ESC HEART FAILURE
ESC Heart Failure (2023)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14471

ORIGINAL ARTICLE

The cost-effectiveness of NT-proBNP for assessment of suspected acute heart failure in the emergency department

Ryan Walkley[1], A. Joy Allen[1]*, Martin R. Cowie[2], Ross Maconachie[3] and Lisa Anderson[4]

[1]*Roche Diagnostics UK and Ireland, Burgess Hill, UK;* [2]*Royal Brompton Hospital, Guy's and St Thomas' NHS Foundation Trust and Faculty of Lifesciences and Medicine, King's College London, London, UK;* [3]*Value, Access and Devolved Nations, Merck Sharp and Dohme (UK) Ltd, London, UK; and* [4]*Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St George's, University of London, St George's Hospital, London, UK*

Abstract

Aims When relying on clinical assessment alone, an estimated 22% of acute heart failure (AHF) patients are missed, so clinical guidelines recommend the use of N-terminal pro-B-type natriuretic peptide (NT-proBNP) for AHF diagnosis. Since publication of these guidelines, there has been poor uptake of NT-proBNP testing in part due to concerns over excessive false positive referrals resulting from the low specificity of a single 'rule-out' threshold of <300 pg/mL. Low specificity can be mitigated by the addition of age-specific 'rule-in' NT-proBNP thresholds.

Methods and results A theoretical hybrid decision tree/semi-Markov model was developed, combining global trial and audit data to evaluate the cost-effectiveness of NT-proBNP testing using age-specific rule-in/rule-out (RI/RO) thresholds, compared with NT-proBNP RO only and with clinical decision alone (CDA). Cost-effectiveness was measured as the incremental cost per quality-adjusted life year (QALY) gained and incremental net health benefit. In the base case, using UK-specific inputs, NT-proBNP RI/RO was associated with both greater QALYs and lower costs than CDA. At a willingness-to-pay threshold of £20 000/QALY, NT-proBNP RO was also cost-effective compared with CDA [incremental cost-effectiveness ratio (ICER) of £8322/QALY], but not cost-effective vs. RI/RO (ICER of £64 518/QALY). Overall, NT-proBNP RI/RO was the most cost-effective strategy. Sensitivity and scenario analyses were undertaken; the conclusions were not impacted by plausible variations in parameters, and similar conclusions were obtained for the Netherlands and Spain.

Conclusions An NT-proBNP strategy that combines an RO threshold with age-specific RI thresholds provides a cost-effective alternative to the currently recommended NT-proBNP RO only strategy, achieving greater diagnostic specificity with minimal reduction in sensitivity and thus reducing unnecessary echocardiograms and hospital admissions.

Keywords NT-proBNP; Emergency department; Acute heart failure; Cost-effectiveness; Diagnosis

Received: 7 November 2022; Revised: 20 June 2023; Accepted: 2 July 2023
**Correspondence to: A. Joy Allen, Roche Diagnostics UK and Ireland, Burgess Hill, UK. Email: Joy.Allen@roche.com*

Introduction

In Europe, heart failure (HF) is prevalent in 1–2% of the population, and rates are increasing as populations age.[1] Acute heart failure (AHF) can develop as a new condition or as a worsening of existing chronic heart failure (CHF)[2] and accounts for over 100 000 admissions in the United Kingdom (UK) annually.[3,4] Diagnosis of HF relies on clinical judgement in combination with appropriate investigations, including electrocardiography, chest X-ray, blood tests, and echocardiography.[5] Echocardiography is considered to be the 'gold standard' tool for supporting the diagnosis of HF.[5,6] However, the most recent data from the UK suggest that 40% of hospitals failed to meet the standard of ≥90% of patients presenting with AHF undergoing echocardiography.[6]

Measuring natriuretic peptides in patients with suspected AHF in the emergency department (ED) is recommended by the National Institute for Health and Care Excellence (NICE) and the European Society of Cardiology (ESC),[2,7] with AHF

diagnosis ruled out at N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels < 300 pg/mL. However, a 2018 review of patients who died in UK hospitals following an admission with AHF found that while natriuretic peptides are available in >80%, it was only measured in 17.9% of newly diagnosed patients, and only 8.5% had natriuretic peptides measured while in the ED.[8] Diagnostic uncertainty led to delays in triage, with patients receiving an array of non-HF investigations and treatments, some of which may be contributed to adverse outcomes.[8]

A barrier to the clinical adoption of NT-proBNP in the ED is the low specificity of the 300 pg/mL rule-in threshold.[8] Clinical demand for HF teams is already high and there are concerns that implementation of NT-proBNP testing could lead to increased false positive referrals and unnecessary echocardiograms. While a result of <300 pg/mL may be diagnostically useful for ruling out AHF, a result of ≥300 pg/mL is not necessarily a good predictor for the presence of AHF, as NT-proBNP rises naturally with age and may be influenced by a range of other cardiac and non-cardiac conditions.[7] ESC guidelines therefore provide additional age-specific rule-in thresholds for the diagnosis of AHF: >450 pg/mL if aged <55 years, >900 pg/mL if aged 55–75 years, and >1800 pg/mL if aged >75 years.[7] Inclusion of these validated age-specific rule-in thresholds to the NT-proBNP testing strategy has the potential to provide greater specificity,[9–11] thus reducing unnecessary admissions and echocardiography referrals and potentially providing cost savings and pathway efficiencies for national healthcare systems.

The objective of this study was therefore to assess the cost-effectiveness, from a European perspective, of an NT-proBNP rule-in/rule-out (RI/RO) strategy vs. an NT-proBNP RO strategy and vs. clinical decision alone (CDA), by updating and modifying the economic model developed for the NICE acute HF guidelines (CG187) in 2014.[2] The updated model has been appraised by Health Technology Wales (HTW), which concluded that NT-proBNP RI/RO is the most cost-effective strategy, and published guidance supporting the routine adoption of NT-proBNP RI/RO in Welsh EDs.[5,12] BNP is also currently recommended by both the NICE and the ESC; this study does not aim to compare the biomarkers directly, but its main aim is to demonstrate the health economic benefit of moving from an RO to RI/RO strategy for NT-proBNP.

