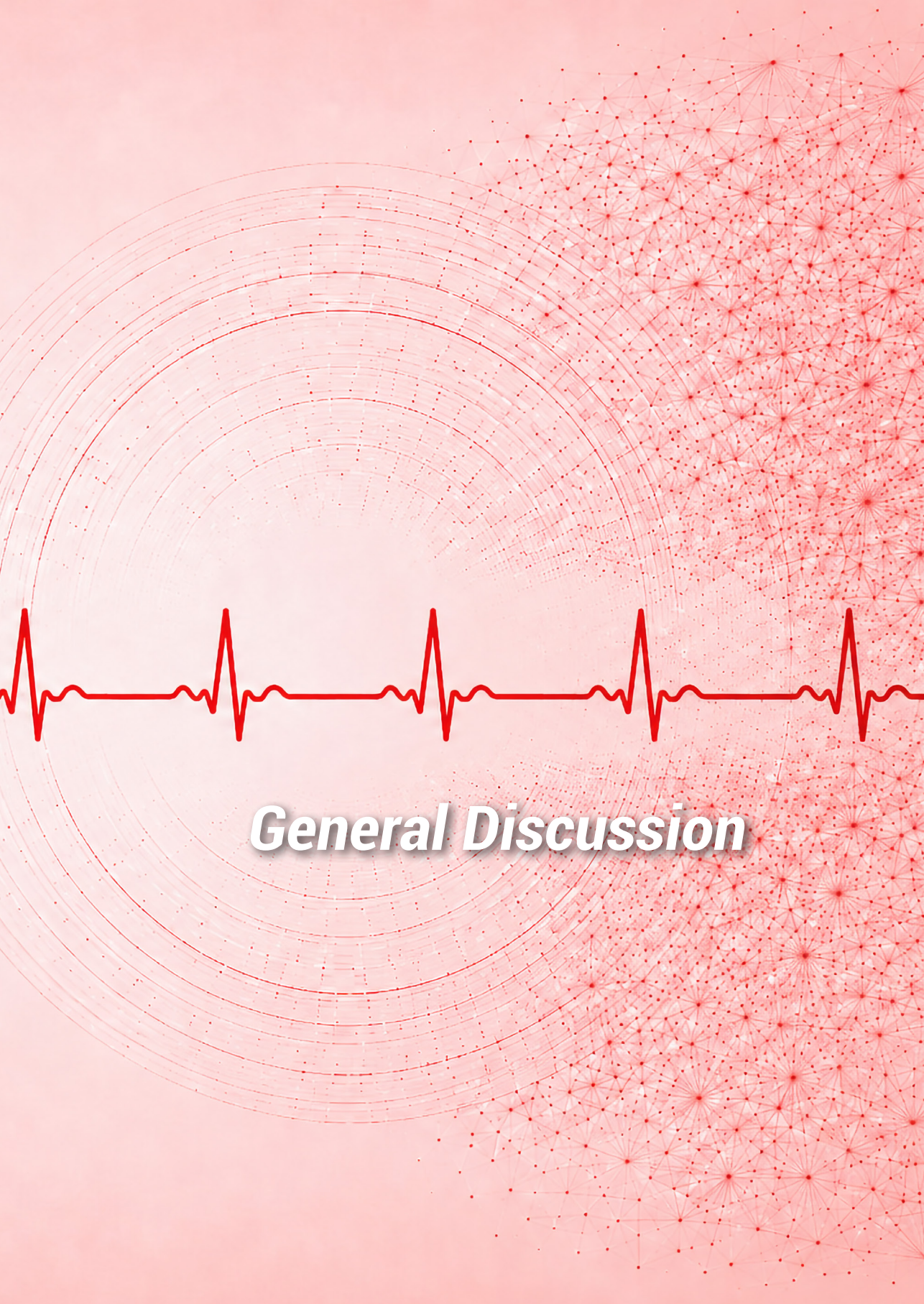
General Discussion

English Summary

Syncope is a sudden and transient loss of consciousness due to temporary global cerebral hypoperfusion, characterized by rapid onset, short duration and complete spontaneous recovery. Within the broader spectrum of transient loss of consciousness (T-LOC), syncope must be distinguished from epileptic seizures, traumatic loss of consciousness and syncope mimics. T-LOC is common in the emergency department (ED) and accounts for an estimated 1–3% of all ED presentations.[1] In primary care, the incidence of first syncope is approximately 1.91 per 1,000 person-years, with serious outcomes within one year in 12.3% of patients.[2]

The diagnostic challenge is considerable, because the causes of T-LOC extend across cardiology, neurology, internal medicine and functional disorders, and because there is no gold standard for the differential diagnosis of syncope. The Amsterdam syncope approach therefore uses multidisciplinary adjudication after structured evaluation and critical follow-up as the best available clinical reference standard. A fully certain diagnosis would ideally be established during a spontaneous T-LOC episode with simultaneous continuous blood pressure and ECG monitoring, but this is rarely feasible in daily practice. By integrating history taking, clinical findings, additional tests and the subsequent clinical course, this adjudication probably comes closest to a reliable diagnosis in clinical syncope care. Precisely for this reason, a standardized and carefully performed initial evaluation is essential: it forms the basis on which further diagnostics, follow-up and final adjudication can be reliably built. The European Society of Cardiology (ESC) guidelines therefore recommend a standardized initial evaluation for every patient with syncope, consisting of careful history taking, physical examination including orthostatic blood pressure measurement, preferably in the form of an active standing test (AST), and a 12-lead electrocardiogram (ECG).[3, 4]

Syncope units (SUs) have been developed to narrow this diagnostic gap. The European Heart Rhythm Association/Heart Rhythm Society (EHRA/HRS) position statement describes an SU as a facility with a standardized approach to the diagnosis and treatment of T-LOC, with dedicated staff, access to appropriate diagnostics and therapy, and a role in education.[5] A structured syncope care pathway can increase diagnostic yield to approximately 97% and may reduce unnecessary additional testing, hospital admissions and healthcare costs.