BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008861
Article Type:	Research
Date Submitted by the Author:	21-May-2015
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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	CARDIOLOGY, Coronary heart disease < CARDIOLOGY, HEALTH ECONOMICS

Ranolazine for the Treatment of Chronic Stable Angina: A Cost-Effectiveness Analysis from the United Kingdom Perspective

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Running Head: Cost-effectiveness of ranolazine in the UK

FUNDING
This work was supported by Menarini International Operations, Luxembourg, SA. The authors maintained full control over the design and performance of the study; collection, management, analysis, and interpretation of the data; and preparation and review of the manuscript. The sponsor reviewed the final manuscript prior to submission. Drs. Coleman and Kohn had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Key words: ranolazine; angina, stable; cost-effectiveness analysis
Word count: 2,650

ABSTRACT

Introduction: Ranolazine decreases angina symptom frequency and nitroglycerin consumption and has a positive impact on patient functioning and quality-of-life. At present, the cost-effectiveness of ranolazine for stable angina has not been assessed from a United Kingdom (UK) perspective. We sought to estimate the cost-effectiveness of ranolazine when added to standard-of-care (SoC) antianginals compared with SoC alone in patients with stable coronary disease experiencing ≥3 attacks/week.

Methods: A Markov model utilizing a UK health-system perspective, a 1-month cycle-length, and a 1-year time horizon was developed to estimate costs (£2014) and quality-adjusted life years (QALYs) for patients receiving and not receiving ranolazine. Patients entered the model in 1 of 4 angina frequency health-states based upon Seattle Angina Questionnaire angina frequency (SAQAF) scores (100=no; 61 to 99=monthly; 31 to 60=weekly; and 0 to 30=daily angina) and were allowed to transition between states or to death based upon probabilities derived from the randomized, controlled Efficacy of Ranolazine in Chronic Angina (ERICA) trial and other published studies. Patients not responding to ranolazine in month 1 (not improving ≥1 SAQAF health-state) were assumed to discontinue ranolazine and behave like SoC patients.

Results: Ranolazine patients accrued a mean of 0.701 QALYs at a cost of £5,208. Those not receiving ranolazine accrued 0.662 QALYs at a cost of £5,318. The addition of ranolazine to SoC was therefore a dominant economic strategy. The incremental cost-effectiveness ratio (ICER) was sensitive to ranolazine cost; exceeding £20,000/QALY when ranolazine's cost was >£203/month. Ranolazine remained a dominant strategy when indirect costs were included and mortality rates were assumed to increase with worsening severity of SAQAF health-states. Monte Carlo simulation found ranolazine to be a dominant economic strategy in ~71% of 10,000 iterations.

Conclusion: Ranolazine added to SoC in patients with weekly or daily angina appears cost-effective from a UK health-system perspective.

Article focus

- To estimate the cost-effectiveness of ranolazine when added to standard-of-care (SoC) antianginals compared with SoC alone in patients with stable coronary disease experiencing ≥3 attacks/week from a United Kingdom (UK) perspective.

Key messages

- The results suggest the addition of ranolazine to SoC therapy is an economically dominant strategy (less costly, more effective) for the treatment of chronic stable angina among patients suffering ≥3 angina attacks/week.
- Ranolazine can be considered an efficacious and cost-effective treatment strategy for stable angina patients experiencing weekly or daily angina symptoms.

Strengths and limitations of the study

- This is the first economic modeling study of ranolazine from the UK perspective
- The model utilized data from the randomized and controlled Efficacy of Ranolazine in Chronic Angina (ERICA) trial.
- It is unclear whether our findings are generalizable to patients with less frequent angina symptoms.
- Results of the short duration ERICA trial were extrapolated to a 1-year time horizon.

The prevalence of stable angina in the United Kingdom (UK) is about 2.1 million people.[1] Stable angina is associated with an unfavorable impact on health-related quality-of-life (HrQoL),[2-4] morbidity and mortality [5] and economic outcomes (increased direct and lost productivity costs);[6,7] with afflicted patients reporting their health to be twice as poor as those who previously suffered a stroke, and direct treatment costs of at least £700 million per year.[8]

Ranolazine is indicated in the UK for the treatment of chronic stable angina. The Combination Assessment of Ranolazine In Stable Angina (CARISA),[9] Efficacy of Ranolazine in Chronic Angina (ERICA) [10] and Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina (TERISA) [11] randomized controlled trials demonstrated ranolazine's ability to significantly reduce weekly angina frequency by 0.4 to 1.2 attacks when added to standard-of-care (SoC) antianginal therapies, as well as, reduce sublingual nitroglycerin consumption. Moreover, in TERISA, ranolazine was found to significantly improve stable angina patient HrQoL, as evidence by an improvement in the physical component sub score of the Short-Form-36.[11]

Here we report the results of a cost-effectiveness analysis from a UK perspective to estimate the costs, quality-adjusted life-years (QALYs) and incremental cost-effectiveness of ranolazine when added to SoC antianginal therapy compared to SoC antianginal therapy alone in stable coronary disease patients experiencing frequent angina attacks.

METHODS

We followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement in reporting this cost-effectiveness analysis.[12]

This Markov model utilized a 1-year time horizon, a cycle length of 1-month and was performed from the UK health-system perspective. It included 5 mutually exclusive health states; 4 related to angina

frequency (no, monthly, weekly and daily angina symptoms) and the absorbing health state of death (**Figure 1**). This model was built using efficacy and tolerability data from the ERICA trial;[10] a randomized controlled trial of 565 patients with stable coronary artery disease experiencing ≥3 angina attacks/week (i.e., 5.6±0.18 episodes/week and consuming 4.7±0.21 nitroglycerin tablets/week) assigned to receive ranolazine (500 mg twice daily for the first week followed by 1,000 mg twice daily thereafter) or placebo in addition to SoC antianginal therapy (including a maximal dose of amlodipine in all patients, 45% and 52% long-acting nitrate and angiotensin-converting enzyme inhibitor use, and no beta-blocker use). As observed in ERICA, patients entering the model started in 1 of 3 of the 4 angina frequency health states (no patients started in the "no angina" state) based upon Seattle Angina Questionnaire Angina Frequency (SAQAF) domain scores.[13] Patients scoring 100 points on the SAQAF were deemed to have no angina symptoms, whereas scores of 61-99, 31-60 and 0-30 represented monthly, weekly and daily angina symptoms, respectively.[14] We utilized the SAQAF to define our model's health states because it was an important patient-reported outcome measure utilized in the ERICA trial [10] and has been used in other angina clinical trials [9,11] and prior stable angina epidemiologic and cost-of-illness analyses.[2,3,5,6,13]

Our model followed patients as they transited between the 4 above-mentioned angina frequency health states and the death state; with potential transitions occurring only once per each 1-month cycle. The model's first month's (cycle's) transition probabilities for movement through the angina frequency health states were calculated directly from the ERICA trial using individual patient data.[10] For patients not receiving ranolazine, the probability of moving from one angina frequency health state to another was calculated based upon those observed in the SoC arm of the ERICA trial (**Table 1**). Transition probabilities for ranolazine patients achieving adequate efficacy on-treatment, defined as improving by at least 1 angina frequency health state (e.g., transitioning from daily to weekly angina symptoms) were calculated based upon rates observed in corresponding ERICA patients (**Table 2**).

		SAQAF EOT Classification			
		No	Monthly	Weekly	Daily
SAQAF Baseline Classification	No	---	---	---	---
	Monthly	2/2 (100%) 95%CI (34%-100%)	---	---	---
	Weekly	13/95 (13.7%) 95%CI (8%-22%)	82/95 (86.3%) 95%CI (78%-92%)	---	---
	Daily	2/47 (4.3%) 95%CI (1%-14%)	10/47 (21.3%) 95%CI (12%-35%)	35/47 (74.5%) 95%CI (60%-85%)	---

Table 1. Transition Probability Matrix for Ranolazine Responders During the First Cycle
CI=confidence interval; EOT=end-of-treatment; SAQAF=Seattle Angina Questionnaire Angina Frequency
The Seattle Angina Questionnaire Angina Frequency Domain category ranolazine responders started in are depicted on the vertical axis (100=no; 61-99=monthly, 31-60=weekly and 0-30=daily symptoms) and the category they finished the double-blind trial period in is depicted on the horizontal axis. For example, 47 ranolazine responders began the study reporting "daily" angina symptoms and 0 (0%), 35 (74.5%), 10 (21.3%) and 2 (4.3%) of these same patients reported having daily, weekly, monthly and no angina symptoms at the end of the trial.

		SAQAF EOT Classification			
		No	Monthly	Weekly	Daily
SAQAF Baseline Classification	No	---	---	---	---
	Monthly	1/20 (5.0%) 95%CI (0.9%-24%)	17/20 (85.0%) 95%CI (64%-95%)	2/20 (10.0%) 95%CI (3.0%-30%)	0/20 (0%) 95%CI (0%-16%)
	Weekly	8/193 (4.1%) 95%CI (2%-8%)	65/193 (33.7%) 95%CI (27%-41%)	112/193 (58.0%) 95%CI (51%-65%)	8/193 (4.1%) 95%CI (2%-8%)
	Daily	2/68 (2.9%) 95%CI (0.8%-10%)	9/68 (13.2%) 95%CI (7%-23%)	33/68 (48.5%) 95%CI (37%-60%)	24/68 (35.3%) 95%CI (25%-47%)

Table 2. Transition Probability Matrix for Standard-of-Care (Plus Placebo) During the First Cycle [reference: 8]
CI=confidence interval; EOT=end-of-treatment; SAQAF=Seattle Angina Questionnaire Angina Frequency
The Seattle Angina Questionnaire Angina Frequency Domain category standard-of-care patients started in are depicted on the vertical axis (100=no; 61-99=monthly, 31-60=weekly and 0-30=daily symptoms) and the category they finished the double-blind trial period in is depicted on the horizontal axis. For example, 68 standard-of-care patients began the study reporting "daily" angina symptoms and 24 (35.3%), 33 (48.5%), 9 (13.2%) and 2 (2.9%) of these same patients reported having daily, weekly, monthly and no angina symptoms at the end of the trial.

Patients receiving ranolazine could also discontinue treatment due to adverse drug reactions or lack of efficacy during, and only during, the first month of treatment. This assumption was based upon the reasoning that patients reporting a lack of efficacy or adverse reactions requiring discontinuation of therapy would most likely do so in the first month [10,11] and data from the TERISA trial [11] suggesting the majority of the effect of ranolazine is seen in the first few weeks of treatment. The rates of ranolazine discontinuation due to adverse reactions and lack of efficacy were derived from the ERICA trial (**Table 3**). For those patients discontinuing ranolazine for any reason, transition probabilities were assumed to follow the same pattern as SoC (plus placebo) patients. In the second month (cycle 2) and onwards, all patients were assumed to stay in the same angina frequency health state for the remainder of the model's time horizon or until death. Thus, no loss or additional efficacy in either treatment group could occur.

