National Institute for Health and Care Excellence

Consultation

Acute coronary syndromes

[H] Evidence review for beta-blockers

NICE guideline

Intervention evidence review

February 2020

Draft for Consultation

This evidence review was developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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1 Beta-blockers

1.1 Review question: What is the optimal duration of beta-blocker therapy to improve outcomes for adults without left ventricular dysfunction after myocardial infarction?

1.2 Introduction

Beta-blockers are competitive antagonists of catecholamines at beta-adrenergic receptors in a wide range of tissues (e.g. heart, peripheral vasculature, bronchi, pancreas and liver). Beta-blockers have long been an integral part of ACS management (acute and long term) due to their anti-arrhythmic, anti-ischaemic and antihypertensive properties and their use has led to a reduction in the rates of mortality and re-infarction. Patients with left ventricular systolic dysfunction and ACS particularly benefit from longer term treatment with beta-blockers. However, patients without left ventricular dysfunction are at lower baseline risk of adverse cardiac outcomes and there is less certainty about the long term benefits of continued beta-blockade in this group of people.

This review will consider how long beta-blockers should be given to people presenting with ACS who do not have evidence of left ventricular dysfunction.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	Adults who have had an MI, have been treated with a beta blocker and have normal LV systolic function Including: • Patients following the acute early phase, providing the patient is stable • STEMI patients • NSTEMI patients
Intervention(s)	Beta-blocker given up to 12 months
Comparison(s)	Beta-blocker given > 12 months
Outcomes	**CRITICAL** • All-cause mortality at 1 year • All-cause mortality at > 1 year • Heart failure at 1 year • Heart failure at > 1 year • Health-related quality of life including EQ5D and SF-36 **IMPORTANT** • All-cause mortality at 30 days • Re-infarction at 1 year • Re-infarction at > 1 year • Revascularisation at 1 year

	• Revascularisation at > 1 year • Cardiogenic shock • New onset diabetes at 1 year
Study design	• Randomised Controlled Trials (RCT) • Systematic Reviews (SR) of RCTs If no evidence from RCTs is found we will look at large well conducted cohort studies that have adjusted for the following confounders: • age • LV function

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[35] Methods specific to this review question are described in the review protocol in Appendix A:

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

No randomised controlled trials were identified. Consequently, non-randomised studies (prospective and retrospective cohort studies) were assessed for eligibility in this review; no non-randomised studies were included.

1.5.2 Excluded studies

Two systematic reviews that were identified through the surveillance review for this guideline were considered.[4, 32] Upon more detailed inspection, we found that the studies included in one of the systematic reviews did not match our review protocol as they compared the use of beta-blockers versus no beta-blockers rather than different durations of beta-blocker administration.[4] The other systematic review was excluded due to the differences in methodology which were not in line with the NICE methods.[32] However, the references were checked and relevant papers were ordered and considered for this review.

Since no randomised controlled trials were identified, prospective and retrospective cohort studies were eligible for inclusion. Five studies were analysed and discussed by the committee although they were ultimately not found to directly address the review question and were subsequently excluded.[5, 8, 41, 42, 48]

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D: forest plots in Appendix E: and GRADE tables in Appendix H:.

See the excluded studies list in Appendix I:.

1.6 Economic evidence

1.6.1 Included studies

No health economic studies were included.

1.6.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G:.

1.6.3 Health economic modelling

This area was not prioritised for new cost-effectiveness analysis.

1.6.4 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Beta blockers that specify ACS usage in the BNF are included in the table. The most commonly used beta blockers based on NHS usage across all indications are atenolol, bisprolol, cardvedilol, metoprolol and propranolol however this is not specific to ACS. The committee noted that bisoprolol is used commonly in current practice after ACS.

Table 2: UK costs of beta-blockers

Drug[(a)]	Preparation	Daily dose[(b)]	Cost per day	Cost per year
Acebutolol	Tablet	400mg	£0.67	£242.73
	Capsule	400mg	£0.69	£250.03
Atenolol[(c)]	Tablet	100mg	£0.02	£6.13
Bisoprolol[(c)]	Tablet	5mg	£0.01	£4.95
Carvedilol[(c)]	Tablet	25mg	£0.04	£13.17
	Tablet	50mg	£0.07	£26.33
Metoprolol[(c)]	Tablet	50mg	£0.02	£8.99
	Tablet	100mg	£0.03	£9.91
	Tablet	200mg	£0.05	£19.81
Propranolol[(c)]	Tablet	160mg	£0.04	£15.51
Timolol	Tablet	10mg	£1.33	£485.82

Source: NHS Drug Tariff prices obtained from the BNF; accessed September 2018[19]
(a) List of beta-blockers obtained from the BNF for long-term management of ACS
(b) Dose obtained from NICE CG172
(c) These beta-blockers are the most commonly used across the NHS based on the Prescription Cost Analysis 2018; however this is not specific to post-ACS as beta-blockers are indicated for various conditions[37]

1.7 Evidence statements

1.7.1 Clinical evidence statements

- No relevant clinical studies were identified for this review.

1.7.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The committee agreed that outcomes critical for decision making were all-cause mortality and heart failure at 1 year and > 1 year and health related quality of life.

Repeat revascularisation and re-infarction at 1 year and > 1 year, cardiogenic shock and new onset diabetes (at 1 year) were considered important outcomes. The committee were also interested to see evidence for mortality at 30 days.

1.8.1.2 The quality of the evidence

No relevant clinical studies were identified for this review.

1.8.1.3 Benefits and harms

There was no clinical evidence included in this evidence review.

The committee reviewed the recommendations from the previous update of the MI guideline (CG172) and decided to not update the recommendations on when to offer beta-blockers as these are still appropriate.

The committee acknowledged the established evidence of benefit from beta-blocker use when given early in the management of ACS. Current recommendations suggest that beta-blockers should then be continued for at least a year, and in many cases the agent is continued beyond this. There is evidence that this is beneficial in the presence of left ventricular dysfunction, but the committee could not find any evidence for or against extending the duration of treatment when left ventricular function is within normal limits. There is a risk of stopping beta-blockade, in that it may have been masking some underlying problem e.g. hypertension, arrhythmia. However, continuing unnecessarily runs the risk of causing side-effects and would be wasteful. It was therefore felt appropriate to produce a recommendation which promotes a decision based on individual circumstances, moving away from the current position in which beta-blockers may be continued by default.

The committee decided to uphold the research recommendation made by the previous CG172 committee, on the basis that the recommended research has not been carried out.

1.8.2 Cost effectiveness and resource use

No economic evaluations were identified for this review.

Unit costs were presented to aid committee consideration of cost-effectiveness. Beta-blockers are available generically at a low cost. The committee indicated that bisoprolol is a commonly prescribed beta blocker for people with ACS, which costs an average of £4.95 per year.

