GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The central finding of this thesis is that high-quality syncope care depends less on isolated diagnostic tests but more on the structured integration of clinical assessment, organisation, technology, and patient-centred outcomes. Syncope is a multidisciplinary symptom explains why diagnostic uncertainty is common, but it also highlights the importance of a standardised initial evaluation. Across all parts of this thesis, the initial syncope evaluation remains the clinical foundation: careful history-taking, physical examination, orthostatic blood pressure assessment or active standing test, and 12-lead electrocardiography.[1-4] Without this fundamental evaluation, additional testing, artificial intelligence, or treatment strategies the risk stratification becomes poorly targeted.

This central role of the initial evaluation is consistent with recent literature. Systematic reviews have shown that both the performance of risk-stratification tools and the diagnostic yield of biomarkers, echocardiography, and rhythm monitoring depend strongly on patient selection and pre-test clinical probability.[5, 6] Orthostatic blood pressure responses also appear to be incompletely stable: in a generally healthy middle-aged population, reproducibility after one year was modest for systolic responses and poor for diastolic responses.[7] A single normal measurement therefore does not exclude orthostatic hypotension when the clinical history remains suggestive. This thesis confirms that the initial evaluation provides the foundation for all subsequent diagnostic and therapeutic steps.

Part 1. Syncope Units: Organisation, Standards, and Referral Patterns

The first part of this thesis shows that syncope care in the Netherlands is delivered by multiple syncope units across the country, including both academic and non-academic hospitals.[8] Although these units do not yet constitute a formal national network, their presence provides an important foundation for developing structured and accessible syncope care beyond tertiary centres. This is important because specialised syncope care should not be restricted to tertiary centres. Most patients with T-LOC are first seen in primary, emergency, or secondary care, and many can be managed effectively when structured diagnostic pathways are available.[1, 2, 4, 8]

The SU-19 translates guideline-based syncope-unit requirements into a practical and measurable quality instrument by assessing structure, diagnostic facilities, and the initial evaluation.[5] Its value lies not only in describing current practice, but also in enabling audit, benchmarking, and future standardisation. A high SU-19 score does not guarantee diagnostic perfection, but it indicates that the core infrastructure for good syncope care is present.

The second part demonstrates why such structure is necessary. Many patients referred to a tertiary syncope unit had no diagnosis, an incomplete diagnosis, or an incorrect diagnosis.[9] Importantly, most final diagnoses were common conditions, such as reflex syncope, initial orthostatic hypotension, or psychogenic pseudosyncope.[6,7] This indicates that the diagnostic problem is often not the absence of advanced tests, but insufficient recognition and interpretation of clinical patterns. Future syncope care should therefore strengthen earlier parts of the care pathway, improve referral quality, and use syncope units as regional

knowledge centres rather than only as last-resort diagnostic clinics.[8, 9]

These findings are consistent with the international development towards structured and risk-guided syncope care. A systematic review published in 2025 showed that risk scores differ substantially in methodological quality and predictive accuracy and should therefore not be applied independently of clinical assessment.[5] The RISC trial builds on this concept by randomizing 640 predefined low- and intermediate-risk patients to either immediate discharge or 24-hour in-hospital rhythm monitoring.[10] The trial evaluates cardiovascular safety and diagnostic yield, as well as healthcare costs and quality of life. Although the RISC trial does not yet provide outcome data, it operationalizes how a standardized initial evaluation can be translated into a prospectively testable discharge strategy.

This thesis complements these developments with a national inventory of syncope care in the Netherlands and the SU-19 as a practical quality instrument. The referral study also demonstrates that diagnostic delay frequently originates before referral. Good organizational infrastructure is therefore insufficient when clinical patterns are not recognized in a timely manner. Future validation should determine whether higher SU-19 scores are associated with better diagnostic accuracy, less unnecessary testing, lower healthcare costs, and better patient-centered outcomes.

Part 2. Artificial Intelligence in Syncope Care: Decision-making and Diagnostic Performance

The second part of this thesis explored whether artificial intelligence could support diagnostic decision-making in syncope, including its performance compared with medical professionals. The findings are promising but cautionary. GPT-4o generated diagnostic suggestions in all referral letters and GPT-5 also showed high diagnostic yield when structured syncope unit information was provided.[11, 12] However, AI often generated broader differential diagnoses than medical professionals. To account for this, a diagnostic performance score was developed that rewarded inclusion of the correct diagnosis but penalised unnecessarily broad or non-specific differential diagnoses. Nevertheless, diagnostic yield is not the same as diagnostic accuracy or clinical safety. Both studies showed limited diagnostic precision, and cardiac syncope remained a particular safety concern.[11, 12]

