Systematic review: prognosis of angina in primary care

Melvyn Jonesa, Greta Raita, Jane Falconerb and Gene Federb


Background. Angina is a common chronic condition, largely managed in primary care in the UK. Mortality data are predominately from population or hospital studies with little known about the prognosis of angina in general practice settings.

Objective. To describe the prognosis of angina in patients identified in primary care.

Methods


Data sources. Medline, PsycINFO, EMBASE, CINAHL, HMIC, WOS, IBSS, UK National Research Register, notification via JISC, CHAIN.

Review methods

Selection criteria. Cohort studies of patients with angina, with >12 months of follow-up, recruited within primary care.

Validity assessment. Database searches and abstracts were reviewed independently by two authors. Papers were assessed according to criteria derived from the cohort methodological literature.

Data abstraction. Data were abstracted by two reviewers.

Data synthesis. Narrative summary. A quantitative synthesis was planned.

Main outcome measures. Total and cardiovascular death; non-fatal myocardial infarction (MI).

Results. Six studies fulfilled our selection criteria. The annual total mortality rate is 2.8–6.6%, an annual cardiovascular death rate of 1.4–6.5% and an annual non-fatal MI rate of 0.3–5.5%. A quantitative synthesis was not possible, because the studies were clinically heterogeneous.

Conclusions. The primary studies have value in determining the prognosis of patients with angina recruited in general practice; however, the studies are old, have small numbers of events and are clinically heterogeneous. The contemporary prognosis of angina in primary care remains a key question, and further research is, therefore, required to estimate the prognosis of angina in this setting and its determinants.

Keywords. Angina pectoris, primary health care, prognosis, systematic review.

Background

Angina pectoris is an important common condition with appreciable morbidity and mortality. Estimates of angina prevalence in UK are 4.8 and 3.4% for men and women, respectively, of all ages.1 The US prevalence is reported at 3.8%.2 The Quality and Outcome framework (QOF) monitoring system for the new UK GP contract recorded 174,000 incident cases of angina in England over 2 years, which gives an incidence rate of angina of 0.33% (0.17% pa).3

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aRoyal Free University College Medical School, Department Of Primary Care and Population Sciences, London, UK; bRoyal Free and University College Medical School, Medical Library, London, UK and cBarts and the London, Queen Mary, University of London, Centre for Health Sciences, London, UK. Correspondence to Melvyn Jones, Royal Free and University College Medical School, Department of Primary Care and Population Sciences, Rowland Hill Street, London NW3 2PF, UK; Email: m.jones@pcps.ucl.ac.uk
Community-based studies suggest that people with diagnosed angina have a better 5 year mortality than survivors of a myocardial infarction (MI; hazard ratios 3.5 and 6.8, respectively), compared with people without manifest ischaemic heart disease.4 The disease severity in terms of risk of mortality falls with years since diagnosis, with a hazard ratio of 3.5 in the first 5 years and 1.2 between 10 and 15 years.4 This finding is supported by the community-based Framingham study5 and from one primary care based study.6 Secondary prevention and revascularisation has improved prognosis and quality of life of people with angina.7,8 However, we know that patients with angina are infrequently referred from primary care to specialist services,9 although this is likely to change with new policy promoting referral of people with new onset angina to secondary care in the UK.10,11

There is a need for a systematic review of angina prognosis in primary care. Estimates of angina prognosis from community-based and hospital-based studies need to be complemented by studies based in primary care, where most patients labelled and diagnosed with angina are managed. A consequence of selective referral from primary to specialist care is that studies measuring prognosis of angina patients in hospital settings are unrepresentative of angina patients in the community. Patients included in this type of study will probably have more severe disease and a worse prognosis. They may also be referred in an early, acute stage, again when their prognosis may be worse, leading to a referral bias. At a population level, among those with angina symptoms, there is evidence that receiving a diagnosis of angina improves prognosis,12 so community-based studies may again appear to indicate a worse prognosis in comparison with a primary care cohort.

The aim of this review was to estimate the prognosis of people with a diagnosis of angina in primary care. The selection criteria for studies were as follows:

**Inclusion criteria:** Cohort studies of patients with angina with follow-up of at least 12 months, based in primary care.