Variable	Base-Case	Range	Reference
SAQAF classification definition			
No	SAQAF=100	NA	6,13
Monthly	SAQAF=61-99	NA	6,13
Weekly	SAQAF=31-60	NA	6,13
Daily	SAQAF=0-30	NA	6,13
SAQAF classification at baseline			6,10
No	0%	NA	6,10
Monthly	6.1%	100%	6,10
Weekly	71.0%	100%	6,10
Daily	22.9%	100%	6,10
Definition of SAQAF responder	Improvement of ≥1 SAQAF classification	20-point change in SAQAF	5,6
Ranolazine non-response	48% during first 4-weeks	42.2%-53.9%	10
Ranolazine discontinuation due to AE	1.1% during first 4-weeks	0.37%-6%	10
All-cause mortality by angina frequency			
No	4.6%/year	3.8%-5.5%	5
Monthly	4.8%/year	3.8%-6.1%	5
Weekly	8.1%/year	6.1%-10.8%	5
Daily	10.9%/year	7.5%-15.4%	5
All-cause mortality for all angina patients	5.8%/year	NA	5
Angina frequency utility (using EOT data)			2,10,15
No	0.87	0.84-0.90	2,10,15
Monthly	0.76	0.75-0.77	2,10,15
Weekly	0.65	0.64-0.66	2,10,15
Daily	0.54	0.52-0.56	2,10,15
Cost of ranolazine twice daily at any dose	£48.98/month	£24.49-£97.96	16
Stable angina direct treatment costs/year (not including ranolazine)			6
No	£3,529	£3,276-£3,786	6
Monthly	£4,711	£4,255-£5,023	6
Weekly	£5,493	£4,765-£6,229	6
Daily	£8,374	£6,754-£9,990	6
Stable angina indirect costs/year			
No	£2,362	£1,011-£3,373	7
Monthly	£4,012	£2,694-£5,395	7
Weekly	£4,271	£2,694-£5,395	7
Daily	£8,194	£5,395-£10,783	7

Table 3. Base-Case Variables and Ranges Used in Sensitivity Analysis

EOT=end-of-treatment; NA=not applicable; SAQAF=Seattle Angina Questionnaire Angina Frequency

During any cycle of the model, patients could transition to the death health state based upon all-cause mortality rates in angina patients, derived from a prospective cohort study of coronary artery disease patients from 6 Veterans Affairs General Internal Medicine Clinics.[5]

Our model determined the mean total cost of treatment accrued by the patient cohorts receiving and not receiving ranolazine separately, as well as the mean number of QALYs. This allowed for the calculation of incremental cost-effectiveness ratios (ICERs) defined as the difference in mean costs between the ranolazine plus SoC and SoC alone (plus placebo) patients divided by the difference in mean QALYs for each treatment. We also provide in this report an ICER defined as the difference in mean costs between the two groups divided by the difference in SAQAF response rate. Since the time horizon did not exceed one-year, no discounting was performed. The model was programmed in TreeAge Pro 2007 (TreeAge Software Inc, Williamstown, MA).

We calculated QALYs by multiplying the time spent in each health state by corresponding EuroQol (EQ)-5D utilities estimates (scores between 1.0 and -0.564, on a scale where 1.0=perfect health and 0.0=death) for each angina frequency health state. EQ-5D utility scores were calculated by taking individual patient data from the ERICA trial and a applying them to a previously derived SAQ to UK EQ-5D mapping equation developed by Goldsmith and colleagues.[2,15]

This cost-effectiveness analysis was performed from the UK health-system perspective, and therefore, included only direct (inpatient, outpatient and drug) costs of treating stable angina. Direct medical costs were based on data from an economic sub-study of the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST Elevation Acute Coronary Syndrome (MERLIN)-TIMI 36 trial [6] which assessed the association between angina frequency and subsequent cardiovascular resource utilization among 5,460 stable outpatients who completed the SAQ 4-months after experiencing an ACS and who were then followed for an additional 8-months. The monthly cost of both doses of ranolazine were set

at published British National Formulary (BNF) pricing, and assumed to be the same for the 750 mg and 1,000 mg doses.[16] Since the CARISA trial [9] suggested no clinically relevant difference in efficacy between the 750 mg and 1,000 mg doses, we assumed the dose of ranolazine was titrated as in the ERICA trial even though the 1,000 mg dose is not approved in the UK. All costs were inflated, when needed, using the Medical Care component of the Consumer Price Index [17] and later expressed in 2014 British Sterling Pounds (£).

We performed one-way sensitivity analysis on all variables in Table 3 over their *a priori* determined plausible ranges. In addition, we performed a number of scenario analyses to test whether: 1) assuming 100% of patients started the model in the daily and weekly angina frequency health states, 2) factoring in indirect costs, 3) allowing mortality rates to vary based upon angina frequency health state severity, and 4) assuming not all patients failing to respond to ranolazine would discontinue therapy would impact the model's overall results and conclusions. We also performed an analysis changing the definition of response to ranolazine to a 20-point change in SAQAF (a previously determined threshold for a minimally important clinical improvement on the SAQAF domain).[14]

For our scenario analyses, lost productivity costs were derived from a published cost-of-illness study of stable angina patients [7]. This study calculated indirect costs, by estimating costs of lost productivity by those with stable angina, as well as all unpaid time devoted to caregiving by family members and friends. Mortality rates stratified by angina frequency published by Spertus and colleagues [5] were used to allow patients to transition to the death health state, conditional upon SAQ angina frequency health state, but not treatment arm.

Finally, we performed a 10,000-iteration Monte Carlo simulation (MCS) to determine the joint uncertainty of model parameters. For each variable in MCS, we assumed a triangle distribution (defined by a likeliest, low and high value) since the true nature of variance for these variables is not well

understood and the triangle distribution (when used appropriately) does not violate the requirements of any variable (i.e., costs cannot be less than $0 and probabilities and utilities must lie between 0 and 1). The results of the MCS are provided as an incremental cost-effectiveness plane, with ICERs <£0 and £20,000/QALY gained considered economically dominant and cost-effective, respectively.

RESULTS

Two hundred and seventy-seven subjects receiving ranolazine in the ERICA trial were analyzable, of whom 144 (52%) improved by at least 1 SAQAF classification during the 6-week double-blind trial period. Only 118 of 281 (42%) subjects in the SoC only (plus placebo) group met the response definition (absolute difference in response rates=10%, 95%CI=2 to 18%). Patients improving at least 1 SAQAF classification (regardless of treatment) experienced a mean 32±14 point change in SAQAF score from baseline. Ranolazine patients accrued a mean of 0.701 QALYs at a cost of £5,208. Those not receiving ranolazine accrued 0.662 QALYs and at a cost of £5,318. Thus, the addition of ranolazine was shown to be a dominant economic strategy.

In performing one-way sensitivity analysis, the ICER was found sensitive to ranolazine cost; exceeding £20,000/QALY when the cost of ranolazine increased to >£203/month (**Table 4**). Upon scenario analysis, ranolazine remained a dominant economic strategy when indirect costs were included in the model; when mortality rates were assumed to increase with worsening severity of SAQAF health states; or when both indirect costs and differences in mortality rates based upon SAQAF were assumed. The model indicated that ranolazine would remain cost-effective, even if 100% of patients classified as non-responders continued on ranolazine past the first month (ICER=£4,051/QALY). When the response to ranolazine was re-defined to incorporate a 20-point change on the SAQAF score (in the base-case analysis, response was defined as improving by at least 1 SAQAF health state), the ICER was £1,692/QALY. Monte Carlo simulation found the addition of ranolazine cost-effective in >99% of

10,000 iterations assuming a £20,000/QALY willingness-to-pay threshold, and a dominant economic strategy in 70.5% of iterations run (**Figure 2**).

Sensitivity or Scenario Analysis	Treatment	Cost	QALY	ICER vs. placebo
Base-Case	Ranolazine	£5,208	0.701	Ranolazine dominant
	SoC+Placebo	£5,318	0.662	---
100% Daily	Ranolazine	£5,915	0.639	Ranolazine dominant
	SoC+Placebo	£6,160	0.614	---
100% Weekly	Ranolazine	£5,058	0.713	Ranolazine dominant
	SoC+Placebo	£5,109	0.672	---
Mortality Differences Assumed	Ranolazine	£5,190	0.700	Ranolazine dominant
	SoC+Placebo	£5,272	0.659	---
Indirect Costs Included	Ranolazine	£9,237	0.701	Ranolazine dominant
	SoC+Placebo	£9,725	0.662	---
Indirect Costs Included and Mortality Differences Assumed	Ranolazine	£9,203	0.700	Ranolazine dominant
	SoC+Placebo	£9,639	0.659	---
20-point change	Ranolazine	£5,362	0.688	£1,692/QALY
	SoC+Placebo	£5,318	0.662	---

Table 4. Results of Base-Case, Sensitivity and Scenario Analyses
Results for the base-case and scenario analysis are depicted above. Incremental cost-effectiveness ratios were calculated as the difference in costs divided by the difference in quality-adjusted life-years between the two treatments. Ranolazine added to standard-of-care therapy was considered cost-effective compared to standard-of-care therapy alone when an Incremental cost-effectiveness ratio was less than £20,000/QALY.

DISCUSSION

The results of our economic analysis suggest that treatment of chronic stable angina with ranolazine is a dominant economic strategy when administered in addition to SoC antianginal in patients reporting daily or weekly angina symptoms. Importantly, our base-case analysis was built on the clinical assumption that patients who do not respond to ranolazine treatment (i.e., continue to suffer the same degree of anginal symptoms) are taken off therapy and behave similarly to placebo patients. This responder type analysis methodology has been utilized in other UK National Health Service/National Institute for Health and Care Excellence (NICE) cost-effectiveness models.[18,19] Of note, our analysis indicates that from a UK perspective, discontinuing therapy in patients not adequately responding to therapy is not necessary to achieve cost-effectiveness.

Importantly, the definition of response used in our analysis (requiring a decrease in symptoms as measured by improving an entire angina frequency classification) is one that is easily translatable to clinical practice by simply questioning patients if their angina frequency is daily, weekly, monthly or absent. Nonetheless, alterative responder definitions merit consideration. One of the scenario analysis we performed utilized an alternative responder definition requiring a 20-point improvement in SAQAF score.[14] Even with this more stringent definition of responder requiring a more robust benefit, the addition of ranolazine was still shown to be cost-effective with an ICER of £1,692/QALY gained.

