took place shortly (mainly a few hours) after unexpected events. The patients

(N=4) received extra TFUs because they were seriously anxious, or because follow-up was needed for a potential life-threatening complication.

Fidelity*:* Prior to conducting the AVRre trial, the content of the 24/7 manuals was analyzed, mainly using findings from the research interviews with former cardiac patients. This pre-trial assessment prompted us to make minor changes in the prioritization of the themes presented in the 24/7 hotline manual (Suppl Table 3). A brief prospective assessment of the calls confirmed that the prioritization of the themes was quite accurate. Thus, we found that the 24/7 manual met the nurses' expectations regarding its purpose. This is evident from the following statements made by some members of the focus group:

"The book we had was very nice!"

"[This book] could actually be really useful in some GPs' [general practitioners'] offices, as well."

In general, TFU nurses were satisfied overall with the manual and viewed it as a valid instrument for its purpose. These findings were supported by the prospectively collected field notes, which showed a high degree of hotline nurse compliance with the planned hotline service, facilitated by the 24/7 manual.

The pilot study did not reveal any substantial concerns regarding the design of the study, neither ones relating to logistics about the web randomization of participants nor ones relating to the TFU part of the intervention. However, the 24/7 hotline received only one call during the pilot study. Although the hotline staff nurses found the 2-hour educational session to be useful, focus group analyses indicated that more pre-trial educational sessions and training would have been useful for preparing the nurses to deliver the hotline service. This was evident from some of the nurses' comments during the focus group:

"I would like to have been trained more before…."

"I don't remember so much from that [2-hour] educational session."

These sentiments are consistent with the field notes, which indicated that more preparatory work would have reduced this possible barrier to delivery fidelity, especially when nurses first start working at the hotline service.

The hotline staff greatly appreciated participating in regular formal meetings, during which cases were discussed, consultations with the project coordinator and physicians we conducted, and educational sessions during the AVRre trial were done. The main conclusions derived from the field notes were that these regular interactions bolstered the nurses' satisfaction, increased their confidence, and helped them to gain knowledge and develop skills to carry out the hotline service well. These conclusions are reflected in the TFU nurses' statements during the focus group:

"The education during the main trial was very good, and it was satisfying to go through the different cases."

"It helped me to advance professionally. Attending the educational sessions— a huge plus."

"I got more confident with time…."

The close follow-up with the project coordinator and availability and consultations were perceived as very good and valuable:

"It was an excellent follow-up… during the trial."

The field notes supported this finding that close follow-up during the hotline service increased the confidence of the nurse staff, likely facilitating the fidelity of the intervention delivery.

The SAVR participants perceived that delivery of the TFU was a valuable service. This was exemplified in the following themes derived from the content analyses: “a necessary service,” “high satisfaction,” “feeling of safety,” and “trustworthiness.” This perception of value was reflected in some comments’ participants made in the questionnaire given 3 months after their surgery:

“I was called twice and that covered my needs.”

“These conversations were very important to me. It worked to calm me.”

Moreover, the themes “reassurance” and “feeling of safety” are in line with the overall high satisfaction participants experienced, as described in the TFU field notes on the delivery of the hotline service.

Mechanisms of impact

In the self-report questionnaire completed 3 months after surgery, the patients who actually used the hotline viewed it as very positive (58%), as a very safe way to access assistance (86%), and as a good and trustworthy post-discharge care option (91%) (Fig. 2). Moreover, the analysis of participants’ responses to the 24/7 hotline showed that they (1) experienced a continuum of care, (2) experienced individualized care, and (3) showed a need for accessing information in the early rehabilitation phase (Table 2). Assessment of participant responses to the 24/7 hotline, as reported by the hotline staff (focus group interviews), could be categorized into three themes: safety (reassurance and availability), high satisfaction, and a need to monitor symptoms after discharge.

The analysis of the participants’ responses to the TFU revealed the following themes in the content analyses: (1) a gap in the transition of care, (2) a need for easy access to secure health information during a vulnerable phase, and (3) a desire for optimized self-care management (Suppl. Table 4). In the questionnaire given at 3 months, the participants in the

intervention group who chose not to use the hotline (i.e., non-callers) had five main reasons. Ordered from most to least frequently, they chose not to because they were: highly satisfied with the TFU, in a rehabilitation facility, afraid to bother the healthcare system unnecessarily, felt safe knowing they had the opportunity to call at will, and had no pressing issues to address during the early rehabilitation phase.

Context

Several discharging hospitals took part in the AVRre trial. In the intervention group, the percentage of readmissions for these hospitals ranged from 0 to 50%, after excluding two local hospitals that had fewer than 10 total discharges (Suppl. Table 5). These two hospitals were located in close proximity and were comparable in size and responsibilities. Despite these similarities, these two local hospitals (nos. 2 and 3) differed significantly in the total proportion of readmissions versus non-readmissions (P= 0.042; Fisher Exact test). These two local hospitals also showed a large difference in mean length of stay (LOS) at 4 versus 7 days.