Methods

Model scope

A hybrid decision tree/semi-Markov model was developed to evaluate the cost-effectiveness of an NT-proBNP RI/RO strategy for the diagnosis of AHF compared with an NT-proBNP RO strategy or CDA. The model was applied to a hypothetical population of 1000 patients presenting to EDs with suspected AHF. Clinical and cost data sources were aligned with the NICE CG187 model and updated using newer trials or datasets where available, including the ICON-RELOADED and BASEL V studies.[9,10] Costs were inflated where necessary using published inflation indices,[13] in line with the NICE guidelines development manual.[14]

The model used a lifetime horizon; costs and quality-adjusted life years (QALYs) were estimated using a healthcare payer perspective and were discounted at an annual rate of 3.5%. Cost-effectiveness results were estimated as incremental cost per QALY gained, as well as net health benefit (NHB), which assigns an opportunity cost to new interventions to account for the fact that funding must be reassigned from other healthcare activities. A higher NHB therefore indicates greater cost-effectiveness. Key base case model parameters are presented in *Table 1*, and additional inputs and methodology are covered in the supporting information.

Model structure

The model comprised a decision tree, covering initial diagnosis and short-term events occurring within the hospital stay, and a longer term semi-Markov component, covering follow-up care and hospital readmission. Within the decision tree, patients were assigned a diagnosis and then entered the downstream pathway where a proportion of patients were admitted and received an echocardiogram (*Figure 1*); patients exiting the decision tree were categorized as true positive (TP), true negative (TN), false positive (FP), or false negative (FN).

Surviving patients entered the semi-Markov model, in which they could occupy one of three health states during each 3 month cycle: 'alive no admission', 'alive with admission', or 'dead'. Each patient then accrued QALYs and healthcare costs according to their hospitalization and follow-up care status. In line with the NICE acute HF guideline (CG187), out-of-hospital follow-up resource use was categorized into four components: drug therapy, hospital outpatient visits, primary care general practitioner visits, and community HF specialist nurse visits. The proportion of admitted patients in any given cycle was dictated by cycle-specific probabilities, and the proportion of surviving patients was determined based on a parametric survival curve.

Diagnostic test accuracy

For CDA, diagnostic accuracy was based on the IMPROVE CHF study of 500 patients with dyspnoea assessed in seven emergency rooms (ERs) in Canada.[15] The prevalence of AHF in the modelled population was based on a meta-analysis of

Table 1 Summary of key base case model parameters

Variable group	Variable		Value	Distribution used in the PSA	Source
Model time horizon			Lifetime	NA	NA
Prevalence of AHF			0.434	Beta: $\alpha = 48$; $\beta = 63$	Meta-analysis (see supporting information)
Diagnostic accuracy	Distribution of NT-proBNP among patients with AHF	> Rule-in threshold	0.844	Dirichlet: $N = 1043$; $k = 880$	BASEL V[10]
		Grey area	0.136	Dirichlet: $N = 1043$; $k = 142$	
		< Rule-out threshold	0.020	Dirichlet: $N = 1043$; $k = 21$	
	Distribution of NT-proBNP among patients without AHF	> Rule-in threshold	0.156	Dirichlet: $N = 1010$; $k = 158$	
		Grey area	0.273	Dirichlet: $N = 1010$; $k = 276$	
		< Rule-out threshold	0.570	Dirichlet: $N = 1010$; $k = 576$	
	Probability that a patient with AHF is above the age-specific rule-in threshold		0.861	Beta: $\alpha = 880$; $\beta = 142$	
	Probability that a patient without AHF is above the age-specific rule-in threshold		0.364	Beta: $\alpha = 158$; $\beta = 276$	
	Clinical decision alone	Sensitivity	0.780	Beta: $\alpha = 91$; $\beta = 26$	IMPROVE-CHF[15]
		Specificity	0.810	Beta: $\alpha = 112$; $\beta = 26$	
	NT-proBNP RO (300 pg/mL)	Sensitivity	0.980	Log normal	Meta-analysis (see supporting information)
		Specificity	0.454		
	Grey zone clinical decision	Sensitivity	0.80	Beta: $\alpha = 196$; $\beta = 49$	Original analysis using data from ICON-RELOADED (see supporting information)
		Specificity	0.60	Beta: $\alpha = 221$; $\beta = 147$	
Costs	Cost of an AHF admission (for TP patients)		£3148.93	Gamma: $\alpha = 16$; $\beta = 234$	NHS Cost Collection[16]
	Cost of a non-AHF admission (for TN patients)		£3625.36	Gamma: $\alpha = 16$; $\beta = 227$	NHS Cost Collection[16]
	Cost of an excess bed day for admitted FP patients		£358.15	Gamma: $\alpha = 96$; $\beta = 3$	NHS Reference Costs: Average excess bed day cost for all conditions[17]
	Cost of an excess bed day for admitted FN patients		£325.21	Gamma: $\alpha = 96$; $\beta = 4$	NHS Reference Costs: Average excess bed day cost for AHF[17]
	Cost of NT-proBNP test		£24.53	Gamma: $\alpha = 6.829$; $\beta = 3.592$	List price
	Cost of echocardiogram		£88.00	NA	NHS Cost Collection: Simple echocardiogram aged 19 and over[16]
Resource use	Proportion or patients receiving echocardiogram		0.860	Beta: $\alpha = 59\,818$; $\beta = 9738$	NICOR 2021[6]
	Length of stay for an AHF admission (for TP patients)		6.52	NA	NHS Reference Costs: Total bed days for AHF admissions/total number of AHF admissions[17]
	Length of stay for a non-AHF admission (for TN patients)		5.59	NA	NHS Reference Costs: Total bed days for non-AHF admissions/ total number of non-AHF admissions[17]
	Bed day increment for FP patients		2	Normal: $\mu = 2$, $\sigma = 0.51$	NICE CG187[2]
	Bed day increment for FN patients		2	Normal: $\mu = 2$, $\sigma = 0.51$	NICE CG187[2]

