Assessing chest pain in primary care

strategies (sensitivity 97.1-98.4). The total number of patients was 2,828 with a 16% incidence of myocardial infarction, which is lower than found in other emergency department populations. Thus, 1 hour exclusion or, in case of an undetectable hs-cTn, direct exclusion appears safe.[78] Except for the single cut-off strategy, all strategies performed well in the challenging subgroup of patients presenting early after onset of complaints.[78] Both strategies where a change was part of the algorithm (the 1-hour and 0/1-hour strategy) showed a high value in including myocardial infarction as well. A multicenter trial (N = 2,222 chest pain patients, 9.7% incidence of myocardial infarction), testing the 0/1-hour rule-out strategy at an emergency department showed 30.6% of patients could be classified as low risk, with 0.5% false negatives.[79] A pooled analysis (N = 9,241 patients, 15.4% incidence of myocardial infarction) testing a combination of negative ECG-findings and a LOD-strategy for hs-cTnT, showed that 64.1% of patients could be classified as low risk, with 2.9% false negatives.[80] These findings lead to the question of what percentage of false negative results is acceptable. Recently, incorporation of blood glucose testing alongside cardiac biomarkers has been reported to be cost-effective in comparison to the ESC-strategy.[81]

To summarise, improvements in the performance of very early rule-out strategies could lead to implementation in the near future. This would lead to a reduction in the time needed to exclude myocardial infarction in an emergency department, making such rule-out strategies more economical. The efficiency of this fast rule-out in terms of reducing the number of patients for further analysis is yet to be determined, although in the study population the test was true-negative in approximately half of the presenting patients, except for the LOD-strategy which had considerably fewer true-negative patients. Whether PoC-devices, with a yes/no indication (qualitative test) or, alternatively, equipped with a reader to obtain a quantitative result, could reach the same level of efficiency in primary care, eliminating unnecessary referrals, is yet to be determined. Of note, PoCTs for troponin that are sensitive enough to measure LODs or low single cut-offs are not yet available.

11.10 Valorisation: how is this thesis related to a chest pain patient in primary care in 2027 A.D.?

Imagine 2027 A.D...
A 50 year old GP in the South of the Netherlands, more specifically in an old Roman city close to the Belgian border, assesses a female patient with chest pain. The patient came walking from her house, 5 minutes from the GP practice. Most probably, there is a mild underlying condition, but the GP cannot rule out ACS. This doctor has been working in general practice for 16 years now and during these years, he has assessed 650 chest pain patients. He has referred 39 patients that eventually had ACS and 52 patients that

eventually only had stomach, chest wall or stress related problems. He has failed to diagnose two cases of ACS, unfortunately in one of these two cases, the patient died after initially not having been referred. At assessment, this patient had hypoglycemia and he recovered after application of glucose.

Late in his fourth decade the GP completed a thesis on this topic. Still, the thesis is now and then seen on book shelves in academic institutions throughout the country. Nowadays, he feels more comfortable with these patients, as in the past few years, assessment of patients suspected of ACS in primary care has become easier. He tells the patient: "not too long ago, I had to refer you for assessment at the hospital during at least half a day, but these days, I can..."

Right there the imagination stops. The crucial point as to what the GP can do in ten years from now, is yet to be answered. But there will be *evolution* in the assessment of chest pain, perhaps even *revolution* at some point. In this section, a light is shed on the (r)evolution and the scientific conditions under which such change could be realised. In other words: where do primary and secondary care meet around the chest pain patient in the future? Notably, the search for advanced diagnostic means in primary care should be seen in the light of today's accurate rule-out capacity of the GP's clinical judgment. Given a NPV for ACS of the GP's clinical judgment of 99.6% as we found in **chapter 4** and an odds ratio of the GP's judgment for correctly categorising a patient as having or not having a life threatening disease of 48 (**table 4.3**), improving this highly accurate clinical judgment as achieved by GPs is not a matter of course.