The intervention and control groups in this cohort, overall, shared similar discharge experiences. However, the data varied regarding their experiences with relevant discharge issues. For example, approximately 40% of the total cohort answered negatively about preparedness in case of complications or what ailments to expect after discharge. Moreover, approximately 25% of them said they were not informed about their actual medication on discharge from hospital. Furthermore, assessment of the TFU-call field notes and the patients' written questionnaire responses 3 months after surgery showed substantial differences in the perceived quality of care between local hospitals. Patients stated:

> *"All in all, very well satisfied with the result, treatment and care, and follow-up afterwards."*

"I am not happy with the follow-up from the local hospital."

Some patients stated that it was too far to travel to the local hospitals for cardiac rehabilitation and that they worried about the GPs' competence to provide adequate follow-up care.

Discussion

The AVRre trial failed to reduce 30-DACR. The high proportion of unavoidable readmissions suggested that this factor was an important part of why the intervention failed [15]. The trend toward more readmissions in the intervention group requires further study. Few clinical RCTs employing a post-discharge follow-up designed to reduce readmissions discuss why the trial failed on the primary outcome; i.e., had no effect on readmissions. It has been suggested that participation bias and lack of power to analyze sub-groups could play a role in such a negative outcome [30]. Moreover, in previous clinical RCTs that reported no or little effect, the presence of Type I errors may explain why a reduction in readmissions were not detected [31]. Another possibility offered was that the intervention itself may have inadvertently heightened participants' awareness of early post-discharge symptoms they were experiencing, prompting them to contact the health system, and thus increase the likelihood of a readmission [31].

Implementation

Evaluation of pilot study

Our process evaluation suggested some positive aspects of trial preparation and some less-than-optimal preparation for the AVRre trial. The 24/7 TFU manual was perceived as a professional tool by the hotline staff, which likely facilitated adequate delivery of the

intervention. The design and content of the 24/7 manual proved to be appropriate, and demonstrated why it is important that end users participate in the developmental phase of an intervention. This early involvement ensured that the intervention content remained the same for the same group of participants. We suggest that the TFU manual had a positive impact on intervention implementation, and at least had no negative effect on the primary outcome. The manual may even have had a positive impact on improving anxiety symptoms of the post-surgical SAVR patients, because of its useful content. This content, in turn, enabled the nurses using the manual to deliver the hotline service with fidelity.

Instruction before implementation of the AVRre trial also had positive aspects and some less-than-optimal aspects. Hotline staff reported that the 2-hour educational session done before the pilot study was useful. However, members of the staff said that if they had received even more instruction and training before the AVRre trial began, they might have been more confident in delivering the service right from the beginning of the intervention. Even though the SAVR participants said they were satisfied with the hotline service, more instruction and training for the hotline staff might have produced even greater participant satisfaction (greater than 58%), and perhaps better primary outcomes. Thus, these process evaluation findings of less-than-optimal intervention preparatory work can be interpreted as a barrier in reducing 30-DACR after SAVR. However, other clinical interventions in the literature reporting low delivery fidelity have produced improved outcomes [16].

Only one incoming patient telephone call was made to the hotline staff during the pilot study. A larger pilot study would have provided more pre-AVRre trial training leading to greater facility in staff handling incoming patient calls from the start. Moreover, a more extensive pilot study could have given us more information about the proportion of unavoidable readmissions to expect. This pre-trial information would have allowed us to

change the primary outcome to only target the avoidable readmission rate. A larger pilot study would have also allowed a more accurate power calculation for this purpose.

Evaluation during the AVRre trial

The range of support available to the hotline staff was appropriate to run the hotline service, and this likely resulted in the intervention being delivered with high fidelity. The ease in learning the intervention allowed the staff to quickly gain confidence in its delivery. Our presumption was confirmed that if experienced nurses had readily available resources, they would actually deliver a high-quality support service [14]. Still, more pre-trial training might have improved the hotline service even more, leading to better primary outcomes. However, the high proportion of unavoidable readmissions in the AVRre trial cohort was likely an important contributing cause to why the intervention delivery had no impact on 30-DACR after SAVR.

The content analysis of the intervention fidelity revealed that the trial participants were mainly highly satisfied and trusted the intervention. Evidence in the literature is mixed about patient satisfaction with post-discharge telephone support [32, 33] and impact of telephone interventions on reducing readmissions [11-13, 34]. Different methods employed in the delivery of telephone support in different contexts might explain some of the heterogeneity regarding satisfaction and readmission outcomes. Therefore, it seems important to include user satisfaction and other PREMs in an evaluation of a delivered health service [35]. Our results show that the mixed methods we used in the process evaluation allowed us to obtain a richer picture of the impact of the intervention.