Use of a beta-blocker post-MI for a longer duration compared to a shorter duration will result in some additional drug costs. However, if it also leads to additional health benefits it may be cost effective. Conversely, if people do not get any additional health benefit after a certain time it will not be cost effective to continue treatment. The clinical review did not identify any direct evidence to address the question of duration of beta-blocker administration in people

who have had an MI but do not have left ventricular dysfunction. Therefore, it was agreed it was not possible to make a judgement on whether continuing beta blockers for more than 12 months compared to 12 months was cost effective. However, the committee agreed that as the cost of beta-blockers is very low, even a small health benefit from longer use would be likely to result in it being cost effective.

The committee highlighted that most people with ACS will receive beta blockers unless they are ineligible. Audit data for 2016/17 recorded over 87,000 myocardial infarctions in England and reported that 97% of people were discharged on beta-blockers. The committee estimated that approximately half of people who have an MI do not have left ventricular dysfunction. Data is not available on the number of people still taking beta-blockers beyond 12 months; however, the committee indicated that many people will continue taking them long-term. It should be noted that some of these people may also have a separate indication for taking them other than ACS.

The committee agreed that the revised recommendations may result in more people stopping beta-blockers at 12 months and this would result in cost-savings for the NHS. However, the magnitude of savings is uncertain as it is currently unclear how many people are taking beta-blockers long-term and how many people have another indication for them.

1.8.3 Other factors the committee took into account

The patient members of the committee described some of the side-effects associated with beta-blocker use, and other potential adverse effects were noted. Although these are generally tolerable they represent a reason for limiting the time for which beta-blockers are taken, assuming no good evidence of continued benefit.

The committee members were aware of several cohort studies which looked at the use of beta blockers after hospital discharge compared to no beta blocker use. None of the studies made it clear if the patients who were discharged on beta blockers were monitored to ensure that they were adhering to this therapy and were indeed still on beta blockers by the end of the study period. These studies however showed that there is a slight relative reduction in risks of mortality at 1, 3 and 5 years, MI at 1 year and revascularisation at 1 and 3 years.

The committee were also aware of a systematic review of RCT's comparing beta-blocker use to no use after an MI [4].This showed benefit from prescription of beta-blockers, but the duration of administration varied between studies. It was not possible to use this evidence to determine the optimal duration of beta-blocker prescription.

References

1. Allen JE, Knight S, McCubrey RO, Bair T, Muhlestein JB, Goldberger JJ et al. Beta-blocker dosage and outcomes after acute coronary syndrome. American Heart Journal. 2017; 184:26-36

2. Andell P, Erlinge D, Smith JG, Sundstrom J, Lindahl B, James S et al. Beta-blocker use and mortality in COPD patients after myocardial infarction: A Swedish nationwide observational study. Journal of the American Heart Association. 2015; 4(4):e001611

3. Bangalore S, Bhatt DL, Steg PG, Weber MA, Boden WE, Hamm CW et al. βeta-blockers and cardiovascular events in patients with and without myocardial infarction: Post hoc analysis from the CHARISMA trial. Circulation: Cardiovascular Quality and Outcomes. 2014; 7(6):872-81

4. Bangalore S, Makani H, Radford M, Thakur K, Toklu B, Katz SD et al. Clinical outcomes with beta-blockers for myocardial infarction: A meta-analysis of randomized trials. American Journal of Medicine. 2014; 127(10):939-53

5. Bao B, Ozasa N, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K et al. Beta-blocker therapy and cardiovascular outcomes in patients who have undergone percutaneous coronary intervention after ST-elevation myocardial infarction. Cardiovascular Intervention and Therapeutics. 2013; 28(2):139-47

6. Chan AY, McAlister FA, Norris CM, Johnstone D, Bakal JA, Ross DB et al. Effect of beta-blocker use on outcomes after discharge in patients who underwent cardiac surgery. Journal of Thoracic and Cardiovascular Surgery. 2010; 140(1):182-7, 187.e1

7. Chatterjee S, Chaudhuri D, Vedanthan R, Fuster V, Ibanez B, Bangalore S et al. Early intravenous beta-blockers in patients with acute coronary syndrome--a meta-analysis of randomized trials. International Journal of Cardiology. 2013; 168(2):915-21

8. Choo EH, Chang K, Ahn Y, Jeon DS, Lee JM, Kim DB et al. Benefit of beta-blocker treatment for patients with acute myocardial infarction and preserved systolic function after percutaneous coronary intervention. Heart. 2014; 100(6):492-9

9. Dai N, Xu D, Zhang J, Wei Y, Li W, Fan B et al. Different beta-blockers and initiation time in patients undergoing noncardiac surgery: a meta-analysis. American Journal of the Medical Sciences. 2014; 347(3):235-44

10. de Matos Soeiro A, de Barros ESPG, Roque EA, Bossa AS, Zullino CN, Simoes SA et al. Mortality reduction with use of oral beta-blockers in patients with acute coronary syndrome. Clinics. 2016; 71(11):635-638

11. Dondo TB, Hall M, West RM, Jernberg T, Lindahl B, Bueno H et al. Beta-blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. Journal of the American College of Cardiology. 2017; 69(22):2710-2720

12. Fallahi B, Beiki D, Akbarpour S, Gholamrezanezhad A, Fard-Esfahani A, Akhzari F et al. Withholding or continuing beta-blocker treatment before dipyridamole myocardial perfusion imaging for the diagnosis of coronary artery disease? A randomized clinical trial. DARU: Journal of Faculty of Pharmacy. 2013; 21(1):8

13. Guay J, Ochroch EA. Beta-blocking agents for surgery: Influence on mortality and major outcomes. A meta-analysis. Journal of Cardiothoracic and Vascular Anesthesia. 2013; 27(5):834-44

14. Hogh A, Lindholt JS, Nielsen H, Jensen LP, Johnsen SP. Beta-blocker use and clinical outcomes after primary vascular surgery: A nationwide propensity score-matched study. European Journal of Vascular and Endovascular Surgery. 2013; 46(1):93-102

15. Hong J, Barry AR. Long-term beta-blocker therapy after myocardial infarction in the reperfusion era: A systematic review. Pharmacotherapy. 2018; 38(5):546-554

16. Hwang D, Lee JM, Kim HK, Choi KH, Rhee TM, Park J et al. Prognostic impact of beta-blocker dose after acute myocardial infarction. Circulation Journal. 2019; 83(2):410-417

17. Iannaccone M, F DA, De Filippo O, Gagliardi M, Southern DA, Raposeiras-Roubin S et al. Optimal medical therapy in patients with malignancy undergoing percutaneous coronary intervention for acute coronary syndrome: a BleeMACS sub-study. American Journal of Cardiovascular Drugs. 2017; 17(1):61-71

18. Iqbal J, Zhang YJ, Holmes DR, Morice MC, Mack MJ, Kappetein AP et al. Optimal medical therapy improves clinical outcomes in patients undergoing revascularization with percutaneous coronary intervention or coronary artery bypass grafting: insights from the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial at the 5-year follow-up. Circulation. 2015; 131(14):1269-77

19. Joint Formulary Committee. British National Formulary (BNF) Online. Available from: http://www.medicinescomplete.com Last accessed: 08/11/2019

