Cost-effectiveness of intravascular ultrasound-guided percutaneous intervention in patients with acute coronary syndromes: a UK perspective

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Background

Use of intravascular ultrasound (IVUS) during percutaneous coronary intervention (PCI) is associated with improved clinical outcomes over angiography alone. Despite this, the adoption of IVUS in clinical practice remains low.

Aims

To examine the cost-effectiveness of IVUS-guided PCI compared to angiography alone in patients with acute coronary syndromes (ACS).

Methods and results

A 1-year decision tree and lifetime Markov model were constructed to compare the cost effectiveness of IVUS-guided PCI to angiography alone for two hypothetical adult populations consisting of 1000 individuals: ST-elevation myocardial infarction (STEMI) and unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) patients undergoing drug- eluting stent (DES) implantation. The United Kingdom (UK) healthcare system perspective was applied using 2019/20 costs. All-cause death, myocardial infarction (MI), repeat PCI, lifetime costs, life expectancy, and quality-adjusted life-years

(QALYs) were assessed. Over a lifetime horizon, IVUS-guided PCI was cost-effective compared to angiography alone in both populations, yielding an incremental cost-effectiveness ratio of £3649 and £5706 per-patient in STEMI and UA/NSTEMI patients, respectively.

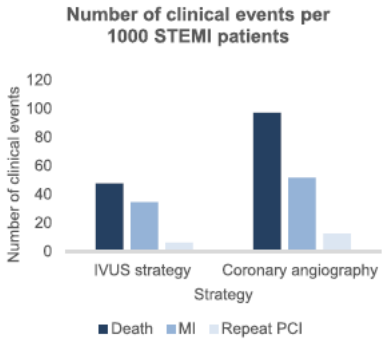
In the 1-year time horizon, the model suggested that IVUS was associated with reductions in mortality, MI, and repeat PCI by 51%, 33%, and 52% in STEMI and by 50%, 29%, and 57% in UA/NSTEMI patients, respectively. Sensitivity analyses demonstrated the robustness of the model with IVUS being 100% cost-effective at a willingness to pay threshold of £20 000 per QALY-gained.

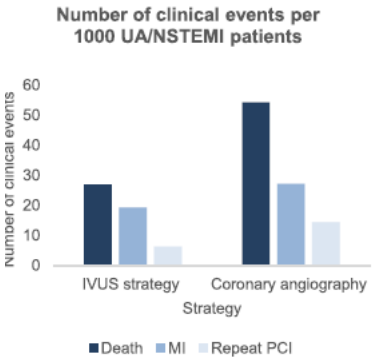
Conclusions

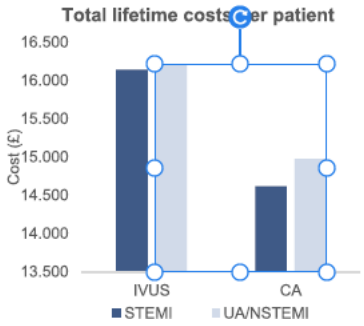
From a UK healthcare perspective, an IVUS-guided PCI strategy was highly cost-effective over angiography alone amongst ACS patients undergoing DES implantation due to the medium- and long-term reduction in repeat PCI, death, and MI.

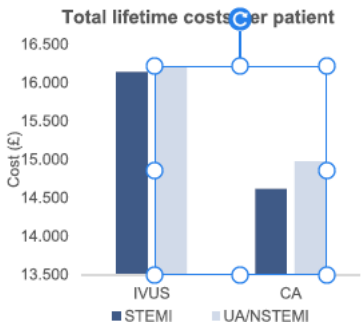
Graphical Abstract

Cost-effectiveness of intravascular ultrasound-guided percutaneous intervention in patients with acute coronary syndromes: A UK perspective

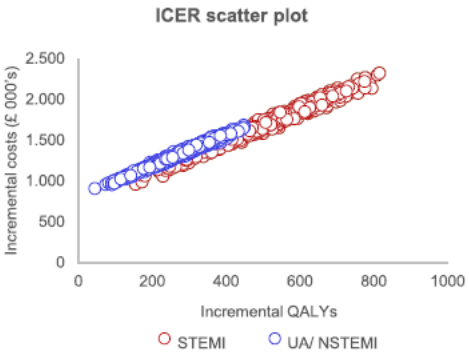








1. Cost estimates were based from specific local NHS England costing values



Take home message

From a UK healthcare perspective, IVUS-guided PCI is highly cost-effective compared to angiography alone in ACS patients undergoing DES implantation, given ICERs of £3,649 and £5,706 per-patient for STEMI and UA/NStemi patients, improving survival, reducing Mis and the likelihood of undergoing repeat revascularisisation.[1]

Cost-effectiveness falls well below the willingness-to pay threshold of £20,000, making it difficult to justify withholding IVUS- guidance in PCI in ACS on cost grounds.

Key learning points

What is already known:

- Clinical evidence has demonstrated that intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) improves angiographic and clinical outcomes compared to angiography alone. European guidelines recommend the use of IVUS for lesion assessment and stent implantation in patients with acute coronary syndromes (ACS); however, adoption in clinical practice remains limited, partly due to perceived high costs.

What this study adds:

- Payers should take a value-based approach to the use of IVUS-guidance in ACS PCI, an approach which, over a lifetime horizon, appears highly cost-effective in the UK setting, given incremental cost-effectiveness ratios of £3649 and £5706 per-patient for ST-elevation myocardial infarction and unstable angina/non-ST-elevation myocardial infarction patients, improving survival, reducing myocardial infarctions and the likelihood of undergoing repeat revascularization.
- Cost-effectiveness falls well below the willingness-to-pay threshold used by National Institute for Health and Care Excellence of £20 000, demonstrating to payers and physicians alike that the use of IVUS in higher risk ACS patients reduces complications and is cost-effective, making it difficult to justify withholding IVUS-guidance in PCI on cost grounds.