A small number of prior European economic analyses performed from the Spanish,[20] Italian [21] and Russian perspectives [22] have also demonstrated the addition of ranolazine to SOC for the treatment of chronic angina patients can be economically substantiated. Two of these analyses [20,21] reported ICERs for ranolazine of ~€8,500/QALY gained; well below the €30,000/QALY gained willingness-to-pay threshold commonly referenced. The third, a Russian model,[22] did not calculated cost/QALY gained but rather used change in angina frequency as its principal measure of effectiveness. This economic model estimated increased expenditures for medication in the ranolazine group, but reduced costs of emergency care and hospitalizations; resulting in a 20% decrease in the cost-effectives ratio for ranolazine added to SOC vs. SOC alone (1,641 RUB vs. 1,965 RUB, respectively). Our model described in this paper is novel and adds important information to the current body of literature. To our knowledge, this is the first report of the cost-effectiveness of ranolazine from the UK health-system perspective. Additionally, the above-mentioned models [20-22] used only direct medical costs; while our model (as a sensitivity analysis) included both direct and indirect costs. The addition of indirect costs to our model yielded an even larger gap (decrease) in treatment costs with the use of ranolazine compared to SOC alone (delta: £488 vs. £110), substantiating the benefit of ranolazine from a societal perspective. Perhaps most importantly, our analysis is the only one to estimate transition probabilities and health utility scores using individual patient level data from the randomized controlled ERICA

trial.[10] Access to this level of data likely increases the internal validity of our model by providing more accurate estimates of transition probabilities across SAQAF health states; as well as, allowing us to map UK EQ-5D equivalent health utility values (the EQ-5D being NICE's preferred health utility measure) needed for calculating QALYs.[15,23]

There are also limitations to consider when putting the results of our model into context. First, our analysis evaluated the cost-effectiveness of ranolazine in those suffering weekly or daily angina. Therefore, it is unclear whether our findings would be generalizable to patients with less frequent angina symptoms (e.g., monthly). This being said, the TERISA trial [11] did support ranolazine's efficacy in a population with a wider range of angina frequencies (an average weekly angina frequency between 1 and 28, and at least 1 angina episode/week). Second, we needed to extrapolate the results of the 7-week double-blind treatment duration of the ERICA trial [10] to a 1-year time horizon. For this reason, we did not attempt to extend the model's time horizon out to longer than 1-year. It is also important to note, randomized trial subjects and data do not always accurately reflect real-life effectiveness and safety because participants may exhibit better adherence and receive superior follow-up. Third, the dosage of ranolazine utilized in ERICA [10] (500 mg twice daily for the first week followed by 1,000 mg twice daily thereafter) differs from the approved dose in Europe (initial dose of 375 mg twice daily, titrated to 500 mg twice daily after 2-4 weeks, and based upon patient response, further titrated to a maximum dose 750 mg twice daily).[23] Importantly, data from the CARISA trial [9] demonstrated greater improvements in exercise duration and reductions in angina attacks and nitroglycerin use compared to placebo with both the 750 mg ($p \leq 0.03$ for all endpoints) and 1,000 mg ($p \leq 0.03$ for all endpoints) twice daily doses of ranolazine at 12-weeks; with no clinically relevant difference in efficacy between the 750 mg and 1,000 mg doses. For this reason, using data from the 1,000 mg twice daily arm of pivotal ERICA trial in this European model seems acceptable. Finally, our model did not directly incorporate the impact of adverse drug reactions to ranolazine. These adverse

events; however, are typically not serious (e.g., usually limited to dizziness, nausea and constipation), and consequently are not likely to have any significant impact on costs or QALYs.[10,11]

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FIGURE LEGENDS

Figure 1. Schematic Representation of the Markov Model

The model was used to determine separately the total cost of treatment and quality-adjusted life-years accrued by the stable angina patients receiving and not receiving ranolazine. Regardless of treatment assignment, patients entered the model in one of 3 angina frequency health states based upon Seattle Angina Questionnaire angina frequency (SAQAF) scores (100=no; 61-99=monthly; 31-60=weekly; 0-30=daily angina; no patients started in "no" angina) and were allowed to transition between states in the first month based upon treatment specific probabilities derived from the Efficacy of Ranolazine in Chronic Angina trial and other studies. Patients not responding to ranolazine in month 1 (i.e., not improving ≥1 SAQAF health state) or experiencing an adverse event requiring discontinuation were assumed to stop taking ranolazine and behave like SoC (plus placebo) patients. Only patients assigned to receive ranolazine at the initiation of the model could discontinue therapy (for lack of efficacy or adverse drug events) and discontinuation could only occur during the first cycle. Patients randomized to SoC (plus placebo) started and had to remain "off drug". In the second through twelfth month, all patients were assumed to stay in the same angina frequency health state for the remainder of the model's time horizon or until death. Transition to death could occur during any cycle.

M=Markov node

Figure 2. Incremental Cost-Effectiveness Plane

Incremental cost-effectiveness plane based on 10,000 Monte Carlo simulation iterations, which drew parameters for each input simultaneously from probability distributions. Incremental cost (2014£) is on the vertical axis and incremental efficacy (quality-adjusted life-years) is on the horizontal axis. As depicted on the incremental cost-effectiveness plane, the probability of ranolazine being cost-effective was >99% (quadrants II and III), assuming a willingness-to-pay (WTP) threshold of £20,000/QALY. We

estimated there was a 70.5% chance the addition of ranolazine to standard of care therapy would be a dominant economic strategy compared to standard of care alone (quadrant III).

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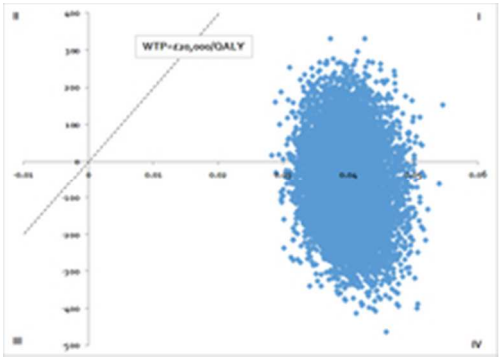
M=Markov node
17x7mm (300 x 300 DPI)



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20x14mm (300 x 300 DPI)

Table 1 – CHEERS checklist—Items to include when reporting economic evaluations of health interventions.

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	page 1/ line 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	page 2/
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	page 4/ line 1-5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page 5/ line 2-8
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page 4/ line 21-22
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page 4/ line 21-22
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	page 5/ line 5-7
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page 4/ line 21-22
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	page 9/ line 9-10
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	page 9/ line 4-9
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	page 5/ line 2, 8-19; page 7/ line 1-11; page 9/ line 1-10
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	page 5/ line 2-15
Estimating resources and costs	13a	*Single study based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	page 9/ line 17-20; page 10/ line 1-6; table 3, page 8
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	page 10/ line 4-6
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	page 4/ line 21-22; page 5/ line 1-3 (Fig); page 5, line 8-21; page 7, line 1-11
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	page 10/ line 7 - page 11/ line 1-4

BMJ Open

Ranolazine for the Treatment of Chronic Stable Angina: A Cost-Effectiveness Analysis from the United Kingdom Perspective

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-008861.R1
Article Type:	Research
Date Submitted by the Author:	19-Aug-2015
Complete List of Authors:	Coleman, Craig; University of Connecticut, School of Pharmacy and Evidence-Based Practice Center Freemantle, Nick; University College London, Department of Primary Care & Population Health Kohn, Christine; University of Saint Joseph, School of Pharmacy
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	CARDIOLOGY, Coronary heart disease < CARDIOLOGY, HEALTH ECONOMICS

Ranolazine for the Treatment of Chronic Stable Angina: A Cost-Effectiveness Analysis from the United Kingdom Perspective

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Running Head: Cost-effectiveness of ranolazine in the UK
Key words: ranolazine; angina, stable; cost-effectiveness analysis
Word count: 2,650

FUNDING

This work was supported by Menarini International Operations, Luxembourg, SA, makers of ranolazine. The authors maintained full control over the design and performance of the study; collection, management, analysis, and interpretation of the data; and preparation and review of the manuscript. The sponsor reviewed the final manuscript prior to submission. Drs. Coleman and Kohn had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

CONTRIBUTORS

Study concept and design: CIC, CGK, NF. Acquisition of data: CIC, CGK, NF. Analysis and interpretation of data: CIC, CGK, NF. Drafting of the manuscript: CIC, CGK. Critical revision of the manuscript for important intellectual content: CIC, CGK, NF. Administrative, technical, or material support: CIC, CGK. Study supervision: CIC. CIC and CGK had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICJME) and were fully responsible for all content and editorial decisions, and were involved in all stages of manuscript development.

CONFLICTS OF INTEREST

Dr. Coleman has received grant funding and consultancy fees from Gilead Sciences Inc., Foster City, CA, USA and Menarini International Operations, Luxembourg, SA. Dr. Freemantle received grant funding from Menarini International Operations, Luxembourg, SA. Dr. Kohn has no conflicts to report.

ABSTRACT

Introduction: Ranolazine decreases angina symptom frequency and nitroglycerin consumption and has a positive impact on patient functioning and quality-of-life. At present, the cost-effectiveness of ranolazine for stable angina has not been assessed from a United Kingdom (UK) perspective. We sought to estimate the cost-effectiveness of ranolazine when added to standard-of-care (SoC) antianginals compared with SoC alone in patients with stable coronary disease experiencing ≥3 attacks/week.

Methods: A Markov model utilizing a UK health-system perspective, a 1-month cycle-length, and a 1-year time horizon was developed to estimate costs (£2014) and quality-adjusted life years (QALYs) for patients receiving and not receiving ranolazine. Patients entered the model in 1 of 4 angina frequency health-states based upon Seattle Angina Questionnaire angina frequency (SAQAF) scores (100=no; 61 to 99=monthly; 31 to 60=weekly; and 0 to 30=daily angina) and were allowed to transition between states or to death based upon probabilities derived from the randomized, controlled Efficacy of Ranolazine in Chronic Angina (ERICA) trial and other published studies. Patients not responding to ranolazine in month 1 (not improving ≥1 SAQAF health-state) were assumed to discontinue ranolazine and behave like SoC patients.

Results: Ranolazine patients accrued a mean of 0.701 QALYs at a cost of £5,208. Those not receiving ranolazine accrued 0.662 QALYs at a cost of £5,318. The addition of ranolazine to SoC was therefore a dominant economic strategy. The incremental cost-effectiveness ratio (ICER) was sensitive to ranolazine cost; exceeding £20,000/QALY when ranolazine's cost was >£203/month. Ranolazine remained a dominant strategy when indirect costs were included and mortality rates were assumed to increase with worsening severity of SAQAF health-states. Monte Carlo simulation found ranolazine to be a dominant economic strategy in ~71% of 10,000 iterations.

Conclusion: Ranolazine added to SoC in patients with weekly or daily angina appears cost-effective from a UK health-system perspective.

ARTICLE SUMMARY

Article focus

- To estimate the cost-effectiveness of ranolazine when added to standard-of-care (SoC) antianginals compared with SoC alone in patients with stable coronary disease experiencing ≥3 attacks/week from a United Kingdom (UK) perspective.

Key messages

- The results suggest the addition of ranolazine to SoC therapy is an economically dominant strategy (less costly, more effective) for the treatment of chronic stable angina among patients suffering ≥3 angina attacks/week.
- Ranolazine can be considered an efficacious and cost-effective treatment strategy for stable angina patients experiencing weekly or daily angina symptoms.

Strengths and limitations of the study

- This is the first economic modeling study of ranolazine from the UK perspective
- The model utilized data from the randomized and controlled Efficacy of Ranolazine in Chronic Angina (ERICA) trial.
- It is unclear whether our findings are generalizable to patients with less frequent angina symptoms.
- Results of the short duration ERICA trial were extrapolated to a 1-year time horizon.

The prevalence of stable angina in the United Kingdom (UK) is about 2.1 million people.[1] Stable angina is associated with an unfavorable impact on health-related quality-of-life (HrQoL),[2-3] morbidity and mortality [4] and economic outcomes (increased direct and lost productivity costs);[5,6] with afflicted patients reporting their health to be twice as poor as those who previously suffered a stroke, and direct treatment costs of at least £700 million per year.[7]

Ranolazine is indicated in the UK for the treatment of chronic stable angina and the National Institute for health and Care Excellence (NICE) endorses it use in persons with stable angina whom cannot tolerate or have contraindications to the first line therapies of beta-blockers or calcium channel blockers, or for persons whom symptoms are not controlled after optimal use of beta-blockers and calcium channel blockers [8]. The Combination Assessment of Ranolazine In Stable Angina (CARISA),[9] Efficacy of Ranolazine in Chronic Angina (ERICA) [10] and Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina (TERISA) [11] randomized controlled trials demonstrated ranolazine's ability to significantly reduce weekly angina frequency by 0.4 to 1.2 attacks when added to standard-of-care (SoC) antianginal therapies, as well as, reduce sublingual nitroglycerin consumption. Moreover, in TERISA, ranolazine was found to significantly improve stable angina patient HrQoL, as evidence by an improvement in the physical component sub score of the Short-Form-36.[11]

Here we report the results of a cost-effectiveness analysis from a UK perspective to estimate the costs, quality-adjusted life-years (QALYs) and incremental cost-effectiveness of ranolazine when added to SoC antianginal therapy compared to SoC antianginal therapy alone in stable coronary disease patients experiencing frequent angina attacks.