20. Kalra PR, Morley C, Barnes S, Menown I, Kassianos G, Padmanabhan S et al. Discontinuation of beta-blockers in cardiovascular disease: UK primary care cohort study. International Journal of Cardiology. 2013; 167(6):2695-9

21. Kernis SJ, Harjai KJ, Stone GW, Grines LL, Boura JA, O'Neill WW et al. Does beta-blocker therapy improve clinical outcomes of acute myocardial infarction after successful primary angioplasty? Journal of the American College of Cardiology. 2004; 43(10):1773-9

22. Khalil CA, Al Suwaidi J, Singh R, Asaad N, Abushahba G, Kunju U et al. Beta-blockers are associated with decreased in-hospital mortality and stroke in acute decompensated heart failure: Findings from a retrospective analysis of a 22-year registry in the middle east (1991-2013). Current Vascular Pharmacology. 2017; 15(1):77-83

23. Konishi H, Miyauchi K, Kasai T, Tsuboi S, Ogita M, Naito R et al. Long-term effect of beta-blocker in ST-segment elevation myocardial infarction in patients with preserved left ventricular systolic function: A propensity analysis. Heart and Vessels. 2016; 31(4):441-8

24. Kontos MC, Diercks DB, Ho PM, Wang TY, Chen AY, Roe MT. Treatment and outcomes in patients with myocardial infarction treated with acute beta-blocker therapy: results from the American College of Cardiology's NCDR(). American Heart Journal. 2011; 161(5):864-70

25. Lang IM, Badr-Eslam R, Greenlaw N, Young R, Steg PG. Management and clinical outcome of stable coronary artery disease in Austria: Results from 5 years of the CLARIFY registry. Wiener Klinische Wochenschrift. 2017; 129(23-24):879-892

26. Lee YH, Park JS, Tahk SJ, Hwang GS, Yoon MH, Choi SY et al. Beta-blocker therapy in the era of primary percutaneous intervention for ST elevation myocardial infarction. Cardiology. 2015; 132(2):91-100

27. Li C, Sun Y, Shen X, Yu T, Li Q, Ruan G et al. Relationship between beta-blocker therapy at discharge and clinical outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Journal of the American Heart Association. 2016; 5(11):e004190

28. Lin T, Hasaniya NW, Krider S, Razzouk A, Wang N, Chiong JR. Mortality reduction with beta-blockers in ischemic cardiomyopathy patients undergoing coronary artery bypass grafting. Congestive Heart Failure. 2010; 16(4):170-4

29. London MJ, Hur K, Schwartz GG, Henderson WG. Association of perioperative beta-blockade with mortality and cardiovascular morbidity following major noncardiac surgery. JAMA. 2013; 309(16):1704-13

30. Maio V, Marino M, Robeson M, Gagne JJ. Beta-blocker initiation and adherence after hospitalization for acute myocardial infarction. European Journal of Cardiovascular Prevention and Rehabilitation. 2011; 18(3):438-45

31. Mateos A, Garcia-Lunar I, Garcia-Ruiz JM, Pizarro G, Fernandez-Jimenez R, Huertas P et al. Efficacy and safety of out-of-hospital intravenous metoprolol administration in anterior ST-segment elevation acute myocardial infarction: insights from the METOCARD-CNIC trial. Annals of Emergency Medicine. 2015; 65(3):318-24

32. Misumida N, Harjai K, Kernis S, Kanei Y. Does oral beta-blocker therapy improve long-term survival in ST-segment elevation myocardial infarction with preserved systolic function? A meta-analysis. Journal of Cardiovascular Pharmacology and Therapeutics. 2016; 21(3):280-5

33. Munkhaugen J, Ruddox V, Halvorsen S, Dammen T, Fagerland MW, Hernaes KH et al. BEtablocker Treatment After acute Myocardial Infarction in revascularized patients without reduced left ventricular ejection fraction (BETAMI): Rationale and design of a prospective, randomized, open, blinded end point study. American Heart Journal. 2019; 208:37-46

34. Nakatani D, Sakata Y, Suna S, Usami M, Matsumoto S, Shimizu M et al. Impact of beta blockade therapy on long-term mortality after ST-segment elevation acute myocardial infarction in the percutaneous coronary intervention era. American Journal of Cardiology. 2013; 111(4):457-464

35. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated October 2018]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

36. Nguyen T, Le KK, Cao HTK, Tran DTT, Ho LM, Thai TND et al. Association between in-hospital guideline adherence and postdischarge major adverse outcomes of patients with acute coronary syndrome in Vietnam: a prospective cohort study. BMJ Open. 2017; 7(10):e017008

37. NHS Digital, Prescribing and Medicines Team. Prescription cost analysis - England, 2018 [PAS]. 2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/2018 Last accessed: 04/06/2019

38. Nicolau JC, Furtado RHM, Baracioli LM, Lara LM, Dalcoquio TF, Scanavini Junior MA et al. The use of oral beta-blockers and clinical outcomes in patients with non-st-segment elevation acute coronary syndromes: A long-term follow-up study. Cardiovascular Drugs and Therapy. 2018; 32(5):435-442

39. Ozasa N, Kimura T, Morimoto T, Hou H, Tamura T, Shizuta S et al. Lack of effect of oral beta-blocker therapy at discharge on long-term clinical outcomes of ST-segment elevation acute myocardial infarction after primary percutaneous coronary intervention. American Journal of Cardiology. 2010; 106(9):1225-33

40. Park KL, Goldberg RJ, Anderson FA, Lopez-Sendon J, Montalescot G, Brieger D et al. Beta-blocker use in ST-segment elevation myocardial infarction in the reperfusion era (GRACE). American Journal of Medicine. 2014; 127(6):503-11

41. Puymirat E, Riant E, Aissaoui N, Soria A, Ducrocq G, Coste P et al. Beta blockers and mortality after myocardial infarction in patients without heart failure: Multicentre prospective cohort study. BMJ. 2016; 354:i4801

42. Raposeiras-Roubin S, Abu-Assi E, Redondo-Dieguez A, Gonzalez-Ferreiro R, Lopez-Lopez A, Bouzas-Cruz N et al. Prognostic benefit of beta-blockers after acute coronary syndrome with preserved systolic function. Still relevant today? Revista Española de Cardiología. 2015; 68(7):585-91

43. Shacham Y, Leshem-Rubinow E, Roth A. Is long-term beta-blocker therapy for myocardial infarction survivors still relevant in the era of primary percutaneous coronary intervention? Israel Medical Association Journal. 2013; 15(12):770-4

44. Shu de F, Dong BR, Lin XF, Wu TX, Liu GJ. Long-term beta blockers for stable angina: Systematic review and meta-analysis. European Journal of Preventive Cardiology. 2012; 19(3):330-41

45. Siu CW, Pong V, Jim MH, Yue WS, Ho HH, Li SW et al. Beta-blocker in post-myocardial infarct survivors with preserved left ventricular systolic function. Pacing and Clinical Electrophysiology. 2010; 33(6):675-80

46. Voko Z, de Brouwer S, Lubsen J, Danchin N, Otterstad JE, Dunselman PH et al. Long-term impact of secondary preventive treatments in patients with stable angina. European Journal of Epidemiology. 2011; 26(5):375-83

47. Wong MCS, Jiang JY, Su X, Wang H, Tang JL, Griffiths SM. Individuals at risk of beta-blocker discontinuation: A cohort study in 19,177 Chinese patients. Clinical Research in Cardiology. 2010; 99(5):277-284

48. Yang JH, Hahn JY, Song YB, Choi SH, Choi JH, Lee SH et al. Association of beta-blocker therapy at discharge with clinical outcomes in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. JACC: Cardiovascular Interventions. 2014; 7(6):592-601

Appendices

Appendix A: Review protocols

Table 3: Review protocol: What is the optimal duration of beta-blocker therapy to improve outcomes for adults without left ventricular dysfunction after myocardial infarction?

