CHAPTER 8

GENERAL DISCUSSION
SUMMARY OF RESULTS

This thesis was divided into two parts. Part 1 focused on a lower middle-income country (LMIC) in Asia, namely Indonesia, and the long-term cardiovascular disease (CVD) burden, as well as the country-specific challenges in prescribing guideline-recommended medications for the secondary prevention of CVD. Part 2 focused on the high-income country of the Netherlands and the challenges in relation to adherence to and the effects of statin therapy, especially in the primary prevention of CVD in the Netherlands.

We estimated the long-term risk (\(> 10\) years) of CVD in Asian populations using a systematic review and meta-analysis of cohort studies (Part 1, Chapter 2). Most studies were from East-Asian regions during a period of time when the prescription of preventive cardiovascular (CV) medications was not strongly advised by clinical guidelines. We observed a high risk of a more than 1 in 5 chance of dying from CVD over a mean risk period of 20 years among Asians (6.35%). Of note, in contrast with most high-income countries, the average long-term incidence rate of any stroke was higher than that of fatal/non-fatal coronary events (3.14 per 1,000 person-years [95% CI 2.12–4.16] vs. 1.51 [0.84–2.18]). We learned from the meta-analysis that only a few risk factors for death due to CVD were statistically significantly related. Male sex, older age (\(\geq 60\) or \(\geq 65\) years old) and current smoking were risk factors for fatal CVD. Importantly, in several studies, the long-term risk factors for fatal stroke were different from those associated with long-term risk of fatal coronary artery disease (CAD). While a higher non-high-density lipoprotein cholesterol level (non-HDL-c = HDL-c subtracted from total cholesterol level) was associated more with fatal CAD, hypertension was associated more with fatal stroke.

In a retrospective cohort study of Indonesian patients with an ST-elevation myocardial infarction (STEMI), 42% were not treated with acute primary percutaneous coronary intervention (pPCI), as is strongly advised by international and national clinical guidelines (Chapter 3). However, 75% of these patients were late hospital-admitters, who are generally underrepresented in clinical trials. Therefore, the benefits of using pPCI and secondary-preventive CV medications in this subset of patients with a high risk of in-hospital mortality were unclear. In our cohort study, we found that one-third of this subpopulation did not receive guideline-recommended preventive
CV medications on hospital admission. After adjustment for potential confounders, the prescription of guideline-recommended medications (dual antiplatelet therapy, anticoagulants, and statins) halved the risk of in-hospital mortality. It was apparent that the acuteness and severity of the STEMI correlated positively with guideline non-adherence.

One-third of patients with STEMI who were admitted to hospital did not receive all five guideline-recommended medications (antiplatelet, clopidogrel, beta-blockers, angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin receptor blockers [ARBs], and statins) at discharge (Chapter 4). The predictors of receiving less than five medications were: the presence of non-anterior MI; age > 65 years; not being treated with acute reperfusion therapy; having a family history of CAD; and having a thrombolysis in myocardial infarction (TIMI) score ≥ 4. Despite the presence of different predictors for separate drug classes, not being treated with acute reperfusion therapy was the most common predictor of not receiving most of the recommended secondary preventive medications. Our finding therefore suggests that prescribers may have different opinions on the benefit-risk of using guideline-recommended medications for different patient groups, and a more personalized approach is required.

We also conducted a small-scale qualitative study to gain insight into the prescribing of statins in primary care in Indonesia from the physicians’ perspective (Chapter 5). Key factors influencing the decision to prescribe statins at the micro level were several patient characteristics, especially a high level of total cholesterol (TC), combined with other characteristics such as clinical symptoms, comorbidities and other risk factors. At the macro level, the physicians appeared to be aware of the relevant guidelines, but there was uncertainty in how to take into account the level of TC in combination with other CV risk factors, such as diabetes and hypertension, as recommended by the guidelines. The recently introduced National Health Insurance System (NHIS), the Jaminan Kesehatan Nasional (JKN), appeared to facilitate the prescription of statins, although information that is more clinical should be integrated into the system’s platform to support a personalized medicine approach and guideline-based prescribing.