[6–8] Against this background, this thesis is built around the question of how syncope care can be better organized, standardized and evaluated in clinical practice. The successive chapters address the organization of syncope units and the role of healthcare and allied health professionals, diagnostic reassessment after referral, the possibilities and limitations of artificial intelligence, the practical performance of autonomic function testing, haemodynamic treatment of hypotensive symptoms and, ultimately, the clinical consequences for health-related quality of life.

Chapter 1 describes the general introduction and outline.

Chapter 2 describes how guideline-based syncope care is organized in the Netherlands. The central message is that specialized syncope care is not limited to tertiary expertise centers. Rather, the study identified multiple syncope units across the country in which cardiology and neurology are usually involved either jointly or complementarily. In this respect, daily practice aligns to a large extent with the ESC guidelines and the EHRA/HRS position statement on syncope units.[3,5] In total, twenty Dutch syncope units were identified: five academic and fifteen non-academic units. Although these units do not constitute a formal national network, they indicate that there is a basis for broader network development and national structuring of syncope care. Seventeen of the twenty reported multidisciplinary involvement in the initial evaluation, while in nineteen units cardiology, neurology or both specialties were responsible for management. The SU-19 score was developed to assess the implementation of best practice across three domains: structure, available diagnostic tests and the initial evaluation. The mean score was high (18.0, SD 1.1), and 45% achieved the maximum score.[9]

The importance of this study lies mainly in the operationalization of guideline implementation. The SU-19 score shows which components are well embedded and where practice variation remains. This variation mainly concerned the performance or availability of active standing measurement, carotid sinus massage, tilt table testing, continuous beat-to-beat blood pressure monitoring and external rhythm monitoring. Such variation is clinically relevant, because standardization of the initial evaluation in particular can increase diagnostic yield and limit unnecessary additional testing.[3, 4, 7, 8]