Mechanism of impact

The overall high patient-reported satisfaction with the AVRre intervention, as supported by the content analyses, adds power to explaining why participants' anxiety symptoms improved

during the intervention period. While delivery of healthcare can sometimes be disjointed and episodic, participants in the AVRre trial experienced their post-discharge care as a continuum of care, which likely contributed to less anxiety. These results are consistent with the finding that providing a continuum of care after cardiac surgery leads to better health outcomes [36]. Our participants reported feeling safe, because they had easy access to secure health information, also likely contributing to less anxiety. An important finding of our process evaluation was that patients in the AVRre trial knew that they were not lost in care transition but rather experienced a continuum of care. More than 90% of the participants reported that the intervention was a good option. This result prompts questions about several aspects of post-discharge care in general.

Gaps in the continuum of care after hospital discharge are well known and reported [37]. Our process evaluation also revealed that participants experienced more individualized care and assistance in monitoring symptoms. This finding might suggest that this aspect is important for reducing symptoms of anxiety after discharge and to achieve greater satisfaction with the intervention. A more individualized approach to post-discharge hospital care has the potential to increase the quality of the care after discharge [38]. However, executing post-discharge care is complex, and interventions that are multimodal are more likely to yield lower readmissions [10, 39]. When looking at the PREM results, issues like patients' adherence to medications and preparedness for coming home appear to be factors to target for quality improvement. Increasing the number of patient-reported outcomes after cardiac surgery is warranted [40].

Context

Our process evaluation results showed great variability in the total proportion of readmissions between the local hospitals. Different discharge management practices/policies of local

hospitals are likely to be an important driver of readmissions after SAVR; our PREM results support this suggestion. Moreover, the significant difference in total proportion of readmissions we observed between two comparable local hospitals (nos. 2 and 3) clearly demonstrates that local hospital contextual factors can influence the readmission rate both positively and negatively. The hospital in the AVRre trial with more readmissions (no. 2) also had shorter LOSs, a similar finding as that in a nationwide Norwegian study, in which shorter LOSs increased the risk of readmissions [41]. However, this finding is at variance with the literature on readmissions, which suggest that shorter LOSs do not predict readmissions [42, 43]. An important future line of research is to determine why hospitals within the same healthcare system have varying readmission rates. Uncovering this answer can provide important information that can be used to optimize discharge care after SAVR.

The quality of care provided locally was perceived as being less good to excellent by AVRre trial participants. We believe this supports our interpretation that different local hospitals' management systems are a barrier to better discharge outcomes. Moreover, this might additionally have had moderator effects on the intervention. Participants having to travel long distances to a local hospital for follow-up seems to be a barrier to engage in local cardiac rehabilitation; this factor potentially impacted post-discharge outcomes. According to some participants' responses, the practices and characteristics of GPs responsible for primary care can be a target for further study on how they impact the outcomes associated with the SAVR treatment. Studies of transcatheter aortic valve replacement (TAVR) patients have similar post-discharge complications as SAVR patients [6]. Thus, our findings on readmission factors affecting optimal post-discharge care for SAVR patients might be valuable for the TAVR population as well.

Methodological considerations

This study has multiple strengths. First, the mixed-methods approach we used allowed us to obtain a broad and deep understanding of the results. This rigorous, multilevel approach also opens up the possibility that our results can be compared in order to confirm and clarify others' findings. Second, the intense follow-up and continuous discussions among staff during the intervention produced reliable data for carrying out a robust process evaluation. Third, using the MRC framework to guide the process evaluation and to structure the collected data was effective for helping us gain a broader understanding of the trial effects. Fourth, we used questions from a well-established PREM questionnaire, allowing comparison and contrast. Fifth, a transparent description of important intervention elements bolsters the possibility for others to conduct good replication studies and to compare results across different studies.

Our study has limitations. First, the process evaluation was not formally integrated initially into the RCT design. More prospective and tailored data collection designed to specifically conduct a process evaluation could have further enriched the findings and could have revealed ones at odds with the present findings. Second, more data on different local hospital discharge management systems could allow for adjustments of potential moderator effects on the primary outcomes. Third, due to partial retrospective data collection, we cannot rule out the possibility of recall bias. Fourth, researcher bias due to preconceptions due to prior knowledge cannot be ruled out. Fifth, lack of more contextual data limits the possibility to adjust for possible confounding effects. Sixth, if we had digital recordings of the hotline calls, this would have allowed us to conduct an even more in-depth analysis of the fidelity of the AVRre trial intervention trial delivery.

Conclusions

The robust follow-up calls and protocol done during the hotline telephone service facilitated an overall well-implemented intervention. The SAVR patients in the study were satisfied and felt safe participating in the intervention, which likely underpinned the reduced anxiety we observed in participants. This observation suggests that in usual care for post-discharge SAVR patients, a gap is present in the care continuum. However, fewer preparations for the hotline service might have been a barrier to the implementation, especially in the beginning of the intervention. The process evaluation findings add knowledge to the importance of integrating user experiences into clinical trials as part of a process evaluation and adding knowledge for optimizing the transition of care after SAVR.