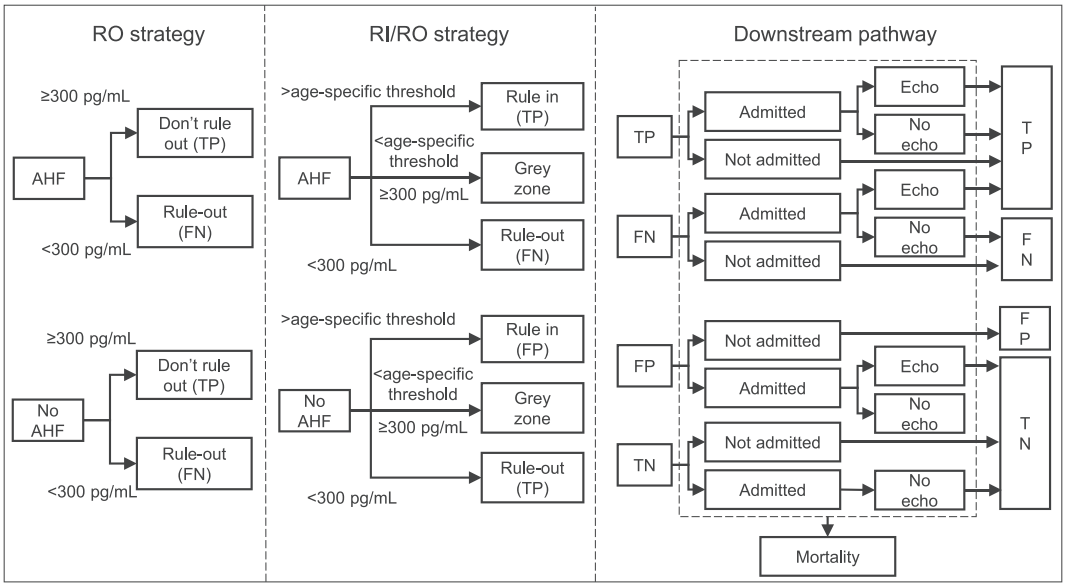
(*Continues*)

Table 1 (continued)

Variable group	Variable		Value	Distribution used in the PSA	Source
Admission probability	Clinical decision alone	TP	0.930	Beta: $\alpha = 150$; $\beta = 11$	ICON-RELOADED economic evaluation[18]
	Clinical decision alone	FN	0.820	Beta: $\alpha = 14$; $\beta = 3$	
	RI/RO strategy:	TN	0.550	Beta: $\alpha = 340$; $\beta = 278$	
	Non-grey zone NT-proBNP	FP	1.000	Uniform: min = 0.8; max = 1	
	result	TP	0.930	Beta: $\alpha = 150$; $\beta = 11$	
	RI/RO strategy:	FN	0.820	Beta: $\alpha = 141$; $\beta = 35$	
	Non-grey zone NT-proBNP	TN	0.410	Beta: $\alpha = 248$; $\beta = 356$	
	result	FP	0.800	Beta: $\alpha = 141$; $\beta = 35$	
	RI/RO strategy:	TP	0.930	Beta: $\alpha = 150$; $\beta = 11$	
	Grey zone clinical decision				
	RI/RO strategy:	FN	0.794	Beta: $\alpha = 51$; $\beta = 13$	Aligned with clinical decision alone
	Grey zone clinical decision				
	RO strategy:	TN	0.679	Beta: $\alpha = 164$; $\beta = 77$	Decision tree used to calculate probabilities to ensure that the overall admission probabilities were consistent with the observed clinical data from the ICON-RELOADED study[9]
	NT-proBNP result	FP	1.000	Uniform: min = 0.8; max = 1	
		TP	0.930	Parameters update automatically when the values for the RI/RO strategy are varied in the PSA	Aligned with clinical decision alone
	RO strategy:	FN	0.797	Parameters update automatically	Decision tree used to calculate
	NT-proBNP result	TN	0.459	when the values for the RI/RO	admission probabilities to
		FP	0.882	strategy are varied in the PSA	ensure that they were consistent with the composite admission probabilities for TP/FN/T (across grey zone and non-N/FPs in the RI/RO strategy grey zone results)
Mortality	Inpatient mortality	Specialist input	0.079	Beta: $\alpha = 4506$; $\beta = 52\,530$	UK, NICOR 2021[6]
		Non-specialist input	0.133	Beta: $\alpha = 246$; $\beta = 1603$	
	Proportion of patients	TP	0.820	Beta: $\alpha = 57\,036$; $\beta = 12\,520$	
	seeing a specialist	FN	0	NA	
Utility values	Utility for CHF ('alive no admission' health state)		0.752	Beta: $\alpha = 966c$; $\beta = 318$	NICE CG187[2]
	Disutility associated with readmission ('alive readmission' health state)		−0.06	Gamma: $\alpha = 16$; $\beta = 0.004$	NICE CG187[2]

AHF, acute heart failure; CHF, chronic heart failure; FN, false negative; FP, false positive; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PSA, probabilistic sensitivity analysis; RI, rule-in; RO, rule-out; TN, true negative; TP, true positive.