**Exclusion criteria:** Non-cohort study designs, studies recruiting patients with unstable angina and cohort studies recruited outside primary care, e.g. within the general population or within hospitals.

**Language:** There were no language restrictions.

**Time limits:** Studies were included if they were published between January 1968 and December 2004. Earlier descriptive or methodological studies that relate to the primary studies are included only where they add useful data.

**Outcomes of interest**
Non-fatal MI, fatal MI, cardiovascular deaths and total mortality.

**Definition of primary care**
Accessible, often first contact, health care, usually provided within the community, which is either comprehensive, coordinated care involving sustained relationship with patients, or undifferentiated by age, gender, disease or organ. This includes comprehensive, co-ordinated care to particular subsets of the population sometimes for a fixed period or care that focuses on sustaining health rather than treating illness.13

**Search strategy**
We used standardized techniques14 to identify studies of prognosis15 and primary care.16 The strategy was developed in Medline, using both MeSH (thesaurus) terms and text words, (Fig. 1) and translated for other databases (available from authors). We searched on the following bibliographic databases:

- National Library of Medicine (NLM) using Medline.
- PsycINFO (The American Psychology Association’s database).
- EMBASE (A bibliographic database produced by Elsevier Science B.V. accessing international literature on pharmacology and biomedicine).
- CINAHL (Cumulative Index to Nursing & Allied Health Literature).
- HMIC (Health Management Information Consortium).
- ISI WOK (Web of Knowledge) conference proceedings.
- IBSS (International Bibliography of the Social Sciences).

<table>
<thead>
<tr>
<th>Table 1 Search results</th>
</tr>
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<tbody>
<tr>
<td>Angina and synonyms</td>
</tr>
<tr>
<td>Medline/OVID</td>
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<tr>
<td>Psycit</td>
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<tr>
<td>EMBASE</td>
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<tr>
<td>HMIC</td>
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<tr>
<td>IBISS</td>
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<tr>
<td>ISI</td>
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<td>CINAHL</td>
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</table>
The UK National Research Register was also searched, using the MeSH term ‘angina pectoris’ (accessed 20 February 2004). ‘Grey’ literature was obtained by searching for theses and conference abstracts from HMIC and WOK. Additionally we notified the Joint Information Systems Committee (JISC; www.jisc.ac.uk) and CHAIN (Contact, Help, Advice, and Information Network for effective health care). JISC and CHAIN are informal email networks for evidence-based care (Fig. 1).17

Citation tracking
Relevant articles were forward tracked through the Web of Knowledge and any articles identified by this process were reviewed. Most studies have reported earlier cross-sectional studies. Data from all papers reporting one of the included studies were used. Author names from identified studies were used as search terms to identify other studies using Medline. We wrote to first or corresponding authors and sought unpublished data (Fig. 2).

All primary studies that were subsequently included were initially found in the search of the NLM database.

Validity assessment
Database searches and abstracts were reviewed independently by two authors (MJ and GR) for papers meeting the inclusion criteria. Full text articles were obtained for possible and probable papers. Where there was disagreement, papers were reviewed and agreement was reached. A third reviewer (GF) was available for adjudication.

Papers were assessed by two reviewers according to consensus quality criteria.14,18–20 Criteria suggested by Lupacis were modified with the MOOSE consensus statement.19 This statement has a wider scope and specifies search strategies and methods of capturing the grey literature. We used these criteria first as inclusion/exclusion criteria and second, if feasible, for sensitivity analyses. In this review all studies of angina in primary care used a clinical diagnosis of angina, which would not fit the criterion of ‘explicit reproducible diagnosis’, so this filter was discarded.

Data from included studies were then abstracted independently by two reviewers (MJ and SC).