Abbreviations

30-DACR: 30-day all-cause readmission; AS: aortic stenosis; AVRre: Aortic Valve Replacement Readmission trial; AVR: aortic valve replacement; GP: general practitioner; LOS: length of stay; MRC: Medical Research Council; ns: not significant; PREM: patient-report experiences measures; RCT randomized controlled trial; TAVI: transcatheter aortic valve implantation; SAVR: surgical aortic valve replacement; StaRI: Standards for Reporting Implementation Studies; TAVR: transcatheter aortic valve replacement; TAVI: transcatheter aortic valve implantation; TFU: telephone follow-up

Declarations

Ethics approval and consent to participate:

The AVRre Study was approved by the Regional Committees for Medical and Health Research Ethics, Health East South, Norway (approval 2013/2031-3), and complied with

the Declaration of Helsinki principles. Participants (former cardiac patients, trial participants and hotline staff) gave their informed consent, included consent for publication under the precondition of anonymity.

Consent for publication: Consent for publication was given as part of the written and verbal consent to participate in the AVRre trial and for the process evaluation of the AVRre trial.

Availability of data and material Competing interests:

The datasets generated and/or analyzed during the current study are not publicly available due to privacy concerns and hospital regulations but are available from the corresponding author on reasonable request.

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Competing interests:

The authors declare that they have no competing interests.

Authors' contributions:

SOD was the project coordinator. Contributions in all part of the work; conception and design, acquisition of data, analyses and interpretation the work and drafting and revising the work.

PM made contribution to the conception, design, interpretation, drafting and revision of the work.

ML made contributions to the revision of the work.

SS made contributions to the interpretation and revision of the work.

TT made contributions to the interpretation and revision of the work.

IL made contributions in conception, analyses, interpretation and revision of the work.

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Figure legends

Figure 1. Design of the process evaluation for the AVRre trial guided by the MRC framework**.**

AVRre trial, Aortic Valve Replacement readmission trial

MRC, Medical Research Council. (Figure is based on the MRC framework for process evaluation of complex interventions; [16].)

Figure 2. Examples and quantitation of AVRre trial participants' comments in the self-report about telephone hotline service.

AVRre trial, Aortic Valve Replacement readmission trial

1. Not at all

Table 1 Overview of the process evaluation of the AVRre trial

Process elements	Scope of the process evaluation	Data type	Data sources	Analysis methods
Implementation	a) What was the process like in delivering the intervention?	Qualitative and quantitative	Field notes and memos, mind maps, [a] registration forms, questionnaires, journal records, and focus group interviews	NVivo and content analysis, qualitative assessments, and descriptive analyses
	b) How was the delivery of the intervention conducted in terms of dose[b] and fidelity[c]?	Qualitative and quantitative		
Mechanisms of impact	How did the patients react to the intervention?	Qualitative and quantitative	Field notes and memos, questionnaires, registration forms, observations, and a focus group interview	NVivo and content analysis, qualitative assessments, and descriptive analyses.
Context	Were there any contextual factors[d] that might have substantially influenced the intervention and the primary outcomes?	Qualitative and quantitative.	Field notes and memos, questionnaires, and a focus group interview	NVivo and content analysis, and descriptive analyses.

AVRre trial, Aortic Valve Replacement readmission trial

[b] Mind map were used to cue respondents' memories before interview

[a] Dose is number of days and calls the intervention was administered

[c] Delivered as planned

[d] Contextual factors, such as length of stay in local hospitals

Table 2 Overview of the content analysis of AVRre trial participants' reactions about the 24/7 telephone hotline

Patient reactions about the 24/7 telephone hotline	
Code	Patient_Hotline_Safe
Category	Patient's experience of safety
Theme	24/7 hotline telephone service made them feel safe
Overarching theme	**Continuum of care**
Code	Patient_Hotline_Satisfaction
Category	Patient's experiences with 24/7 hotline service
Theme	I was treated professionally by staff of the hotline service
Overarching theme	**Individualized care**
Code	Patient_Hotline_Need
Category	Post-discharge service
Theme	I want easy access to health information after hospital discharge
Overarching theme	**Information needed for the early rehabilitation phase**

AVRre trial, Aortic Valve Replacement readmission trial

Table 3 AVRre trial participants' self-reports about hospital discharge experiences 3 months after surgery