METHODS

We followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement in reporting this cost-effectiveness analysis.[12]

This Markov model utilized a 1-year time horizon, a cycle length of 1-month and was performed from the UK health-system perspective. It included 5 mutually exclusive health states; 4 related to angina frequency (no, monthly, weekly and daily angina symptoms) and the absorbing health state of death (**Figure 1**). This model was built using efficacy and tolerability data from the ERICA trial;[10] a randomized controlled trial of 565 patients with stable coronary artery disease experiencing ≥3 angina attacks/week (i.e., 5.6±0.18 episodes/week and consuming 4.7±0.21 nitroglycerin tablets/week) assigned to receive ranolazine (500 mg twice daily for the first week followed by 1,000 mg twice daily thereafter) or placebo in addition to SoC antianginal therapy (including a maximal dose of amlodipine in all patients, 45% and 52% long-acting nitrate and angiotensin-converting enzyme inhibitor use, and no beta-blocker use). As observed in ERICA, patients entering the model started in 1 of 3 of the 4 angina frequency health states (no patients started in the "no angina" state) based upon Seattle Angina Questionnaire Angina Frequency (SAQAF) domain scores.[13] Patients scoring 100 points on the SAQAF were deemed to have no angina symptoms, whereas scores of 61-99, 31-60 and 0-30 represented monthly, weekly and daily angina symptoms, respectively.[14] We utilized the SAQAF to define our model's health states because it was an important patient-reported outcome measure utilized in the ERICA trial [10] and has been used in other angina clinical trials [9,11] and prior stable angina epidemiologic and cost-of-illness analyses.[2-5,13]

Our model followed patients as they transited between the 4 above-mentioned angina frequency health states and the death state. The model's first set of 12, one-month cycle-length transition probabilities were calculated directly from the ERICA trial using individual patient data.[10] Transition probabilities for ranolazine patients achieving adequate efficacy on-treatment, defined as improving by

at least 1 angina frequency health state (e.g., transitioning from daily to weekly angina symptoms) were calculated based upon rates observed in corresponding ERICA patients (**Table 2**). For patients not receiving ranolazine, the probability of moving from one angina frequency health state to another was calculated based upon those observed in the SoC arm of the ERICA trial (**Table 1**).

		SAQAF EOT Classification			
		No	Monthly	Weekly	Daily
SAQAF Baseline Classification	No	---	---	---	---
	Monthly	2/2 (100%) 95%CI (34%-100%)	---	---	---
	Weekly	13/95 (13.7%) 95%CI (8%-22%)	82/95 (86.3%) 95%CI (78%-92%)	---	---
	Daily	2/47 (4.3%) 95%CI (1%-14%)	10/47 (21.3%) 95%CI (12%-35%)	35/47 (74.5%) 95%CI (60%-85%)	---

Table 1. Transition Probability Matrix for Ranolazine Responders During the First Cycle
CI=confidence interval; EOT=end-of-treatment; SAQAF=Seattle Angina Questionnaire Angina Frequency
The Seattle Angina Questionnaire Angina Frequency Domain category ranolazine responders started in are depicted on the vertical axis (100=no; 61-99=monthly, 31-60=weekly and 0-30=daily symptoms) and the category they finished the double-blind trial period in is depicted on the horizontal axis. For example, 47 ranolazine responders began the study reporting "daily" angina symptoms and 0 (0%), 35 (74.5%), 10 (21.3%) and 2 (4.3%) of these same patients reported having daily, weekly, monthly and no angina symptoms at the end of the trial.

		SAQAF EOT Classification			
		No	Monthly	Weekly	Daily
SAQAF Baseline Classification	No	---	---	---	---
	Monthly	1/20 (5.0%) 95%CI (0.9%-24%)	17/20 (85.0%) 95%CI (64%-95%)	2/20 (10.0%) 95%CI (3.0%-30%)	0/20 (0%) 95%CI (0%-16%)
	Weekly	8/193 (4.1%) 95%CI (2%-8%)	65/193 (33.7%) 95%CI (27%-41%)	112/193 (58.0%) 95%CI (51%-65%)	8/193 (4.1%) 95%CI (2%-8%)
	Daily	2/68 (2.9%) 95%CI (0.8%-10%)	9/68 (13.2%) 95%CI (7%-23%)	33/68 (48.5%) 95%CI (37%-60%)	24/68 (35.3%) 95%CI (25%-47%)

Table 2. Transition Probability Matrix for Standard-of-Care (Plus Placebo) During the First Cycle
CI=confidence interval; EOT=end-of-treatment; SAQAF=Seattle Angina Questionnaire Angina Frequency
The Seattle Angina Questionnaire Angina Frequency Domain category standard-of-care patients started in are depicted on the vertical axis (100=no; 61-99=monthly, 31-60=weekly and 0-30=daily symptoms) and the category they finished the double-blind trial period in is depicted on the horizontal axis. For example, 68 standard-of-care patients began the study reporting "daily" angina symptoms and 24 (35.3%), 33 (48.5%), 9 (13.2%) and 2 (2.9%) of these same patients reported having daily, weekly, monthly and no angina symptoms at the end of the trial.

Starting the second month (cycle 2) onwards, all patients were assumed to stay in the same angina frequency health state (no loss or additional efficacy in either treatment group could occur) for the remainder of the model's time horizon unless they died. During any cycle of the model, patients could transition to the death health state based upon all-cause mortality rates in angina patients, derived from a prospective cohort study of coronary artery disease patients from 6 Veterans Affairs General Internal Medicine Clinics.[4]

Patients receiving ranolazine could also discontinue treatment due to adverse drug reactions or lack of efficacy during, and only during, the first month of treatment. This assumption was based upon the reasoning that patients reporting a lack of efficacy or adverse reactions requiring discontinuation of therapy would most likely do so in the first month [10,11] and data from the TERISA trial [11] suggesting the majority of the effect of ranolazine is seen in the first few weeks of treatment. The rates of ranolazine discontinuation due to adverse reactions and lack of efficacy were derived from the ERICA trial (**Table 3**). For those patients discontinuing ranolazine for any reason, transition probabilities were assumed to follow the same pattern as SoC (plus placebo) patients.

Variable	Base-Case	Range	Reference
SAQAF classification definition			
No	SAQAF=100	NA	6,13
Monthly	SAQAF=61-99	NA	6,13
Weekly	SAQAF=31-60	NA	6,13
Daily	SAQAF=0-30	NA	6,13
SAQAF classification at baseline			6,10
No	0%	NA	6,10
Monthly	6.1%	100%	6,10
Weekly	71.0%	100%	6,10
Daily	22.9%	100%	6,10
Definition of SAQAF responder	Improvement of ≥1 SAQAF classification	20-point change in SAQAF	5,6
Ranolazine non-response	48% during first 4-weeks	42.2%-53.9%	10
Ranolazine discontinuation due to AE	1.1% during first 4-weeks	0.37%-6%	10
All-cause mortality by angina frequency			
No	4.6%/year	3.8%-5.5%	5
Monthly	4.8%/year	3.8%-6.1%	5
Weekly	8.1%/year	6.1%-10.8%	5
Daily	10.9%/year	7.5%-15.4%	5
All-cause mortality for all angina patients	5.8%/year	NA	5
Angina frequency utility (using EOT data)			2,10,15
No	0.87	0.84-0.90	2,10,15
Monthly	0.76	0.75-0.77	2,10,15
Weekly	0.65	0.64-0.66	2,10,15
Daily	0.54	0.52-0.56	2,10,15
Cost of ranolazine twice daily at any dose	£48.98/month	£24.49-£97.96	16
Stable angina direct treatment costs/year (not including ranolazine)			6
No	£3,529	£3,276-£3,786	6
Monthly	£4,711	£4,255-£5,023	6
Weekly	£5,493	£4,765-£6,229	6
Daily	£8,374	£6,754-£9,990	6
Stable angina indirect costs/year			
No	£2,362	£1,011-£3,373	7
Monthly	£4,012	£2,694-£5,395	7
Weekly	£4,271	£2,694-£5,395	7
Daily	£8,194	£5,395-£10,783	7

Table 3. Base-Case Variables and Ranges Used in Sensitivity Analysis

EOT=end-of-treatment; NA=not applicable; SAQAF=Seattle Angina Questionnaire Angina Frequency

Our model determined the mean total cost of treatment accrued by the patient cohorts receiving and not receiving ranolazine separately, as well as the mean number of QALYs. This allowed for the calculation of incremental cost-effectiveness ratios (ICERs) defined as the difference in mean costs between the ranolazine plus SoC and SoC alone (plus placebo) patients divided by the difference in mean QALYs for each treatment. We also provide in this report an ICER defined as the difference in mean costs between the two groups divided by the difference in SAQAF response rate. Since the time horizon did not exceed one-year, no discounting was performed. The model was programmed in TreeAge Pro 2007 (TreeAge Software Inc, Williamstown, MA).

We calculated QALYs by multiplying the time spent in each health state by corresponding EuroQol (EQ)-5D utilities estimates (scores between 1.0 and -0.564, on a scale where 1.0=perfect health and 0.0=death) for each angina frequency health state. EQ-5D utility scores were calculated by taking individual patient data from the ERICA trial and a applying them to a previously derived SAQ to UK EQ-5D mapping equation developed by Goldsmith and colleagues.[2,15]

This cost-effectiveness analysis was performed from the UK health-system perspective, and therefore, included only direct (inpatient, outpatient and drug) costs of treating stable angina. Direct medical costs were based on data from an economic sub-study of the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST Elevation Acute Coronary Syndrome (MERLIN)-TIMI 36 trial [6] which assessed the association between angina frequency and subsequent cardiovascular resource utilization among 5,460 stable outpatients who completed the SAQ 4-months after experiencing an ACS and who were then followed for an additional 8-months. The monthly cost of both doses of ranolazine were set at published British National Formulary (BNF) pricing, and assumed to be the same for the 750 mg and 1,000 mg doses.[16] Since the CARISA trial [9] suggested no clinically relevant difference in efficacy between the 750 mg and 1,000 mg doses, we assumed the dose of ranolazine was titrated as in the

ERICA trial even though the 1,000 mg dose is not approved in the UK. All costs were inflated, when needed, using the Medical Care component of the Consumer Price Index [17] and later expressed in 2014 British Sterling Pounds (£).

We performed one-way sensitivity analysis on all variables in Table 3 over their *a priori* determined plausible ranges. In addition, we performed a number of scenario analyses to test whether: 1) assuming 100% of patients started the model in the daily and weekly angina frequency health states, 2) factoring in indirect costs, 3) allowing mortality rates to vary based upon angina frequency health state severity, and 4) assuming not all patients failing to respond to ranolazine would discontinue therapy would impact the model's overall results and conclusions. We also performed an analysis changing the definition of response to ranolazine to a 20-point change in SAQAF (a previously determined threshold for a minimally important clinical improvement on the SAQAF domain).[14]

For our scenario analyses, lost productivity costs were derived from a published cost-of-illness study of stable angina patients [6]. This study calculated indirect costs, by estimating costs of lost productivity by those with stable angina, as well as all unpaid time devoted to caregiving by family members and friends. Mortality rates stratified by angina frequency published by Spertus and colleagues [4] were used to allow patients to transition to the death health state, conditional upon SAQ angina frequency health state, but not treatment arm.