A second important message is the growing role of allied professionals. In these Dutch syncope units, nurse specialists or physician assistants were involved in tilt table testing and in the initial evaluation. This increases the scalability of syncope care, provided that protocols, education, supervision and quality control are clearly defined. The study therefore supports the concept of a multidisciplinary syncope unit as a recognizable, auditable and reproducible care structure.[5, 9]

Chapter 3 focuses on a persistent problem in syncope care: many patients are referred to a tertiary syncope unit without a diagnosis or with a diagnosis that proves to be incorrect or incomplete after critical reassessment. The study analyzed the referral diagnosis, the diagnosis after history taking and evaluation in the syncope unit, additional autonomic function tests and the adjudicated diagnosis after long-term follow-up by a multidisciplinary panel.[10]

In an in-depth analysis of the FAST II study, a prospective cohort of consecutive adult patients with T-LOC referred to the tertiary syncope unit of Amsterdam UMC, the referral diagnosis from the referral letter was compared with the final diagnosis after stepwise evaluation. This evaluation consisted of history taking, autonomic function testing when indicated, and critical follow-up over 1.5–2 years, with assessment by a multidisciplinary committee. The final diagnosis was established on the basis of all available clinical data and follow-up, and was considered the best available clinical reference standard. A fully certain diagnosis would ideally require documentation of a spontaneous T-LOC episode with simultaneous continuous blood pressure and ECG monitoring, but this is rarely feasible in daily

practice. Therefore, critical follow-up with multidisciplinary adjudication provides a pragmatic approach to establishing the diagnosis as reliably as possible. This reference standard also forms the basis for the comparison with artificial intelligence in the subsequent chapters. Of the 264 referred patients, 51% had no diagnosis at referral. In the remaining patients, a working diagnosis was present, yet 80% of this group nevertheless regarded their condition as unexplained. Ultimately, most patients had reflex syncope, initial orthostatic hypotension or psychogenic pseudo syncope. These are not exceptional diagnoses, but common causes of T-LOC that are often insufficiently recognized in daily care.[10–12]

Importantly, specialized syncope care can still provide diagnostic clarity in a large proportion of patients. Previous FAST research showed that a guideline-based syncope unit approach can achieve a diagnostic yield of up to 97% after history taking, initial evaluation and additional autonomic function testing.[6,13,14] This study shows that this yield is not only technically diagnostic, but also clinically meaningful: it shortens diagnostic uncertainty and enables targeted treatment or reassurance.

A notable finding was that cardiac syncope as a referral diagnosis was not confirmed in 17 of the 18 cases after adjudicated assessment. The message is therefore twofold. On the one hand, cardiac syncope must never be missed because of its potential risk; on the other hand, a cardiac explanation should not be labelled causal too readily when the relationship with the loss of consciousness is insufficiently substantiated. A structured syncope unit can better maintain this balance by combining history taking, risk stratification, targeted additional testing and critical follow-up.[3, 10, 15]

Chapter 4 examines whether a large language model, GPT-4o, can provide diagnostic support based on general practitioner referral letters in patients referred to a syncope unit. The background is that artificial intelligence and natural language processing are increasingly being studied as tools for triage, risk stratification and diagnostic decision-making, including within syncope care.[16–20] This analysis was performed in an existing database of patients referred for syncope care within three hospitals in the Haaglanden region. For each case, an adjudicated final diagnosis was available, established after structured review of the clinical data and 1.5 years of critical follow-up by a multidisciplinary panel. This adjudicated diagnosis served as the reference standard. In total, 55 anonymized referral letters were assessed by GPT-4o and by eighteen medical professionals, including physicians and other healthcare professionals. The diagnostic yield of AI was subsequently compared with that of the medical professionals. This assessment evaluated whether a diagnosis was provided, whether the correct diagnosis was included in the differential diagnosis, and to what extent the proposed diagnosis corresponded with the adjudicated final diagnosis.[16]