Introduction

Acute coronary syndromes (ACS) represent an increasing proportion of percutaneous coronary intervention (PCI) procedures in the United Kingdom (UK), accounting for 72% of all PCI procedures in 2020–21.[1] This is partly due to increased diagnosis of ACS and partly due to a stabilization of the rate of intervention for patients receiving PCI for chronic coronary syndromes

(CCS), which may have been related to the publication of studies such as COURAGE and ISCHEMIA, which suggest limited prognostic utility of PCI in CCS.[2, 3]

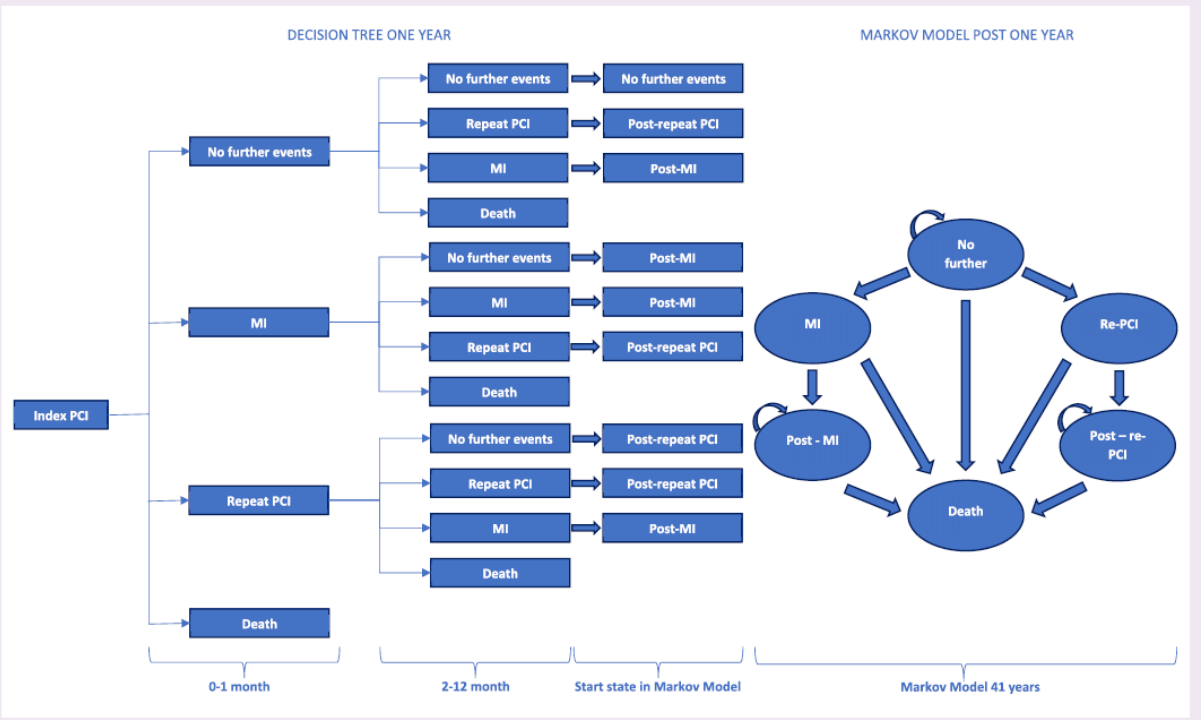


Figure 1 Model structure of decision tree and post 1-year Markov model. Decision tree representing the first year after index percutaneous coronary intervention with drug-eluting stent implantation. The structure of the decision tree remained consistent but costs and clinical events varied by comparator. The long-term Markov model was used to extrapolate clinical events beyond 1-year and consisted of six health states; no further event, MI, post-MI, repeat PCI, post-repeat PCI, and death. Arrows represented possible movements between health states during each cycle. Abbreviations: MI, myocardial infarction; and PCI, percutaneous coronary intervention

Coronary angiography (CA) remains the gold standard for treatment guidance during PCI.[3–5] However, intravascular ultrasound (IVUS) provides superior visual assessment of the coronary arteries compared to angiography alone, allowing the optimization of stent implantation and identification of stent-related complications, both of which have been proven to improve clinical outcomes in multiple clinical studies.[6] Evidence suggests that IVUS-guided PCI leads to fewer repeat revascularizations in patients with ACS and in those with complex lesions.[7] However, despite a large body of observational data and well conducted randomised clinical trials all showing clinical outcome benefit, the adoption of IVUS in clinical practice remains relatively low, with IVUS only being utilized in 13% of all PCI procedures in the UK, in 2020–21, according to data from the British Cardiovascular Intervention Society (BCIS).[1, 8, 9] This is despite recent guidelines and consensus statements sup- porting the use of IVUS in ACS patients and complex lesion subsets.[10]

An international survey of over 1000 interventional cardiologists from Europe and Japan indicated that perceived high cost of adoption (65.9%), prolongation of the procedure (35.0%), and lack of operator experience (17.1%) were contributing factors impeding the adoption of IVUS.[11] This suggests that perceived costs may be a barrier to improved clinical outcomes in an era where payers, providers, and policymakers must ensure that patients receive the highest quality care within the constraints of limited budgets. Currently, there are no economic evaluations that focus on the use of IVUS within higher-risk ACS patients, where expected benefits from devices may be higher given their higher long-term event rates. This study aims to

examine the cost-effectiveness of IVUS-guided PCI compared to angiography alone in patients with ACS undergoing PCI with drug-eluting stent (DES), from the UK healthcare system perspective.