	Intervention (N=119) [a]	**Control** [b] **(N=119)**
Informed about what you could do at home in the event of a relapse?		
To a very large extent, N (%)	10 (8.40)	3 (2.50)
Largely, N (%)	26 (21.8)	21 (17.6)
To some extent, N (%)	30 (25.2)	21 (17.6)
To a small extent, N (%)	19 (16.0)	33 (27.7)
Not at all, N (%)	18 (15.1)	29 (24.4)
Not applicable, N (%)	16 (13.4)	12 (10.1)
Informed about what ailments to expect after discharge?		
To a very large extent, N (%)	12 (10.1)	6 (5.10)
Largely, N (%)	30 (25.2)	29 (24.6)
To some extent, N (%)	34 (28.6)	37 (31.4)
To a small extent, N (%)	18 (15.1)	20 (16.9)
Not at all, N (%)	20 (16.8)	22 (18.6)
Not applicable, N (%)	5 (4.20)	4 (3.40)
When hospital staff evaluated my healthcare needs after discharge, did they consider what I and my relatives wanted?		
To a very large extent, N (%)	14 (11.7)	13 (10.8)
Largely, N (%)	40 (33.3)	28 (23.3)
To some extent, N (%)	14 (11.7)	26 (21.7)
To a small extent, N (%)	17 (14.2)	14 (11.7)
Not at all, N (%)	12 (10.0)	14 (11.7)
Not applicable, N (%)	23 (19.2)	25 (20.8)
At time of discharge, I clearly understood my responsibility for own health.		
To a very large extent, N (%)	31 (25.8)	33 (28.0)
Largely, N (%)	56 (46.7)	46 (39.0)
To some extent, N (%)	25 (20.8)	24 (20.3)
To a small extent, N (%)	4 (3.3)	9 (7.6)
Not at all, N (%)	2 (1.7)	4 (3.4)
Not applicable, N (%)	2 (1.7)	2 (1.7)
At time of discharge from hospital, I clearly understood my medication.		
To a very large extent, N (%)	44 (36.7)	45 (38.5)
Largely, N (%)	54 (45.0)	37 (31.6)
To some extent, N (%)	14 (11.7)	21 (17.9)
To a small extent, N (%)	2 (1.7)	10 (8.50)
Not at all, N (%)	4 (3.3)	1 (0.9)
Not applicable, N (%)	2 (1.7)	3 (2.6)
Were you informed about your actual medication when discharged from hospital?		
Not applicable, N (%)	2 (1.7)	2 (1.7)
Yes, N (%)	85 (70.8)	89 (76.1)
No, N (%)	33 (27.5)	26 (22.2)

[a] Eight participants were unavailable to provide self-reports at the 3-month assessment, accounting for the difference in the 127 intervention participants who received the planned structured TFUs on days 2 and 9 after discharge from the local hospitals

[a] Participants in the control group received usual care [14].