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	What is the optimal duration of beta-blocker therapy to improve outcomes for adults without left ventricular dysfunction after myocardial infarction?
2.	Review question	What is the optimal duration of beta-blocker therapy to improve outcomes for adults without left ventricular dysfunction after myocardial infarction?
3.	Objective	To assess the long term clinical effectiveness and safety of beta blocker therapy in adults without left ventricular dysfunction beyond 1 year.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by:

		• English language • Human studies • Letters and comments are excluded. Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Acute coronary syndromes
6.	Population	Adults who have had an MI, have been treated with a beta blocker and have normal LV systolic function Including: • Patients following the acute early phase, providing the patient is stable • STEMI patients • NSTEMI patients Exclusions: • Patients diagnosed as having a type 2, 3, 4a, 4b or 5 MI as per the universal definition of myocardial infarction if

		mentioned, if not we'll assume that type I. • Patients with left ventricular dysfunction (applies to RCTs only)
7.	Intervention/Exposure/Test	Beta –blocker - include papers that use intravenous or oral beta-blocker in hospital but oral only after discharge • Acebutolol • Atenolol • Bisoprolol • Carvedilol • Celiprolol • Esmolol • Labetalol • Metoprolol • Nadolol • Nebivolol • Oxprenolol • Propranolol • Pindolol • Sotalol • Timolol
8.	Comparator/Reference standard/Confounding factors	• Beta-blocker compared to same beta-blocker (as per list above) given for up to 12 months vs > 12 months
9.	Types of study to be included	• Systematic reviews of RCTs • RCTs • If no evidence from RCTs is found we will look at large (>1000 participants) well conducted cohort studies that have

		adjusted for the following confounders: ○ age ○ LV function • Cross over trials will be excluded.
10.	Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	• All-cause mortality at 1 year • All-cause mortality at > 1 year • Heart failure at 1 year • Heart failure at > 1 year • Health-related quality of life including EQ5D and SF-36. All data for the stated quality of life measures will be collected. Only overall scores will be reported for meta-analysis and GRADE.
13.	Secondary outcomes (important outcomes)	• All cause mortality at 30 days • Re-infarction at 1 year • Re-infarction at > 1 year • Revascularisation at 1 year • Revascularisation at > 1 year • Cardiogenic shock • New onset diabetes at 1 year
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

		An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be

		used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
17.	Analysis of sub-groups	• Type of treatment of MI (PCI or CABG or medical) • Age <75 years vs. >75 years • STEMI/NSTEMI • Length of time since MI
18.	Type and method of review	☒ Intervention ☐ Diagnostic

		☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	12/04/19		
22.	Anticipated completion date	14/05/20		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐ ☐	☑ ☑
		Piloting of the study selection process	☐ ☐	☑ ☑
		Formal screening of search results against eligibility criteria	☐ ☐	☑ ☑
		Data extraction	☐ ☐	☑ ☑
		Risk of bias (quality) assessment	☐ ☐	☑ ☑

		Data analysis	☐ ☐	☑ ☑
24.	Named contact	**5a. Named contact** National Guideline Centre **5b Named contact e-mail** Acutecoronarysyndromes@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: • Dr Bernard Higgins [Guideline lead] • Dr Saoussen Ftouh/Ms Sedina Lewis [Senior Systematic Reviewers] • Ms Annabelle Davies/Ms Kate Lovibond [Health economist; Health economists lead] • Ms Agnes Cuyas/Ms Jill Cobb [Information specialists]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be		

		published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Acute coronary syndrome, NSTEMI, STEMI, beta-blockers, treatment duration
33.	Details of existing review of same topic by same authors	N/A
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated

		☐ Discontinued
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

1

2 **Table 4: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2003 that were included in the previous guidelines will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[35] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and

	methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. • The following will be rated as 'Very serious limitations' and excluded: economic analyses undertaken as part of clinical studies that are excluded from the clinical review; economic models where relative treatment effects are based entirely on studies that are excluded from the clinical review.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014.[35]

For more information, please see the Methods report published as part of the accompanying documents for this guideline

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well

described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 22 July 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 22 July 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 7 of 7 CENTRAL to 2019 Issue 7 of 7	None

Medline (Ovid) search terms

1.	Acute Coronary Syndrome/ or Angina Pectoris/ or Angina, Unstable/ or Coronary Thrombosis/ or exp Myocardial Infarction/
2.	Heart Arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.
7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	(NSTE-ACS or STE-ACS).ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16
18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.

28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	limit 36 to English language
38.	exp Adrenergic beta-Antagonists/
39.	(Acebutolol or Atenolol or Bisoprolol or Carvedilol or Celiprolol or Esmolol or Labetalol or Metoprolol or Nadolol or Nebivolol or Oxprenolol or Propranolol or Pindolol or Sotalol or Timolol).ti,ab.
40.	(beta adj3 block*).ti,ab.
41.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj (block* or antagonist*)).ti,ab.
42.	(b adj3 block*).ti,ab.
43.	(beta adj2 antagonist*).ti,ab.
44.	or/38-43
45.	37 and 44
46.	randomized controlled trial.pt.
47.	controlled clinical trial.pt.
48.	randomi#ed.ti,ab.
49.	placebo.ab.
50.	randomly.ti,ab.
51.	Clinical Trials as topic.sh.
52.	trial.ti.
53.	or/46-52
54.	Meta-Analysis/
55.	exp Meta-Analysis as Topic/
56.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
57.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
58.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
59.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
60.	(search* adj4 literature).ab.
61.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
62.	cochrane.jw.
63.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
64.	or/54-63
65.	Epidemiologic studies/
66.	Observational study/
67.	exp Cohort studies/
68.	(cohort adj (study or studies or analys* or data)).ti,ab.