Methods

This cost-effectiveness model was designed to conform to the National Institute for Health and Care Excellence (NICE) Guide to the Methods of Technology Appraisal (April 2013) and the NICE reference case criteria.[12] Health benefits were expressed in terms of life-years (LYs) gained and quality-adjusted life-years (QALYs) saved. Cost-effectiveness was expressed in terms of incremental cost per QALY gained. Cost-effectiveness for a willingness to pay (WTP) threshold of £20 000 was expressed as the net monetary benefit (NMB). The comparator with the highest NMB is the option that provides the highest number of QALYs at an acceptable cost.

The UK National Health Service (NHS) perspective was applied using a 2019/20 cost year. Data collection occurred between 2020 and 2021. Both costs and QALYs were discounted at a rate of 3.5% per annum. The model assumed exclusively use of DES as it is the most common type of stent currently used for primary PCI in the UK, with most centres reporting greater than 90% usage.[11]

Table I Cost of IVUS technology

Staff	Unit cost	IVUS guidance (hours)	No IVUS guidance (hours)	Incremental IVUS	Source
Nurse	£31.00	1	0.75	£7.75	Hospital-based nurses—band 4[18]
Radiographer	£67.00	1	0.75	£16.75	Hospital-based scientific and professional staff—band 7 (team manager)[18]
Cardiologist	£114.00	1	0.75	£28.50	
Registrar	£50.00	1	0.75	£12.50	Hospital-based scientific and professional staff[18]
Scrub nurse	£50.00	1	0.75	£12.50	Hospital-based nurses—band 6 (specialist)[18]
Total				**£78.00**	
Consumables	**Unit cost**	**IVUS guidance (units per patient)**	**No IVUS guidance (units per patient)**	**Incremental IVUS**	**Source**
IVUS catheter	£696.00[a]	1	0	£696	Philips list price (data on file)[16]
Stent	£250.00	1.81	1.76	£12.50	
Coronary balloon[b]	£115.65[a]	2.53	1.42	£128.37	
Wires[b]	£35.10	2.16	2.37	−£7.37	
Guide catheter[b]	£31.67	2.26	1.58	£21.54	
Total				**£851.04**	
Total cost IVUS				**£929.04**	

[a] Based on Philips 2021 list price.
[b] No data on the current cost of balloons, wires, and catheter was retrieved; the model assumed a cost reduction of 55% similar to the reduction of cost for stents from the date of the source study (1998) to the date of the source for cost of stents (2020).

Population

Ethics approval was not required for this study as two hypothetical adult populations were modelled, the first consisting of 1000

ACS patients undergoing PCI for ST-elevation myocardial infarction (STEMI) and the second consisting of 1000 patients undergoing PCI for unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI).

Baseline demographic and clinical data from the ULTIMATE trial are previously published.[8] However, we replicate key data in the Supplement for reader benefit. The baseline characteristics (Supplementary material online, Table S2) were well matched between the 2 groups.

Model structure

A two-part cost-effectiveness model was developed to assess the cost- effectiveness of IVUS. The first part was a decision tree estimating clinical events in the first year (0–30 days and from 31 days until 1 year). The second part was a Markov model estimating long-term costs and QALYs (Figure 1).

Treatment effects , mortality, and data sources

The 1-year decision tree was used to reflect the first year after index PCI.

The patient populations were modelled separately to account for prob- able differences in baseline risks, which were estimated from real-world UK patient populations that underwent PCI with angiography-guidance alone.[13, 14] Differences in rates of clinical events with adjunctive IVUS were estimated by applying relative effects (odds ratios; OR) from the ULTIMATE trial (Table 2) to obtain the probability of events occurring in the IVUS intervention arms.[8]

The vast majority of STEMI patients received PCI. Patients with UA/NSTEMI were risk assessed and a proportion were selected for angiography based on risk, appropriateness, and local factors, with a proportion of these patients subsequently selected for PCI.[13, 14] The economic analysis did not consider UA/NSTEMI patients that were medically managed. The pivotal ULTIMATE trial, comparing IVUS vs. angiography guided PCI for DES implantation, demonstrated that the reduction in clinical events were sustained throughout a 3-year follow-up period. The study included 1448 patients, of which 78.5% presented with ACS. As the model assumes no effect of IVUS after the first year, the 1 year OR for cardiac death (OR 0.50, 95% Confidence Interval (CI) 0.17–1.45, p = 0.19), myocardial infarction (MI) (OR 0.63, 95% CI 0.25–1.64, p = 0.34) and clinically driven total lesion revascularization (TLR) (OR 0.47, 95% CI 0.21–1.03, p = 0.05) from this study were applied to the model.[8]

In the first year, all-cause mortality, MI and repeat PCI were assumed to vary between IVUS and angiography. Repeat PCI was used as a conservative proxy for stent failure. Baseline risk data for repeat PCI were extracted from the EXAMINATION trial and applied to both STEMI and UA/NSTEMI populations.[15] The EXAMINATION trial used non-protocol driven PCI based on clinical assessment, which is more rigorous than self- reported BCIS data. This approach was recommended in NICE's evidence review for the clinical and cost-effectiveness of drug-eluting stents (DES) in patients with ACS (NG185) (Table 2).[16] Coronary artery bypass grafting and medical treatment were excluded, as they were not in scope of the model.

The Markov model was run over 40 years in order to calculate lifetime costs and QALYs, at the end of which the majority of the cohort would have died. The model extrapolated the impact of differences in clinical events in the first year to a lifetime horizon. Even assuming no further difference in the risk of clinical events between comparators, costs and QALYs would vary between intervention arms beyond the first year.

