Off-hour presentation and outcomes in patients with acute myocardial infarction: systematic review and meta-analysis

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STUDY QUESTION

Do patients with acute myocardial infarction presenting to hospital during off-hours (weekends and nights) have higher mortality than those presenting during regular hours, and do patients with ST elevation myocardial infarction (STEMI) have longer door to balloon time during off-hours than in regular hours?

SUMMARY ANSWER

Patients with acute myocardial infarction presenting during off-hours have higher mortality, and patients with STEMI have longer door to balloon times during off-hours.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Past studies have suggested that patients with acute myocardial infarction may or may not have higher mortality when they present to the hospital during off-hours compared with regular hours. This systematic review suggests that mortality is higher for patients with acute myocardial infarction who present during off-hours compared with regular hours; this finding may be partially attributed to longer door to balloon times during off-hours for patients with STEMI.

Selection criteria for studies

We searched Medline in-process and other non-indexed citations, Medline, Embase, Cochrane Database of Systematic Reviews, and Scopus from database inception to April 2013. We included any study (with any language and design) that evaluated the association between time of presentation to a healthcare facility and mortality or door to balloon times among adult patients with acute myocardial infarction.

Primary outcome(s)

The main outcomes were in-hospital or 30 day mortality and door to balloon times.

Main results and role of chance

The meta-analysis included 48 cohort studies with fair quality enrolling 1 896 859 patients. Off-hour presentation for patients with acute myocardial infarction was associated with higher in-hospital or 30 day mortality (odds ratio 1.06, 95% confidence interval 1.04 to 1.09). Patients with STEMI presenting during off-hours were less likely to receive percutaneous coronary intervention within 90 minutes (odds ratio 0.40, 0.35 to 0.45) and had longer door to balloon time by 14.8 (10.7 to 19.0) minutes. A diagnosis of STEMI (odds ratio 1.12, 1.03 to 1.22) was associated with a larger increase in mortality during off-hours compared with non-STEMI (0.96, 0.91 to 1.02). Studies in Europe (odds ratio 1.08, 1.02 to 1.15) and other regions (1.25, 1.15 to 1.36) seemed to be associated with a larger off-hour increase in mortality compared with North America (1.03, 1.01 to 1.04). Meta-regression showed a significant association between the mid-year of patient enrolment and the effect size, suggesting a larger off-hour increase in mortality in recent years (P=0.03).

Bias, confounding, and other reasons for caution

The results were derived from observational studies in which patients were not randomised, and studies used different variables for adjustment of outcomes. Therefore, the difference in mortality between off-hours and regular hours may be confounded by patients' clinical characteristics. High heterogeneity reduces the validity of the study findings, and the pooled effect size of this study should be viewed as an average estimate expected across a range of different settings such as countries, institutions, and population demographics. Publication bias is likely in small studies, favouring positive association between off-hour presentation and higher mortality. Potential exists for overlapping of patients across the cohorts.

Study funding/potential competing interests

The study did not receive any extramural funding.

Summary of outcomes of meta-analysis

Outcome	No of cohorts	Measure	Point estimate (95% CI)	I^2 (%)
Mortality:				
In-hospital or 30 day	42	Odds ratio	1.06 (1.04 to 1.09)	74
In-hospital	35	Odds ratio	1.05 (1.03 to 1.08)	55
30 day	18	Odds ratio	1.05 (1.02 to 1.09)	83
Door to balloon time:				
% <90 minutes	7	Odds ratio	0.40 (0.35 to 0.45)	41
Mean	29	Mean difference	14.8 (10.7 to 19.0) min	99

Red flags to screen for malignancy and fracture in patients with low back pain: systematic review

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STUDY QUESTION

What are the best red flags to indicate the possibility of fracture or malignancy in patients presenting with low back pain in primary, secondary, or tertiary care?

SUMMARY ANSWER

Older age, prolonged corticosteroid use, severe trauma, and presence of a contusion or abrasion increase the likelihood of spinal fracture (likelihood was higher with multiple red flags); a history of malignancy increases the likelihood of spinal malignancy.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Guidelines recommend red flags to screen for spinal fracture or malignancy in patients presenting with low back pain but do not agree on which ones to use. In a summary of the evidence on diagnostic accuracy, this article showed that only a few of these red flags are informative.