69.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
70.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
71.	Controlled Before-After Studies/
72.	Historically Controlled Study/
73.	Interrupted Time Series Analysis/
74.	(before adj2 after adj2 (study or studies or data)).ti,ab.
75.	exp case control study/
76.	case control*.ti,ab.
77.	Cross-sectional studies/
78.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
79.	or/65-78
80.	45 and (53 or 64 or 79)

1 **Embase (Ovid) search terms**

1.	acute coronary syndrome/ or angina pectoris/ or unstable angina pectoris/ or coronary artery thrombosis/ or exp heart infarction/
2.	heart arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.
7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	(NSTE-ACS or STE-ACS).ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	Case report/ or Case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	Nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental animal/

30.	Animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	limit 34 to English language
36.	exp *beta adrenergic receptor blocking agent/
37.	(Acebutolol or Atenolol or Bisoprolol or Carvedilol or Celiprolol or Esmolol or Labetalol or Metoprolol or Nadolol or Nebivolol or Oxprenolol or Propranolol or Pindolol or Sotalol or Timolol).ti,ab.
38.	(beta adj3 block*).ti,ab.
39.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj (block* or antagonist*)).ti,ab.
40.	(b adj3 block*).ti,ab.
41.	(beta adj2 antagonist*).ti,ab.
42.	or/36-41
43.	35 and 42
44.	random*.ti,ab.
45.	factorial*.ti,ab.
46.	(crossover* or cross over*).ti,ab.
47.	((doubl* or singl*) adj blind*).ti,ab.
48.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
49.	crossover procedure/
50.	single blind procedure/
51.	randomized controlled trial/
52.	double blind procedure/
53.	or/44-52
54.	systematic review/
55.	meta-analysis/
56.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
57.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
58.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
59.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
60.	(search* adj4 literature).ab.
61.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
62.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
63.	cochrane.jw.
64.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
65.	or/54-64
66.	Clinical study/
67.	Observational study/
68.	family study/
69.	longitudinal study/
70.	retrospective study/

71.	prospective study/
72.	cohort analysis/
73.	follow-up/
74.	cohort*.ti,ab.
75.	73 and 74
76.	(cohort adj (study or studies or analys* or data)).ti,ab.
77.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
78.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
79.	(before adj2 after adj2 (study or studies or data)).ti,ab.
80.	exp case control study/
81.	case control*.ti,ab.
82.	cross-sectional study/
83.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
84.	or/66-72,75-83
85.	43 and (53 or 65 or 84)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Acute Coronary Syndrome] this term only
#2.	MeSH descriptor: [Angina Pectoris] this term only
#3.	MeSH descriptor: [Angina, Unstable] this term only
#4.	MeSH descriptor: [Coronary Thrombosis] this term only
#5.	MeSH descriptor: [Myocardial Infarction] explode all trees
#6.	(or #1-#5)
#7.	MeSH descriptor: [Heart Arrest] this term only
#8.	(acute coronary near/2 syndrome*):ti,ab
#9.	((myocardial or heart) next infarct*):ti,ab
#10.	(heart next (attack* or event*)):ti,ab
#11.	((heart or cardiac) next arrest*):ti,ab
#12.	(coronary near/2 thrombos*):ti,ab
#13.	(stemi or st-segment or st segment or st-elevation or st elevation):ti,ab
#14.	non-ST-segment elevation:ti,ab
#15.	(non-STEMI or NSTEMI or nonSTEMI):ti,ab
#16.	Q wave myocardial infarction:ti,ab
#17.	non Q wave MI:ti,ab
#18.	(NSTE-ACS or STE-ACS):ti,ab
#19.	(subendocardial near/3 infarct*):ti,ab
#20.	((unstable or variant) near/2 angina*):ti,ab
#21.	(unstable near/2 coronary):ti,ab
#22.	(or #6-#21)
#23.	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#24.	(Acebutolol or Atenolol or Bisoprolol or Carvedilol or Celiprolol or Esmolol or Labetalol or Metoprolol or Nadolol or Nebivolol or Oxprenolol or Propranolol or Pindolol or Sotalol or Timolol):ti,ab
#25.	(beta near/3 block*):ti,ab
#26.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) next (block* or

	antagonist*)):ti,ab
#27.	(b near/3 block*):ti,ab
#28.	(beta near/2 antagonist*):ti,ab
#29.	(OR #23-#28)
#30.	#22 AND #29

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a search relating to acute coronary syndromes population combined with terms for interventions in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase using a filter for health economics studies.

Table 6: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 18 June 2019	Exclusions Health economics studies
Embase	01 January 2014 – 18 June 2019	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 2003 – 31 March 2018 NHSEED - 2003 to 31 March 2015	None

Medline (Ovid) search terms

1.	Acute Coronary Syndrome/ or Angina Pectoris/ or Angina, Unstable/ or Coronary Thrombosis/ or exp Myocardial Infarction/
2.	Heart Arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.
7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	NSTE-ACS.ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16

18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	limit 36 to English language
38.	Economics/
39.	Value of life/
40.	exp "Costs and Cost Analysis"/
41.	exp Economics, Hospital/
42.	exp Economics, Medical/
43.	Economics, Nursing/
44.	Economics, Pharmaceutical/
45.	exp "Fees and Charges"/
46.	exp Budgets/
47.	budget*.ti,ab.
48.	cost*.ti.
49.	(economic* or pharmaco?economic*).ti.
50.	(price* or pricing*).ti,ab.
51.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
52.	(financ* or fee or fees).ti,ab.
53.	(value adj2 (money or monetary)).ti,ab.
54.	or/38-53
55.	37 and 54
56.	*Angiography/
57.	Angiocardiography/
58.	Coronary Angiography/

59.	Angiograph*.ti.
60.	Arteriograph*.ti.
61.	Angiocardiograph*.ti,ab.
62.	Coronary Angiograph*.ti,ab.
63.	Angiogram*.ti,ab.
64.	Cardioangiograph*.ti,ab.
65.	Angiocardiogram.ti,ab.
66.	Angio Cardiograph*.ti,ab.
67.	Coronary Arteriogra*.ti,ab.
68.	Coronarograph*.ti,ab.
69.	*Myocardial Revascularization/
70.	Angioplasty, Balloon, Coronary/
71.	(Myocardial adj revasculari?ation).ti,ab.
72.	PCI.ti,ab.
73.	Percutaneous coronary intervention.ti,ab.
74.	Percutaneous Transluminal Coronary Angioplasty.ti,ab.
75.	PTCA.ti,ab.
76.	exp Angioplasty/
77.	Blunt microdissection.ti,ab.
78.	((laser or patch) adj angioplasty).ti,ab.
79.	Percutaneous Transluminal Angioplasty.ti,ab.
80.	Transluminal Coronary Angioplasty.ti,ab.
81.	(Balloon adj3 coronary).ti,ab.
82.	(Balloon adj3 angioplasty).ti,ab.
83.	exp STENTS/
84.	stent*.ti,ab.
85.	Or/56-84
86.	aspirin/
87.	(aspirin or acetylsalicylic acid).ti,ab.
88.	(clopidogrel or plavix).ti,ab.
89.	(ticagrelor or brilique).ti,ab.
90.	(prasugrel or efient or effient or prasita).ti,ab.
91.	Prasugrel Hydrochloride/
92.	platelet aggregation inhibitors/
93.	(Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA).ti,ab.
94.	exp Platelet Glycoprotein GPIIb-IIIa Complex/
95.	exp Receptors, Fibrinogen/
96.	(Abciximab or Reopro or Eptifibatide or Integrelin or Integrilin or Intrifiban or Tirofiban or Aggrastat).ti,ab.
97.	exp adrenergic beta-antagonists/
98.	(propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or

	betim).ti,ab.
99.	propranolol/ or acebutolol/ or atenolol/ or bisoprolol/ or celiprolol/ or labetalol/ or metoprolol/ or nadolol/ or nebivolol/ or oxprenolol/ or pindolol/ or sotalol/ or timolol/
100.	(beta adj3 block*).ti,ab.
101.	(b adj3 block*).ti,ab.
102.	(beta adj2 antagonist*).ti,ab.
103.	Antithrombins/
104.	Antithrombin*.ti,ab.
105.	(thrombin adj3 inhibitor*).ti,ab.
106.	Hirudins/
107.	Hirudin*.ti,ab.
108.	Hirulog.ti,ab.
109.	Bivalirudin.ti,ab.
110.	Or/86-109
111.	55 and (85 or 110)