GPT-4o provided a diagnostic suggestion in all cases, often with a broad list of differential diagnoses. This increased the likelihood that the adjudicated diagnosis appeared somewhere in the list and therefore resulted in a very high diagnostic yield. However, diagnostic precision was limited. The model relatively often included the adjudicated diagnosis within the differential diagnosis, but also produced many less appropriate alternatives. As a result, the Diagnostic

Precision Score was low and even negative. In practical terms, this means that GPT-4o functioned well as a broad hypothesis generator, but insufficiently as a clinically calibrated assessor that weighs diagnoses according to probability and risk.[16,17]

The safety message is essential: GPT-4o missed three of the four cardiac diagnoses and incorrectly labelled these as reflex syncope. Medical professionals were more selective and had higher precision, but there was variation among them as well. The study therefore does not support autonomous AI-based diagnosis based on referral letters, but does support a possible role as structured support under human supervision. Because a large language model interprets text, the quality and completeness of the input are crucial. When the model receives more and better structured clinical information, such as a complete history, active standing measurement, ECG and additional findings, the output is expected to become more reliable.[16, 20–23]

Chapter 5 builds directly on the findings from **Chapter 4**. Whereas GPT-4o assessed only general practitioner referral letters in that chapter, **Chapter 5** used GPT-5 and structured clinical information from the syncope unit. The choice of GPT-5 was logical because newer large language models are being developed with better instruction following, broader context processing and potentially better clinical pattern recognition. At the same time, it had to be examined whether this theoretical improvement translated into safe diagnostics within a protocolized syncope pathway.[16, 22, 23]

GPT-5 and a syncope expert assessed the same case information after "core evaluation" and "extended evaluation". Core evaluation consisted of history taking, physical examination, active standing measurement and an ECG. Extended evaluation consisted of core evaluation supplemented by transthoracic echocardiography and exercise ergometry when feasible, while additional investigations such as Holter monitoring or tilt table testing were performed when clinically indicated. The adjudicated reference standard was established after systematic follow-up, as described in **Chapter 4**, and in line with guideline-based assessment.[3, 4, 16]

In 54 patients with complete follow-up, the diagnostic yield of GPT-5 was high: 100% after core evaluation and 96% after extended evaluation, compared with 94% for the syncope expert in both phases. However, actual diagnostic quality lagged behind. GPT-5 included the adjudicated diagnosis in 52% after core evaluation and 57% after extended evaluation, whereas the syncope expert achieved 67%. The Diagnostic Precision Score remained negative, and among the four patients with adjudicated cardiac syncope, GPT-5 selected the correct cardiac diagnosis only once, compared with three of four by the syncope expert.

An important contribution of this study is the fivefold reanalysis of identical case information. This analysis shows that GPT-5 is not fully consistent: the same input could lead to different diagnostic labels across repeated runs. This is clinically important, because it shows that a single LLM output should not be regarded as a stable diagnosis. The findings therefore support a supportive role within a clinician-led, protocolized care pathway, but not independent diagnostic use. The study also shows that additional tests have value mainly when they

are deployed in a targeted manner based on clinical probability, and not as an untargeted diagnostic expansion. After all, the diagnosis made by the syncope expert did not change after extended evaluation, which emphasizes that history taking, physical examination, active standing measurement and ECG remain the core of diagnostic assessment.[6, 13, 22, 23]

Chapter 6 is a practical review of tilt table testing. This test has existed for decades and remains valuable for assessing short-term regulation of blood pressure and heart rate during orthostatic provocation. Tilt table testing can provoke vasovagal syncope, but can also assist in orthostatic hypotension, postural orthostatic tachycardia syndrome (POTS; an excessive rise in heart rate on standing without a clear fall in blood pressure) and syncope mimics (formerly psychogenic pseudosyncope).[24,25]