Subsections **11.9.3** and **11.9.4** outline the development of CDRs combining signs, symptoms and PoCTs (**11.9.3**), and the development of high-sensitive biomarker regimes available in highly equipped laboratories as seen in hospital settings (**11.9.4**). The optimal CDR or biomarker regime has yet to be determined and its economic value has to be assessed after validation. However, classical clinical assessment combined with two point biomarker tests with high interval times of up to 6 hours will be replaced by accurate and fast rule-out regimes in the near future of secondary care assessment. From a primary care perspective, one of two possible scenarios molded by the introduction of 'the ideal rule-out schedule' could become daily practice.

The first possible effect of a fast rule-out schedule in secondary care, with a strong negative predictive value for ACS within one hour after presentation, is a fast and less expensive assessment after referral to secondary care. Ambulance transport will still be necessary, however cost reductions will be realised by shorter assessment at the emergency room. For example, assessment could start in the ambulance by taking the initial blood samples.[82] Assessment could even take place outside the hospital, with experienced specialists working in outpatient clinics with lower overhead costs.[83] This type of highly efficient specialist care, positioned 'in between' primary and secondary care, is becoming more common in non-acute settings and could in the near future evolve in

acute medicine as well. An ideal environment to monitor a patient with suspected ACS, and fast access to specialist care when needed, would be close to, even perhaps within the walls of, but technically not inside the hospital. For example, primary care OOH services are often located close to, or even inside, the hospital and could provide this type of care. Thus, **the potential role of specialist care outside the hospital with lower overhead costs, using fast rule-in and rule-out tests for ACS, could be a subject of future studies (point 14 in section 11.11).** If rule-out strategies become faster and specialist care is becoming less expensive due to shorter assessment times and lower overhead costs, new workup models do not necessarily have to be established in primary care to be cost-efficient. In the Netherlands, GPs with a post academic education for both emergency medicine and cardiovascular disease are available and could possibly have a role as well as cardiologists, in the same way they are presently working outside the hospital in non-acute matters.[83]

The second possible consequence of a very fast rule-out regime (a CDR, incorporating a high sensitive biomarker-based PoCT) could be its availability in primary care directly. It seems unlikely for a CDR without incorporation of a PoCT, to gain sufficient NPV. Perhaps, even a combination of two or more different biomarkers should be tested at once to reach a high NPV, e.g. the combination of H-FABP and cTnI. Earlier work has shown that these markers identify distinct patients, so possibly their combined evaluation shows increased performance in a rule-out strategy.[84] Note that the analytical challenge to rapidly and accurately measure both H-FABP (in ng/mL) and cTnI (in pg/mL, i.e. a 1,000-fold lower concentration) has recently been overcome in a pilot study (details not yet available). Therefore, a **highly accurate CDR incorporating a single-measurement, high-sensitive PoCT device would be an effective solution to the high number of ACS-negative referrals and the incidentally occurring ACS-positive non-referrals. A combination of two or more markers in one device may be even more effective (point 6 in section 11.11).**

Biomarker tests are becoming more and more accurate. Yet, these tests thrive on high-sensitive quantitative measurements, with a low variance around the cut-off value. Performance of similar qualitative tests in an easily accessible PoCT format seems to lag behind the accurate (combinations of) biomarker tests available in laboratories, which measure the whole blood biomarker values which modern fast rule-out regimes are based on.[85] **Translating early rule-out strategies based on highly specialist laboratory measurements into easy to use PoCTs and maintaining accuracy of the laboratory tests, is challenging (point 4 in section 11.11).** Perhaps extremely low cut-off values for such easy to use PoCTs or utilisation of a combination of biomarkers in one test could gain sufficient NPV. However, in our RAPIDA-study, the cut-off value was lower than the 99th percentile and the test still failed in ruling out ACS. One of the D-Dimer PoCTs investigated in ruling out pulmonary embolism in primary care is based on a cut-off value of 80 ng/ml, which is less than 20% of the cut-off values usually used in whole blood meas-