Figure 1 Decision tree structure for AHF diagnosis for the RO and RI/RO NT-proBNP strategies and downstream patient pathway. The decision tree for CDA is equivalent to the RO strategy, with the exception that TP/FN/TN/FP categorization is based on clinician's assessment in the absence of NT-proBNP testing. AHF, acute heart failure; CDA, clinical decision alone; FN, false negative; FP, false positive; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RI, rule-in; RO, rule-out; TN, true negative; TP, true positive.



diagnostic test accuracy studies identified in a systematic review (conducted for the 2014 NICE CG187 model) along with additional recent studies. Diagnostic accuracy for the RO strategy was also based on a meta-analysis of these studies. For the RI/RO strategy, the central estimates of sensitivity and specificity from the RO meta-analysis were first used to quantify the proportion of patients with and without AHF falling below the 300 pg/mL threshold. In the base case, the BASEL V study of more than 2000 patients presenting with acute dyspnoea to two Swiss hospitals was used to inform the proportion of patients that were above the age-specific thresholds.[10]

The RI/RO strategy also has a 'grey zone', in which test results may be higher than the RO threshold but lower than the age-specific RI threshold. For these patients, it was assumed that positive/negative status would be determined based on clinical decision. However, it is expected that the accuracy of clinical decision for grey zone patients would be lower than in the CDA strategy, as the grey zone would not include those patients with extreme NT-proBNP results who may have a clearer clinical presentation. To account for this, a logistic regression model was produced using individual patient data for grey zone patients from the ICON-RELOADED study of almost 1500 patients with acute dyspnoea assessed in 19 ERs in North America.[9,19] A point at the shoulder of the modelled curve was then used to estimate a sensitivity/specificity pair of around 80/60% for grey zone clinical decision.[18] Alternative values were explored in scenario analyses.

Downstream patient pathway

Modelled admission probabilities varied depending on both the strategy and the patient's TP/FP/TN/FN categorization. For non-grey zone TP/FP/TN/FNs in the CDA and RI/RO strategies, admission probabilities were aligned with the ICON-RELOADED economic evaluation.[18] For the RI/RO strategy grey zone, admission probabilities for TP/FPs were set equal to the CDA strategy, and the decision tree was then used to calculate admission probabilities for TN/FNs that would result in an overall admission probability equal to the observed clinical data from the ICON-RELOADED study.[9] For the RO strategy, admission probabilities for TP/FN/TN/FPs were aligned with the composite admission probabilities (across both non-grey zone and grey zone results) for TP/FN/TN/FPs in the RI/RO strategy. This assumption ensures that any differences in admission rates between NT-proBNP strategies are due to differences in the proportion of TP/FN/TN/FPs, rather than differences in the likelihood of TP/FN/TN/FPs being admitted within each strategy.

Following admission, it was assumed that 86% of TP/FPs[6] and 80% of FNs would receive an echocardiogram during their hospital stay, in line with CG187. The latter assumption was varied to zero and 100% in sensitivity analysis. Echocardiography was assumed to be 100% accurate, such that all assessed FPs were converted to TNs and all assessed FNs to TPs.

Mortality

Inpatient mortality was applied to admitted patients in the decision tree, using mortality data from a UK-wide annual HF admission audit dataset (NICOR).[6] Mortality was weighted by the proportion of patients who saw a specialist; it was assumed that no FNs would see a specialist. As a further simplifying assumption, mortality for non-admitted patients was applied in line with admitted patients. Both assumptions were varied in sensitivity analysis.

In the longer term semi-Markov model, survival for TPs was based on a parametric curve fitted to a Kaplan–Meier analysis of AHF patients diagnosed in the UK.[20] The survival curve for FNs was calculated by applying weighted hazard ratios to the survival curve for TPs, as these patients have AHF but would not benefit from disease modifying interventions.

Costs and resource use

In the decision tree, resource use included costs of NT-proBNP testing, admission, and echocardiography. All patients in the NT-proBNP strategies received a single NT-proBNP test. The cost of initial admissions and length of stay for TP/TNs were estimated from NHS reference costs.[16,17] Initial admission costs for FNs and FPs were assumed to be equal to TPs and TNs, respectively, with the additional cost of two excess bed days due to delayed diagnosis (in line with CG187, and sourced from NHS reference costs).[16]

The longer term model included costs associated with out-of-hospital follow-up and readmissions. Drug therapies included angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, aldosterone antagonists, and sacubitril/valsartan. Drug costs were estimated in line with the methodology from CG187, using updated cost, dosing, and prescribing sources.[2,21–23] For cardiology and HF specialist nurse follow-up, probabilities were sourced from national audit data,[6] resource use estimates were sourced from CG187, and unit costs were sourced from appropriate reference costs.[13,16]

Hospital readmission rates were based on cycle-dependent probabilities. For TPs, readmission probability was aligned with CG187, based on 4 year follow-up data from a UK study of AHF patients.[24] Beyond 4 years, the admission rate was assumed to remain constant. For FNs, readmissions were adjusted by applying intervention-related weighted hazard ratios to the survival curve for TPs, down-weighted by the proportion of TPs receiving the interventions.[6] Costs of readmission were assumed equal to initial admission costs for TPs.

Health-related quality of life

In line with CG187, patients in the 'alive no admission' health state were assigned a utility value for CHF, patients in the 'alive readmission' experienced a disutility relative 'alive no admission' health state, and patients in the 'dead' health state were assigned a utility of zero.

Accounting for false negatives/false positives

In the long-term model, all FNs received an elevated mortality risk for one cycle, after which they converted to TPs (in line with CG187). Time to conversion was explored in sensitivity analysis. Due to a lack of data on the negative effects of false positivity, FPs were conservatively assumed to incur the cost of one cycle of follow-up and lose zero QALYs. FN/FPs were also assigned a 2 day length of stay penalty during admission, in line with CG187.