Part 2 presented studies using the PharmLines Initiative, a database linking the Netherlands Lifelines Cohort Study and the IADB.nl community prescription
database (Chapter 6), finding that there are potential disparities between the sexes in CVD prevention. Among all first-time statin users, we found that statin therapy was significantly more effective in increasing HDL-c levels in women than in men, irrespective of their previous history of CVD. The proportion of men and women who achieved the LDL-c treatment goal recommended by the Dutch guidelines ($\leq 2.5$ mmol/L) was just below 40% without statistically significant differences between the sexes. The level of adherence to statin therapy in both subgroups (of men and women) was low. Using the same database, we found that the level of adherence was similarly associated with LDL-c response in first-time statin users of a standard-dose and a low-dose group (Chapter 7). However, the same level of adherence was associated with a significantly slower rate of reduction of LDL-c among male participants than among female participants. In the standard-dose group, adherence was associated with a reduction of LDL-c response at follow-up at a significantly faster rate in women than in men. In the low-dose group, there was no significant difference between the sexes in the rate of LDL-c reduction.

**STRENGTHS AND LIMITATIONS**

Our literature review was based on a comprehensive search strategy aiming to include studies from all Asian countries and a selection of cohort studies with participants free from CVD at baseline. This enabled the estimation of absolute risks, especially the burden of CVD in the general population, to inform strategy for the primary prevention of CVD (Part 1, Chapter 1).

Published studies of high-risk Indonesian patients focusing on the prevalence of use of preventive CV medications, their effectiveness and predictors of the suboptimal utilization are very limited to almost non-existent. We are the first to provide more solid evidence on their use, as well as the challenges (Part 1, Chapters 2 and 3) and their effectiveness (Part 1, Chapter 2). One important strength was that we examined patients in a real-world setting, which is different to a clinical trial, where recommendations in guidelines are commonly used as the basis for treatment. We used the Jakarta Acute Coronary Syndrome (JAC) Registry, which has been set up since 2007. The JAC Registry prospectively collected and managed data on patients with STEMI admitted to the emergency department (ED) of the National Cardiovascular Center
Harapan Kita (NCCHK), which is the largest tertiary cardiac referral hospital in Jakarta, the capital of Indonesia. The data were collected using a standardized form and verified regularly. The hospital is JCI (Joint Committee International) accredited. Consequently, the risk of information bias is low, the results of the studies were more representative of clinical practice, and they more accurately reflect the clinical event rates. Furthermore, our qualitative study is the first to explore physicians’ perspectives on how they come to the decision to prescribe a specific preventive CV medication in a clinical practice setting in Indonesia (Part 1, Chapter 4).

For our studies on the effect of statin therapy on lipid parameters in a Dutch population, we used the PharmLines Initiative database, which linked IADB.nl and the Lifelines Cohort databases. The data in IADB and the Lifelines Cohort were collected prospectively. IADB data has been proven to be valid and representative of the overall population of the Netherlands, and the Lifelines adult population is representative of the adult population in the northern Netherlands. The recruitment strategy means that the selection bias is low and that the results obtained from Lifelines can be applied to the Dutch general population (Part 2, Chapters 5 and 6). The amount of data on demographic, clinical, physical and medication characteristics for each patient is large (more than 4000 variables per person), which makes such databases suitable for accurate causal and predictive studies.

Nevertheless, several limitations need to be addressed. In the systematic review, most of the indexed articles eligible for analysis were in English as the main language. Due to a relatively small number of articles included, we were not able to detect the potential for publication bias. It is possible that we may have overlooked some information from unpublished articles in other languages, including Asian countries such as Indonesia, although the influence on the observed associations is unclear.