1 **Embase (Ovid) search terms**

1.	acute coronary syndrome/ or angina pectoris/ or unstable angina pectoris/ or coronary artery thrombosis/ or exp heart infarction/
2.	heart arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.
7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	NSTE-ACS.ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	Case report/ or Case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	Nonhuman/

28.	exp Animal Experiment/
29.	exp Experimental animal/
30.	Animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	limit 34 to English language
36.	health economics/
37.	exp economic evaluation/
38.	exp health care cost/
39.	exp fee/
40.	budget/
41.	funding/
42.	budget*.ti,ab.
43.	cost*.ti.
44.	(economic* or pharmaco?economic*).ti.
45.	(price* or pricing*).ti,ab.
46.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
47.	(financ* or fee or fees).ti,ab.
48.	(value adj2 (money or monetary)).ti,ab.
49.	or/36-48
50.	35 and 49
51.	angiography/
52.	angiocardiography/
53.	coronary angiography/
54.	Angiograph*.ti.
55.	Arteriograph*.ti.
56.	Angiocardiograph*.ti,ab.
57.	Coronary Angiograph*.ti,ab.
58.	Angiogram*.ti,ab.
59.	Cardioangiograph*.ti,ab.
60.	Angiocardiogram.ti,ab.
61.	Angio Cardiograph*.ti,ab.
62.	Coronary Arteriogra*.ti,ab.
63.	Coronarograph*.ti,ab.
64.	*heart muscle revascularization/
65.	transluminal coronary angioplasty/
66.	(Myocardial adj revasculari?ation).ti,ab.
67.	PCI.ti,ab.
68.	Percutaneous coronary intervention.ti,ab.
69.	Percutaneous Transluminal Coronary Angioplasty.ti,ab.

70.	PTCA.ti,ab.
71.	*angioplasty/
72.	Blunt microdissection.ti,ab.
73.	((laser or patch) adj angioplasty).ti,ab.
74.	Percutaneous Transluminal Angioplasty.ti,ab.
75.	Transluminal Coronary Angioplasty.ti,ab.
76.	(Balloon adj3 coronary).ti,ab.
77.	(Balloon adj3 angioplasty).ti,ab.
78.	exp STENTS/
79.	stent*.ti,ab.
80.	Or/51-79
81.	acetylsalicylic acid/
82.	(aspirin or acetylsalicylic acid).ti,ab.
83.	(clopidogrel or plavix).ti,ab.
84.	(ticagrelor or brilique).ti,ab.
85.	(prasugrel or efient or effient or prasita).ti,ab.
86.	prasugrel/
87.	antithrombocytic agent/
88.	(Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA).ti,ab.
89.	exp fibrinogen receptor/
90.	(Abciximab or Reopro or Eptifibatide or Integrelin or Integrilin or Intrifiban or Tirofiban or Aggrastat).ti,ab.
91.	abciximab/ or eptifibatide/ or tirofiban/
92.	exp beta adrenergic receptor blocking agent/
93.	(propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
94.	propranolol/ or acebutolol/ or atenolol/ or bisoprolol/ or bisoprolol fumarate/ or carvedilol/ or celiprolol/ or esmolol/ or labetalol/ or metoprolol/ or nadolol/ or nebivolol/ or oxprenolol/ or pindolol/ or sotalol/ or timolol/ or timolol maleate/
95.	(beta adj3 block*).ti,ab.
96.	(b adj3 block*).ti,ab.
97.	(beta adj2 antagonist*).ti,ab.
98.	antithrombin/
99.	Antithrombin*.ti,ab.
100.	(thrombin adj3 inhibitor*).ti,ab.
101.	hirudin derivative/
102.	Hirudin*.ti,ab.
103.	Hirulog.ti,ab.
104.	Bivalirudin.ti,ab.
105.	Or/81-104

106.	50 and (80 or 105)

