New approaches to the implementation of cardiovascular disease prevention
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SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES
SUMMARY AND DISCUSSION

Cardiovascular disease (CVD) remains one of the biggest contemporary health problems. As stated in the introduction of this thesis, the implementation of primary and secondary prevention is currently far from optimal. Therefore, in this thesis, we have presented the findings of a number of studies investigating new approaches to the implementation of CVD prevention.

PART 1
Risk assessment in primary prevention

In part 1, we perform a comprehensive analysis of SCORE, a risk estimator for CVD mortality endorsed for primary prevention in Europe by the European Society of Cardiology. SCORE estimates 10-year CVD mortality, and according to the European guidelines, the initiation or intensification of preventive measures (pharmacological or non-pharmacological) should be guided by an individuals’ SCORE.

In chapter 2, we found that the UK has correctly been reclassified as a low-risk country when predicting CVD risk using SCORE. We compared the high-risk and low-risk algorithms of SCORE, and found that the high-risk algorithm overestimates the risk of 10-year CVD mortality as compared with the low-risk algorithm. Overall, the discriminatory ability was high for both SCORE algorithms, but calibration was suboptimal for both, albeit superior using the low-risk algorithm. Therefore, our findings support the reclassification of the UK as a low-risk country.

In chapter 3, we found that estimating only CVD mortality leads to a serious underestimation of the total burden of CVD. While fatal CVD is clearly the most robust outcome for any risk score, non-fatal CVD is just as relevant for patients, providers of healthcare, policy makers and insurance companies. The current European guidelines suggest that a multiplier (3x) can be used to calculate fatal- and non-fatal risk from fatal risk alone. In our analysis in the EPIC-Norfolk cohort, a large population-based cohort in the UK, we found that the ratios of fatal to fatal- and non-fatal CVD are highly dependent on gender and age. Especially in younger individuals, these ratios are very high (28.5 in women, 11.7 in men). Our findings do not support using a fixed multiplier to calculate total CVD risk based on CVD mortality risk, and caution is warranted when extrapolating the risk of CVD mortality to the risk of total CVD. Future guidelines may be revised to reflect these relationships.

In chapter 4, we evaluated the current Dutch country-specific SCORE charts using the ratios of fatal to fatal- and non-fatal CVD as presented in chapter 3. The current multidisciplinary guidelines on CVD risk management (CVRM) in the Netherlands recommend using a modified version of the SCORE charts to estimate 10-year risk of fatal and non-fatal CVD. The Dutch SCORE charts predict fatal CVD in addition to (non-fatal) myocardial infarction, cerebrovascular disease and congestive heart failure. These charts have been constructed using multipliers (5x the SCORE predicted fatal CVD for individuals aged 35-45 years, 4x for individuals aged 45-65 years, and 3x for individuals aged >65 years) based on data from two national cohorts, and overall risk is presented in the charts, coded by colour. These multipliers have not been validated in other, large population-based studies, and include only 3 clinical manifestations of non-fatal CVD. Using the ratios
presented in chapter 3, we found that including a broader range of clinically relevant CVD leads to a marked increase in high-risk (i.e., >20% risk of 10-year CVD) categories in the risk charts. We conclude that the 10-year risk of clinically relevant CVD in an individual is significantly greater than is currently estimated based on the current Dutch SCORE-charts. Even when analyses are restricted to CVD events that require hospitalization, true 10-year risks are more than double the currently estimated risks. Caution is advised when using the current risk charts, especially in young individuals, as a low risk according to the current risk charts may not reflect a low risk of clinically relevant CVD. Future guidelines may need to be revised to reflect these findings.

PART 2
Nurse coordinated secondary prevention after an acute coronary syndrome

In part 2, we present the methods and outcomes of the RESPONSE (Randomised Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists) trial, a large, multicenter randomized trial in 754 patients in the Netherlands.

In chapter 5, the study design, objectives and expected results of the RESPONSE trial are described as they were published at the outset of the study. The RESPONSE trial was designed to evaluate the effect of a practical, hospital-based nurse coordinated prevention programme on top of usual care (intervention), as compared with usual care alone (control). Nurses saw patients up to 4 times in the first 6 months after an acute coronary syndrome, focusing on healthy lifestyles (including smoking cessation), blood pressure targets, lipid targets and screening for diabetes, in addition to medication use. The intervention included medication titration of blood pressure- and lipid lowering medication in cooperation with the treating physician, and counseling on healthy lifestyles. The primary outcomes of our trial were Systematic COronary Risk Evaluation (SCORE) and the number of risk factors on target at 12 months after the acute coronary syndrome.

In chapter 6, we present the main outcomes of the RESPONSE trial. The main finding of our study was that a nurse coordinated prevention programme on top of usual care is a successful new strategy in secondary prevention, which leads to a reduction in cardiovascular risk in patients after an acute coronary syndrome. This effect was most pronounced in blood pressure and LDL-cholesterol management, possibly due to titration of medication or better compliance in the intervention group. For the (self-reported) lifestyle targets, patients attending the nurse coordinated prevention program reported a higher level of physical activity, fruit- and vegetable consumption. However, no effect was seen on smoking cessation or weight loss. Attendance to the programme was excellent, and patients were willing to visit the clinic and to complete the programme. Also, locally selected registered nurses with limited additional training were able to execute the programme and were comfortable with the protocol. Surprisingly, we also observed a reduction in hospital readmissions for non-ACS chest pain and visits to the cardiac emergency ward, potentially reflecting the effectiveness of the counseling component of the nurse programme in preventing unnecessary hospital readmissions and emergency room visits. Factors such as increased patient confidence, reduced anxiety, better information, and better access to outpatient care may explain this reduction.