Table 2 Model input parameters

Input Parameters	Data	Source
Perspective	UK NHS and PSS	[12]
Time horizon	Lifetime	
Discount rate	Costs: 3.5% Outcomes: 3.5%	
Baseline risks angiography alone 0–30 days		
STEMI		
Repeat PCI	0.12%	[15]
All-cause mortality	6.15%	[14]
MI	2.91%	[13]
UA/NSTEMI		
Repeat PCI	0.12%	[15]
All-cause mortality	1.79%	[14]
MI[a]	1.00%	[13]
Baseline risks angiography alone 31 days to 1 year		
STEMI		
Repeat PCI	1.34%	[15]
All-cause mortality[b]	3.80%	[14]
MI[c]	3.88%	[13]
UA/NSTEMI		
Repeat PCI	1.34%	[15]
All-cause mortality[b]	3.71%	[14]
MI[c]	3.28%	[13]
Relative treatment effects IVUS at year one vs angiography alone (odds ratios; 95% CI)		
Repeat PCI	0.47 (0.21–1.03)	[8]
All-cause mortality	0.50 (0.17–1.45)	
MI	0.63 (0.25–1.64)	
Transition probabilities excluding death in post year one Markov model (day 31 to 1 year)		
STEMI		
Repeat PCI[d]	1.46%	Probability for 31 days to 1 year, converted to a one year probability using standard formulae assuming a constant underlying rate
All-cause mortality[d]	4.13%	
MI[d]	4.22%	
UA/NSTEMI		
Repeat PCI[d]	1.46%	Probability for 31 days to 1 year, converted to a 1-year probability using standard formulae assuming a constant underlying rate
All-cause mortality[d]	4.04%	
MI[d]	3.57%	
Transition probabilities to dead state		
General population mortality[e]	Age and sex dependent Age entering Markov model: **STEMI**: Male/Female: 64 years **UA/NSTEMI:** Male/Female: 64 years **% male entering Markov model** *STEMI:* 75% *UA/NSTEMI:* 75%	[30]
No further event SMR	2.00 (1.99–2.01)	[31]
Myocardial infarction SMR	4.50 (4.43–4.57)	
Post-MI SMR	3.00 (2.95–3.05)	

Table 2 Continued

Input Parameters	Data	Source
Quality of life (utilities)		
No further event	0.8420	20
Repeat PCI	0.8364	21
MI	0.7790	20
Post-repeat PCI	0.8420	21
Post-MI	0.8210	20
Age-adjustment (general population utility by age)[f]	Age and sex dependent	32
Costs of interventions per year (£)		
IVUS[f]	929.04	17,33
CA	—	—
Model costs[g]		
Cost repeat PCI (0–30 days and 31 days-12 months)[h]	3451.61	34
Cost no further event (0–30 days)[h]	1129.32	
Cost no further event (31 days–12 months)[h]	494.26	
MI (0–30 days month cost)[h]	4608.18	
MI (31 days–12 months cost) [h]	741.65	18,19
Cost no further event Markov[h]	988.52	
Cost MI Markov[h]	5349.83	
Cost post MI Markov[h]	1483.30	
Cost post repeat PCI Markov[h]	1483.30	

Abbreviations: CA, coronary angiography; IVUS, intravascular ultrasound; MI, myocardial infarction; NHS, National Health Service; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PSS, personal social services; SMR, standardized mortality ratios; STEMI, ST-elevation myocardial infarction; and UA, unstable angina.

[a] Calculated based on 1 year rate from NICE CG9440 using PLATO and SwedeHeart rates.[16,35,36]

[b] Mortality tracked BCIS PCI audit data.[1]

[c] Recalculated based on 30-day events.

[d] Assumption: Probability of 31 days to 1 year converted to a 1-year probability using standard formulae assuming a constant underlying rate.

[e] Standardized mortality ratios were applied to cycle-specific general population mortality rates, which meant that mortality was dependent on sex and increased with age. During the first year, only event-related mortality was applied. From years 2 to 40, patients could die not only from background mortality but also event related mortality, therefore assuming that patients experiencing an event have a higher mortality rate. Rates were converted to probabilities using standardized conversion methods (Supplementary material online, *Table S5*).

[f] Applied multiplicatively with health state weights. Calculated using formulae from Ara and Brazier (2010)[32]

[g] For the year one decision tree, it was assumed that events occurring between 31 days and 1 year occurred around 6 months. Therefore, costs were attributed assuming that the first 6-month costs were determined by events occurring between 0 and 30 days and the second 6-months costs were determined by events occurring between 31 days to 1 year.

[h] Costs inflated to 2019/20.

Figure 1 and Supplementary material online, *Table S3* illustrates the Markov model structure and the possible transitions between health states . The Markov model used a 1-year cycle length. A half- cycle correction was applied, assuming that people transitioned between states halfway through a cycle, on average.

Repeat PCI and MI were treated as tunnel health states , meaning that people only remained in that health state for one cycle, after which they transitioned to dead or post-MI/post-repeat PCI health states . Differential intervention effects were assumed to apply in the first year only. Therefore, event probabilities post 1-year did not vary between intervention arms. In the Markov model, death was sex- and age-dependent and changed in each cycle.

The transition matrices applied in the Markov model for STEMI and UA/NSTEMI are detailed in Supplementary material online, *Table S3*. Certain assumptions regarding the application of relative treatment effects, subsequent events, event probabilities, and costs of events were considered in order to simplify the model. These assumptions are detailed in the Supplement (Supplementary material online, *Table S4*).

Costs and resource utilization

A micro-costing approach was adapted to the UK setting was used to estimate IVUS-related costs along with prior precedent.[17] Procedural time associated with IVUS consumables and staff were applied and unit costs were based on local UK cost data.[17–19] All cost inputs are summarized in *Table 1* .

Health-related qua lit y of life

Utilities were applied to patients who experienced no additional event, reinfarction, or repeat PCI in the first-year decision tree and first post- year Markov model.[20,21] In the Markov model, individuals who had not experienced a previous event could experience an event (tunnel states) and the same associated utility value was applied. After experiencing the event, patients went to the post-event health states where they did not experience any further event, in which they stayed or moved to the dead state. Individuals in these post-health states had higher utilities considering utilities decreased after experiencing an event. In the post-event, utilities returned to the baseline values.