Analysis
Data from included studies were abstracted and means of annual total mortality, cardiovascular mortality and non-fatal MI rates, and their confidence intervals were calculated, if not reported. Forest plots were then constructed for the data. In addition to the narrative analysis, we planned to use a random effects model to produce a pooled estimate of mean event rates. We abstracted data and examined in detail, the Methods section of the included reports to look at study methods and the selection criteria for those recruited to the studies to ascertain whether there was clinical heterogeneity between studies.
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Fry</th>
<th>Lambert</th>
<th>Hobkirk</th>
<th>Clarke</th>
<th>Gill</th>
<th>Mozaffarian</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type</strong> cohort (exclude other methodologies)*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (499 of 6586 sub sample with notes verification)</td>
<td>Yes</td>
<td>Veteran’s Affairs general internal medicine</td>
</tr>
<tr>
<td>Based/ recruited from primary care*</td>
<td>Yes (1 practice in Bromley, SE London, UK)</td>
<td>Yes (1 practice in Keighley, Yorks, UK)</td>
<td>Yes (20 practices in northern England, UK)</td>
<td>Yes (Nottingham health district, UK)</td>
<td>Yes (1 practice in Oxford, UK)</td>
<td>Yes (6 Veterans’ Affairs Medical Centres, USA)</td>
</tr>
<tr>
<td>‘Representativeness’ selected from a representative population—described?</td>
<td>GP diagnosis of AP</td>
<td>GP diagnosis of AP</td>
<td>GP diagnosis of AP</td>
<td>Receipt of prescription of nitrates and GP notes verification</td>
<td>10% sample of notes reviewed for evidence of AP</td>
<td>Self-reported chd events</td>
</tr>
<tr>
<td>Well defined sample/Explicit inclusion criteria</td>
<td>Incident cases</td>
<td>Incident cases</td>
<td>Prevalent cases (31% &gt; 5 years, 10% &gt;10 years duration)</td>
<td>Prevalent cases (duration not recorded)</td>
<td>Prevalent and incident cases</td>
<td>Prevalent cases (duration not recorded)</td>
</tr>
<tr>
<td>Duration of illness/symptoms</td>
<td>Average 11 years (range 0–20+)</td>
<td>3 years</td>
<td>4 years</td>
<td>7 years</td>
<td>2 years prospectively</td>
<td>2 years</td>
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<td><strong>Secondary guides</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective unbiased outcomes mortality (CHD and non-CHD)</td>
<td>GP records and autopsy records</td>
<td>GP records/ autopsy records</td>
<td>GP records</td>
<td>FHSAs (health authority records) &amp; Office of Population Census and Surveys data</td>
<td>GP records</td>
<td>Veteran’s Affairs computer records</td>
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<tr>
<td></td>
<td>ECG/ enzyme/ history records</td>
<td>GP and hospital records</td>
<td>ECG/ enzyme markers</td>
<td>GP records</td>
<td>GP records</td>
<td>Veteran’s Affairs health information systems and Technology Architecture) and Beneficiary Identification Records Locator Subsystem</td>
</tr>
<tr>
<td>Outcomes morbidity e.g. AMI (biochemical /ECG marker of MI, blinded observer?)</td>
<td>GP records</td>
<td>ECG/ enzyme/ history records</td>
<td>GP and hospital records</td>
<td>ECG/ enzyme markers</td>
<td>GP records</td>
<td>Veterans Affairs system inc. hospital records</td>
</tr>
<tr>
<td>Adjustment for important prognostic factors</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Prognostic factors: demographic</td>
<td>Mode 70+</td>
<td>Mode 50–54</td>
<td>75 (range 33–95)</td>
<td>45–74 defined range</td>
<td>68 mean</td>
<td></td>
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<tr>
<td>Age range of sample described</td>
<td>65</td>
<td>Mode 50–54</td>
<td>75 (range 33–95)</td>
<td>45–74 defined range</td>
<td>68 mean</td>
<td></td>
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<tr>
<td>Gender distribution described</td>
<td>64% male</td>
<td>56% male</td>
<td>3:1 m:f</td>
<td>58% male</td>
<td>58% male</td>
<td>93% male</td>
</tr>
</tbody>
</table>
Results

We reviewed 3411 abstracts and 136 full papers. Five abstracts in languages other than English potentially fulfilled our inclusion criteria and were translated into English. They did not fulfill our inclusion criteria and were excluded. Our correspondence with authors added no further data to the published reports.

Six papers fulfilled all our quality criteria (Table 2). The most common reasons for exclusion of full papers, identified as potential primary studies from the abstracts, were: studies examining a broader range of CHD diagnoses (e.g. post MI, undifferentiated chest pain), based in secondary care, cross-sectional or community surveys. A few studies were excluded as they had <12 months follow-up (Table 3).

