Prehospital management of patients suspected for non ST-elevation acute coronary syndrome

Ambulance care professionals are very frequently confronted in their work with patients who have complaints of chest pain. Because a potentially dangerous acute coronary syndrome (ACS) cannot be quickly ruled out during telephone triage in the case of chest pain, an ambulance is often sent immediately with urgency. Ambulance personnel must make an on-scene decision which care pathway is best and safest for the patient. This is often done based on anamnestic data and an electrocardiogram (ECG) taken at the scene. Many times a professional consideration of what to do is made based on experience and clinical judgment. This thesis is an outline of research done in ambulance care to use a risk stratification tool, the HEART score (History, ECG, Age, Risk factors, Troponin), in this triage. This HEART score was already clinically proven to be a very easy and reliable tool in identifying both low- and high-risk patients on major adverse cardiac event (MACE) endpoints. By using this validated instrument already in ambulance care, combined with a point-of-care (POC) determination of troponin, a reliable prehospital prediction can be made. This can help in prehospital decision-making whether or not to refer a patient to the hospital. This has the potential to reduce unnecessary transport of patients to the hospital but also to better harmonize care in the chain so that the turnaround time of patients at the emergency department (ED) will be faster.

Chapter 1 of this thesis describes the developments in acute cardiac care in recent years that have formed the basis for the various research in ambulance care. These studies and interpretations focus on prehospital triage in ambulance care with the HEART score in combination with a POC determination of cardiac troponin.

The first phase of the FamouS Triage study is described in **chapter 2**. The main focus of this phase was the feasibility of risk stratification in ambulance care by ambulance care professionals using the HEAR(T) score for this purpose. In this phase, the HEAR elements were determined prospectively by ambulance personnel. The score was then completed at the hospital where the troponin result was determined from a blood sample collected prehospital. Of the 600 patients with suspected non-ST-elevation acute coronary syndrome (NSTE-ACS), 140 patients (23%) were classified as low-risk, 342 (57%) as intermediate-risk and 119 (20%) as high-risk. A 30-day follow-up period showed that the incidence of MACE in these groups was 2.9%, 19% and 45% ($p < 0.001$), respectively, with an area under the curve (AUC) of 0.77 (95% CI 0.73-0.81) for predicting MACE with a prehospital HEART score.

In the second phase of the FamouS Triage study, the complete HEART score was determined in the ambulance by the ambulance care professional, using troponin determination on a POC device for the troponin element of the score. **Chapter 3** describes the results of this study. In this prospective observational study, a full HEART score was recorded prehospital in 700 patients with suspected NSTE-ACS. A total of 172 patients (24.6%) were thereby stratified as low-risk, the remaining 528 patients (75.4%) as intermediate to high-risk. In 5 patients (2.9%) of the low-risk group, MACE endpoints occurred during a follow-up period of 45 days, this occurred in 111 (21%) intermediate/high-risk patients ($p < 0.001$). No deaths were reported in the low-risk group and the incidence of acute myocardial infarction was 1.2%. For the first time, it was discussed which

(cardiac) endpoints should be classified as MACE. Studies handle this in different ways which can confound the interpreting of presented MACE rates. At this stage of the study, there were no consequences in decision making to refer patients to the hospital based on HEART score classification. All patients were transported to the ED of the hospital where they received usual care. It was concluded that prehospital risk stratification with the HEART score by ambulance care professionals is accurate in differentiating between low- and intermediate to high-risk for MACE endpoints. In addition, it was mentioned that further training is important and that in the case of the POC device used for troponin, the sensitivity of this test necessitates a second measurement if the symptoms are of short duration. All this to decrease the MACE rate in the low-risk group. Further research will have to show whether transport to the hospital of low-risk patients can be avoided.

Chapter 4 reviews several Dutch studies, all focusing on prehospital triage of patients with chest pain. Overcrowding of EDs is a major and growing problem worldwide. Developments in prehospital risk stratification and chain collaboration between healthcare stakeholders may offer a solution to reduce the number of referrals to EDs. Although results of research are promising, questions are also raised about the reliability of existing POC tests for troponin. It is expected that the reliability of risk stratification will further increase if POC devices that determine high-sensitivity cardiac troponin are used (see also **chapter 9** of this thesis).