Sensitivity and scenario analysis

Probabilistic sensitivity analysis (PSA) was performed using 5000 runs employing probability distributions for input parameters. One-way sensitivity analyses (OWSAs) were performed by varying key parameters to plausible extremes to evaluate their effect on the incremental NHB. Scenario analyses using alternate assumptions or sources for input parameters included examining poorer sensitivity/specificity of clinical decision in the grey zone; adjusting the length of stay penalty associated with FN or FP hospital admissions; exclusion of the admission node such that 100% of patients were admitted from the ED (in line with CG187); modelling two alternative European countries (the Netherlands and Spain); and exploring a societal perspective in the Netherlands. Additional details are provided in the supporting information.

Results

Base case analysis

The RI/RO strategy had a substantially higher estimated specificity than the RO strategy, with only a small reduction in estimated sensitivity due to imperfect decision-making in the grey zone (*Table 2*). Use of echocardiography was 15.9% lower with the RI/RO strategy compared with the RO strategy. The RI/RO strategy also had the lowest number of initial admissions, approximately 6% fewer admissions than the RO strategy and 1.5% fewer than the CDA strategy.

At the standard willingness-to-pay (WTP) threshold for the UK healthcare setting of £20 000/QALY gained, both

NT-proBNP strategies were cost-effective compared with CDA, with RI/RO being both less costly and more effective than CDA (*Table 3*). NT-proBNP RO was marginally the most effective strategy as, in the base case, no QALY penalties were modelled for FPs and thus the most sensitive strategy produced the most QALYs. However, NT-proBNP RI/RO was the most cost-effective strategy, as the incremental cost-effectiveness ratio (ICER) for RO vs. RI/RO was £64 518/QALY, substantially above the WTP threshold.

Table 2 Intermediate outcomes predicted by the model

Intermediate outcomes	Clinical decision alone	NT-proBNP RO strategy	NT-proBNP RI/RO strategy
Sensitivity	78.0%	98.0%	95.3%
Specificity	81.0%	45.4%	66.2%
PPV	75.9%	57.9%	68.4%
NPV	82.8%	96.7%	94.8%
HF deaths during the decision tree	42.7	38.9	39.4
Initial admissions	753	793	742
Total bed days during initial admissions	4945	5367	4888
Total echocardiograms during initial admissions	417	579	487
Readmissions	337	343	342
Life years for AHF patients in the long-term model	1955	1991	1968

AHF, acute heart failure; HF, heart failure; NPV, negative predictive value; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PPV, positive predictive value; RI, rule-in; RO, rule-out.

Total costs were lower with RI/RO than with RO or CDA, largely driven by a reduction in bed days. When opportunity cost was set equal to the WTP threshold, the RI/RO strategy was associated with the highest NHB. This implies that QALYs gained by switching from the RI/RO to the RO strategy would be insufficient to outweigh QALYs lost by moving the necessary funding away from other healthcare activities.

Probabilistic sensitivity analysis

Cost-effectiveness acceptability curves (CEACs) generated from the PSA show that the RI/RO strategy has the highest likelihood of being the most cost-effective strategy at WTP thresholds up to approximately £64 000 (*Figure 2*). At a £20 000/QALY WTP threshold, the PSA estimated RI/RO was the most cost-effective strategy in all 5000 simulations, with 55% of simulations finding RI/RO to be not only cost-effective but also cost-saving vs. CDA.

One-way sensitivity analysis

The OWSA results indicate that there are no parameters that plausibly influence the conclusion that the NT-proBNP strategies are cost-effective compared with CDA (*Figure 3*). The per-test cost for NT-proBNP could be varied up to ~£430 (€500) without the NT-proBNP strategies becoming cost-ineffective, which is highly implausible given the **list** price

Table 3 Cost-effectiveness results

Country	UK	The Netherlands	Spain
Cost inputs			
Cost of an AHF admission (for TP patients)	£3149	€4920	€3396
Cost of a non-AHF admission (for TN patients)	£3625	€3269	€2157
Cost of an excess bed day for admitted FP patients	£358	€479	€386
Cost of an excess bed day for admitted FN patients	£325	€479	€386
Cost of echocardiogram	£88	€117	€137
Clinical decision alone			
Cost	£4 418 157	€5 823 430	€4 842 477
QALYs	1251	1378	1263
NHB	1030	1262	1102
NT-proBNP RI/RO			
Cost	£4 403 196	€5 964 560	€4 973 426
QALYs	1271	1401	1285
NHB	1051	1281	1119
NT-proBNP RO			
Cost	£4 615 078	€6 403 897	€5 295 815
QALYs	1274	1405	1288
NHB	1044	1277	1111
ICER			
RI/RO vs. clinical decision alone	RI/RO dominates	€6252	€6339
RO vs. clinical decision alone	£8322	€22 135	€18 890
RO vs. RI/RO	£64 518	€120 368	€96 523

AHF, acute heart failure; FN, false negative; FP, false positive; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QALYs, quality-adjusted life years; RI, rule-in; RO, rule-out; TN, true negative; TP, true positive; UK, United Kingdom.
NHB = incremental gain in QALYs − (incremental cost/opportunity cost threshold). Opportunity cost threshold: UK £20 000; the Netherlands €50 000; Spain €30 000.

Figure 2 Cost-effectiveness acceptability curves showing the probability that each strategy was cost-effective at different WTP thresholds. NT-proBNP, N-terminal pro-B-type natriuretic peptide; WTP, willingness-to-pay.