Utilities were age-adjusted, accounting for a decrease in quality of life as people age and to avoid overestimating QALYs (*Table 2*). This method has been applied by economic models accepted by NICE.[22]

Sensitivity analyses

One-way sensitivity analyses were performed to assess the impact of individual input parameter estimates on the model and identify the main factors driving the cost-effectiveness of IVUS. In total, [26] parameters were included and the base case point estimates for each parameter were varied by 20%, as per standard health economics practice. Uncertainty of model parameters was also assessed by means of probabilistic sensitivity analyses (PSA). The variables included in the PSA and their distributional parameters are detailed in the Supplement (Supplementary material online, *Table S5*).

The percentage of time each comparator was more cost-effective at a threshold of £20 000 was recorded and cost-effectiveness acceptability curves (CEAC) were provided

Scenario analyses

Different time horizons were considered to examine their impact on cost- effectiveness, including 1-year decision tree, 1-year decision tree plus 2 years Markov model, 1-year decision tree plus 3 years Markov model, 1- year decision tree plus 5 years Markov model, and lifetime horizon.

Results

Base case results

Results of the base case analysis for the STEMI and UA/NSTEMI patient populations are presented in *Table 3* . Although the initial cost of IVUS-guided PCI was higher than angiography alone, use of IVUS was cost-effective in both populations over a lifetime horizon. In the STEMI population, IVUS-guided PCI was associated with 0.417 QALYs gained and 0.837 LYs gained at an incremental cost of £1522.57 with an incremental cost-effectiveness ratio of (ICER) per patient of £3649 per QALY gained. In the UA/NSTEMI population, IVUS-guided PCI resulted in 0.216 QALYs gained and 0.424 LYs gained at an incremental cost of £1234.12 with an ICER of £5706 per-patient. A positive incremental NMB per-patient, or the difference in NMB between interventions, of £6821.58 and £3091.49 at a WTP threshold of £20 000, for STEMI and UA/NSTEMI populations, respectively, further indicates the cost-effectiveness of IVUS-guided PCI.

The cost-effectiveness of IVUS-guided PCI was driven by a reduction in adverse clinical events during the first year (*Table 4*). In the STEMI population, use of IVUS was associated with relative

reductions in mortality, MI, and repeat PCI of 51%, 33%, and 52%, respectively, compared with angiography alone. In the UA/NSTEMI population, use of IVUS was associated with reductions in mortality, MI, and repeat PCI of 51%, 29%, and 57%, respectively.

Sensitivity analyses

One way sensitivity analyses

In the STEMI population, utility value of no further events and probability of death from 0 to 30 days were the main drivers of cost- effectiveness in both intervention arms (*Figure 2 A*). For UA/NSTEMI, probability of all-cause mortality from day 31 to 1 year and relative risk of all-cause mortality from day 31 to 1 year in the IVUS group were the main drivers of cost-effectiveness (*Figure 2 B*). The ICER value did not reach above £6500 in either case and fell below the WTP threshold of £20 000, confirming the robustness of the results.

Probabilistic sensitivity analyses

Results from the PSA similarly support the cost-effectiveness of IVUS- guided PCI in both patient populations. In the STEMI population, the CEAC illustrates that IVUS has a 100% probability of being cost-effective from a WTP of £10 500 upwards (*Figure 3 A*). In the UA/NSTEMI population, the CEAC illustrates that IVUS has a 100% probability of being cost-effective from a WTP of £13 000 upwards (*Figure 3 B*).

Scenario analyses

The model also explored the role of time horizon for the cost- effectiveness of IVUS-guided PCI. As expected, the upfront cost of the IVUS technology drove the cost-effectiveness results, whereby, during the first year, IVUS was not cost-effective at a threshold of £20 000 in the STEMI population (ICER £23 882) or the UA/NSTEMI population (ICER £42 403). However, at 3 years, IVUS-guided PCI became a cost-effective strategy, with an ICER of £9413 and £17 296 in the STEMI and UA/NSTEMI population, respectively. This improves dramatically over a lifetime horizon.

Table 3 Base case lifetime results—STEMI and UA/NSTEMI populations

				Incremental analysis			Net monetary benefit		Incremental life-years gained	
Population	Strategy	Total cost (£)	Total QALY	Incremental cost (£)	Incremental QALY	ICER (£)	WTP (£)	ST iNMB (£)	Life-years	Life-years gained
Results reported for entire cohort (per 1000 patients)										
STEMI	IVUS	£16 141 884	7925	£1 522 573	417	£3649	20 000	£6 821 575	15 773	837
	CA	£14 619 312	7508						14 935	
UA/NSTEMI	IVUS	£16 210 263	8168	£1 234 121	216	£5706	20 000	£3 091 494	16 303	424
	CA	£14 976 142	7951						15 879	

Abbreviations: ICER, incremental cost-effectiveness ratio; iNMB, incremental net monetary benefit; NSTEMI, non-ST-elevation myocardial infarction; QALY, quality-adjusted life year; STEMI, ST-elevation myocardial infarction; UA, unstable angina; and WTP, willingness to pay.

Table 4 Absolute reduction of clinical events in year one—STEMI and UA/NSTEMI populations

Absolute reduction of clinical events year one in a cohort of 1000 hypothetical patients			
Number clinical events No. (%)	**Death**	**MI**	**Repeat PCI**
STEMI Population			
IVUS strategy	47.9 (4.79)	34.5 (3.45)	6.1 (0.61)
Coronary angiography	97.1 (9.71)	51.7 (5.17)	12.6 (1.26)
Avoided events with IVUS	49.2 (50.68)	−17.2 (33.28)	−6.5 (51.72)
UA/NSTEMI Population			
IVUS strategy	26.9 (2.69)	19.3 (1.93)	6.2 (0.62)
Coronary angiography	54.3 (5.43)	27.2 (2.72)	14.4 (1.44)
Avoided events with IVUS	27.4 (50.45)	7.9 (28.98)	8.2 (56.88)

Abbreviations: IVUS, intravascular ultrasound; MI, myocardial infarction; NSTEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; and UA, unstable angina

Discussion

To our knowledge, this is the first dedicated cost effectiveness study on the use of IVUS vs. angiography alone in an ACS population, using a modelling strategy recommended by NICE. The results of this study confirmed that IVUS-guided PCI is cost-effective in a STEMI and UA/NSTEMI population. This positive incremental NMB per patient for both populations further indicate the cost-effectiveness of IVUS- guided PCI.