Selection criteria for studies

Medline, OldMedline, Embase, and CINAHL were searched from earliest available up to 1 October 2013. Primary diagnostic studies comparing red flags for fracture or malignancy to an acceptable reference standard in any language were included. Three independent reviewers extracted data from qualifying studies and assessed quality with QUADAS.

Primary outcome

We generated diagnostic accuracy statistics and post-test probabilities for each red flag identified and matched these to guideline recommendations for the use of red flags involving the diagnosis of low back pain.

Main results

We included 14 studies (eight from primary care, two from secondary care, four from tertiary care) evaluating 53 red flags; only five studies evaluated combinations of red flags. Pooling of data was not possible because of index test heterogeneity. Study quality items that were often inadequately covered or unclear were an acceptable delay between index and reference tests, partial verification, differential verification, reference standard blinding, reporting uninterpretable results, and explaining withdrawals. Point prevalence we used to calculate post-test probability was determined by extracting prevalence from a reduced set of methodologically robust studies for fracture and cancer and by considering a value that could be readily applied in the clinical setting (fracture: 1% for primary care, 5% for secondary and tertiary care; malignancy: 0.5% for primary care, 1.5% for secondary and tertiary care). Many red flags in current guidelines provide virtually no change in probability of fracture. Example post-test probabilities are spinal tenderness (2%, 95% confidence interval 1% to 3%) and spasm (1%, 0% to 4%). The red flags with the highest post-test probability for detection of fracture were older age (9%, 95% confidence interval 3% to 25%), prolonged corticosteroid use (33%, 10% to 67%), severe trauma (11%, 8% to 16%), and presence of a contusion or abrasion (62%, 49% to 74%). The probability of spinal fracture was higher when multiple red flags were present (90%, 34% to 99%); but this approach is not endorsed in current guidelines. Many red flags in current guidelines provide little or virtually no change in probability of malignancy. Examples are unexplained weight loss (1%, 95% confidence interval 0% to 5%), insidious onset (1%, 0% to 1%), and failure to improve after one month (2%, 1% to 3%). The red flag with the highest post-test probability for detection of spinal malignancy was history of malignancy (33%, 22% to 46%).

Bias, confounding, and other reasons for caution

In this review we graphically portray the post-test probability and 95% confidence intervals for investigated red flags. Our results enable clinicians to easily interpret the informativeness of red flags to screen for spinal fracture and malignancy. A limitation of this approach is that prevalence of fracture and malignancy varied considerably between studies (fracture: from 0.7% to 11.0%; malignancy: from 0% to 7.0%) and depended on study methods and setting. Therefore values for prevalence and post-test probability in our review might not generalise to every setting.

Study funding/potential competing interests

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Red flags with highest probability for detection of fracture or malignancy in patients with low back pain

Pathology and red flag	Setting	Probability* (%) When absent	Probability* (%) When present
Fracture			
Prolonged use of corticosteroid	Primary care	0.8	32.9
Combination†	Primary care	0.6	90.2
Contusion/abrasion	Emergency department	0.8	62.1
Malignancy			
History of malignancy	Primary care	0.1	32.5

*Probabilities presume prevalence of fracture is 1% in primary care, 5% in secondary and tertiary care; and prevalence of malignancy is 0.5% in primary care, 1.5% in secondary and tertiary care.
†Any three of female, age >70, severe trauma, prolonged use of corticosteroids.

Severe bereavement stress during the prenatal and childhood periods and risk of psychosis in later life: population based cohort study

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- Research: Course of bereavement over 8-10 years in first degree relatives and spouses of people who committed suicide: longitudinal community based cohort study (*BMJ* 2013;347:f5519)
- Practice: Recognition and management of psychosis and schizophrenia in children and young people: summary of NICE guidance (*BMJ* 2013;346:f150)
- Research: Early interventions to prevent psychosis: systematic review and meta-analysis (*BMJ* 2013;346:f185)
- Editorial: Can we identify and treat "schizophrenia light" to prevent true psychotic illness? (*BMJ* 2013;346:f304)

STUDY QUESTION

What are the risks to offspring of subsequent psychosis associated with severe prenatal and postnatal maternal bereavement stress between conception and adolescence, and with different causes of death?

SUMMARY ANSWER

Postnatal, but not prenatal, severe bereavement stress was associated with an increased risk of later psychosis in offspring. Risks were especially high for affective psychosis after suicide in a nuclear family member, an effect which was not explained by family psychiatric history.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The largest previous study showed no effect of prenatal maternal bereavement stress on a range of psychopathological outcomes, but it did not distinguish between loss of a close compared with more distant relative or between causes of death. We found that the risk of psychosis increased significantly if a close family member died suddenly during an offspring's childhood, particularly if a parent committed suicide before the child was 3; this finding was not explained by a family history of mental illness or suicide.