We also only used a single registry from a tertiary cardiac-referral academic hospital in the largest urban area in Indonesia. Patients referred to this type of hospital may have different characteristics than those referred to secondary referral hospitals, non-pPCI hospitals, non-academic hospitals, or other types of hospitals in other urban areas of a smaller size and population than Jakarta. In a study with an extended population beyond the JAC Registry it was reported that the proportion of non-reperfused STEMI patients with a TIMI score ≥ 4 and onset of MI ≥ 12 hours were
significantly higher at pPCI centres than at non-pPCI centres in Jakarta. The mean ‘door-to-device’ time of STEMI patients who were reperfused with pPCI at academic centres was shorter than that at non-academic centres. The proportion of STEMI patients reperfused with a drug-eluting stent and who received thrombectomy were also significantly higher at academic centres compared to non-academic centres. Although the clinical outcomes, including in-hospital death, were not significantly different between these centres,6 these possible differences in baseline patient characteristics limit the generalizability of our findings.

Another limitation is the unavailability of some clinical information, which hinders us from assessing the contraindication of using preventive CV medications. Although several studies did not consider a contraindication when assessing guideline adherence, our estimation of the level of adherence might underestimate the true prevalence, assuming that contraindicated patients were not adequately prescribed such medications. As is inherent to observational studies, we cannot rule out the possibility of other unmeasured potential confounders that were not included in our studies. We may therefore have overestimated the preventive effects of the medications on CVD deaths.

Regarding the qualitative study, we only reached a code saturation with interviews of physicians who had relatively homogenous characteristics and came from one city in one province in Indonesia. Although this survey is sufficient to support further quantitative studies, a larger sample size is needed to attain a meaningful saturation if the aim is to gain a deeper understanding of physicians’ prescribing behaviour.9

One of the main limitations of our studies using the PharmLines Initiative database was the relatively small number of participants who met our strict inclusion criteria. This might have caused a lack of statistical power to detect smaller differences between groups, and hence low precision in the estimates. Finally, a lack of information on medications dispensed at hospitals in the IADB.nl database might have led to the misclassification of a potential confounder, such as the use of other CV medications, and might inadvertently have excluded potential participants who started statins for the first time at the hospital.
IMPLICATIONS FOR CLINICAL PRACTICE AND FURTHER RESEARCH

Our knowledge of the burden of CVD in Indonesia is mostly derived from cross-sectional studies or country report profiles. Data on the prevalence rates of CVD subtypes and risk factors were self-reported. In addition to increasing the risk of information bias, such data do not permit the calculation of an absolute risk estimate of short-term or long-term CVD and their subtypes. Furthermore, death registration data were unavailable or unusable due to quality issues. Moreover, different country reports published by different networks of investigators have provided different estimations of the CVD burden. The report by the Institute for Health Metrics and Evaluation identified the top two causes of most deaths and premature deaths as stroke followed by CAD, and this position had not changed since 2007. In contrast, the World Health Organization reported CAD to have caused more deaths than stroke since 2000. This conflicting information might confuse policymakers who are responsible for the creation of intervention strategies for CVD prevention, as the approaches to the prevention of each disease are not the same.

Recent studies have analysed data from the hospital-based JAC Registry. To our knowledge, there are only two well-known registries for acute coronary syndrome available in Indonesia and they are designed to manage STEMI patients in Jakarta. The presence of MI registries has been proven to improve the quality of care for STEMI patients, such as an increase in interhospital referral to a PCI-capable facility and the use of pPCI as the reperfusion strategy. Such registries are known to serve as ‘best practice’ and can improve guideline implementation. These evidence-based practices might also be investigated through a sound research methodology. As the registries are hospital-based, a study of these registries will provide more evidence on the secondary prevention of CVD. Therefore, this area of research should continue, and the development of more registries in other regions in Indonesia should be encouraged.