1 **NHS EED and HTA (CRD) search terms**

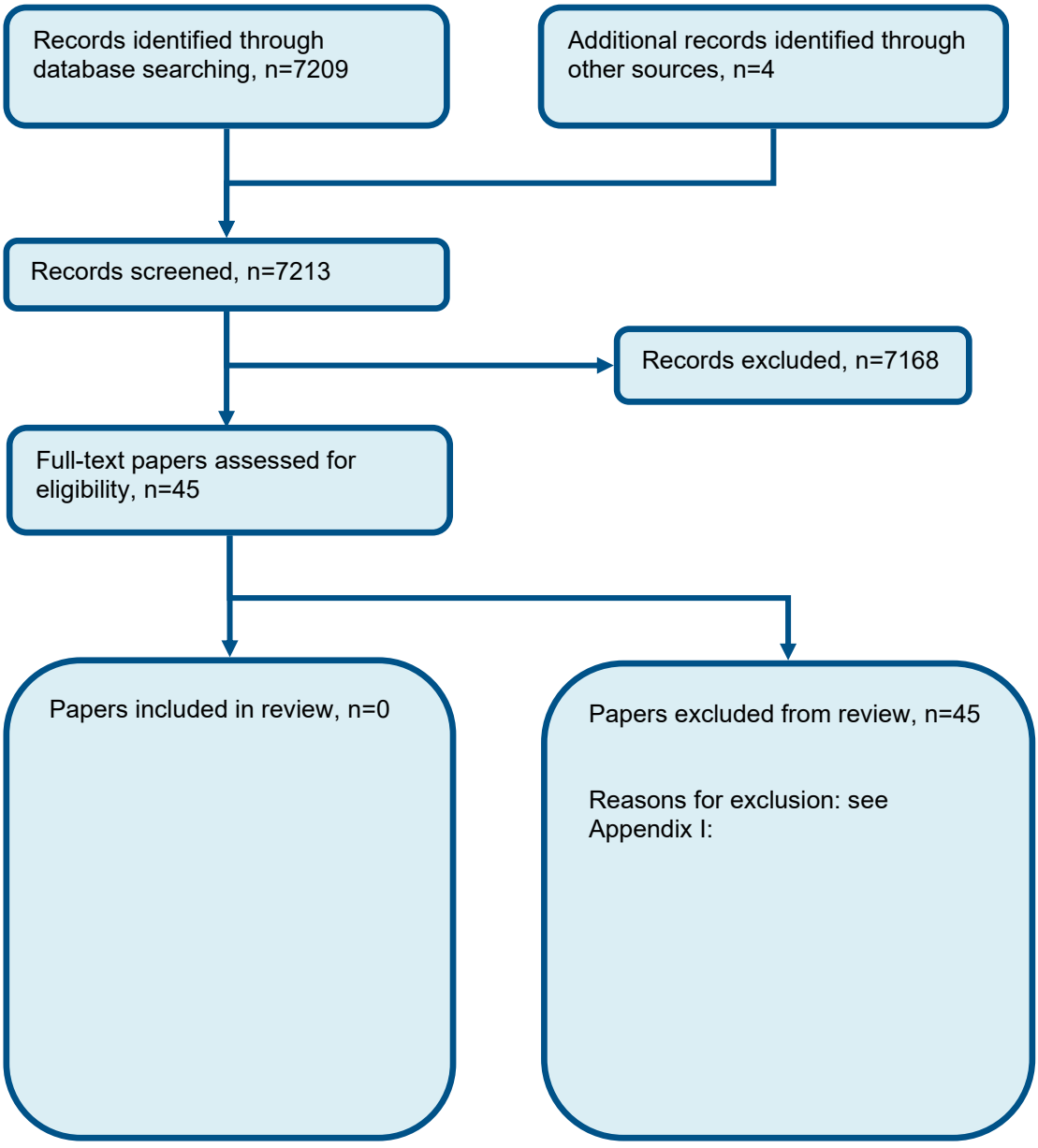
#1.	MeSH DESCRIPTOR Acute Coronary Syndrome
#2.	(MeSH DESCRIPTOR angina pectoris)
#3.	(MeSH DESCRIPTOR Angina, Unstable)
#4.	(MeSH DESCRIPTOR Coronary Thrombosis)
#5.	MeSH DESCRIPTOR Myocardial Infarction EXPLODE ALL TREES
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(MeSH DESCRIPTOR Heart Arrest)
#8.	((acute coronary adj2 syndrome*))
#9.	(((myocardial or heart) adj infarct*))
#10.	((heart adj (attack* or event*)))
#11.	(((heart or cardiac) adj arrest*))
#12.	((coronary adj2 thrombos*))
#13.	((stemi or st-segment or st segment or st-elevation or st elevation))
#14.	("non-ST-segment elevation")
#15.	((non-STEMI or NSTEMI or nonSTEMI))
#16.	("Q wave myocardial infarction")
#17.	("non Q wave MI")
#18.	(NSTE-ACS)
#19.	(STE-ACS)
#20.	(((subendocardial adj3 infarct*)))
#21.	((((unstable or variant) adj2 angina*)))
#22.	(((unstable adj2 coronary)))
#23.	(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
#24.	(MeSH DESCRIPTOR Angiography)
#25.	(MeSH DESCRIPTOR Angiocardiography)
#26.	((MeSH DESCRIPTOR Coronary Angiography))
#27.	((Angiograph*))
#28.	((Arteriograph*))
#29.	((Angiocardiograph*))
#30.	((Coronary Angiograph*))
#31.	((Angiogram*))
#32.	((Cardioangiograph*))
#33.	((Angiocardiogram))
#34.	((Angio Cardiograph*))
#35.	((Coronary Arteriogra*))
#36.	((Coronarograph*))
#37.	(MeSH DESCRIPTOR Myocardial Revascularization)
#38.	(MeSH DESCRIPTOR Angioplasty, Balloon, Coronary)
#39.	(((Myocardial adj revasculari?ation)))
#40.	((PCI))
#41.	((Percutaneous coronary intervention))
#42.	((Percutaneous Transluminal Coronary Angioplasty))

#43.	((PTCA))
#44.	(MeSH DESCRIPTOR Angioplasty EXPLODE ALL TREES)
#45.	((Blunt microdissection))
#46.	(((((laser or patch) adj angioplasty)))
#47.	((Percutaneous Transluminal Angioplasty))
#48.	((Transluminal Coronary Angioplasty))
#49.	(((Balloon adj3 coronary)))
#50.	((Balloon adj3 angioplasty))
#51.	(MeSH DESCRIPTOR Stents EXPLODE ALL TREES)
#52.	((stent*))
#53.	(#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52)
#54.	(MeSH DESCRIPTOR Aspirin)
#55.	((aspirin or acetylsalicylic acid))
#56.	((clopidogrel or plavix))
#57.	((ticagrelor or brilique))
#58.	((prasugrel or efient or effient or prasita))
#59.	MeSH DESCRIPTOR Prasugrel Hydrochloride
#60.	MeSH DESCRIPTOR Platelet Aggregation Inhibitors
#61.	((Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA))
#62.	MeSH DESCRIPTOR Platelet Glycoprotein GPIIb-IIIa Complex EXPLODE ALL TREES
#63.	MeSH DESCRIPTOR Receptors, Fibrinogen EXPLODE ALL TREES
#64.	((Abciximab or Reopro or Eptifibatide or Integrelin or Integrilin or Intrifiban or Tirofiban or Aggrastat))
#65.	MeSH DESCRIPTOR Adrenergic beta-Antagonists EXPLODE ALL TREES
#66.	((propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim))
#67.	(MeSH DESCRIPTOR propranolol)
#68.	(MeSH DESCRIPTOR acebutolol)
#69.	(MeSH DESCRIPTOR atenolol)
#70.	(MeSH DESCRIPTOR bisoprolol)
#71.	(MeSH DESCRIPTOR celiprolol)
#72.	(MeSH DESCRIPTOR labetalol)
#73.	(MeSH DESCRIPTOR metoprolol)
#74.	(MeSH DESCRIPTOR nadolol)
#75.	(MeSH DESCRIPTOR nebivolol)
#76.	(MeSH DESCRIPTOR oxprenolol)
#77.	(MeSH DESCRIPTOR pindolol)
#78.	(MeSH DESCRIPTOR sotalol)
#79.	(MeSH DESCRIPTOR timolol)
#80.	((beta adj3 block*))

#81.	((b adj3 block*))
#82.	((beta adj2 antagonist*))
#83.	MeSH DESCRIPTOR Antithrombins
#84.	(Antithrombin*)
#85.	((thrombin adj3 inhibitor*))
#86.	MeSH DESCRIPTOR Hirudins
#87.	(Hirudin*)
#88.	(Hirulog)
#89.	(Bivalirudin)
#90.	#54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89
#91.	(#23 AND (#53 OR #90))

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of optimal duration of beta-blocker therapy to improve outcomes for adults without left ventricular dysfunction after myocardial infarction



Appendix D: Clinical evidence tables

No relevant evidence identified.