There is extensive evidence from both observational and randomised studies that IVUS-guided PCI improves both angiographic and clinical outcomes when compared to angiography alone.[8,9,23–27] Despite these well-established benefits, adoption of IVUS is limited, partly by perceived high technology-related costs.[11]

Studies examining the economic benefits of IVUS remain limited, particularly in ACS patients who represent the significant majority of the global population undergoing PCI in the contemporary era and in whom post-procedural event rates are the highest. These patients potentially have the most to gain from strategies that might reduce complications and given that cost appears to be a barrier to adoption in this higher risk cohort, we modelled this cost effectiveness analysis specifically to re-assure physicians that the use of IVUS in these populations does indeed appear highly cost effective.

We identified two published economic evaluations on the cost- effectiveness of IVUS-guided PCI for DES implantation.[17,28] Alberti *et al.* found that IVUS-guided PCI was a dominant treatment strategy compared to angiography alone in Italy, especially in patients at higher risk of restenosis, specifically patients with diabetes, chronic kidney disease and ACS.[28] Similarly, Zhou *et al.* found that IVUS guidance for DES implantation was cost-effective in all-comer patients under- going PCI in Australia, with an incremental cost-effectiveness ratio of AUD $17 539 (USD $12 730) per QALY gained.[17] Our results concur with these studies and extend their findings by focusing on the ACS population using an analogous model to those used by NICE. Specifically, we demonstrated that adjunctive IVUS is cost-effective compared to angiography alone amongst patients with ACS over a lifetime horizon, with ICERs of £3649 and £5706 per QALY gained in the STEMI and UA/NSTEMI population, respectively. It is important to note that the main driver of IVUS cost-effectiveness was the reduction of mortality, which becomes more apparent when considering a medium/long term perspective after the initial cost associated with the use of IVUS technology has eroded. In contrast to these studies, we implemented a single-study approach and applied relative treatment effects from the multicentre randomized ULTIMATE trial, where over 78% of the included population presented with ACS. If mortality

event rates were applied from a meta-analysis of ACS patients alone, such as from the recently published meta-analysis by Groen- land *et al* ., then IVUS would have demonstrated to be even more cost-effective.[29]

However, given that the meta-analysis by Groenland *et al*. included almost exclusively primarily observational studies, with only one RCT containing just 80 patients and excluded ULTIMATE data, we opted to utilize outcomes from ULTIMATE.

Our model can be compared to that developed by Zhou *et al* . in showing that IVUS-guided PCI can provide long-term value, however the meta-analysis performed by Zhou *et al* . to estimate relative risks of outcomes focused on all-comers with less than 60% of the overall patient pool presenting with ACS.[17] Both models indicated that during the first year, IVUS was not cost-effective due to the up-front cost of the technology. However, these costs were offset in the longer term by reduced clinical event rates in the IVUS group. In the Zhou *et al*. model, IVUS became the economically favourable option (ICER less than AUD $50 000) from 7 years onwards. In contrast, IVUS became cost-effective from 3 years onwards in both ACS patient populations in our study. In the STEMI population, IVUS may be cost-effective during the first year if the standard is set at £30 000, given our model depicts an ICER of £29 000 per QALY gained.

Further health-economic studies should consider the long-term value of IVUS in different patient populations to support the transition from an acquisition cost approach (short-term) to a value-based approach (long-term) in which patients and providers can benefit from the clinical and economic superiority of IVUS-guided PCI compared to angiography alone.

Our study has limitations , but several that we describe only serve to emphasize the conservative nature of our modelling process.

First, we used the relative treatment effects for mortality, MI, and repeat PCI from the ULTIMATE trial. The ORs applied for both death and MI had wide confidence internals, exceeding 1.0, introducing higher uncertainty into model. Despite this, PSA results aligned with base-case results and demonstrated that IVUS has a 100% probability of being cost-effective in both STEMI and UA/NSTEMI patients at a WTP below the threshold of £20 000.

Second, the ULTIMATE trial included all-comers from a non- western cohort, though to our knowledge this was the best available data at the time and contained a large volume of ACS patients when compared to other studies.[8] Although IVUS-XPL had a more balanced cohort, it included a non-western cohort with only 49% ACS presentation.9 Over 50% of patients included in ADAPT-DES had ACS, however, the study was non-randomized.25 The global meta- analysis by Darmoch *et al*. included a mix of RCTs and observational studies, one of which was the ULTIMATE trial, though less than 50% of the patient pool had ACS and a moderate level of heterogeneity was observed with MI and TLR.[26] If ACS event rates were applied from either of these meta-analyses in our model, it would have rendered IVUS as cost-effective. However, due to the limitations cited, we chose to apply event rates from ULTIMATE data, resulting in the application of lower event rates, which would serve only to weaken the already demonstrated cost-effectiveness of IVUS. Our analysis is thus a conservative representation and yet still shows high degrees of cost effectiveness by NICE standards.