urements of D-Dimer concentrations.[86] Theoretically, such a low cut-off value seems impractical. Such a test would rarely be negative, when looking at the usual results of 100-400 ng/ml that are obtained in whole blood measurements, where a cut-off value of around 500 ng/ml is utilised. Still, the test proved to be considerably effective in ruling out pulmonary embolism when combined with the Well's score. From this example, one could learn that **cut-off values cannot be directly translated from whole blood quantitative measurements to qualitative point of care devices (point 2 in section 11.11).**

Altogether, it is yet unclear whether a GP in 2027 tells his patient that referral has to take place for fast rule-out of ACS in a hospital or another specialist setting, or the GP rules out the ACS in his own practice. Nevertheless, rule-out will become much faster and more accurate, thereby increasing patient and doctor comfort.

11.11 Fourteen points of attention for future research

The next traveler exploring the field of chest pain in primary care could consider the following 14 points of attention:

Development of biomarker based PoC tests:
1. Seamless evolution of biomarker tests from 'bench' to 'bedside' should be covered in unambiguous study pathways incorporating both the experimental and the implementational phase of development. Before developing and implementing a new biomarker test, defining its clinical need should be a 'conditio sine qua non'.
2. Cut-off values cannot be directly translated from whole blood quantitative measurements to qualitative point of care devices.
3. The optimal cut-off value of H-FABP for AMI -and therefore for ACS in a clinical setting in primary care - was set at 4 ng/ml: a cut-off even lower than the 99th percentile in a normal reference population. This strategy seems recommendable when aiming at safe rule-out of ACS in primary care.
4. Translating early rule-out strategies based on highly specialist laboratory measurements into easy to use PoCTs and maintaining accuracy of the laboratory tests, is challenging.

Rationale of a CDR:
5. In the Netherlands, 50,000 patients annually are referred to secondary care facilities to rule out ACS that eventually is excluded. Ruling out ACS in these patients at the GP's office, thereby preventing an ambulance transport and examinations in secondary care, is valuable to both the patient and the health system at large.
6. A highly accurate CDR incorporating a single-measurement, high-sensitive biomarker based PoCT-device would be an effective solution to the high number of

ACS-negative referrals and the incidentally occurring ACS-positive non-referrals. A combination of two or more biomarkers in one device may be of added value.

7. With an estimated cost price of a PoCT of €45, a reduction of ACS negative referrals from 10.8% to 7.7% of all chest pain patients would make the test cost-neutral.

Study methods in PoC test research in primary care:

8. Researchers and medical ethical boards should keep the procedures as simple as possible in studies involving acute medicine, where the very short time window to include patients as well as the acute setting is challenging.
9. Patient inclusion improves when nurses take over study activities from the GP and are free to perform the necessary consent procedures to enroll patients (without interfering too much with the handling of the GP).
10. In studies on diagnostic tools in chest pain patients in primary care, venous blood sampling in non-referred patients - rather than a negative clinical follow-up period - to definitively rule out ACS is recommended.
11. To find diagnostic tools in acute chest pain suspected of ACS, patient selection should focus on including these patients and this should be reflected in an incidence of ACS in the study population of at least 10%.
12. Predicting factors possibly contributing to a CDR to rule in and out ACS should be derived by multivariate analysis with ACS – not a heterogeneous mixture of CHD patients – as a main outcome measure.

Future implementation:

13. A new PoC test to rule in and out ACS should be accompanied by clear instructions on when (e.g. for what indication) and how (e.g. as part of a clinical decision rule (CDR)) to use it. Furthermore, it should be clear what action should follow a certain test result.
14 The potential role of specialist care outside the hospital with lower overhead costs, using fast rule-in and rule-out tests for ACS when available, could be a subject of future studies.