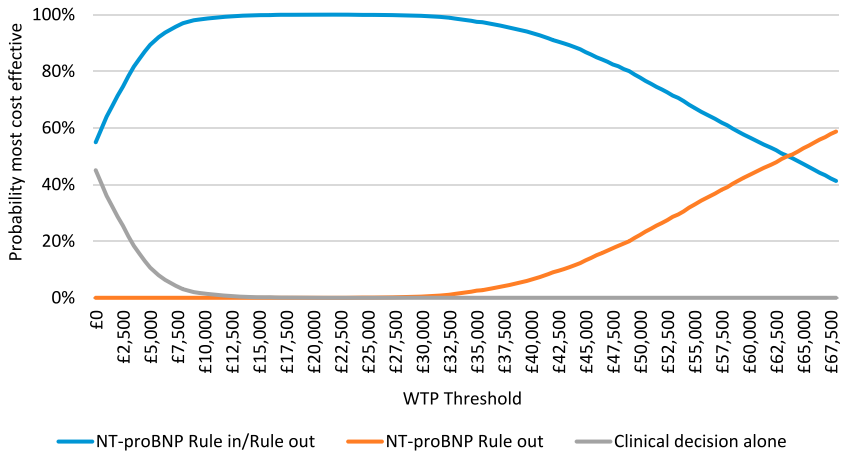
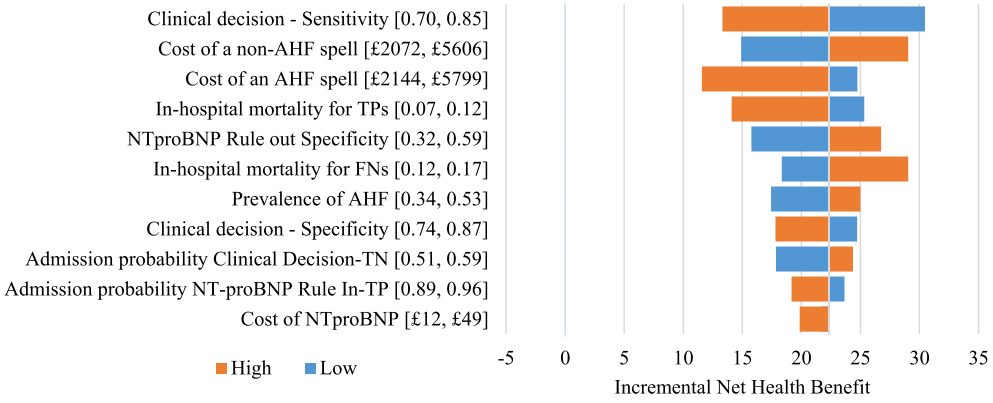


Figure 3 Tornado diagram of the 10 most impactful parameters and NT-proBNP cost varied in the OWSA for RI/RO vs. CDA. AHF, acute heart failure; CDA, clinical decision alone; FNs, false negatives; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OWSA, one-way sensitivity analysis; RI, rule-in; RO, rule-out; TPs, true positives.



(£24.53; €29). There were also no parameters that plausibly influenced the conclusion that the RI/RO strategy is cost-effective compared with RO alone.

Scenario analyses, including the Netherlands and Spain

Across scenario analyses, NHB was always the highest for RI/RO, and the only scenario in which the RO strategy had an NHB lower than CDA was when the prevalence of AHF was reduced to 19%, sourced from the ICON-RELOADED study. This shows that the conclusions of the analysis are highly insensitive to alternate input parameters or plausible variations in model assumptions. When considering resource use and cost estimates for both the Netherlands and Spain, RI/RO was still the most cost-effective strategy in both countries, although it no longer dominated CDA (*Table 3*). When exploring societal costs in the Netherlands (results presented in the supporting information), RI/RO remained the most cost-effective strategy, with both RI/RO and RO likely to dominate CDA due to the productivity loss of working age patients dying due to the lower sensitivity of CDA vs. NT-proBNP.

Discussion

The poor and inconsistent uptake of NT-proBNP testing is likely due to clinician's concerns regarding its lower specificity vs. CDA resulting in greater resource costs, due to increased false positive HF referrals, unnecessary echocardiography referrals, and increased hospital admissions. However,

maintaining the status quo of CDA means that a substantial proportion of patients with AHF are missed (22%), preventing them from rapidly accessing specialist care and full guideline-directed medical therapy (GDMT). Improved detection in the ED leads to better triage, more appropriate place of care, specialist review, and GDMT, thus resulting in improved survival and fewer admissions overall. The RI/RO strategy can mitigate the specificity concerns of NT-proBNP testing through the addition of age-specific RI thresholds and may be cost-saving, largely driven by a reduction in bed days.

Other published economic analyses have evaluated the cost-effectiveness or cost impacts associated with NT-proBNP,[2,15,18,19,25,26] but to our knowledge, this model represents the first analysis comparing an NT-proBNP strategy incorporating age-specific RI thresholds with an NT-proBNP strategy using only a fixed RO threshold. As with NICE's approach, the analysis did not attempt to directly compare NT-proBNP with BNP, both are recommended by the NICE and the ESC, with NICE demonstrating the cost-effectiveness of BNP vs. CDA.[2] The paper's aim is not to advocate for one biomarker over another but to demonstrate that moving from a single NT-proBNP cut-off to RI/RO is a cost-effective option. Similar results may be seen with this approach for BNP, but little evidence both exploring and validating age-specific BNP cut-offs exists.

There are some data limitations that may increase uncertainty in the model's conclusions. The post-2014 studies used to update the diagnostic test accuracy meta-analysis are believed to represent the totality of the evidence base; however, no systematic review of diagnostic test accuracy trials was undertaken. It is therefore possible that additional trials may have been published since 2014 that were not included in the updated meta-analysis informing NT-proBNP diagnosis test accuracy. The central estimates were very similar to those reported in NICE CG187 as the new studies had a similar proportion of positive and negative patients with NT-proBNP $<$ 300 pg/mL; it is therefore expected that the addition of any further studies would not have a substantial impact on the model inputs.