In addition, studies are also needed on the total burden of CVD in Indonesia in the general population. To date, we know of only one study that has estimated this burden in the general population. The study was a cross-sectional survey, in which data were collected through a household visit, interviewing subjects from the general
population aged ≥ 40 years in eight purposively selected villages in the second largest district of the province of East Java. From the total of 22,093 participants, about 25% had a high clinical risk of CVD. This number might under- or over-estimate the real prevalence due to the bias of self-reported data. Cohort studies are needed to obtain more accurate information on the incidence and prevalence of CVD and CV risk factors such as diabetes, hypertension and dyslipidaemia.

Findings from cohort studies are needed to guide and strengthen the prevention of CVD in primary care. The JKN, which encourages primary health care facilities to take a role on the front line of the health system, can follow this up. This new NHIS means CVD-related health care services and medications for the primary and secondary prevention of CVD will be subsidized and covered by the JKN. We would then expect a rise in the utilization of CVD-related health care services, including clinical guidelines, as well as the use of preventive CV medications in primary health care facilities. This would subsequently lead to a substantial increase in the government costs to cover this burden. Therefore, further research on the health services is needed to investigate the extent of CVD prevention covered by the JKN in primary care, as well as the clinical and economic impacts of the system, with the aim of developing and evaluating suitable interventions for the promotion of CVD primary prevention in primary care.

One review of a small number of studies in Indonesia concluded that CVD-related health care services were insufficient and unequally distributed, including the supply of preventive CV medications, across the entire nation. Between 2015 and 2016, it was estimated that there were only 1.5 cardiologists, 0.38 neurologists and 0.4 endocrinologists per million Indonesians. The total number of Indonesian cardiologists was only 365, with most practising in Jakarta, for a population of around 260 million in Indonesia. For the sake of rough comparison, the cardiologist/inhabitant ratio in Indonesia is 35 times less than the ratio in the Netherlands (around 900 cardiologists for around 17 million in 2014). Another study reflects these findings for Indonesia, with the mean number of certified cardiologists reported to be 2.74 per million Indonesians, and only 88 hospitals equipped with percutaneous coronary intervention (PCI) measures (mean population per PCI centre = 2.7 million) in 2014. In Jakarta, however, the mean number of certified cardiologists was 18.9 per million and the mean population per PCI centre was 392.9.
care by a PCI facility is readily available throughout the country (at least 600 PCI procedures per year). Moreover, another study revealed there were considerable unmet needs for CVD care in the Indonesian population aged ≥ 40 years. Of all participants at risk of CVD, only one-third received the treatment needed. However, this study did not clearly explain what needs were unmet and what treatment was needed. The possibility of primary and secondary care overload in the JKN era needs to be anticipated and carefully examined.

Although the JKN will make health care services more accessible to the general population, there are other barriers to potential patients even arriving at the access point, especially in rural and remote areas in Indonesia. Geographical difficulties and out-of-pocket transport expenses have been found to play a significant role in delaying timely treatment for acute myocardial infarction and acute stroke, which might result in death or long-term disabilities. Our findings reflect this, with many STEMI patients non-reperfused, while a majority were late presenters. Non-reperfusion itself predicted a less optimal prescription of medications to STEMI patients at discharge. Since the main therapy for STEMI patients strongly recommended by clinical guidelines is acute pPCI in a very timely manner, the reasons behind non-reperfusion need to be further explored in quantitative studies to support the development of suitable interventions to improve care.