Finally, we performed a 10,000-iteration Monte Carlo simulation (MCS) to determine the joint uncertainty of model parameters. For each variable in MCS, we assumed a triangle distribution (defined by a likeliest, low and high value) since the true nature of variance for these variables is not well understood and the triangle distribution (when used appropriately) does not violate the requirements of any variable (i.e., costs cannot be less than $0 and probabilities and utilities must lie between 0 and

1). The results of the MCS are provided as an incremental cost-effectiveness plane, with ICERs <£0 and £20,000/QALY gained considered economically dominant and cost-effective, respectively.

RESULTS

Two hundred and seventy-seven subjects (97% from Eastern Europe) receiving ranolazine in the ERICA trial were analyzable, of whom 144 (52%) improved by at least 1 SAQAF classification during the 6-week double-blind trial period. Only 118 of 281 (42%) subjects in the SoC only (plus placebo) group met the response definition (absolute difference in response rates=10%, 95%CI=2 to 18%). Patients improving at least 1 SAQAF classification (regardless of treatment) experienced a mean 32±14 point change in SAQAF score from baseline. Ranolazine patients accrued a mean of 0.701 QALYs at a cost of £5,208. Those not receiving ranolazine accrued 0.662 QALYs and at a cost of £5,318. Thus, the addition of ranolazine was shown to be a dominant economic strategy.

In performing one-way sensitivity analysis, the ICER was found sensitive to ranolazine cost; exceeding £20,000/QALY when the cost of ranolazine increased to >£203/month (**Table 4**). Upon scenario analysis, ranolazine remained a dominant economic strategy when indirect costs were included in the model; when mortality rates were assumed to increase with worsening severity of SAQAF health states; or when both indirect costs and differences in mortality rates based upon SAQAF were assumed. The model indicated that ranolazine would remain cost-effective, even if 100% of patients classified as non-responders continued on ranolazine past the first month (ICER=£4,051/QALY). When the response to ranolazine was re-defined to incorporate a 20-point change on the SAQAF score (in the base-case analysis, response was defined as improving by at least 1 SAQAF health state), the ICER was £1,692/QALY. Monte Carlo simulation found the addition of ranolazine cost-effective in >99% of 10,000 iterations assuming a £20,000/QALY willingness-to-pay threshold, and a dominant economic strategy in 70.5% of iterations run (**Figure 2**).

Table 4. Results of Base-Case, Sensitivity and Scenario Analyses

Results for the base-case and scenario analysis are depicted above. Incremental cost-effectiveness ratios were calculated as the difference in costs divided by the difference in quality-adjusted life-years between the two treatments. Ranolazine added to standard-of-care therapy was considered cost-effective compared to standard-of-care therapy alone when an Incremental cost-effectiveness ratio was less than £20,000/QALY.

Sensitivity or Scenario Analysis	Treatment	Cost	QALY	ICER vs. placebo
Base-Case	Ranolazine	£5,208	0.701	Ranolazine dominant
	SoC+Placebo	£5,318	0.662	---
100% Daily	Ranolazine	£5,915	0.639	Ranolazine dominant
	SoC+Placebo	£6,160	0.614	---
100% Weekly	Ranolazine	£5,058	0.713	Ranolazine dominant
	SoC+Placebo	£5,109	0.672	---
Mortality Differences Assumed	Ranolazine	£5,190	0.700	Ranolazine dominant
	SoC+Placebo	£5,272	0.659	---
Indirect Costs Included	Ranolazine	£9,237	0.701	Ranolazine dominant
	SoC+Placebo	£9,725	0.662	---
Indirect Costs Included and Mortality Differences Assumed	Ranolazine	£9,203	0.700	Ranolazine dominant
	SoC+Placebo	£9,639	0.659	---
20-point change	Ranolazine	£5,362	0.688	£1,692/QALY
	SoC+Placebo	£5,318	0.662	---

DISCUSSION

The results of our economic analysis suggest that treatment of chronic stable angina with ranolazine is a dominant economic strategy when administered in addition to SoC antianginal in patients reporting daily or weekly angina symptoms. Importantly, our base-case analysis was built on the clinical assumption that patients who do not respond to ranolazine treatment (i.e., continue to suffer the same degree of anginal symptoms) are taken off therapy and behave similarly to placebo patients. This responder type analysis methodology has been utilized in other UK National Health Service/National Institute for Health and Care Excellence (NICE) cost-effectiveness models.[18,19] Of note, our analysis indicates that from a UK perspective, discontinuing therapy in patients not adequately responding to therapy is not necessary to achieve cost-effectiveness.

Importantly, the definition of response used in our analysis (requiring a decrease in symptoms as measured by improving an entire angina frequency classification) is one that is easily translatable to clinical practice by simply questioning patients if their angina frequency is daily, weekly, monthly or

absent. Nonetheless, alterative responder definitions merit consideration. One of the scenario analysis we performed utilized an alternative responder definition requiring a 20-point improvement in SAQAF score.[14] Even with this more stringent definition of responder requiring a more robust benefit, the addition of ranolazine was still shown to be cost-effective with an ICER of £1,692/QALY gained.

A small number of prior European economic analyses performed from the Spanish,[20] Italian [21] and Russian perspectives [22] have also demonstrated the addition of ranolazine to SOC for the treatment of chronic angina patients can be economically substantiated. Two of these analyses [20,21] reported ICERs for ranolazine of ~€8,500/QALY gained; well below the €30,000/QALY gained willingness-to-pay threshold commonly referenced. The third, a Russian model,[22] did not calculated cost/QALY gained but rather used change in angina frequency as its principal measure of effectiveness. This economic model estimated increased expenditures for medication in the ranolazine group, but reduced costs of emergency care and hospitalizations; resulting in a 20% decrease in the cost-effectives ratio for ranolazine added to SOC vs. SOC alone (1,641 RUB vs. 1,965 RUB, respectively). Our model described in this paper is novel and adds important information to the current body of literature. To our knowledge, this is the first report of the cost-effectiveness of ranolazine from the UK health-system perspective, and our findings are supportive of NICE's current recommendation for ranolazine use in stable angina [8]. Additionally, the above-mentioned models [20-22] used only direct medical costs; while our model (as a sensitivity analysis) included both direct and indirect costs. The addition of indirect costs to our model yielded an even larger gap (decrease) in treatment costs with the use of ranolazine compared to SOC alone (delta: £488 vs. £110), substantiating the benefit of ranolazine from a societal perspective. Perhaps most importantly, our analysis is the only one to estimate transition probabilities and health utility scores using individual patient level data from the randomized controlled ERICA trial.[10] Access to this level of data likely increases the internal validity of our model by providing more accurate estimates of transition probabilities across SAQAF health states; as well as,

allowing us to map UK EQ-5D equivalent health utility values (the EQ-5D being NICE's preferred health utility measure) needed for calculating QALYs.[15,23]

There are also limitations to consider when putting the results of our model into context. First, our analysis evaluated the cost-effectiveness of ranolazine in those suffering weekly or daily angina. Therefore, it is unclear whether our findings would be generalizable to patients with less frequent angina symptoms (e.g., monthly). This being said, the TERISA trial [11] did support ranolazine's efficacy in a population with a wider range of angina frequencies (an average weekly angina frequency between 1 and 28, and at least 1 angina episode/week). Second, we needed to extrapolate the results of the 7-week double-blind treatment duration of the ERICA trial [10] to a 1-year time horizon. Because the duration to which ranolazine will remain efficacious is unclear, we did not attempt to extend the model's time horizon out to longer than 1-year. The fact that ~85% of patients in the Ranolazine Open Label Experience (ROLE) remained on therapy and only 4.2% of 746 ranolazine-treated patients electively discontinued therapy at 1-year suggests our 1-year time horizon may be justifiable [24]. It is also important to note that we assumed UK patients as a group would have similar response to ranolazine as patients enrolled in the multinational ERICA trial. Unfortunately, data to test this assumption was not available in ERICA. Third, the dosage of ranolazine utilized in ERICA [10] (500 mg twice daily for the first week followed by 1,000 mg twice daily thereafter) differs from the approved dose in Europe (initial dose of 375 mg twice daily, titrated to 500 mg twice daily after 2-4 weeks, and based upon patient response, further titrated to a maximum dose 750 mg twice daily).[23] Importantly, data from the CARISA trial [9] demonstrated greater improvements in exercise duration and reductions in angina attacks and nitroglycerin use compared to placebo with both the 750 mg ($p \leq 0.03$ for all endpoints) and 1,000 mg ($p \leq 0.03$ for all endpoints) twice daily doses of ranolazine at 12-weeks; with no clinically relevant difference in efficacy between the 750 mg and 1,000 mg doses. For this reason, using data from the 1,000 mg twice daily arm of pivotal ERICA trial in this European model seems acceptable.

Fourth, in the ERICA trial, beta-blockers were not used to treat angina and therefore we could not assess the cost-effectiveness of adding ranolazine to beta-blocker therapy (which is often effective and inexpensive). Importantly, the TERISA trial provides data suggesting ranolazine remained efficacious when added to ~90% beta-blocker background therapy [11]. Despite this, additional cost-effectiveness analyses based on TERISA data would helpful in demonstrating ranolazine's cost-effectiveness in heavily beta-blocker treated population (as well as in a wider range of angina symptom frequencies and diabetic patients). Finally, our model did not directly incorporate the impact of adverse drug reactions to ranolazine. These adverse events; however, are typically not serious (e.g., usually limited to dizziness, nausea and constipation), and consequently are not likely to have any significant impact on costs or QALYs.[10,11]

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FIGURE LEGENDS

Figure 1. Schematic Representation of the Markov Model

The model was used to determine separately the total cost of treatment and quality-adjusted life-years accrued by the stable angina patients receiving and not receiving ranolazine. Regardless of treatment assignment, patients entered the model in one of 3 angina frequency health states based upon Seattle Angina Questionnaire angina frequency (SAQAF) scores (100=no; 61-99=monthly; 31-60=weekly; 0-30=daily angina; no patients started in "no" angina) and were allowed to transition between states in the first month based upon treatment specific probabilities derived from the Efficacy of Ranolazine in Chronic Angina trial and other studies. Patients not responding to ranolazine in month 1 (i.e., not improving ≥1 SAQAF health state) or experiencing an adverse event requiring discontinuation were assumed to stop taking ranolazine and behave like SoC (plus placebo) patients. Only patients assigned to receive ranolazine at the initiation of the model could discontinue therapy (for lack of efficacy or adverse drug events) and discontinuation could only occur during the first cycle. Patients randomized to SoC (plus placebo) started and had to remain "off drug". In the second through twelfth month, all patients were assumed to stay in the same angina frequency health state for the remainder of the model's time horizon or until death. Transition to death could occur during any cycle.

M=Markov node

Figure 2. Incremental Cost-Effectiveness Plane

Incremental cost-effectiveness plane based on 10,000 Monte Carlo simulation iterations, which drew parameters for each input simultaneously from probability distributions. Incremental cost (2014£) is on the vertical axis and incremental efficacy (quality-adjusted life-years) is on the horizontal axis. As depicted on the incremental cost-effectiveness plane, the probability of ranolazine being cost-effective

was >99% (quadrants II and III), assuming a willingness-to-pay (WTP) threshold of £20,000/QALY. We estimated there was a 70.5% chance the addition of ranolazine to standard of care therapy would be a dominant economic strategy compared to standard of care alone (quadrant III).