Outcome 1: total mortality
All-cause mortality rate varied from 2.8 to 6.6% per annum. The studies were found to exhibit considerable clinical heterogeneity; therefore, a pooled estimate would not be statistically appropriate (Fig. 3).

Outcome 2: cardiovascular mortality
The cardiovascular death rate varied from 1.4 to 6.5% per annum (Fig. 4).

Outcome 3: non-fatal MI
The non-fatal MI rate varied from 0.3 to 5.5% per annum. We have only reported data from four studies as the non-fatal MI data were not reported in two of the studies (Fig. 5).

Clinical heterogeneity
We identified clinical heterogeneity in these studies. There is variation in cohort identification and recruitment in the primary studies. Lambert’s study was a non-randomized comparison of beta blocker usage in angina (but reported total events).21–24 Hobkirk’s study has an age range with a young upper limit (59 years).25,26 As most deaths and events would be expected to occur in the older age group, this may explain the reduced event rates in this study. The Mozaffarian study recruited patients with recall of a CHD diagnosis, (i.e. no independent confirmation of the diagnosis).27–29 However, there is evidence that there is good agreement between patient recall and clinical diagnoses.30 The Mozaffarian study also followed patients up on the basis of their Seattle Angina Questionnaire (SAQ) angina score and not specifically an angina diagnosis (Table 4). This study has the largest sample in this review and is the most robust methodologically, but the participants are different from the UK studies. All had served in the US armed forces, 98% were male and 15% were African Americans. This group will, therefore, have a different risk of cardiac events in comparison with other studies. Overall there is marked clinical heterogeneity between studies rendering a pooled estimate inappropriate.

Discussion
The main findings of this systematic review are the morbidity and mortality rates; the range of total mortality rate in angina patients identified in primary care is 2.8–6.6% per annum, cardiovascular death rates...
ranged from 1.4 to 6.5% per annum and the non-fatal MI rate ranged from 0.3 to 5.5% per annum.

There are some limitations in the primary studies, which may have an impact on the outcome rates we have reported. There is a wide range of percentage cardiovascular deaths (32–98%), which suggests there have been problems in recording this data. In Clarke’s study,9 approximately one-third of patients had an unknown cause of death. It is likely that a high proportion of these deaths were cardiac in origin, and so this might explain the low percentage of cardiovascular deaths (32%) in this study compared with the other included studies.

The reports of percentage non-fatal MI rates show an almost 20-fold difference from the highest to lowest estimate. The lower estimate comes from Fry who collected data from patients starting in the 1950s.6 Fry’s study may give a low estimate, due to under-recognition or under-recording of non-fatal MI as a cause. Historically, MI was largely a clinical diagnosis and patients were infrequently hospitalized with suspected MI. If we exclude Fry’s non-fatal MI data the estimate range is a slightly narrower 1.8–5.5% pa.

We have presented the data in an approximate chronological order, but this is not the strict publishing date order as the data collection covered large, and in some cases overlapping, periods of time. This is particularly the case for Fry’s work, which recruited patients from the 1950s onwards, but was published in the mid 1970s.

MI before or after the diagnosis of angina, is highlighted by other investigators as an important prognostic factor.31 Only one study reported this association with a univariate odds ratio of 1 year morality of 1.4.29 Hobkirk’s study reports data suggesting an odds ratio of subsequent cardiac events (cardiac death and non-fatal MI) of 1.2 in relation to previous MI.25 Diabetes is associated with an increased death rate in the Mozaffarian study (OR 1.52). Hobkirk indicates a 33% mortality over 4 years amongst the patients with diabetes suggesting a 2-fold increase over their total published mortality rate. Other known important prognostic factors such as heart failure, medication and smoking status are similarly poorly reported apart from the Mozaffarian study (so are not reported again in this review).27

Age, probably the most important predictor of outcome, is reported in three studies but using different analyses and differing age bands, making comparisons difficult (see Table 4). Overall these studies report an increasing death rate with age, but, interestingly, Fry reports a falling observed/expected death rate in older patients. This might suggest that the prognosis of angina for older patients is more to do with general age-related processes rather than their underlying coronary artery disease.
There are potential problems with systematic reviews of observational data such as confounding and selection bias, which can distort the findings. There are no validated quality criteria for such studies, but there are consensus statements, which we have used as study ‘quality filters’.\(^{14,18,19}\) The possibility of publication bias must also be considered.

