



Sex Differences in Acute Coronary Syndrome Presentation and Management: Twenty Years On, What Has Actually Narrowed

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Introduction

Sex differences in acute coronary syndrome (ACS) have been documented since the early 2000s: women present with somewhat different symptoms, wait longer for reperfusion, receive guideline-directed medical therapy (GDMT) less often, and have historically fared worse after myocardial infarction (MI) than men. Two decades on, cardiology has produced a substantial further body of registry data and meta-analyses on this question. What has rarely been asked as directly is whether any of these specific gaps has actually narrowed, or whether 'awareness' of the disparity has simply become part of the literature without changing the numbers underneath it.

This review sets six sources spanning 1995 through 2024 -- covering symptom presentation, reperfusion delay, discharge prescribing, and long-term outcome -- side by side to ask, domain by domain, which sex gaps have measurably closed and which have not.

The distinction matters clinically as well as historically. A gap in symptom recognition argues for different triage heuristics; a persistent gap in door-to-balloon time or discharge prescribing argues for a systems failure that has had twenty years to be fixed and has not been; a gap in raw mortality that disappears once treatment is equalized argues that the sex difference was never biological in the first place. Conflating these three kinds of gap into one general claim of 'disparity' obscures which lever actually needs to move.

Material and Methods

This is a narrative review drawing on six published sources identified through targeted literature search and citation tracking: a 2020 systematic review and meta-analysis of symptom presentation in ACS, a national US registry study and a 2022 systematic review of sex differences in door-to-balloon time, two reports from the Swedish SWEDEHEART registry spanning 1995-2014 and 2003-2013, and a 2024 meta-analysis of sex differences in myocardial infarction with nonobstructive coronary arteries (MINOCA). There was no pre-registered protocol or systematic search string across all domains. All percentages, odds ratios, hazard ratios, and confidence intervals reported here are taken directly from the cited sources; none has been invented, estimated, or extrapolated.

Sources were prioritized for inclusion when they either directly compared women and men on a single, well-defined process or outcome measure with an adjusted effect estimate, or when they explicitly tested whether a previously reported sex gap had changed over a defined follow-up period. That second criterion is why the Get With The Guidelines-Coronary Artery Disease registry, the 2022 door-to-balloon systematic review, and the Western Sweden SWEDEHEART report were selected together as a triangulating set on reperfusion and discharge prescribing, rather than any single one of them being treated as representative of the full twenty-year period on its own.

Results

Symptom presentation: real differences, wide overlap

A systematic review and meta-analysis pooling 27 studies found that, compared with men, women with confirmed ACS had higher odds of presenting with interscapular or shoulder-blade pain (OR 2.15, 95% CI 1.95-2.37), nausea or vomiting (OR 1.64, 95% CI 1.48-1.82), and shortness of breath (OR 1.34, 95% CI 1.21-1.48), and lower odds of chest pain (OR 0.70, 95% CI 0.63-0.78) and diaphoresis (OR 0.84, 95% CI 0.76-0.94) [1]. Despite these real differences, chest pain remained the most common presenting symptom in both sexes -- pooled prevalence 79% in men versus 74% in women [1]. Figure 1 sets this prevalence out directly, and Figure 2 sets the pooled odds ratios for each individual symptom out alongside it. The review's authors note that these sex differences have been established since the early 2000s, and that newer studies included in their cumulative meta-analysis did not materially change the pooled estimates [1] -- symptom presentation is, in that specific sense, a domain that has not changed, because it did not need to: the gap was real from the outset and remains real, but modest, and heavily overlapping between sexes.

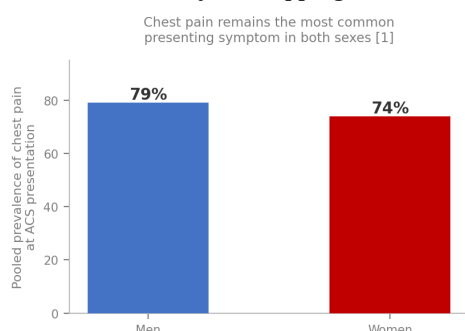


Figure 1: Pooled prevalence of chest pain at ACS presentation, by sex, across 27 studies [1].