Fig.1

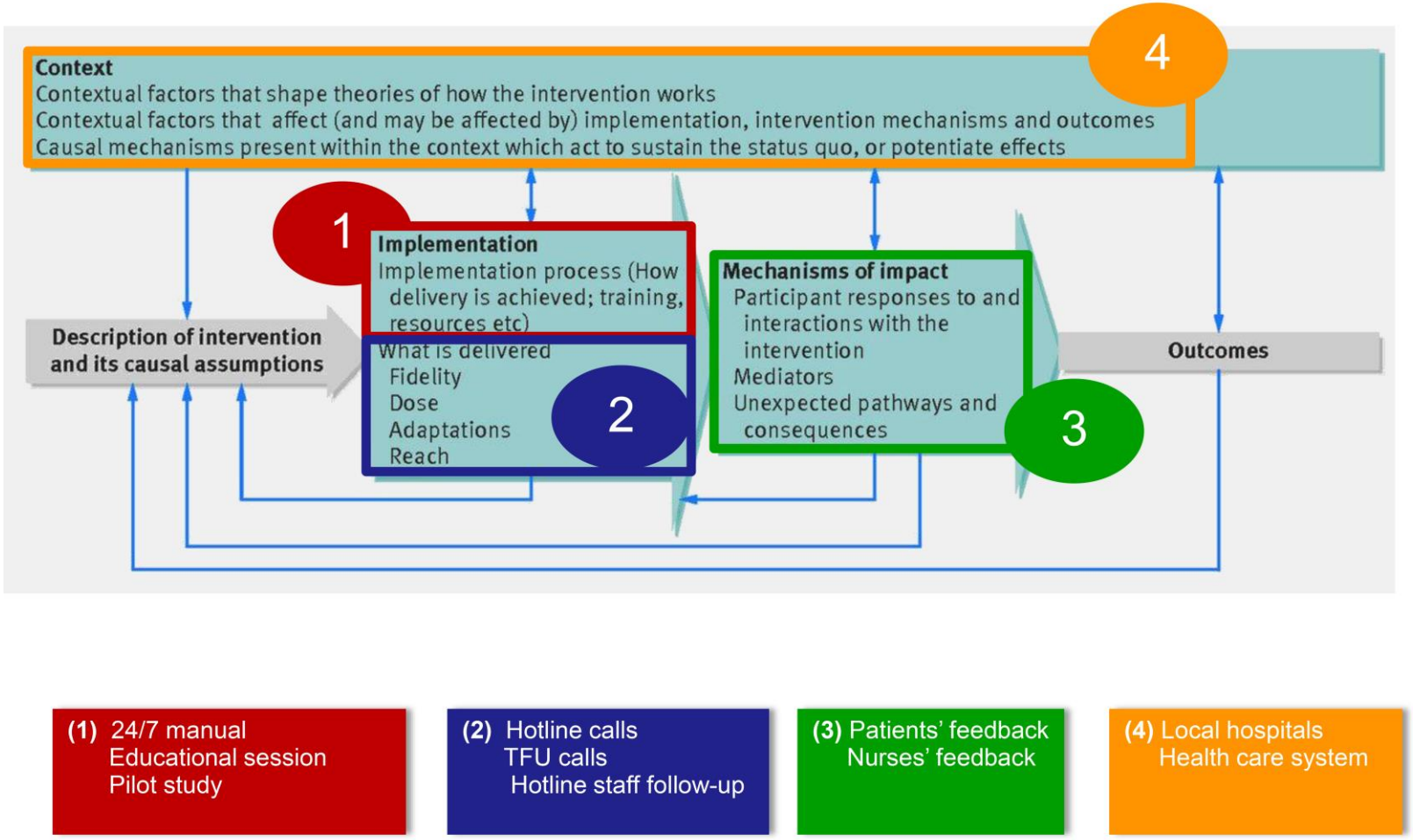
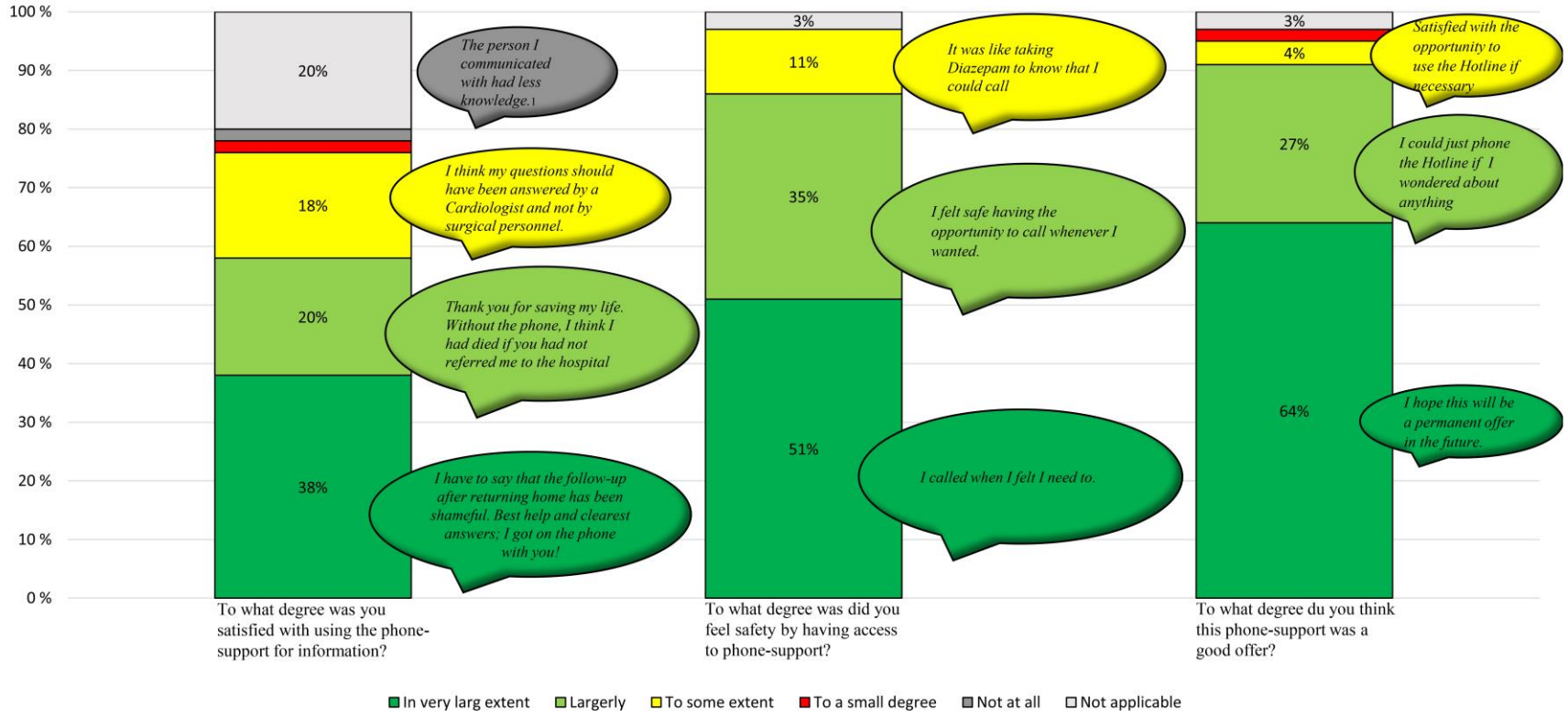
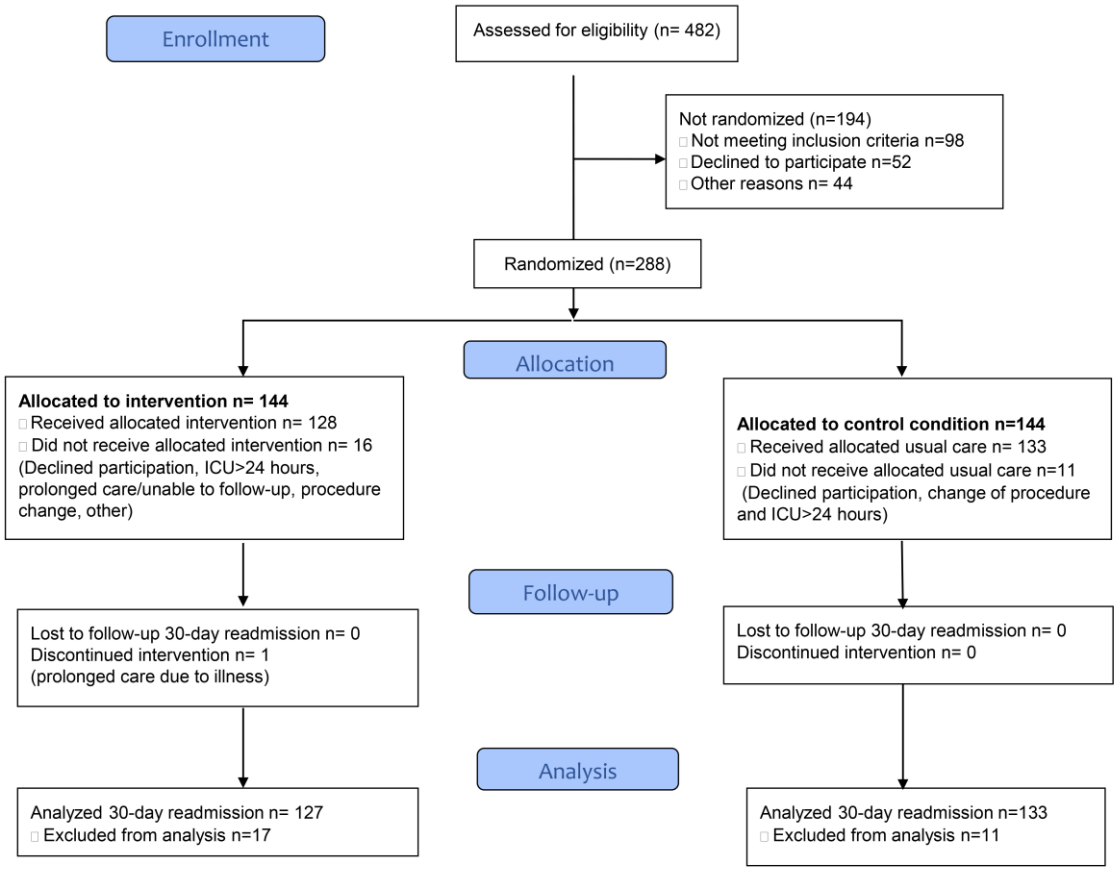