The key message is that tilt table testing supports history taking, but never replaces it. The minimum requirements are a safe tilt table with the capacity for rapid return to the supine position, continuous beat-to-beat blood pressure monitoring, continuous ECG monitoring and trained staff. Interpretation requires clinical context: a positive test is particularly meaningful when the provoked symptoms are recognizable to the patient or witness and correspond with the measured haemodynamics.[3,4,25,26]

In vasovagal syncope (the common faint), the test helps to characterize the mechanism according to vasodepressor components (dominant blood pressure fall due to insufficient vasoconstriction or peripheral vasodilatation) and cardioinhibitory components (dominant bradycardia or asystole due to vagal activation). The VASIS classification provides a practical framework for this, but the result is influenced by the test protocol, the duration of provocation and the use of nitroglycerine.[27,28]

An important point is reproduction of the spontaneous attack. Classically, reproduction of syncope is considered necessary to support the diagnosis. This can, however, be debated: in some patients, reproduction of recognizable prodromes, in combination with appropriate blood pressure and heart rhythm changes, may be clinically sufficient and complete loss of consciousness can potentially be avoided. This is relevant to patient safety and test comfort. Tilt table testing also has therapeutic value, for example through biofeedback: patients learn to recognize prodromes and to apply counterpressure manoeuvres in time.[25, 26]

Chapter 7 focuses on carotid sinus massage, a long-established autonomic function test whose performance varies markedly in practice. In patients older than 40 years with unexplained syncope and a suspected reflex mechanism, carotid sinus massage can be valuable, but only when the test is performed in a standardized and safe manner with adequate haemodynamic monitoring.[3,4]

The proposed Six-Step Method standardizes the procedure into a reproducible protocol: checking for contraindications, correct positioning of the head, palpation of the carotid sinus, massage for 10 seconds, continuous recording of blood pressure and heart rate, and a sufficient interval between consecutive massages. The test should be performed on both the left and right side, both supine and, if

non-diagnostic, in a standing or tilted position.[4,25,29]
The diagnostic value lies not only in demonstrating carotid sinus hypersensitivity, but especially in combining a haemodynamic response with recognizable symptoms. This is consistent with the method of symptoms: a test result acquires clinical meaning only when the provoked response corresponds with the spontaneous presentation. This prevents overdiagnosis in asymptomatic hypersensitivity, which may occur particularly in older individuals.[30-32]

Safety is a second key point. Carotid sinus massage is safe when contraindications, such as TIA, stroke or myocardial infarction in the preceding three months, or relevant carotid stenosis, are carefully excluded and when continuous monitoring and trained staff are present. The available literature shows that complications are rare, but the test should not be performed as an informal bedside manoeuvre. The strength of the protocol is precisely that it translates an old test into modern, reproducible syncope-unit practice.[30,33]

Chapter 8 shifts the focus from diagnostics to treatment of the hypotensive phenotype in reflex syncope and orthostatic intolerance. Hypotensive susceptibility (the tendency to develop relevant blood pressure falls in daily life or during orthostatic stress, leading to insufficient cerebral perfusion) can become visible on 24-hour ambulatory blood pressure monitoring. This fits with the concept that, in a subset of patients, insufficient blood pressure stability rather than a primary rhythm disorder is central.[15, 34-36]

Treatment does not start with medication. Lifestyle measures must first have been implemented consistently: adequate fluid intake, salt intake where appropriate, avoidance of triggers, physical counterpressure manoeuvres, training in prodrome recognition and withdrawal or adjustment of blood pressure-lowering or vasodilator medication. Only when these measures have insufficient effect should blood pressure-raising medication such as fludrocortisone or midodrine be considered.[3,15,37-39]

Previous research showed that interventions aimed at increasing mean 24-hour systolic blood pressure can reduce the number of blood pressure drops in patients with reflex syncope and orthostatic intolerance.[34, 40] **Chapter 8** builds on this by specifically investigating the haemodynamic effects of fludrocortisone and midodrine. In this proof-of-efficacy study, 53 patients were treated with fludrocortisone, midodrine or a combination of both agents. All patients had recurrent syncope or symptoms consistent with hypotension and predefined systolic blood pressure drops on ambulatory blood pressure monitoring. A second measurement within six months showed that fludrocortisone increased mean 24-hour systolic blood pressure and clearly reduced the number of blood pressure drops. Midodrine also showed a reduction in blood pressure drops, although its effect on mean 24-hour systolic blood pressure was less pronounced.