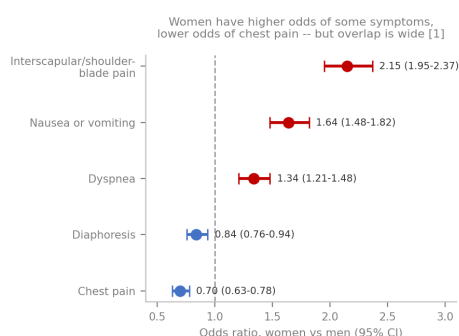


Figure 2: Pooled odds ratios for individual presenting symptoms, women versus men, across 27 studies [1].

Reperfusion delay: a gap unchanged from 2003 to 2022

In the American Heart Association's Get With The Guidelines-Coronary Artery Disease registry, 104,817 ACS patients treated between 2003 and 2008 at PCI-capable US hospitals were assessed for door-to-balloon (DTB) time. Women achieved a DTB time of 90 minutes or less in 51.7% of cases versus 56.9% of men, an adjusted OR of 0.85 (95% CI 0.80-0.91) [2]. Figure 3 sets this gap out directly. Both sexes improved substantially over the five-year study period -- DTB90 rates rose 24 to 35 absolute percentage points across sex and age groups -- but the gap between them did not converge [2]. A subsequent systematic review, published in 2022 and pooling the contemporary literature on this question, reached the same qualitative conclusion: women referred for primary PCI experienced longer DTB and symptom-to-balloon times than men across the studies it reviewed [3]. Nearly two decades separate these two assessments, and the direction of the finding has not changed.

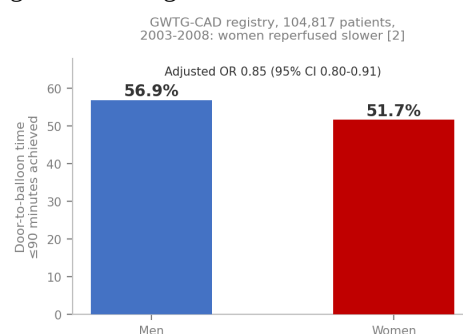


Figure 3: Door-to-balloon time of 90 minutes or less achieved, by sex, Get With The Guidelines-Coronary Artery Disease registry, 2003-2008 [2].

Not every metric in the same registry showed a sex gap of this size. Aspirin administration, already at a high baseline of 87%-91% across sex and age groups, increased a further 9-11% over the 2003-2008 study period for both women and men, with consistent uptake across sex and age strata [2]. The contrast is instructive: a simple, low-cost, protocol-driven intervention like early aspirin administration reached near-universal, sex-equal uptake over the same years that a time-critical, resource-dependent intervention like primary PCI did not. This suggests the persistent door-to-balloon gap is not a failure of guideline awareness in general, but a specific bottleneck in how quickly women are triaged to the catheterization laboratory once a STEMI is suspected.

Guideline-directed therapy: no narrowing across a full 20-year window

The SWEDEHEART registry's Western Sweden report, covering 48,118 patients with acute MI treated between 1995 and 2014 (35.4% women), found that women were less likely than men to be prescribed beta-blockers, ACE inhibitors or angiotensin receptor blockers, statins, and P2Y12 antagonists at hospital discharge ($P < 0.001$ for every drug class) [4]. Younger women and women with ST-elevation MI were also more likely to develop prehospital cardiogenic shock than their male counterparts (adjusted OR 1.67, 95% CI 1.30-2.16, and adjusted OR 1.31, 95% CI 1.16-1.48, respectively) [4]. Critically, this is the one source in this review with a full two-decade span built into its own design, and its authors tested explicitly for change over time: differences in treatment between the sexes did not decrease across the 20-year study period ($P > 0.1$ for every treatment class examined) [4]. Figure 4 places this alongside the reperfusion-delay finding in a single schematic of the ACS care pathway, since both concern what is actually done for a patient once the diagnosis is made, and both show the same pattern: stable sex gaps in favor of men across a period long enough that a slow secular narrowing should have been detectable if one were occurring.

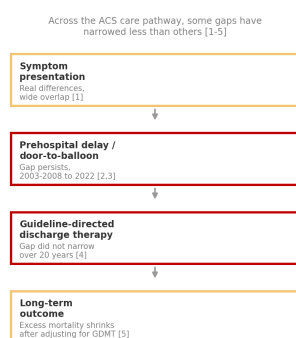


Figure 4: The ACS care pathway from presentation to outcome, with the direction of change in the sex gap at each stage as reported by the sources reviewed here [1-5].