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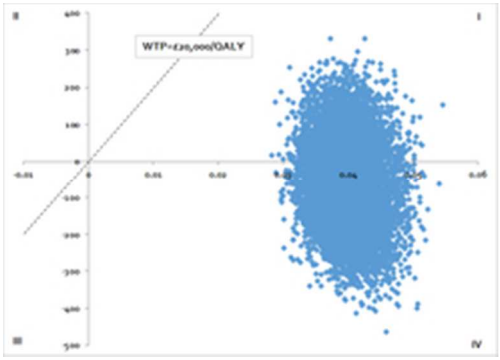
M=Markov node
17x7mm (300 x 300 DPI)



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20x14mm (300 x 300 DPI)

Table 1 – CHEERS checklist—Items to include when reporting economic evaluations of health interventions.

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	page 1/ line 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	page 2/
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	page 4/ line 1-5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page 5/ line 2-8
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page 4/ line 21-22
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page 4/ line 21-22
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	page 5/ line 5-7
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page 4/ line 21-22
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	page 9/ line 9-10
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	page 9/ line 4-9
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	page 5/ line 2, 8-19; page 7/ line 1-11; page 9/ line 1-10
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	page 5/ line 2-15
Estimating resources and costs	13a	*Single study based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	page 9/ line 17-20; page 10/ line 1-6; table 3, page 8
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	page 10/ line 4-6
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	page 4/ line 21-22; page 5/ line 1-3 (Fig); page 5, line 8-21; page 7, line 1-11
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	page 10/ line 7 - page 11/ line 1-4

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-008861.R2
Article Type:	Research
Date Submitted by the Author:	21-Sep-2015
Complete List of Authors:	Coleman, Craig; University of Connecticut, School of Pharmacy and Evidence-Based Practice Center Freemantle, Nick; University College London, Department of Primary Care & Population Health Kohn, Christine; University of Saint Joseph, School of Pharmacy
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	CARDIOLOGY, Coronary heart disease < CARDIOLOGY, HEALTH ECONOMICS

Ranolazine for the Treatment of Chronic Stable Angina: A Cost-Effectiveness Analysis from the United Kingdom Perspective

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Running Head: Cost-effectiveness of ranolazine in the UK
Key words: ranolazine; angina, stable; cost-effectiveness analysis
Word count: 2,650

ABSTRACT

Objectives: To estimate the cost-effectiveness of ranolazine when added to standard-of-care (SoC) antianginals compared with SoC alone in stable coronary disease patients experiencing ≥3 attacks/week.

Setting: An economic model utilizing a United Kingdom (UK) health-system perspective, a 1-month cycle-length and a 1-year time horizon.

Participants: Stable coronary disease patients experiencing ≥3 attacks/week starting in 1 of 4 angina frequency health-states based upon Seattle Angina Questionnaire angina frequency (SAQAF) scores (100=no; 61-99=monthly; 31-60=weekly; 0-30=daily angina).

Intervention: Ranolazine added to SoC or SOC alone. Patients were allowed to transition between SAQAF states (first cycle only) or death (any cycle) based upon probabilities derived from the randomized, controlled Efficacy of Ranolazine in Chronic Angina trial and other studies. Patients not responding to ranolazine in month 1 (not improving ≥1 SAQAF health-state) discontinued ranolazine and were assumed to behave like SoC patients.

Primary and secondary outcomes measures: Costs (£2014) and quality-adjusted life-years (QALYs) for patients receiving and not receiving ranolazine.

Results: Ranolazine patients lived a mean of 0.701 QALYs at a cost of £5,208. Those not receiving ranolazine lived 0.662 QALYs at a cost of £5,318. The addition of ranolazine to SoC was therefore a dominant economic strategy. The incremental cost-effectiveness ratio (ICER) was sensitive to ranolazine cost; exceeding £20,000/QALY when ranolazine's cost was >£203/month. Ranolazine remained a dominant strategy when indirect costs were included and mortality rates were assumed to increase with worsening severity of SAQAF health-states. Monte Carlo simulation found ranolazine to be a dominant strategy in ~71% of 10,000 iterations.

Conclusion: Although UK specific data on ranolzine's efficacy and safety are lacking, our analysis suggest ranolazine added to SoC in patients with weekly or daily angina is likely cost-effective from a UK health-system perspective.

ARTICLE SUMMARY

Article focus

- To estimate the cost-effectiveness of ranolazine when added to standard-of-care (SoC) antianginals compared with SoC alone in patients with stable coronary disease experiencing ≥3 attacks/week from a United Kingdom (UK) perspective.

Key messages

- The results suggest the addition of ranolazine to SoC therapy is an economically dominant strategy (less costly, more effective) for the treatment of chronic stable angina among patients suffering ≥3 angina attacks/week.
- Ranolazine can be considered an efficacious and cost-effective treatment strategy for stable angina patients experiencing weekly or daily angina symptoms.

Strengths and limitations of the study

- This is the first economic modeling study of ranolazine from the UK perspective.
- The model utilized data from the randomized and controlled Efficacy of Ranolazine in Chronic Angina (ERICA) trial.
- As a simplifying assumption, angina states were assumed not to change after the first month.
- It is unclear whether our findings are generalizable to patients with less frequent angina symptoms.
- Results of the short duration ERICA trial were extrapolated to a 1-year time horizon.

The prevalence of stable angina in the United Kingdom (UK) is about 2.1 million people.[1] Stable angina is associated with an unfavorable impact on health-related quality-of-life (HrQoL),[2-3] morbidity and mortality [4] and economic outcomes (increased direct and lost productivity costs);[5,6] with afflicted patients reporting their health to be twice as poor as those who previously suffered a stroke, and direct treatment costs of at least £700 million per year.[7]

Ranolazine is indicated in the UK for the treatment of chronic stable angina and the National Institute for health and Care Excellence (NICE) endorses it use in persons with stable angina whom cannot tolerate or have contraindications to the first line therapies of beta-blockers or calcium channel blockers, or for persons whom symptoms are not controlled after optimal use of beta-blockers and calcium channel blockers [8]. The Combination Assessment of Ranolazine In Stable Angina (CARISA),[9] Efficacy of Ranolazine in Chronic Angina (ERICA) [10] and Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina (TERISA) [11] randomized controlled trials demonstrated ranolazine's ability to significantly reduce weekly angina frequency by 0.4 to 1.2 attacks when added to standard-of-care (SoC) antianginal therapies, as well as, reduce sublingual nitroglycerin consumption. Moreover, in TERISA, ranolazine was found to significantly improve stable angina patient HrQoL, as evidence by an improvement in the physical component sub score of the Short-Form-36.[11]

Here we report the results of a cost-effectiveness analysis from a UK perspective to estimate the costs, quality-adjusted life-years (QALYs) and incremental cost-effectiveness of ranolazine when added to SoC antianginal therapy compared to SoC antianginal therapy alone in stable coronary disease patients experiencing frequent angina attacks.

METHODS

We followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement in reporting this cost-effectiveness analysis.[12]

This economic decision model utilized a 1-year time horizon, a cycle length of 1-month and was performed from the UK health-system perspective. It included 5 mutually exclusive health states; 4 related to angina frequency (no, monthly, weekly and daily angina symptoms) and the absorbing health state of death (**Figure 1**). This model was built using efficacy and tolerability data from the ERICA trial;[10] a randomized controlled trial of 565 patients with stable coronary artery disease experiencing ≥3 angina attacks/week (i.e., 5.6±0.18 episodes/week and consuming 4.7±0.21 nitroglycerin tablets/week) assigned to receive ranolazine (500 mg twice daily for the first week followed by 1,000 mg twice daily thereafter) or placebo in addition to SoC antianginal therapy (including a maximal dose of amlodipine in all patients, 45% and 52% long-acting nitrate and angiotensin-converting enzyme inhibitor use, and no beta-blocker use). As observed in ERICA, patients entering the model started in 1 of 3 of the 4 angina frequency health states (no patients started in the "no angina" state) based upon Seattle Angina Questionnaire Angina Frequency (SAQAF) domain scores.[13] Patients scoring 100 points on the SAQAF were deemed to have no angina symptoms, whereas scores of 61-99, 31-60 and 0-30 represented monthly, weekly and daily angina symptoms, respectively.[14] We utilized the SAQAF to define our model's health states because it was an important patient-reported outcome measure utilized in the ERICA trial [10] and has been used in other angina clinical trials [9,11] and prior stable angina epidemiologic and cost-of-illness analyses.[2-5,13]

Patients transited between the 4 above-mentioned angina frequency health states and the death state during the first cycle. After this, patients were assumed to remain in the same health state, apart from those who died. The model's first set of 12, one-month cycle-length transition probabilities were

calculated directly from the ERICA trial using individual patient data.[10] Transition probabilities for ranolazine patients achieving adequate efficacy on-treatment, defined as improving by at least 1 angina frequency health state (e.g., transitioning from daily to weekly angina symptoms) were calculated based upon rates observed in corresponding ERICA patients (**Table 1**). For patients not receiving ranolazine, the probability of moving from one angina frequency health state to another was calculated based upon those observed in the SoC arm of the ERICA trial (**Table 2**).

		SAQAF EOT Classification			
		No	Monthly	Weekly	Daily
SAQAF Baseline Classification	No	---	---	---	---
	Monthly	2/2 (100%) 95%CI (34%-100%)	---	---	---
	Weekly	13/95 (13.7%) 95%CI (8%-22%)	82/95 (86.3%) 95%CI (78%-92%)	---	---
	Daily	2/47 (4.3%) 95%CI (1%-14%)	10/47 (21.3%) 95%CI (12%-35%)	35/47 (74.5%) 95%CI (60%-85%)	---

Table 1. Transition Probability Matrix for Ranolazine Responders During the First Cycle
CI=confidence interval; EOT=end-of-treatment; SAQAF=Seattle Angina Questionnaire Angina Frequency
The Seattle Angina Questionnaire Angina Frequency Domain category ranolazine responders started in are depicted on the vertical axis (100=no; 61-99=monthly, 31-60=weekly and 0-30=daily symptoms) and the category they finished the double-blind trial period in is depicted on the horizontal axis. For example, 47 ranolazine responders began the study reporting "daily" angina symptoms and 0 (0%), 35 (74.5%), 10 (21.3%) and 2 (4.3%) of these same patients reported having daily, weekly, monthly and no angina symptoms at the end of the trial.