Participants and setting

All children born alive in Sweden between 1 October 1973 and 31 December 1985.

Design, size, and duration

In a cohort of 1 045 336, offspring exposed to severe maternal bereavement stress six months before conception or during pregnancy, or to loss of a close family member subsequently from birth to 13 years of age were followed until 2006.

Main results and the role of chance

Maternal bereavement stress occurring preconception or during the prenatal period was not associated with a significant excess risk of psychosis in offspring (adjusted odds ratio, preconception 1.24, 95% confidence interval 0.96 to 1.62; first trimester 0.95, 0.58 to1.56; second trimester 0.79, 0.46 to 1.33; third trimester 1.14, 0.78 to 1.66). Risks increased modestly after exposure to the loss of a close family member from birth to adolescence for all psychoses (adjusted odds ratio 1.17, 1.04 to 1.32). The pattern of risk was generally similar for non-affective and affective psychosis. Thus, estimates were higher after death in the nuclear compared with death in the extended family, but remained non-significant for prenatal exposure; and higher the earlier the exposure to death in the nuclear family occurred in childhood (all psychoses: adjusted odds ratio, birth to 2.9 years 1.84, 1.41 to 2.41; 3-6.9 years 1.47, 1.16 to 1.85; 7-12.9 years 1.32, 1.10 to 1.58) and after suicide. Following suicide, risks were especially higher for affective psychosis (birth to 2.9 years 3.33, 2.00 to 5.56; 6.9 years 1.84, 1.04 to 3.25; 7-12.9 years 2.68, 1.84 to 3.92).

Crude and adjusted odds ratios for risk of all psychoses after exposures to bereavement stress during prenatal and postnatal periods (n=946 994)

Exposure status	No of cases	Adjusted odds ratio* (95% CI)
Unexposed	2710	—
Any time	1725	1.16 (1.09 to 1.23)
Any prenatal	115	1.10 (0.91 to 1.32)
Any postnatal	1610	1.16 (1.09 to 1.24)
Preconception	58	1.24 (0.96 to 1.62)
First trimester	16	0.95 (0.58 to 1.56)
Second trimester	14	0.79 (0.46 to 1.33)
Third trimester	27	1.14 (0.78 to 1.66)
Birth-2.9 years	312	1.17 (1.04 to 1.32)
3-6.9 years	491	1.21 (1.09 to 1.33)
7-12.9 years	807	1.13 (1.04 to 1.23)

Total exposed n=321 249; total unexposed n=625 745.
*Generated by logistic regression; adjusted for sex, year of birth, country of birth, presence or absence of siblings, any family psychiatric history, urban birth, highest education of parents, receipt of welfare, and maternal and paternal age.

Bias, confounding, and other reasons for caution

Adjustment for key confounders attenuated but did not explain risk associations. We did not have enough cases to calculate risks separately by trimester after the death of nuclear family members.

Generalisability to other populations

Findings may not generalise to other prenatal and maternal environmental exposures, such as nutritional deficiencies.

Study funding/potential competing interests

Data linkage and staff costs in Sweden were supported by grants from the Swedish Research Council (CD) and Swedish Council for Working Life and Social Research (2003-0376). ES acknowledges support received as Lisa Oehler visiting professor, Department of Psychiatry, University of Göttingen, Germany. We have no competing interests.

Long term duration of protective effect for HPV negative women: follow-up of primary HPV screening randomised controlled trial

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- Research: Detection rates of precancerous and cancerous cervical lesions within one screening round of primary human papillomavirus DNA testing (*BMJ* 2012;345:e7789)
- Research: Primary screening for human papillomavirus compared with cytology screening for cervical cancer in European settings: (*BMJ* 2012;344:e670)

STUDY QUESTION

Does the increased sensitivity of screening for human papillomavirus (HPV) represent overdiagnosis, and what is the long term duration of the protective effect against cervical intraepithelial neoplasia grade 2 or worse (CIN2+) in HPV based and cytology based screening?