However, the studies of diagnostic test accuracy that were identified were heterogeneous in terms of patient characteristics, with no UK-specific data, and the average age of patients diagnosed with AHF in hospital in the UK is 81 years,[6] which is somewhat older than the population in the studies. Furthermore, although there is a degree of convergent validity in the estimates for the sensitivity and specificity of CDA, none are from high-quality UK sources, and there were no data available on the differential accuracy of clinical decision in the grey zone vs. CDA. Despite this uncertainty, extensive sensitivity and scenario analyses were undertaken and the model's conclusions were not found to be sensitive to any plausible variations in these parameters. The conclusions were also consistent following adaptation for the Netherlands and Spain, and it is therefore likely that this strategy will be cost-effective in any country that closely follows ESC guidelines and has a WTP threshold in the range of £20 000–£50 000/QALY.

An additional area of uncertainty is the assumption that a small number of FP patients will continue into the longer term model, either because they are not admitted or because they are admitted but do not receive an echocardiogram. There is also no mortality applied to FP patients during the decision tree. It is therefore possible that the number of FPs entering the longer term model is overestimated relative to clinical practice. However, as these FP patients were conservatively associated with only one cycle of follow-up costs and no loss of QALYs, this is not expected to alter the model's conclusions.

Furthermore, the methods used for the modelling match those used for decision-making in the UK,[2,14] and the model was submitted to HTW as part of their 'Natriuretic peptides to rule-in and rule-out a diagnosis of acute heart failure' appraisal process.[5] As such, the model has been appraised by the HTW health economics team and committee. Following their appraisal of NT-proBNP, HTW published a recommendation for the routine adoption of NT-proBNP RI/RO in the diagnosis of AHF in the ED setting, stating that NT-proBNP measurement may reduce length of hospital stay and the rate of re-hospitalizations.[12] These findings have wider implications for decision-makers as they demonstrate that the RI/RO strategy can both mitigate concerns about the specificity of NT-proBNP and provide a cost-effective strategy for the diagnosis of AHF in the ED. NT-proBNP testing may also be associated with other plausible benefits that were not explicitly modelled, such as faster diagnosis, improved risk stratification, and enhanced prioritization of patients.

Conclusions

NT-proBNP-aided clinical decision represents a marked improvement in the ability to diagnose AHF in the ED, preventing missed diagnoses of AHF compared with CDA. Concerns about the low specificity of NT-proBNP resulting in potentially unnecessary increases in resource use can be mitigated through the addition of age-specific RI cut-offs. A combined RI/RO strategy is cost-saving vs. CDA, and the small reduction in sensitivity vs. a single RO threshold is outweighed by a large gain in specificity, resulting in reductions in unnecessary admissions and echocardiography referrals. This model therefore demonstrates that age-specific NT-proBNP RI thresholds could be a cost-effective addition to the diagnostic pathway for AHF in EDs in the UK, the Netherlands, and Spain.

Acknowledgements

We thank Rachel Crosby (Mtech Access) who provided medical writing services in the preparation of the manuscript. We would also like to thank Professor James Januzzi for granting approval of the grey zone analysis using ICON-RELOADED patient data and contributing to the statistical methods and approach used on this dataset.

Conflict of interest

A.J.A. is both employed by Roche Diagnostics Ltd and owns shares in Roche. R.M. was an employee of Roche Diagnostics Ltd until June 2020. R.W. is both employed by Roche Diagnostics Ltd and owns shares in Roche. M.R.C. has provided consultancy advice to Roche Diagnostics, Abbott, AstraZeneca, Medtronic, Novartis, and Servier. As from 1 August 2022, he is a full-time employee of AstraZeneca.

Funding

This work was supported by Roche Diagnostics Ltd. Mtech Access is an independent market access consultancy and received payment from Roche Diagnostics Ltd to provide writing services.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1: Forest plot of acute heart failure prevalence among those presenting with symptoms.
Figure S2: Forest plot for diagnostic accuracy (sensitivity) of the NT-proBNP rule out threshold (300 pg/mL).
Figure S3: Forest plot for diagnostic accuracy (specificity) of the NT-proBNP rule out threshold (300 pg/mL).
Figure S4: Proportion of patients with AHF that are ruled in (TPs).
Figure S5: Proportion of patients without AHF that are ruled in (FPs).
Figure S6: ROC curves for all models in the analysis.
Table S1: AUC statistics for all models in the analysis.
Figure S7: Parametric curves fitted to the NICOR Kaplan–Meier curves, with AIC and BIC.
Table S2: Mortality hazard ratios by follow-up intervention.
Table S3: Proportion of TPs receiving follow-up interventions.
Table S4: Readmission relative risk ratios by follow-up drug therapy.
Table S5: Probability of readmission for heart failure by patient status.
Table S6: Resource use for follow-up services.
Table S7: Follow-on resource use cost.
Table S8: Weighted daily cost of follow up drug therapy.
Table S9: Alternative model parameters for European country scenario analyses.
Table S10: Intermediate results for the Netherlands and Spain.
Table S11: Cost-effectiveness results for Netherlands societal perspective scenario analysis.
Table S12: NHB for the three strategies in scenario analysis.
Table S13: Cost-effectiveness results for NICE structural sensitivity analysis.