This distinction is clinically important. In syncope, missing a cardiac diagnosis may have serious consequences, whereas overcalling cardiac syncope may lead to unnecessary diagnostic uncertainty, additional investigations, and increase of health care costs.[1, 11] Current large language models appear useful as broad hypothesis generators, but not as autonomous diagnostic systems.[11-13] The GPT-5 study also showed that identical clinical information may lead to different outputs across repeated runs. This inconsistency limits the role of AI as an independent clinical decision-maker.[12]

Nevertheless, the findings of this thesis suggest that AI may have a future role in syncope care, particularly as a structured support tool rather than as an autonomous diagnostic system. Potential applications include improving referral letters, identifying missing information, summarising clinical histories,

flagging red flags, assisting triage, and checking whether the initial evaluation is complete.[11-13] These applications should be regarded as hypotheses for future implementation rather than established conclusions from the present thesis. Future implementation should therefore focus on clinician-led AI, validated against adjudicated diagnoses, with explicit safety checks for cardiac syncope and clear reporting of uncertainty.[11, 12]

These findings should be interpreted against the background of the rapidly expanding literature on generative AI. A 2025 meta-analysis of 83 diagnostic studies reported a pooled accuracy of 52.1%. Generative AI did not perform better than physicians as an overall group and performed significantly worse than medical experts; moreover, most studies had a high risk of bias.[14] A syncope-focused review similarly highlighted its potential for risk stratification and test interpretation, but also the lack of external validation, transparency, and demonstrated clinical safety.[15] This thesis supports this cautious position and adds limited reproducibility and inadequate recognition of cardiac syncope as important safety concerns.

Another machine-learning model correctly classified 80.8% of T-LOC diagnoses using information provided by patients and witnesses, but did not perform significantly better than the initial clinical assessment and was considered insufficiently accurate for routine care.[16] AI may therefore be most promising for clearly defined tasks, such as identifying missing components of the initial evaluation, structuring descriptions of events, and flagging cardiac red flags. Prospective studies should assess not only average accuracy, but also diagnosis-specific sensitivity, reproducibility, and the clinical consequences of errors.

Part 3. Bedside Provocation, Diagnostic Methodology, and Haemodynamic Stabilisation

The third part of this thesis emphasises that autonomic testing is valuable when tailored on the initial syncope evaluation. Tilt table testing and carotid sinus massage are not simple positive-or-negative tests. Their diagnostic value depends on whether the provoked symptoms reproduce the spontaneous event and whether the haemodynamic response fits the context of the clinical presentation.[17, 18] Tilt table testing remains useful for investigating reflex syncope, orthostatic hypotension, postural orthostatic tachycardia syndrome, and syncope mimics.[17] However, it should support the clinical history, not replace it.[17] Similarly, carotid sinus massage should be performed according to the Six-Step-Method which provides a reproducible and safe protocol, including exclusion of contraindications, correct positioning, standardised massage duration, and continuous blood pressure and heart rate monitoring.[18]

The contextual interpretation of autonomic function tests is supported by a recent review of head-up tilt testing. Differences in protocol, test duration, and pharmacological provocation result in varying diagnostic yields, while limited reproducibility remains an important limitation.[19] The value of the test therefore lies not only in the haemodynamic response, but also in symptom recognition and concordance with the spontaneous events.

An international scientific statement published in 2026 confirms that carotid sinus massage remains underused or is performed without standardization

outside specialized syncope facilities.[20] The statement provides indications, contraindications, and a step-by-step methodology and emphasizes that carotid sinus syndrome can only be diagnosed when spontaneous symptoms are reproduced. An asymptomatic response should be classified as carotid sinus hypersensitivity and has insufficient diagnostic specificity on its own. Recent cohorts reported only three reversible neurological complications per 10,000 procedures, indicating that the test can be considered safe when appropriate patient selection and standardized methodology are applied.[20]

The Six-Step-Method therefore directly aligns with this recent international consensus. The contribution of this thesis lies mainly in methodological harmonization: uniform performance and reporting may reduce differences between centers and improve differentiation between clinically relevant carotid sinus syndrome and incidentally identified carotid sinus hypersensitivity.[18]

This part of the thesis also moves from diagnosis to treatment. In some patients, the dominant mechanism is not a primary rhythm disorder but a hypotensive phenotype: a tendency to develop blood pressure drops sufficient to compromise cerebral perfusion.[21, 22] Ambulatory blood pressure monitoring can identify this pattern and may guide treatment.[21, 22] The haemodynamic study of fludrocortisone and midodrine suggests that blood pressure-raising therapy can reduce systolic blood pressure drops in selected patients.[21] Future syncope care should therefore become more phenotype-based, linking clinical presentation, haemodynamic measurements, and treatment response.[21, 22]

Recent literature supports the transition from a solely etiological diagnosis towards haemodynamic phenotyping. The combination of 24-hour ambulatory blood pressure monitoring and a short autonomic function assessment can distinguish hypotensive, bradycardic, and mixed mechanisms.[23] At the same time, the study of orthostatic blood pressure responses demonstrated that individual measurements may vary substantially over time.[7] In that study, none of the nine participants who met the criteria for orthostatic hypotension at reassessment had met these criteria at baseline. This supports repeated measurements in patients with new or persistent symptoms and an interpretation in which symptoms and haemodynamics are considered together.