Context
Contextual factors that shape theories of how the intervention works
Contextual factors that affect (and may be affected by) implementation, intervention mechanisms and outcomes
Causal mechanisms present within the context which act to sustain the status quo, or potentiate effects
4
1
Implementation
Implementation process (How delivery is achieved; training, resources etc)
Description of intervention and its causal assumptions
What is delivered
Fidelity
Dose
Adaptations
Reach
2
Mechanisms of impact
Participant responses to and interactions with the intervention
Mediators
Unexpected pathways and consequences
3
Outcomes
(1) 24/7 manual
Educational session
Pilot study
(2) Hotline calls
TFU calls
Hotline staff follow-up
(3) Patients' feedback
Nurses' feedback
(4) Local hospitals
Health care system

Fig.2


100 %
90 %
80 %
70 %
60 %
50 %
40 %
30 %
20 %
10 %
0 %
20%
18%
20%
38%
The person I communicated with had less knowledge.1
I think my questions should have been answered by a Cardiologist and not by surgical personnel.
Thank you for saving my life. Without the phone, I think I had died if you had not referred me to the hospital
I have to say that the follow-up after returning home has been shameful. Best help and clearest answers; I got on the phone with you!
To what degree was you satisfied with using the phone-support for information?
3%
11%
35%
51%
It was like taking Diazepam to know that I could call
I felt safe having the opportunity to call whenever I wanted.
I called when I felt I need to.
To what degree was did you feel safety by having access to phone-support?
3%
4%
27%
64%
Satisfied with the opportunity to use the Hotline if necessary
I could just phone the Hotline if I wondered about anything
I hope this will be a permanent offer in the future.
To what degree du you think this phone-support was a good offer?
In very larg extent
Largerly
To some extent
To a small degree
Not at all
Not applicable

Supplemental Material 1

Supplemental Fig. 1. CONSORT flow chart for participant selection and group assignments for the AVRre study



Supplemental Table 1 Proportion of unavoidable readmissions in the AVRre trial and cause of 30-DACR