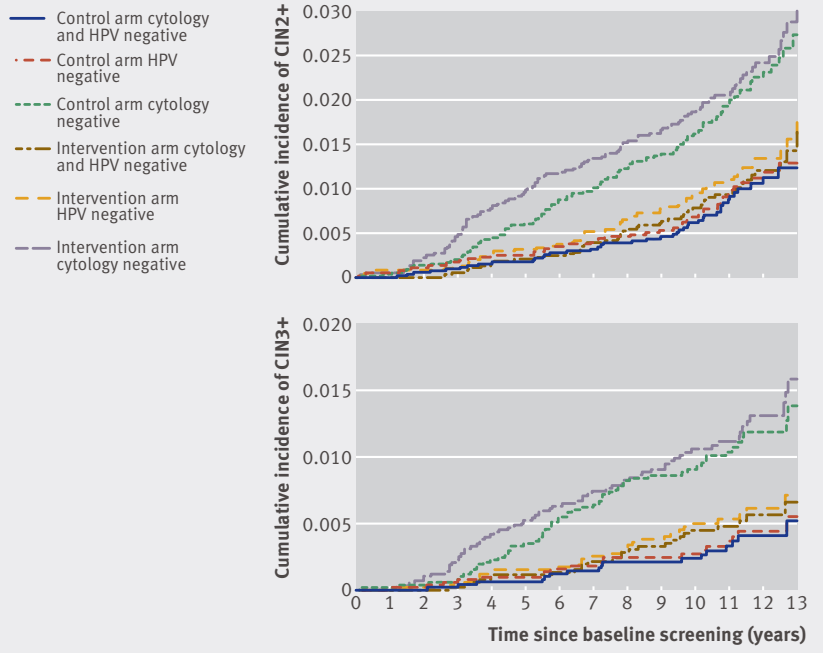
SUMMARY ANSWER

Over 13 years' follow-up, the cumulative incidence of CIN2+ was the same for HPV screening as for cytology, implying that the increased sensitivity of HPV screening for CIN2+ reflects earlier detection rather than overdiagnosis. We found low long term risks for CIN2+ among women testing negative in HPV screening, and this supports screening intervals of five years for such women.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The long term risks for CIN2+ and CIN3+ in HPV negative women are low, but data from randomised trials are limited. In this follow-up study of a randomised controlled trial of primary cervical screening, the cumulative incidence of CIN2+ at 13 years was the same for HPV based screening as for cytology based screening, indicating that increased sensitivity reflects earlier detection rather than overdiagnosis; the sensitivity of HPV based screening for CIN2+ after five years was similar to cytology based screening after three years.

Cumulative incidence of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) or grade 3 or worse (CIN3+) over 13 years of follow-up



Design

A double blind randomised controlled trial of HPV testing in primary cervical screening. 12 527 enrolled women were randomised 1:1 to HPV and cytology double testing (intervention arm, n=6257) or cytology only, with samples frozen for future HPV testing (control arm, n=6270). Women were followed through comprehensive registry based follow-up for all cervical cytological and histopathological diagnoses.

Participants and setting

Women aged 32-38 attending organised cervical cancer screening in five regions of Sweden.

Primary outcome

Cumulative incidence of CIN2+ and CIN3+ (Kaplan Meier curves). Longitudinal test characteristics were calculated for cytology only, HPV testing only, and cytology and HPV testing combined, adjusting for censoring.

Main results and the role of chance

The increased detection of CIN2+ in the intervention arm decreased over time. After six years the cumulative incidence of CIN3+ was similar in both trial arms and after 11 years the cumulative incidence of CIN2+ became similar in both arms. The longitudinal sensitivity of cytology for CIN2+ in the control arm at three years was similar to that of HPV testing at five years of follow-up in the intervention arm (85.9%, 95% confidence interval 76.9% to 91.8%) versus 86.4% (79.2% to 91.4%).

Bias, confounding, and other reasons for caution

The study targeted a limited age range. We used routine histopathological diagnoses, which could include some misclassification of endpoints but might provide results more directly generalisable to actual screening programmes.

Generalisability to other populations

Because this trial was nested within a population based organised screening programme in Sweden, the results should be generalisable to real life screening programmes.

Study funding/potential competing interests

This study was supported by the PREHDICT and CoheaHr projects (EU FP7 programmes), Swedish Cancer Society, and Swedish Foundation for Strategic Research. The funders had no role in the study design, analyses, interpretation, or decision to submit. JD has received grants from Merck/SPMSD for unconditional studies and LAD has received grants from Merck/SPMSD and GlaxoSmith-Kline for unconditional studies.

Trial registration number

Clinicaltrials.gov NCT00479375.