	SAQAF EOT Classification				
		No	Monthly	Weekly	Daily

SAQAF Baseline Classification	No	---	---	---	---
	Monthly	1/20 (5.0%) 95%CI (0.9%-24%)	17/20 (85.0%) 95%CI (64%-95%)	2/20 (10.0%) 95%CI (3.0%-30%)	0/20 (0%) 95%CI (0%-16%)
	Weekly	8/193 (4.1%) 95%CI (2%-8%)	65/193 (33.7%) 95%CI (27%-41%)	112/193 (58.0%) 95%CI (51%-65%)	8/193 (4.1%) 95%CI (2%-8%)
	Daily	2/68 (2.9%) 95%CI (0.8%-10%)	9/68 (13.2%) 95%CI (7%-23%)	33/68 (48.5%) 95%CI (37%-60%)	24/68 (35.3%) 95%CI (25%-47%)

Table 2. Transition Probability Matrix for Standard-of-Care (Plus Placebo) During the First Cycle
CI=confidence interval; EOT=end-of-treatment; SAQAF=Seattle Angina Questionnaire Angina Frequency
The Seattle Angina Questionnaire Angina Frequency Domain category standard-of-care patients started in are depicted on the vertical axis (100=no; 61-99=monthly, 31-60=weekly and 0-30=daily symptoms) and the category they finished the double-blind trial period in is depicted on the horizontal axis. For example, 68 standard-of-care patients began the study reporting "daily" angina symptoms and 24 (35.3%), 33 (48.5%), 9 (13.2%) and 2 (2.9%) of these same patients reported having daily, weekly, monthly and no angina symptoms at the end of the trial.

Starting the second month (cycle 2) onwards, all patients were assumed to stay in the same angina frequency health state (no loss or additional efficacy in either treatment group could occur) for the remainder of the model's time horizon unless they died. During any cycle of the model, patients could transition to the death health state based upon all-cause mortality rates in angina patients (5.8%/year), derived from a prospective cohort study of coronary artery disease patients from 6 Veterans Affairs General Internal Medicine Clinics.[4]

Patients receiving ranolazine could also discontinue treatment due to adverse drug reactions or lack of efficacy during, and only during, the first month of treatment. This assumption was based upon the reasoning that patients reporting a lack of efficacy or adverse reactions requiring discontinuation of therapy would most likely do so in the first month [10,11] and data from the TERISA trial [11] suggesting the majority of the effect of ranolazine is seen in the first few weeks of treatment. The rates of ranolazine discontinuation due to adverse reactions and lack of efficacy were derived from the ERICA trial (**Table 3**). Patients discontinuing ranolazine for any reason were assumed to follow the same pattern as SoC (plus placebo) patients.

Variable	Base-Case	Range	Reference
SAQAF classification definition			
No	SAQAF=100	NA	6,13
Monthly	SAQAF=61-99	NA	6,13
Weekly	SAQAF=31-60	NA	6,13
Daily	SAQAF=0-30	NA	6,13
SAQAF classification at baseline			6,10
No	0%	NA	6,10
Monthly	6.1%	100%	6,10
Weekly	71.0%	100%	6,10
Daily	22.9%	100%	6,10
Definition of SAQAF responder	Improvement of ≥1 SAQAF classification	20-point change in SAQAF	5,6
Ranolazine non-response	48% during first 4-weeks	42.2%-53.9%	10
Ranolazine discontinuation due to AE	1.1% during first 4-weeks	0.37%-6%	10
All-cause mortality by angina frequency			
No	4.6%/year	3.8%-5.5%	5
Monthly	4.8%/year	3.8%-6.1%	5
Weekly	8.1%/year	6.1%-10.8%	5
Daily	10.9%/year	7.5%-15.4%	5
All-cause mortality for all angina patients	5.8%/year	NA	5
Angina frequency utility (using EOT data)			2,10,15
No	0.87	0.84-0.90	2,10,15
Monthly	0.76	0.75-0.77	2,10,15
Weekly	0.65	0.64-0.66	2,10,15
Daily	0.54	0.52-0.56	2,10,15
Cost of ranolazine twice daily at any dose	£48.98/month	£24.49-£97.96	16
Stable angina direct treatment costs/year (not including ranolazine)			6
No	£3,529	£3,276-£3,786	6
Monthly	£4,711	£4,255-£5,023	6
Weekly	£5,493	£4,765-£6,229	6
Daily	£8,374	£6,754-£9,990	6
Stable angina indirect costs/year			
No	£2,362	£1,011-£3,373	7
Monthly	£4,012	£2,694-£5,395	7
Weekly	£4,271	£2,694-£5,395	7
Daily	£8,194	£5,395-£10,783	7

Table 3. Base-Case Variables and Ranges Used in Sensitivity Analysis

EOT=end-of-treatment; NA=not applicable; SAQAF=Seattle Angina Questionnaire Angina Frequency

Our model determined the mean total cost of treatment accrued by the patient cohorts receiving and not receiving ranolazine separately, as well as the mean number of QALYs. This allowed for the calculation of incremental cost-effectiveness ratios (ICERs) defined as the difference in mean costs between the ranolazine plus SoC and SoC alone (plus placebo) patients divided by the difference in mean QALYs for each treatment. We also provide in this report an ICER defined as the difference in mean costs between the two groups divided by the difference in SAQAF response rate. Since the time horizon did not exceed one-year, no discounting was performed. The model was programmed in TreeAge Pro 2007 (TreeAge Software Inc, Williamstown, MA).

We calculated QALYs by multiplying the time spent in each health state by corresponding EuroQol (EQ)-5D utilities estimates (scores between 1.0 and -0.564, on a scale where 1.0=perfect health and 0.0=death) for each angina frequency health state. EQ-5D utility scores were calculated by taking individual patient data from the ERICA trial and a applying them to a previously derived SAQ to UK EQ-5D mapping equation developed by Goldsmith and colleagues.[2,15]

This cost-effectiveness analysis was performed from the UK health-system perspective, and therefore, included only direct (inpatient, outpatient and drug) costs of treating stable angina. Direct medical costs were based on data from an economic sub-study of the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST Elevation Acute Coronary Syndrome (MERLIN)-TIMI 36 trial [6] which assessed the association between angina frequency and subsequent cardiovascular resource utilization among 5,460 stable outpatients who completed the SAQ 4-months after experiencing an ACS and who were then followed for an additional 8-months. The monthly cost of both doses of ranolazine were set at published British National Formulary (BNF) pricing, and assumed to be the same for the 750 mg and 1,000 mg doses.[16] Since the CARISA trial [9] suggested no clinically relevant difference in efficacy between the 750 mg and 1,000 mg doses, we assumed the dose of ranolazine was titrated as in the

ERICA trial even though the 1,000 mg dose is not approved in the UK. All costs were inflated, when needed, using the Medical Care component of the Consumer Price Index [17] and later expressed in 2014 British Sterling Pounds (£).

We performed one-way sensitivity analysis on all variables in Table 3 over their *a priori* determined plausible ranges. In addition, we performed a number of scenario analyses to test whether: 1) assuming 100% of patients started the model in the daily and weekly angina frequency health states, 2) factoring in indirect costs, 3) allowing mortality rates to vary based upon angina frequency health state severity, and 4) assuming not all patients failing to respond to ranolazine would discontinue therapy would impact the model's overall results and conclusions. We also performed an analysis changing the definition of response to ranolazine to a 20-point change in SAQAF (a previously determined threshold for a minimally important clinical improvement on the SAQAF domain).[14]

For our scenario analyses, lost productivity costs were derived from a published cost-of-illness study of stable angina patients [6]. This study calculated indirect costs, by estimating costs of lost productivity by those with stable angina, as well as all unpaid time devoted to caregiving by family members and friends. Mortality rates stratified by angina frequency published by Spertus and colleagues [4] were used to allow patients to transition to the death health state, conditional upon SAQ angina frequency health state, but not treatment arm.

Finally, we performed a 10,000-iteration Monte Carlo simulation (MCS) to determine the joint uncertainty of model parameters. For each variable in MCS, we assumed a triangle distribution (defined by a likeliest, low and high value) since the true nature of variance for these variables is not well understood and the triangle distribution (when used appropriately) does not violate the requirements of any variable (i.e., costs cannot be less than $0 and probabilities and utilities must lie between 0 and

1). The results of the MCS are provided as an incremental cost-effectiveness plane, with ICERs <£0 and £20,000/QALY gained considered economically dominant and cost-effective, respectively.

RESULTS

Two hundred and seventy-seven subjects (97% from Eastern Europe) receiving ranolazine in the ERICA trial were analyzable, of whom 144 (52%) improved by at least 1 SAQAF classification during the 6-week double-blind trial period. Only 118 of 281 (42%) subjects in the SoC only (plus placebo) group met the response definition (absolute difference in response rates=10%, 95%CI=2 to 18%). Patients improving at least 1 SAQAF classification (regardless of treatment) experienced a mean 32±14 point change in SAQAF score from baseline. Ranolazine patients lived a mean of 0.701 QALYs at a cost of £5,208. Those not receiving ranolazine lived 0.662 QALYs and at a cost of £5,318. Thus, the addition of ranolazine was shown to be a dominant economic strategy.

In performing one-way sensitivity analysis, the ICER was found sensitive to ranolazine cost; exceeding £20,000/QALY when the cost of ranolazine increased to >£203/month (**Table 4**). Upon scenario analysis, ranolazine remained a dominant economic strategy when indirect costs were included in the model; when mortality rates were assumed to increase with worsening severity of SAQAF health states; or when both indirect costs and differences in mortality rates based upon SAQAF were assumed. The model indicated that ranolazine would remain cost-effective, even if 100% of patients classified as non-responders continued on ranolazine past the first month (ICER=£4,051/QALY). When the response to ranolazine was re-defined to incorporate a 20-point change on the SAQAF score (in the base-case analysis, response was defined as improving by at least 1 SAQAF health state), the ICER was £1,692/QALY. Monte Carlo simulation found the addition of ranolazine cost-effective in >99% of 10,000 iterations assuming a £20,000/QALY willingness-to-pay threshold, and a dominant economic strategy in 70.5% of iterations run (**Figure 2**).

Table 4. Results of Base-Case, Sensitivity and Scenario Analyses
Results for the base-case and scenario analysis are depicted above. Incremental cost-effectiveness ratios were calculated as the difference in costs divided by the difference in quality-adjusted life-years between the two treatments. Ranolazine added to standard-of-care therapy was considered cost-effective compared to standard-of-care therapy alone when an Incremental cost-effectiveness ratio was less than £20,000/QALY.

Sensitivity or Scenario Analysis	Treatment	Cost	QALY	ICER vs. placebo
Base-Case	Ranolazine	£5,208	0.701	Ranolazine dominant
	SoC+Placebo	£5,318	0.662	---
100% Daily	Ranolazine	£5,915	0.639	Ranolazine dominant
	SoC+Placebo	£6,160	0.614	---
100% Weekly	Ranolazine	£5,058	0.713	Ranolazine dominant
	SoC+Placebo	£5,109	0.672	---
Mortality Differences Assumed	Ranolazine	£5,190	0.700	Ranolazine dominant
	SoC+Placebo	£5,272	0.659	---
Indirect Costs Included	Ranolazine	£9,237	0.701	Ranolazine dominant
	SoC+Placebo	£9,725	0.662	---
Indirect Costs Included and Mortality Differences Assumed	Ranolazine	£9,203	0.700	Ranolazine dominant
	SoC+Placebo	£9,639	0.659	---
20-point change	Ranolazine	£5,362	0.688	£1,692/QALY
	SoC+Placebo	£5,318	0.662	---

DISCUSSION

The results of our economic analysis suggest that treatment of chronic stable angina with ranolazine is a dominant economic strategy when administered in addition to SoC antianginal in patients reporting daily or weekly angina symptoms. Importantly, our base-case analysis was built on the clinical assumption that patients who do not respond to ranolazine treatment (i.e., continue to suffer the same degree of anginal symptoms) are taken off therapy and behave similarly to placebo patients. This responder type analysis methodology has been utilized in other UK National Health Service/National Institute for Health and Care Excellence (NICE) cost-effectiveness models.[18,19] Of note, our analysis indicates that from a UK perspective, discontinuing therapy in patients not adequately responding to therapy is not necessary to achieve cost-effectiveness.