Appendix E: Forest plots

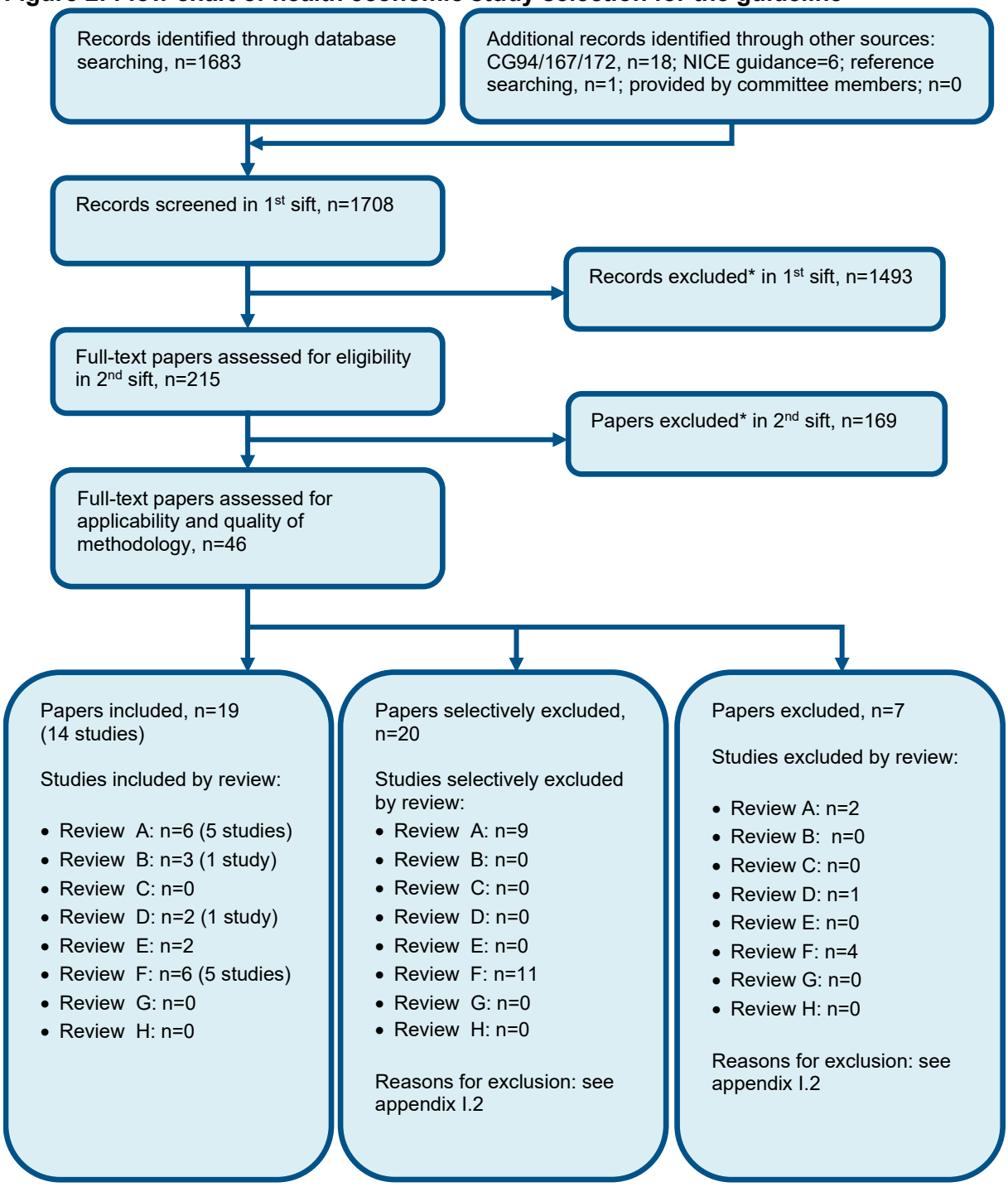
No relevant evidence identified.

Appendix F: GRADE tables

No relevant evidence identified.

Appendix G: Health economic evidence selection

Figure 2: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Review A = dual-antiplatelet therapy; Review B = early invasive investigation for UA/NSTEMI; Review C = antithrombins in UA/NSTEMI; Review D = bivalirudin in STEMI; Review E = multi-vessel PCI; Review F = drug-eluting stents; Review G = combination of antiplatelets and anticoagulants; Review H = beta-blocker therapy.

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 7: Studies excluded from the clinical review

Study	Exclusion reason
Allen 2017[1]	Incorrect study design (inappropriate variable adjustments)
Andell 2015[2]	Incorrect comparison (COPD versus no COPD)
Bangalore 2014[3]	Incorrect comparison
Bangalore 2014[4]	Systematic review: Studies included are not relevant (incorrect comparison)
Bao 2013[5]	Does not answer clinical review question
Chan 2010[6]	Incorrect population
Chatterjee 2013[7]	Incorrect comparison
Choo 2014[8]	Does not answer clinical review question
Dai 2014[9]	Systematic review: Studies included are not relevant (incorrect comparison)
de Matos Soeiro 2016[10]	No relevant outcome data
Dondo 2017[11]	No relevant outcome data
Fallahi 2013[12]	Incorrect comparison
Guay 2013[13]	Systematic review: Studies included are not relevant (incorrect comparison)
Hogh 2013[14]	Incorrect population (vascular surgery)
Hong 2018[15]	Systematic review: Studies included are not relevant (incorrect comparison)
Hwang 2019[16]	Incorrect study design (inappropriate variable adjustments)
Iannaccone 2017[17]	Incorrect study design (less than 1,000 participants)
Iqbal 2015[18]	Incorrect comparison
Kalra 2013[20]	No relevant outcome data
Kernis 2004[21]	No relevant outcome data
Khalil 2017[22]	No relevant outcome data
Konishi 2016[23]	Incorrect study design (less than 1,000 participants)
Kontos 2011[24]	No relevant outcome data
Lang 2017[25]	Incorrect study design (less than 1,000 participants)
Lee 2015[26]	No relevant outcome data
Li 2016[27]	Incorrect study design (inappropriate variable adjustments)
Lin 2010[28]	Incorrect study design (inappropriate variable adjustments)
London 2013[29]	Incorrect population (non-cardiac surgery)
Maio 2011[30]	No relevant outcome data
Mateos 2015[31]	Incorrect comparison
Misumida 2016[32]	Incorrect comparison
Munkhaugen 2019[33]	Incorrect comparison
Nakatani 2013[34]	Incorrect study design (inappropriate variable adjustments)
Nguyen 2017[36]	Incorrect study design (less than 1,000 participants)

Study	Exclusion reason
Nicolau 2018[38]	No relevant outcome data
Ozasa 2010[39]	Incorrect study design (less than 1,000 participants)
Park 2014[40]	No relevant outcome data
Puymirat 2016[41]	Does not answer clinical review question
Raposerias-Roubin 2015[42]	Does not answer clinical review question
Shacham 2013[43]	Incorrect study design
Shu de 2012[44]	Incorrect comparison
Siu 2010[45]	Incorrect study design (less than 1,000 participants)
Voko 2011[46]	Incorrect comparison
Wong 2010[47]	No relevant outcome data
Yang 2014[48]	Does not answer clinical review question

I.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 8: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Appendix J: Research recommendations

The research recommendation from CG172 has been upheld. Information about the research recommendation can be found in NICE guideline CG172.