Type of readmission	**Intervention group (N=32)**	**Control group (N=26)**	***P***
Avoidable, N (%)	1 (3.1)	4 (15.4)	0.160[a]
Unavoidable, N (%)	26 (81.3)	18 (69.2)	
Disagreement, N (%)	5 (15.6)	4 (15.4)	
Cause of readmission			
Cardiac related cause for readmission, N (%)	20 (62.5)	13 (50)	0.427[b]
Non-cardiac related cause for readmission, N (%)	12 (37.5)	13 (50)	

AVRre trial, Aortic Valve Replacement readmission trial

30-DACR, 30-day all-cause readmission

[a] Fisher Exact test between groups on avoidable and unavoidable readmissions

[b] Fisher Exact test

Supplemental Table 2 Distribution of AVRre trial participants at local discharge hospitals

	Intervention (N=127)	**Control (N=133)**
Local hospital 1	19	15
Local hospital 2	8	9
Local hospital 3	8	5
Local hospital 4	22	22
Local hospital 5	9	17
Local hospital 6	18	15
Local hospital 7	16	20
Local hospital 8	13	12
Local hospital 9	9	13
Local hospital 10	4	5
Local hospital 11	1	0
Total	127	133

AVRre trial, Aortic Valve Replacement readmission trial

Supplemental Table 3 Themes and headings in the 24/7 telephone manual for hotline nurses to use in the AVRre trial

	Themes	Symptoms/clinical signs/questions			Advice to patient	Tips for nurse	References
01	Dyspnea						
02	Heart rhythm						
03	Pain						
04	Medication						
05	Infection						
06	Anxiety, depression, memory						
07	Activity						
08	Nutrition/lifestyle						
09	Social network						
10	Sexuality						

AVRre trial, Aortic Valve Replacement readmission trial

Supplemental Table 4 Overview of content analysis of SAVR patient participant reactions of the TFU in the AVRre trial

Patient reactions on the TFU	
Code	Patient_STFU_Satisfaction
Category	Patient experience of STFU (Satisfaction)
Theme	I was satisfied with being followed up by phone after discharge
Overarching theme	**A gap in care transition for SAVR patients**
Code	Patient_STFU_Safety
Category	Patient feeling safe (Safety)
Theme	It was comforting being followed by phone
Overarching theme	**Need for easy access to secure health information in a vulnerable phase**
Code	Patient_STFU_Self-care (Need)
Category	Symptom questions
Theme	I have questions I need answers on.
Overarching theme	**Patients desire to optimize their self-care management**

TFU, Telephone follow-up

AVRre trial, Aortic Valve Replacement readmission trial

Supplement Table 5 Distribution of readmissions and non-readmissions in the AVRre trial and local hospitals

	Intervention group		**Control group**		**Total**
	No readmission	Readmission (%)	No readmission	Readmission (%)	
Local hospital 1	12	7 (37)	10	5 (50)	34
Local hospital 2	**4**	**4 (50)**	**5**	**4 (44)**	**17**
Local hospital 3	**8**	**0 (0)**	**4**	**1 (20)**	**13**
Local hospital 4	15	7 (32)	20	2 (10)	44
Local hospital 5	9	0 (0)	15	2 (13)	26
Local hospital 6	14	4 (22)	14	1 (7)	33
Local hospital 7	14	2 (13)	15	5 (25)	36
Local hospital 8	10	3 (23)	7	5 (42)	25
Local hospital 9	6	3 (33)	12	1 (8)	22
Local hospital 10	3	1 (33)	5	0 (0)	9
Local hospital 11	0	1 (100)	0	0 (0)	1
	95	**32**	**107**	**26**	**260**

AVRre trial, Aortic Valve Replacement readmission trial

Suppl.2.

Semi-structured interview guide: Focus group -AVRre Trial

Retrospective focus group discussion guide to obtain data on the nurses' experiences of the preparation and their performance on the 24/7 telephone hotline service.

- How did you experience preparations for the intervention?
    - Possible follow-up: Should we have done anything different?
- How did you experience your performance during the delivery of the intervention?
    - Possible follow-up: Was it different from that expected? If it was different, why is it different from what you expected?
- How did you experience the follow-up during the intervention?
- Was there anything that, or someone who, made it difficult for you to perform the service you were trained to do?
- What kind of impression do you have of the participants' experiences of the hotline and follow-up telephone service?
- If you were to summarize what you were involved in, what would you say?

Suppl.3.

Semi-structured interview guide: Experiences after discharge from hospital as a cardiac surgery patient

Retrospective focus group/in-depth interview guide to obtain data on what former cardiac surgery patients (i.e., not AVRre trial participants) experienced when they first got home after discharge (especially experiences in the first month).

- Do you remember how you were discharged from the hospital?
    - Anything about the discharge you would like to comment on especially?
- What do you remember from the time you first got home after hospital discharge?
    - Can I look at your mind map?
    - Can you say something about what you perceived about the care after discharge?
- Should the hospital have done anything different when you were discharged?
- What kind of impressions do you have of the rehabilitation care offers you were given?
- If you were to summarize what you experienced when you first got home after hospital discharge, what would you say?

Suppl.4.

Mind map used to interview former cardiac patients' in the AVRre Trial