A qualitative study of community pharmacists (public primary health centres [Puskesmas] and pharmacies) in East Java revealed the pharmacists’ perceptions of their role in CVD prevention. Not wishing to be confused with physicians, some pharmacists perceived that their role was limited to providing medication counselling and monitoring medication use only. They also perceived negative attitudes of both physicians and patients towards pharmacists playing a greater role, which made them hesitant to adopt a more ‘clinical’ role. Pharmacists also had mixed perceptions on whether their skills were adequate for this role. There were also several organizational barriers, including work overload, lack of incentive and support from the professional pharmacy body and government, and the perception that most patients who needed CVD-related care went to the secondary health care facilities, with Puskesmas only providing basic health care services.
Our findings provided insights into the factors from a physicians’ perspective. In addition to non-reperfusion, several baseline patient characteristics, such as older age (> 65 years old), non-anterior MI, having a family history of CAD and a TIMI score ≥ 4, were independent predictors of receiving less medication at discharge. This suggests that physicians could stratify patients based on these baseline characteristics and treat them accordingly. However, as the default treatment of STEMI patients is acute pPCI, there is no information on risk stratification to guide in-hospital management and, even more, at-discharge therapy.

Furthermore, the national guidelines in Indonesia adopted international guidelines that drew their recommendations from studies in Western populations, with different burden and risk factors. This may lead to different opinions on the benefit-risk of using guideline-recommended medications among physicians. In our qualitative study, physicians had different opinions, for example, on the cut-off of total cholesterol required to initiate statin therapy in primary health care settings. Terms such as ‘ guideline ’ and ‘ risk-assessment ’ were not mentioned, unless directly asked, as key factors in prescribing statins. The JKN and its platforms were also considered when prescribing medication. These findings suggest that prescribing preventive CV medications in STEMI patients according to guidelines involves many internal and external factors related to the physicians. Thus, the factors that inform a physician’s decision and the external barriers in the health system need to be investigated further.

Considering other previous and limited studies, we conclude that CVD prevention in Indonesia, especially through the primary care setting, still has a long way to go. In the JKN era, when primary health care facilities are readily accessible and covered, the size of the population at risk still needs to be accurately estimated. The improved use of guidelines, JKN platforms and properly designed research are still required. While secondary prevention of CVD needs to be strengthened by continuing the use of evidence-based procedures and medications, the reasons behind discordances need to be investigated further to identify the risk group who might need different approaches.

In the Dutch context, despite many years since the establishment of guidelines on prevention of CVD, which strongly advises the use of statins for CVD prevention in the Netherlands, 77% of the high-risk Dutch general population (primary prevention)
and 31% with CVD (secondary prevention) from a Lifelines database study did not report receiving lipid-lowering agents (statins and ezetimibe) in accordance with the guideline. In another study using the PHARMO, a GP database, 67% of high-risk Dutch participants with or without CVD were given lipid-lowering agents, which were usually statins. In the population treated by statins – on average one daily defined dose – 45% did not reach the LDL-c treatment target according to the guidelines. Moreover, there was no significant difference in LDL-c target attainment between a standard-potency and high-potency group. Due to the nature of the database, the actual use of the drug by the patients, which might influence LDL-c target attainment, could not be assessed.

By using the PharmLines database, which includes the IADB.nl data reporting actual dispensing of the medication, we could measure whether factors such as adherence might have different effects in different statin dosing groups or different patient risk groups. Using this database, we observed differences between men and women in the effectiveness of statins on increasing the level of HDL-c. An interaction between sex and adherence to statin therapy appeared to have influenced the LDL-c response to statins. This finding might prompt further studies with a larger sample size in order to identify whether sex-specific guidelines for statin therapy are needed.

**CONCLUSIONS**

This thesis provided insights into the current challenges to using guideline-recommended preventive CV medications in high-risk populations in Indonesia and the Netherlands. In Indonesia, a substantial percentage of high-risk patients did not receive secondary preventive CVD medications recommended by the guidelines. The reasons behind this need to be investigated further to be able to design an efficient intervention programme. In the Netherlands, differences between the sexes in the effect of statins on LDL-c response appeared to be present when adherence to statin therapy and the statin dose level were taken into account. These findings suggest that a more personalized approach taking sex differences into account is needed, but this should be confirmed through larger studies.
REFERENCES


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A wax model of a sectioned heart in situ (Marinkovic S. et al. Folia Morphol 2014; 73(2): 103-12) [used with permission].