A pharmacological review published in 2025 concluded that fludrocortisone and midodrine may be effective in selected patients, but that average treatment effects remain limited and patient selection is essential.[24] This thesis adds mechanistic data by describing the effects of both drugs on systolic blood pressure drops. It does not, however, establish that these haemodynamic changes result in fewer episodes of syncope, less pre-syncope, or improved quality of life. Future intervention studies should therefore investigate whether objective haemodynamic characteristics predict treatment response.

Part 4. Clinical Consequences

The final part of this thesis addresses the patient-level consequences of structured syncope care. Diagnostic yield alone is not enough. Patients need fewer symptoms, less fear, better functioning, and improved health-related quality of life.[25] The longitudinal quality-of-life study showed improvement in syncope-specific burden, SF-12 summary scores, and several RAND-36 domains after

syncope-unit care.[25] However, recovery was not uniform, indicating that a correct diagnosis does not always equal full clinical recovery.[25]

This is an important clinical message in favour for syncope units. Syncope may occur intermittently, but its impact can be continuous. Patients may restrict work, driving, social activities, or physical exertion because of fear of recurrence.[25] A syncope unit therefore offers more than a diagnostic label: it provides explanation, reassurance, risk stratification, targeted treatment, and a coherent framework for understanding symptoms.[1, 2, 4, 25] Patient-reported outcome measures such as the SFSQ, RAND-36, and SF-12 should therefore be used more often to evaluate whether syncope care improves outcomes that matter to patients.

This focus on patient-centered outcomes is consistent with recent literature in which autonomic syncope is associated with injury, anxiety, functional limitations, and reduced quality of life.[26] The international relevance of disease-specific measurement is further supported by the recent validation of a new language version of the SFSQ.[27] This thesis adds longitudinal data over 18 months and demonstrates, using both disease-specific and generic instruments, that improvement involves multiple physical and psychosocial domains.

Because of the observational design and the absence of an untreated control group, this improvement cannot be attributed entirely to syncope-unit care. Natural recovery, regression to the mean, fluctuations in symptoms, and changes in coping may also have contributed. Nevertheless, the consistent improvement across different instruments suggests that explanation, reassurance, and a coherent understanding of symptoms are clinically relevant components of care. Diagnostic success and patient-centered recovery should therefore be regarded as separate outcomes.

In conclusion, this thesis supports a model of syncope care built on four principles. First, the initial evaluation remains essential.[1,2] Second, syncope units require measurable standards, for which the SU-19 score provides a practical foundation.[8] Third, AI will probably become increasingly important, but mainly as decision support within clinician-led pathways.[11-13] Fourth, diagnostic success should be judged not only by the final label, but also by patient-centred recovery.[25] The future of syncope care lies not in more indiscriminate testing, but in better integration of structure, clinical reasoning, technology, haemodynamic phenotyping, and patient-reported outcomes.

In relation to the recent literature, this thesis confirms the importance of a structured, clinically guided, and patient-centered approach to syncope. It makes the organizational quality of syncope units measurable, quantifies the limitations of AI in realistic clinical cases, standardizes provocation testing, and connects diagnosis with haemodynamic phenotyping and patient-reported outcomes. At the same time, it challenges the assumptions that more diagnostic testing automatically leads to a better diagnosis, that more clinical information automatically makes AI more reliable, and that a correct etiological diagnosis is equivalent to complete recovery.

The next step should be the development of a national network of syncope units with uniform quality criteria, regional referral pathways, and structured knowledge exchange. Within this network, the SU-19 should be prospectively validated against diagnostic accuracy, hospital admissions, healthcare costs,

and patient-reported outcomes, while the RISC trial may guide the safe and efficient discharge of low- and intermediate-risk patients. Artificial intelligence should first be evaluated prospectively, preferably in a silent-mode setting, and may subsequently develop into multimodal decision support combining clinical information with ECG data, blood pressure profiles, and wearable sensor data. At the same time, treatment should be increasingly tailored to objectively identified haemodynamic phenotypes, with repeated orthostatic blood pressure measurements accounting for the variability of orthostatic responses. Finally, syncope units should fulfil a regional educational role in addition to providing diagnosis and treatment, while patient-reported outcomes, functioning, and social participation should be incorporated into a standardized core outcome set for both clinical care and future research.

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