The results are consistent with the idea that ambulatory blood pressure monitoring can guide not only diagnosis but also treatment. It can help with patient selection, objective assessment of hypotensive susceptibility and evaluation of treatment. Because the study was not randomized and the treatment groups were small, a direct comparison between fludrocortisone and midodrine should be interpreted cautiously. The clinical added value lies mainly in making a treatable

haemodynamic pattern visible.[34, 37-40]

In **Chapter 9**, this brings us to the question of what these developments in syncope care ultimately mean for the patient. The preceding chapters describe organization, diagnostics, autonomic function testing, artificial intelligence and treatment. All these components are essential, but their value becomes fully apparent only when they lead to clinical consequences: a better diagnosis, more targeted treatment, less uncertainty and lower disease burden. Health-related quality of life is therefore a logical endpoint to examine whether syncope-unit care provides more than a diagnostic label alone.[41-47]

We investigated the longitudinal development of quality of life after structured syncope-unit care. The study combines two independent cohorts: 367 patients from three general hospitals within the Haaglanden Syncope Unit database and 264 patients from a tertiary academic syncope unit. These cohorts differed in clinical setting, patient case mix, referral patterns and period of data collection, but both underwent a comparable guideline-based initial evaluation. Generic quality of life was measured with the RAND 36-Item Health Survey (RAND-36) in secondary care and the 12-item Short Form Health Survey (SF-12) in tertiary care; syncope-specific disease burden was measured in both cohorts with the Syncope Functional Status Questionnaire (SFSQ).[3, 48, 49]

The main finding is that syncope-specific disease burden decreased in both secondary and tertiary care, despite differences in patient case mix and referral patterns between the two settings.

The setting-specific SFSQ trajectories showed reductions in functional impairment, fear and worry, and the overall Syncope Dysfunction Score in both cohorts. However, the absolute disease burden and the precise course of change differed between the cohorts. Because cohort differences and time-by-cohort interactions had been demonstrated statistically before pooling, the pooled SFSQ results, based on 1,703 questionnaires, were adjusted for cohort. In this combined analysis, impairment, fear/worry and the Syncope Dysfunction Score also decreased significantly.

In tertiary care, both physical and mental SF-12 summary scores improved.

In secondary care, RAND-36 trajectories were domain-specific, with improvements in physical role functioning, energy/fatigue and emotional well-being, whereas general health declined during follow-up. The generic RAND-36 and SF-12 outcomes therefore supported the overall improvement in syncope-specific quality of life, while also showing that recovery did not occur uniformly across all health domains.

The interpretation is clinically nuanced. An important proportion of the improvement occurred within three to six months, whereas fear, worry and certain physical outcomes continued to improve thereafter. Diagnostic clarity, explanation, reassurance and targeted treatment may have contributed to these developments. Yet recovery was not uniform, and some outcomes improved later or remained limited.

The central message is therefore not only that quality of life changed during follow-up, but particularly that a consistent reduction in syncope-specific disease burden was observed in two clinically distinct care settings. This finding supports

the clinical value of structured syncope-unit care irrespective of the clinical setting, although the magnitude and time course of recovery differed between settings and individual patients.

Patient-reported outcome measures such as the SFSQ, RAND-36 and SF-12 make these patient-centred outcomes visible. Syncope-specific and generic questionnaires have complementary roles and together form a bridge between diagnostic quality and clinical relevance.[41-49]

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