For such an important condition with an enormous impact on individuals and health services, there are surprisingly few studies of prognosis from primary care populations. Those that do exist are of a lower quality and are relatively small. Most of the UK work is no longer contemporary and predates recent medical and surgical advances that have improved prognosis.

**Relationship to other literature**

The range in prognosis in our primary studies encompasses estimates from studies investigating angina prognosis in other settings or using other methodologies. For example, the Framingham study in the US, a population cohort, reported a 30% mortality rate over 8 years in those >55 with angina. This approximates to a death rate of 3.8% per annum. The study is now
quite old and does report a higher initial death rate, falling with years from diagnosis, so such estimates of average death rates must be treated with caution.\textsuperscript{31}

Tiernay’s retrospective US cohort study patients with IHD, which was defined as MI, angina or coronary artery disease, but which was based in primary care found an 18% mortality over 5 years (which approximates to 3.6% pa).\textsuperscript{32} A UK study of fish oil exposure for male patients with angina identified by their GP and self-selected (and therefore excluded from this review) gave an approximate death rate of 3.7% pa.\textsuperscript{33}

In the UK, the British Regional Heart Study group reported a total mortality for diagnosed angina of 3.0% per year.\textsuperscript{4} This was a population cohort of middle-aged men who were screened for cardiovascular symptoms and risk factors, including a doctor diagnosis of angina. A Swedish community study of angina reports 148 deaths over 16 years among 314 men with angina (but no pre-existing MI), which approximates to 3.0% deaths pa.\textsuperscript{34} A recent community study from Finland of patients with angina, defined as those on nitrates or who are ‘test positive’ (ECG or angiogram) reports data, which would suggest a lower death rate of those with angina of 1.6% pa.\textsuperscript{35}

Not all other studies reported mortality in our range. For example, Gandhi’s study of patients with angina recruited from primary care but required referral to a quasi-secondary care clinic, similar in nature to contemporary rapid-access chest-pain clinics (hence its non-inclusion in this review). They reported a 7% non-fatal MI rate per year and a 4% total death rate per year.\textsuperscript{36} These higher rates in comparison with our results would suggest a referral bias in favour of the sicker patient. However, two recent studies looking at angina prognosis in secondary care report quite low death rates of 1.1–1.67% pa (and 1.8% in angiographically confirmed angina).\textsuperscript{37,38}

The implication for practice is that angina remains a disease with appreciable mortality and morbidity. The implication for research is that a contemporary cohort

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**TABLE 4**  
Age specific mortality data

<table>
<thead>
<tr>
<th>Age range</th>
<th>observed/expected [E&amp;W] rates</th>
<th>Mortality by age group (person years) [% 95% CI]</th>
<th>Age band</th>
<th>Mortality by age band [% 95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–&lt;49</td>
<td>4</td>
<td>&lt;60</td>
<td>104/4015 (2.6% [2.1–3.1])</td>
<td>60–69</td>
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<tr>
<td>50–&lt;59</td>
<td>2.3</td>
<td>240/5406 (4.4% [3.6–4.9])</td>
<td>60–69</td>
<td>240/5406 (4.4% [3.6–4.9])</td>
</tr>
<tr>
<td>60–&lt;69</td>
<td>1.9</td>
<td>61–70</td>
<td>240/5406 (4.4% [3.6–4.9])</td>
<td>70–79</td>
</tr>
<tr>
<td>&gt;80</td>
<td>0.9</td>
<td>&gt;70</td>
<td>552/7856 (7.0% [6.4–7.6])</td>
<td>&gt;70</td>
</tr>
</tbody>
</table>

*over 3 years

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**FIGURE 5**  
Forest plot of mean non-fatal MI rate
study of angina is required to examine the impact of changes in management (use of statins, anti-platelet agents and coronary artery procedures) away from tightly controlled trial environments. It is vital this occurs in a primary care setting, where most patients with angina receive their care.

Acknowledgements

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References