References

1. European Heart Network (EHN). Heart failure and cardiovascular diseases—a European Heart Network paper. 2019. Available from: https://ehnheart.org/publications-and-papers/publications/1202:heart-failure-and-cardiovascular-diseases.html. Accessed on: 27 January 2022.
2. National Institute for Health and Care Excellence (NICE). Acute heart failure: diagnosis and management (CG187). 2014. Available from: https://www.nice.org.uk/guidance/cg187. Accessed on: 25 January 2022.
3. NHS Wales. Cardiovascular Atlas of Variation. 2019. Available from: https://collaborative.nhs.wales/networks/wales-cardiac-network/cardiac-network-documents/cardiovascularatlasofvariation-march2019-pdf/. Accessed on: 27 January 2022.
4. British Heart Foundation (BHF). Heart failure: a blueprint for change. 2020. Available from: https://www.bsh.org.uk/wp-content/uploads/2020/10/Heart-Failure-A-Blueprint-For-Change-Oct-2020-3.pdf. Accessed on: 27 January 2022.
5. Health Technology Wales (HTW). Evidence appraisal report: natriuretic peptides to rule-in and rule-out a diagnosis of acute heart failure in adults in the emergency department setting. 2021. Available from: https://healthtechnology.wales/wp-content/uploads/2021/11/EAR026-BNP-and-NTproBNP.pdf. Accessed on: 27 January 2022.
6. The National Institute for Cardiovascular Outcomes Research (NICOR). National Cardiac Audit Programme National Heart Failure Audit (NHFA) 2021 Summary Report (2019/20 data). 2021. Available from: https://www.nicor.org.uk/wp-content/uploads/2021/10/NHFA-Domain-Report_2021_FINAL.pdf. Accessed on: 25 January 2022.
7. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.*; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2021;**42**:3599–3726.
8. National Confidential Enquiry into Patient Outcome and Death (NCEPOD). Failure to function: a review of the care received by patients who died in hospital

following an admission with acute heart failure. 2018. Available from: https://www.ncepod.org.uk/AHF%20full%20report.pdf. Accessed on: 27 January 2022.
9. Januzzi JL, Chen-Tournoux AA, Christenson RH, Doros G, Hollander JE, Levy PD, *et al.* N-terminal pro–B-type natriuretic peptide in the emergency department: the ICON-RELOADED study. *J Am Coll Cardiol*. 2018;**71**:1191–1200.
10. Kozhuharov N, Sabti Z, Wussler D, Nowak A, Badertscher P, Twerenbold R, *et al*. Prospective validation of N-terminal pro B-type natriuretic peptide cut-off concentrations for the diagnosis of acute heart failure. *Eur J Heart Fail*. 2019;**21**:813–815.
11. Ibrahim I, Kuan WS, Frampton C, Troughton R, Liew OW, Chong JPC, *et al*. Superior performance of N-terminal pro brain natriuretic peptide for diagnosis of acute decompensated heart failure in an Asian compared with a Western setting. *Eur J Heart Fail*. 2017;**19**:209–217.
12. Health Technology Wales (HTW). Health Technology Wales (HTW) Guidance 026 (October 2021): natriuretic peptides to rule-in and rule-out a diagnosis of acute heart failure in adults in the emergency department setting. 2021. Available from: https://healthtechnology.wales/wp-content/uploads/2021/11/GUI026-NTproBNP-and-BNP-Guidance.pdf. Accessed on: 31 January 2022.
13. Jones KC, Burns A. Unit costs of health and social care 2021. 2021.
14. National Institute for Health and Care Excellence (NICE). Developing NICE guidelines: the manual. 2014 (Last Updated 2022). Available from: https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869. Accessed on: 31 January 2022.
15. Moe GW, Howlett J, Januzzi JL, Zowall H. N-terminal pro–B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. *Circulation*. 2007;**115**:3103–3110.
16. NHS. 2019/20 National Cost Collection. 2020. Available from: https://www.england.nhs.uk/national-cost-collection/. Accessed on: 25 January 2022.
17. NHS Improvement. Reference Costs 2017/18. 2018. Available from: https://webarchive.nationalarchives.gov.uk/ukgwa/20200501111106mp_/https://improvement.nhs.uk/documents/6468/201718_reference_costs_data_and_guidance.zip. Accessed on: 25 January 2022.
18. Siebert U, Milev S, Zou D, Litkiewicz M, Gaggom H, Tirapelle L, *et al*. PMU18 economic evaluation of an NT-proBNP-supported diagnostic strategy among dyspneic patients suspected of acute heart failure in the emergency department. *Value Health*. 2020;**23**:S236.
19. Siebert U, Milev S, Zou D, Litkiewicz M, Gaggin HK, Tirapelle L, *et al*. Economic evaluation of an N-terminal pro B-type natriuretic peptide-supported diagnostic strategy among dyspneic patients suspected of acute heart failure in the emergency department. *Am J Cardiol*. 2021;**147**:61–69.
20. The National Institute for Cardiovascular Outcomes Research (NICOR). National Heart Failure Audit April 2013–March 2014. 2015. Available from: https://www.nicor.org.uk/wp-content/uploads/2019/02/hfannual13-14-updated.pdf. Accessed on: 8 July 2022.
21. NHS Business Services Authority. NHS Electronic Drug Tariff. 2021. Available from: http://www.drugtariff.nhsbsa.nhs.uk/#/00446515-DC_2/DC00446511/Home. Accessed on: 25 January 2022.
22. British National Formulary (BNF). Available from: https://bnf.nice.org.uk/. Accessed on: 25 January 2022.
23. NHS Business Services Authority. Prescription cost analysis—England 2020/21. 2020. Available from: https://www.nhsbsa.nhs.uk/statistical-collections/prescription-cost-analysis-england/prescription-cost-analysis-england-202021. Accessed on: 25 January 2022.
24. Cowie M, Fox K, Wood D, Metcalfe C, Thompson S, Coats A, *et al*. Hospitalization of patients with heart failure. A population-based study. *Eur Heart J*. 2002;**23**:877–885.
25. Siebert U, Januzzi JL Jr, Beinfeld MT, Cameron R, Gazelle GS. Cost-effectiveness of using N-terminal pro-brain natriuretic peptide to guide the diagnostic assessment and management of dyspneic patients in the emergency department. *Am J Cardiol*. 2006;**98**:800–805.
26. Rutten JH, Steyerberg EW, Boomsma F, van Saase JL, Deckers JW, Hoogsteden HC, *et al*. N-terminal pro–brain natriuretic peptide testing in the emergency department: beneficial effects on hospitalization, costs, and outcome. *Am Heart J*. 2008;**156**:71–77.