Third, the baseline risk data for reinfarction (only in STEMI) were for all events rather than non-fatal events, potentially leading to an overestimation of the number of people that were alive

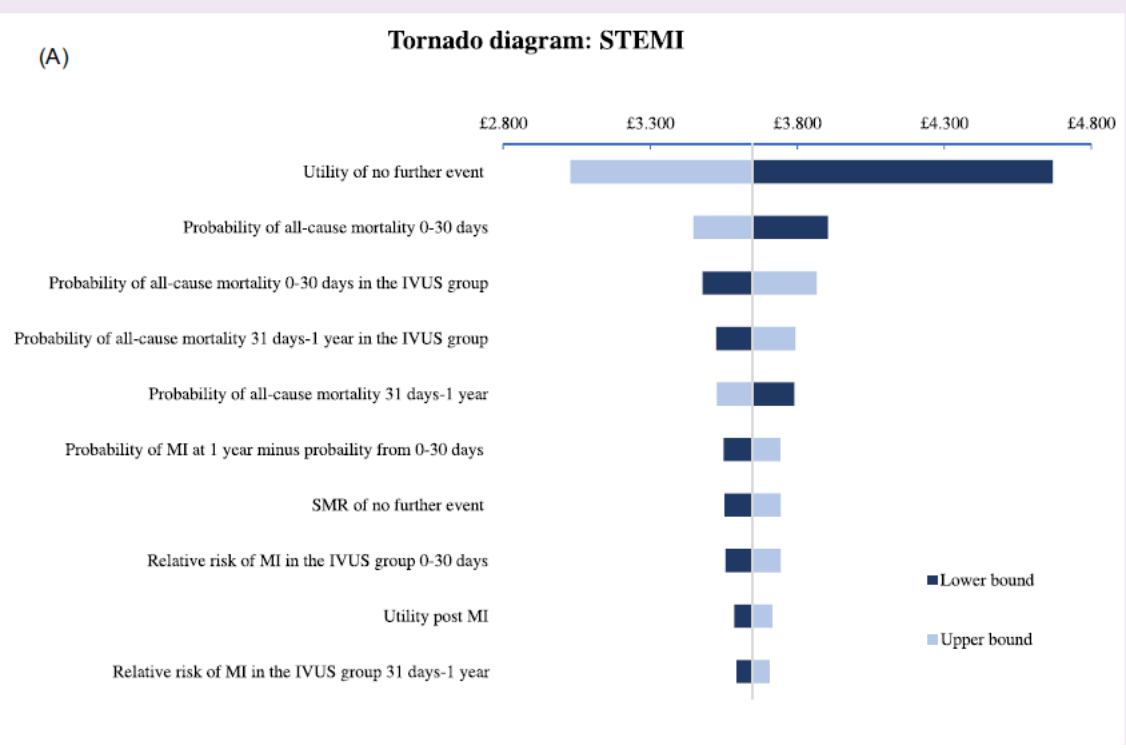
with an event at the end of the decision tree and entering the Markov model. This may have elevated the ICER since post-reinfarction results in higher costs and lower quality of life.

Fourth, the risk of reinfarction beyond 1 year was assumed to be equal to that between 31 days and 1 year. The model did not allow for repeat events after 1 year and only allowed people in the 'no further event' health state to have a reinfarction or repeat PCI (i.e. the model did not allow for one patient to experience additional events). This approach does not reflect reality as people can experience repeat reinfarctions and repeat PCIs. However, this simplification has been implemented in models accepted by NICE and may be considered reasonable due to limited data available to model repeat events beyond 1 year. Given the cost-effectiveness of IVUS, the inclusion of secondary events would likely further increase cost-effectiveness.

Furthermore, when selecting health state cost data, costs incorporating downstream events were used if available. Given that IVUS reduces the first episode of repeat PCI, it is unlikely that the pattern of additional repeat PCIs in the ACS population would render the model less cost-effective.

Fifth, ST was not modelled as a separate health state as it is a low frequency event captured with repeat MI. Nonetheless, ST may significantly increase resource utilization, potentially impacting overall costs and, in turn, cost-effectiveness. IVUS has been associated with a reduction in the rate of ST and so the model could prove even more favourable towards IVUS if differential costs were incurred over other types of MI.[7]

Lastly, in order to estimate the costs of wires , balloons , and catheters, we adjusted previously published rates to 2019/2020 costs. In order to assess the robustness of our results, we conducted an internal analysis using local costings, based on commercially sensitive data, from a single NHS centre and single supplier and found little variance (data available upon request).