In chapter 7, we present the outcomes of the RESPONSE trial for health-related quality of life and depression. We found that attendance to the nurse coordinated prevention programme is associated with a modest but statistically significant increase in health-related quality of life. This improve-
ment was seen across the emotional, physical and social dimensions of health-related quality of life. Furthermore, we found that there was a decrease of depressive symptoms in the patients in the intervention group as compared with the control group. Both of these parameters are highly relevant to patients. The improvement in health-related quality of life and depressive symptoms was seen on top of the reduction of risk and hospital admissions reported in chapter 6. In any case, the increased attention to preventive measures is not associated with loss of quality of life.

In chapter 8, we describe a specific part of the trial design, which was implemented to reduce a Hawthorne-effect and contamination. When patients and physicians are aware of the fact that their actions are observed and recorded in a trial, this can induce behavioral changes (a Hawthorne effect). Furthermore, when evaluating trials where double blinding is not possible due to the nature of the interventions, such as behavioral interventions, contamination can occur. To minimize Hawthorne effects and contamination in the RESPONSE-trial, information about the nature of the intervention was largely withheld from participating patients. After completion of the trial, participants were fully informed of the design of the study and of the reasons for withholding information, and they were interviewed on their perspectives on this approach. After disclosure of the study design, nearly all patients stated that they would still have participated, and that they found the reasons for withholding this information to be valid and understandable. Only a small percentage of the patients stated that they had identified the design of the other treatment arm. In future trials, comparable strategies to minimize contamination and a Hawthorne effect can be considered.

In chapter 9, we describe a factor often overlooked in clinical trials: the experiences and perspectives of the nurses who participated in the prevention programme. We found that nurses participating in such a programme acknowledge the importance and effectiveness of the programme, and are confident about their abilities to achieve drug-related treatment targets. Nurses view treatment to-target of LDL-cholesterol, systolic blood pressure and medication adherence as the most successful components, consistent with the observed impact on these risk factors as measured in the RESPONSE trial. Room for improvement is reported for weight reduction, smoking cessation and achieving adequate regular physical activity. Furthermore, room for improvement is reported for facilitating collaboration with general practitioners and for screening for anxiety and depression. The findings of our study provide a basis for the further development and evaluation of nurse coordinated prevention programmes. To our knowledge, this is the first study to investigate nurses’ perspectives on running such programmes.

FUTURE PERSPECTIVES

Based on our findings, a nurse coordinated prevention program should be implemented into daily practice for patients after an acute coronary syndrome. In addition, since the risk factors for atherosclerotic complications in other arterial territories are largely the same as in coronary artery disease, a comparable approach may be considered for patients with cerebral and peripheral arterial disease.

While the results of the RESPONSE trial are encouraging, there is room for improvement. Weight loss was disappointing in our patient population, in spite of an increase in self-reported adequate physical exercise and improved food choices in the intervention group. The large number of smokers who quit (in both groups) could potentially have been a factor limiting weight loss. In a secondary analysis in our study (not included in this thesis), Snaterse et al. found that of the patients who smoke prior to their acute coronary event, those who immediately stop are the most successful.
In the future, more intensive interventions could potentially benefit from targeting patients who are not motivated to quit immediately after their event.

Given the encouraging results in the pharmacological components of the nurse programme, the most important opportunities for further improvement are found in lifestyle parameters. In particular, there is an unmet need for strategies for weight loss, physical activity and smoking cessation. As a consequence of this, we are currently conducting the RESPONSE 2 trial. The RESPONSE 2 trial aims to evaluate the impact of 3 community-based lifestyle programs in patients after hospitalization for coronary artery disease. It is a multicenter (n = 15), randomized trial that has recruited 824 patients to test the efficacy of up to 3 widely available commercial lifestyle programs, aimed at patients and their partners, on top of usual care. These programs are aimed at smoking cessation (Luchtsignaal®), weight loss (Weight Watchers®), and improving physical activity (Philips Direct-Life®). The results of this trial will be available by the end of 2016.

SCORE was a pioneer project developing a tool for risk estimation for CVD in European populations. Now, more than 13 years after the publication of SCORE, there are a multitude of risk estimation tools available, with different outcomes and durations of follow-up. Recently, the United States opted for a new risk model ("Pooled cohort atherosclerotic cardiovascular disease risk equation"), which predicts fatal- and non-fatal CVD. While SCORE might be a valid tool for short-term risk estimation in individuals of middle age and intermediate or higher risk, several other options should be considered to optimally estimate risk of CVD.

In the future, the two main approaches to prevention – the high-risk approach and the population based approach should both be considered.

The personalized approach using SCORE knows several limitations, as presented in this thesis, next to the limitations of a high-risk approach in general. However, if regularly reassessed, SCORE can still aid caregivers when to initiate and intensify preventive measures. It should be kept in mind that almost all individuals will qualify for preventive measures, including pharmacological interventions, based on increasing age alone. With the development of risk estimation tools for long-term risk (lifetime) and algorithms including non-fatal outcomes, it could be helpful to use different risk estimation tools in young individuals with a relatively high risk.

The population-based approach replaces or complements personalized risk prediction, and instead focuses on population-broad initiatives. The polypill is such an approach. Comparable to tooth brushing, the whole population eligible for primary prevention is offered a single pill for daily consumption. This pill includes a combination of low-dose preventive medication (i.e. statin, aspirin, blood-pressure lowering agents). In theory, the reduction in CVD from such an approach could be drastic and cost-efficient. The first results of such an approach in large study populations will be published at the ACC in April 2016.