Importantly, the definition of response used in our analysis (requiring a decrease in symptoms as measured by improving an entire angina frequency classification) is one that is easily translatable to clinical practice by simply questioning patients if their angina frequency is daily, weekly, monthly or

absent. Nonetheless, alterative responder definitions merit consideration. One of the scenario analysis we performed utilized an alternative responder definition requiring a 20-point improvement in SAQAF score.[14] Even with this more stringent definition of responder requiring a more robust benefit, the addition of ranolazine was still shown to be cost-effective with an ICER of £1,692/QALY gained.

A small number of prior European economic analyses performed from the Spanish,[20] Italian [21] and Russian perspectives [22] have also demonstrated the addition of ranolazine to SOC for the treatment of chronic angina patients can be economically substantiated. Two of these analyses [20,21] reported ICERs for ranolazine of ~€8,500/QALY gained; well below the €30,000/QALY gained willingness-to-pay threshold commonly referenced. The third, a Russian model,[22] did not calculated cost/QALY gained but rather used change in angina frequency as its principal measure of effectiveness. This economic model estimated increased expenditures for medication in the ranolazine group, but reduced costs of emergency care and hospitalizations; resulting in a 20% decrease in the cost-effectives ratio for ranolazine added to SOC vs. SOC alone (1,641 RUB vs. 1,965 RUB, respectively). Our model described in this paper is novel and adds important information to the current body of literature. To our knowledge, this is the first report of the cost-effectiveness of ranolazine from the UK health-system perspective, and our findings are supportive of NICE's current recommendation for ranolazine use in stable angina [8]. Additionally, the above-mentioned models [20-22] used only direct medical costs; while our model (as a sensitivity analysis) included both direct and indirect costs. The addition of indirect costs to our model yielded an even larger gap (decrease) in treatment costs with the use of ranolazine compared to SOC alone (delta: £488 vs. £110), substantiating the benefit of ranolazine from a societal perspective. Perhaps most importantly, our analysis is the only one to estimate transition probabilities and health utility scores using individual patient level data from the randomized controlled ERICA trial.[10] Access to this level of data likely increases the internal validity of our model by providing more accurate estimates of transition probabilities across SAQAF health states; as well as,

allowing us to map UK EQ-5D equivalent health utility values (the EQ-5D being NICE's preferred health utility measure) needed for calculating QALYs.[15,23]

There are also limitations to consider when putting the results of our model into context. First, we needed to extrapolate the results of the 7-week double-blind treatment duration of the ERICA trial [10] to a 1-year time horizon. Because the duration to which ranolazine will remain efficacious is unclear, we did not attempt to extend the model's time horizon out to longer than 1-year and thus this model should be considered hypothesis generating. The fact that ~85% of patients in the Ranolazine Open Label Experience (ROLE) [24] remained on therapy and only 4.2% of 746 ranolazine-treated patients electively discontinued therapy at 1-year suggests our 1-year time horizon may be justifiable, as does longer-term follow-up data from the MERLIN trial which shows stability in SAQAF, physical limitation and quality-of-life domain scores in stable coronary disease patients over 12-months [6, 14, 25]. Second, our analysis evaluated the cost-effectiveness of ranolazine in those suffering weekly or daily angina. Therefore, it is unclear whether our findings would be generalizable to patients with less frequent angina symptoms (e.g., monthly). This being said, the TERISA trial [11] did support ranolazine's efficacy in a population with a wider range of angina frequencies (an average weekly angina frequency between 1 and 28, and at least 1 angina episode/week). It is also important to note that we assumed UK patients as a group would have similar response to ranolazine as patients enrolled in the multinational ERICA trial. Unfortunately, data to test this assumption was not available in ERICA. Third, the dosage of ranolazine utilized in ERICA [10] (500 mg twice daily for the first week followed by 1,000 mg twice daily thereafter) differs from the approved dose in Europe (initial dose of 375 mg twice daily, titrated to 500 mg twice daily after 2-4 weeks, and based upon patient response, further titrated to a maximum dose 750 mg twice daily).[23] Importantly, data from the CARISA trial [9] demonstrated greater improvements in exercise duration and reductions in angina attacks and nitroglycerin use compared to placebo with both the 750 mg ($p \leq 0.03$ for all endpoints) and 1,000 mg ($p \leq 0.03$ for all

endpoints) twice daily doses of ranolazine at 12-weeks; with no clinically relevant difference in efficacy between the 750 mg and 1,000 mg doses. For this reason, using data from the 1,000 mg twice daily arm of pivotal ERICA trial in this European model seems acceptable. Fourth, in the ERICA trial, beta-blockers were not used to treat angina and therefore we could not assess the cost-effectiveness of adding ranolazine to beta-blocker therapy (which is often effective and inexpensive). Importantly, the TERISA trial provides data suggesting ranolazine remained efficacious when added to ~90% beta-blocker background therapy [11]. Despite this, additional cost-effectiveness analyses based on TERISA data would helpful in demonstrating ranolazine's cost-effectiveness in heavily beta-blocker treated population (as well as in a wider range of angina symptom frequencies and diabetic patients). Finally, our model did not directly incorporate the impact of adverse drug reactions to ranolazine. These adverse events; however, are typically not serious (e.g., usually limited to dizziness, nausea and constipation), and consequently are not likely to have any significant impact on costs or QALYs.[10,11]

FUNDING

This work was supported by Menarini International Operations, Luxembourg, SA, makers of ranolazine. The authors maintained full control over the design and performance of the study; collection, management, analysis, and interpretation of the data; and preparation and review of the manuscript. The sponsor reviewed the final manuscript prior to submission. Drs. Coleman and Kohn had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

CONTRIBUTORS

Study concept and design: CIC, CGK, NF. Acquisition of data: CIC, CGK, NF. Analysis and interpretation of data: CIC, CGK, NF. Drafting of the manuscript: CIC, CGK. Critical revision of the manuscript for important intellectual content: CIC, CGK, NF. Administrative, technical, or material support: CIC, CGK. Study supervision: CIC. CIC and CGK had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICJME) and were fully responsible for all content and editorial decisions, and were involved in all stages of manuscript development.

CONFLICTS OF INTEREST

Dr. Coleman has received grant funding and consultancy fees from Gilead Sciences Inc., Foster City, CA, USA and Menarini International Operations, Luxembourg, SA. Dr. Freemantle received grant funding from Menarini International Operations, Luxembourg, SA. Dr. Kohn has no conflicts to report.

DATA SHARING

No additional data available.

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FIGURE LEGENDS

Figure 1. Schematic Representation of the Economic Decision Model

The model was used to determine separately the total cost of treatment accrued and quality-adjusted life-years lived by the stable angina patients receiving and not receiving ranolazine. Regardless of treatment assignment, patients entered the model in one of 3 angina frequency health states based upon Seattle Angina Questionnaire angina frequency (SAQAF) scores (100=no; 61-99=monthly; 31-60=weekly; 0-30=daily angina; no patients started in "no" angina) and were allowed to transition between states in the first month based upon treatment specific probabilities derived from the Efficacy of Ranolazine in Chronic Angina trial and other studies. Patients not responding to ranolazine in month 1 (i.e., not improving ≥1 SAQAF health state) or experiencing an adverse event requiring discontinuation were assumed to stop taking ranolazine and behave like SoC (plus placebo) patients. Only patients assigned to receive ranolazine at the initiation of the model could discontinue therapy (for lack of efficacy or adverse drug events) and discontinuation could only occur during the first cycle. Patients randomized to SoC (plus placebo) started and had to remain "off drug". In the second through twelfth month, all patients were assumed to stay in the same angina frequency health state for the remainder of the model's time horizon or until death. Transition to death could occur during any cycle.

M=Markov node

Figure 2. Incremental Cost-Effectiveness Plane

Incremental cost-effectiveness plane based on 10,000 Monte Carlo simulation iterations, which drew parameters for each input simultaneously from probability distributions. Incremental cost (2014£) is on the vertical axis and incremental efficacy (quality-adjusted life-years) is on the horizontal axis. As depicted on the incremental cost-effectiveness plane, the probability of ranolazine being cost-effective

was >99% (quadrants II and III), assuming a willingness-to-pay (WTP) threshold of £20,000/QALY. We estimated there was a 70.5% chance the addition of ranolazine to standard of care therapy would be a dominant economic strategy compared to standard of care alone (quadrant III).

Figure 1. Schematic Representation of the Markov Model
The model was used to determine separately the total cost of treatment and quality-adjusted life-years accrued by the stable angina patients receiving and not receiving ranolazine. Regardless of treatment assignment, patients entered the model in one of 3 angina frequency health states based upon Seattle Angina Questionnaire angina frequency (SAQAF) scores (100=no; 61-99=monthly; 31-60=weekly; 0-30=daily angina; no patients started in "no" angina) and were allowed to transition between states in the first month based upon treatment specific probabilities derived from the Efficacy of Ranolazine in Chronic Angina trial and other studies. Patients not responding to ranolazine in month 1 (i.e., not improving ≥1 SAQAF health state) or experiencing an adverse event requiring discontinuation were assumed to stop taking ranolazine and behave like SoC (plus placebo) patients. Only patients assigned to receive ranolazine at the initiation of the model could discontinue therapy (for lack of efficacy or adverse drug events) and discontinuation could only occur during the first cycle. Patients randomized to SoC (plus placebo) started and had to remain "off drug". In the second through twelfth month, all patients were assumed to stay in the same angina frequency health state for the remainder of the model's time horizon or until death. Transition to death could occur during any cycle.
M=Markov node
17x7mm (300 x 300 DPI)

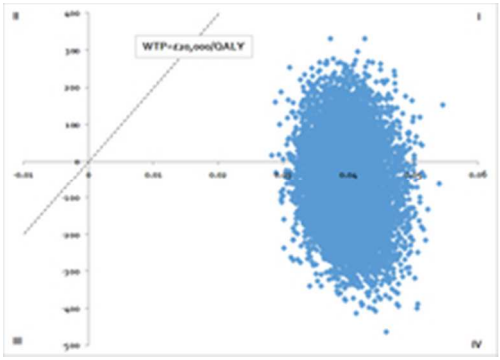

Figure 2. Incremental Cost-Effectiveness Plane
Incremental cost-effectiveness plane based on 10,000 Monte Carlo simulation iterations, which drew parameters for each input simultaneously from probability distributions. Incremental cost (2014£) is on the vertical axis and incremental efficacy (quality-adjusted life-years) is on the horizontal axis. As depicted on the incremental cost-effectiveness plane, the probability of ranolazine being cost-effective was >99% (quadrants II and III), assuming a willingness-to-pay (WTP) threshold of £20,000/QALY. We estimated there was a 70.5% chance the addition of ranolazine to standard of care therapy would be a dominant economic strategy compared to standard of care alone (quadrant III).
20x14mm (300 x 300 DPI)

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Pg 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Pg 3-4
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Pg 6
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Pg 7
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Pg 7
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Pg 7
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Pg 7
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Pg 7
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Pg 11
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Pg 8
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Pgs 7, 16-17

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	PG 11
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	PG 11
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	PG 12
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	PG 7, FIGURE 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	PG 7-9
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	NA
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	PG 10 / TABLE 3
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	PG 13
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	~~Pg 13, TABLE 4~~ NA
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Pg 13, TABLE 4
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Pg 14, 16-17
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Pg 1
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Pg 2

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

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The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.