In both phase 1 and 2 of FamouS Triage, there was no impact on decision making for the ambulance care professionals yet. All patients where prehospital risk stratification with the HEART score was performed were still taken to the ED for further evaluation. **Chapter 5** outlines the design of the third phase of the FamouS Triage study. The aim of this study is to no longer refer patients classified as low-risk for a NSTE-ACS to the hospital. This non-inferiority study evaluates whether this form of prehospital management in patients with chest pain is feasible and no worse than the previously described cohorts in which patients were still transported to the hospital. **Chapter 6** describes the results of this phase 3 of the FamouS Triage study. In phase 3, including 536 patients, 149 of them (28%) were not transported to the hospital based on a low-risk classification with the HEART score. The MACE rate among low-risk patients was 2.9% in phase 2 and 1.3% in phase 3. After adjusting for possible confounders in baseline characteristics, the hazard ratio (HR) for 45-day MACE was 0.88 (95% CI 0.63-1.25) in phase 3 compared with phase 2. It was therefore concluded that prehospital risk stratification in patients suspected for NSTE-ACS, in which a substantial number of low-risk patients are no longer transported to the hospital, seems feasible and no worse than transporting all patients to the hospital.

In **chapter 7**, an editorial commentary takes a closer look at a publication by the HART-c research group from Leiden, the Netherlands. The HART-c project shows that prehospital triage in patients with cardiac symptoms, using prehospital data in combination with consultation with a cardiologist in the hospital, contributes to leaving more patients safely at home. In addition, the cardiologists

on call for consultation also had insight into the admission capacity of different hospitals in the region. This made it easier to decide which hospital to refer patients to if they still required hospital evaluation. This led to a significant decrease in the number of interhospital transports by the ambulance services. This study confirms the important role for ambulance services in triage of patients with cardiac symptoms. It also underlines the importance of cooperation in the chain of acute cardiac care, of which consultation with a doctor in the hospital is a good example.

Chapter 8 outlines the added value of troponin determination within the prehospital HEART score. The mean HEAR score was 4.5 ± 1.6, and the mean HEART score was 4.7 ± 1.7. Employing the HEAR score, 183 patients (26%) were classified as low-risk, whereas utilizing the HEART score, 172 patients (25%) fell into the low-risk category ($p = 0.001$). In both low-risk groups, no fatalities occurred within 45 days. With the HEAR assessment, 13 patients (7%) in the low-risk group experienced MACE, while using the HEART score, MACE occurred in 5 patients (3%, $p < 0.001$) within the low-risk group. The HEART score (AUC 0.74) demonstrated superior predictive capability compared to HEAR (AUC 0.65, $p < 0.001$) for MACE. The conclusion was that in patients with suspected NSTE-ACS, the prehospital troponin component of the HEART score provides significant additional predictive value.

Thanks to ongoing technological developments, it has now also become possible to determine cardiac troponin on a POC device with high-sensitivity. **Chapter 9** describes research results using a modified HEART score based on different cut-off values for troponin. In this way, justice is done to the ongoing development in sensitivity of troponin determinations. The results show that based on the modified HEART score, the number of low-risk patients becomes slightly lower, but the sensitivity and negative predictive values improve. Considering the prehospital situation with a POC determination of troponin, the number of patients with low-risk for MACE score changes from about 25% to about 19%. In doing so, the sensitivity and negative predictive values of the test increase from 96.5 and 97.7 in the conventional HEART score to 98.8 and 99.0 in the modified HEART score, respectively. This suggests improved safety in prehospital ruling out NSTE-ACS in suspected patients.

Finally, **chapter 10** provides insight into how all these developments could contribute to a new prehospital management system to triage and risk stratify patients with chest pain in ambulance care. All developments are compared with current in-hospital guidelines that could also be implemented prehospital due to technological developments and increased scientific evidence. A collaborative and chain-wide approach has the potential to contribute to a significant reduction of hospital referrals, decrease in length of stay and observation in an ED (and thus overcrowding) and decrease in hospital admissions.