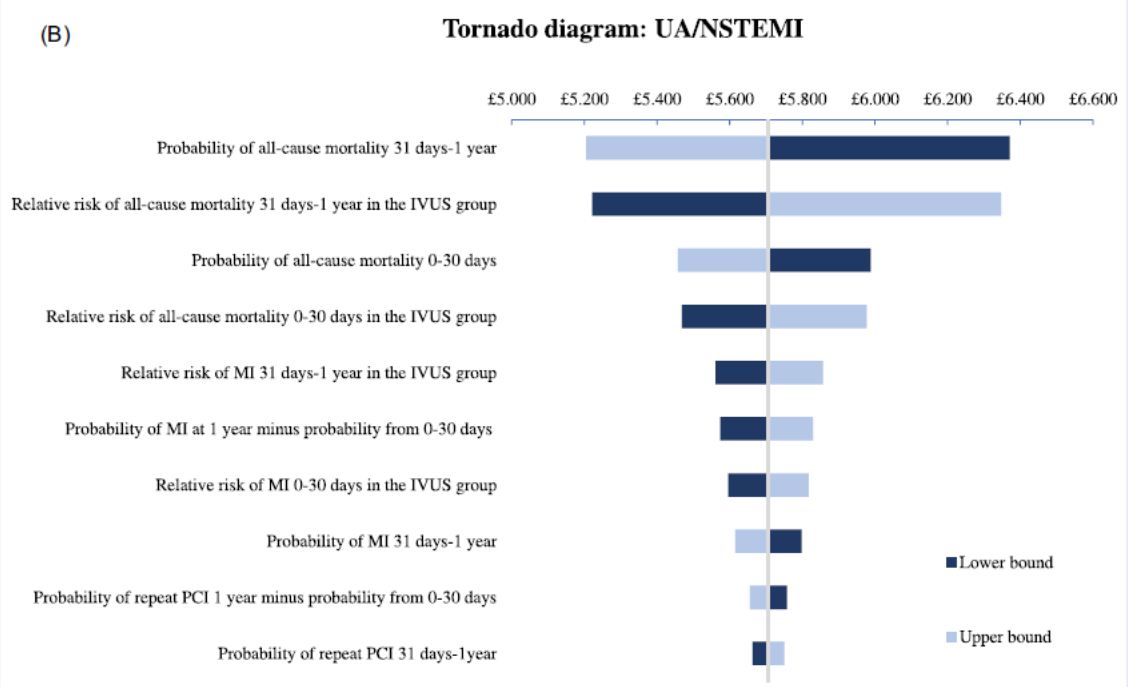


Figure 2 One way sensitivity analyses results. The tornado diagram highlights the parameters that have biggest impact on the incremental cost-effectiveness ratio after varying them 20% in (A) STEMI population (B) UA/NSTEMI population. Abbreviations: CA, coronary angiography; ICER, incremental cost-effectiveness ratio; IVUS, intravascular ultrasound; MI, myocardial infarction; and QALY, quality-adjusted life-year.

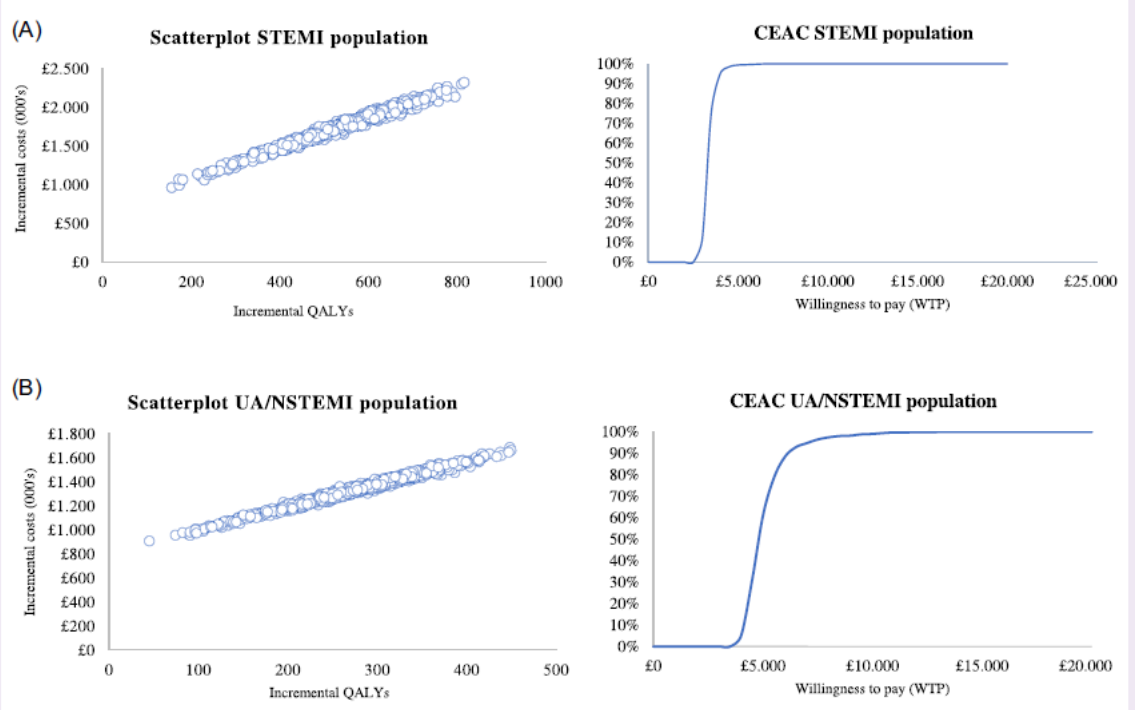


Figure 3 Probabilistic sensitivity analysis results. The probabilistic ICER scatterplot demonstrates that the base case ICER deviates less than 10% from the deterministic ICER in (A) STEMI population (B) UA/NSTEMI population. The CEAC illustrates that IVUS has a 100% probability of being cost-effective from a WTP of £4500 upwards in the STEMI population and from a WTP of £5752 in the UA/STEMI population. Abbreviations: CEAC, cost-effectiveness acceptability curve; ICER, incremental cost-effectiveness ratio; NSTEMI, non- ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; and UA, unstable angina.

Conclusion

From a UK healthcare system perspective, an IVUS-guided PCI strategy is a highly cost-effective alternative to angiography alone in ACS patients undergoing DES implantation. IVUS is cost-

effective with a favourable ICER of £3649 and £5706 per patient in the STEMI and UA/NSTEMI population, respectively, with the initial costs of technology adoption clearly offset by health benefits and over a lifetime horizon. Costs should therefore not be a barrier to the increased use of IVUS-guided PCI in ACS patients.

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Conflict of interest: A.S.P.S. is a consultant to Medtronic, Recor Medical, Philips, Boston Scientific, and Penumbra; N.C. has received unrestricted research grants from Boston Scientific, Haemonectics, HeartFlow & Beckmann Coulter; speaker fees/consultancy from Abbott, Boston, Edwrads; travel sponsorship from Medtronic, Biosensors; Abbott; HeartFlow; R. A . and J.E. A . report consulting for Philips; H.V.B is an employee at Philips Healthcare; T.K. and M. A .M. report no conflicts of interest pertaining to this manuscript.

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Data availability

The data underlying this article are available in the article and in its online supplementary material. The data pertaining to the economic model in this article will be shared on reasonable request to the corresponding author.

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