It is worth being precise about what the Western Sweden report's $P > 0.1$ finding actually rules out. This was not a single snapshot comparison at one point in time: the authors tested explicitly for change across the full 1995-2014 span and found none [4], for every one of the four discharge medication classes examined. A null finding of that kind, repeated across twenty years and four separate drug classes rather than derived from one comparison at one moment, is considerably harder to explain away as a statistical artifact of case-mix or a short observation window than a single cross-sectional comparison would be.

Outcome: excess mortality narrows once treatment is accounted for

A national Swedish cohort using SWEDEHEART data from 2003 to 2013 found no statistically significant sex difference in age- and comorbidity-adjusted all-cause mortality at 1 or 5 years for either ST-elevation MI (STEMI) or non-ST-elevation MI (NSTEMI) [5]. However, when mortality was compared against a matched background population -- the excess mortality rate ratio (EMRR) -- women showed substantially higher excess mortality than men: EMRR 1.89 (95% CI 1.66-2.16) at 1 year and 1.60 (95% CI 1.48-1.72) at 5 years for STEMI, and 1.20 (95% CI 1.16-1.24) at 1 year and 1.26 (95% CI 1.21-1.32) at 5 years for NSTEMI [5]. Figure 5 sets both the unadjusted and treatment-adjusted trajectories out together. After further adjustment for the use of guideline-indicated treatments, the excess mortality attenuated markedly: for NSTEMI, it was no longer statistically significant at 1 year (EMRR 1.01, 95% CI 0.97-1.04) and only slightly elevated at 5 years (EMRR 1.07, 95% CI 1.02-1.12); for STEMI it fell to 1.43 (95% CI 1.26-1.62) at 1 year and 1.31 (95% CI 1.19-1.43) at 5 years, still elevated but substantially reduced from the unadjusted figure [5]. The authors conclude directly that improved adherence to guideline-recommended MI treatment may reduce premature cardiovascular death among women [5] -- in other words, this particular outcome gap looks less like a fixed sex difference and more like a downstream consequence of the treatment gap documented above.

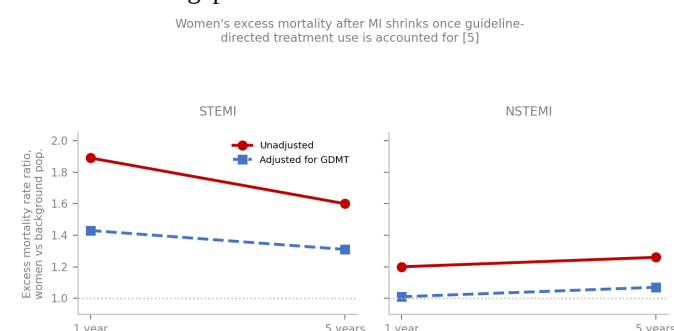


Figure 5: Excess mortality rate ratio (women versus matched background population), unadjusted and adjusted for use of guideline-indicated treatments, by follow-up duration, STEMI and NSTEMI, national SWEDEHEART cohort 2003-2013 [5].

The choice of excess mortality rather than raw all-cause mortality as the primary metric in this SWEDEHEART analysis is itself worth underlining, because it is what let the finding emerge at all. Comparing women's and men's absolute mortality directly found essentially no sex difference at 1 or 5 years for either STEMI or NSTEMI [5]; only by benchmarking each sex's mortality against its own matched background population did the analysis reveal that women were dying at a rate further above their expected baseline than men were above theirs [5]. A raw same-mortality comparison, of the kind commonly reported in smaller registries, would have missed this gap entirely.

MINOCA: more common in women, but converging long-term outcomes

A 2024 meta-analysis pooled nine studies totaling 30,281 patients with myocardial infarction with nonobstructive coronary arteries (MINOCA), of whom 18,079 (59.7%) were women and 12,202 (40.3%) were men [6]. Figure 6 sets this composition out directly. Women with MINOCA were older and had a higher prevalence of hypertension, diabetes, and prior stroke than men with MINOCA [6]. Despite these baseline differences, pooled analysis found no statistically significant sex difference in long-term all-cause mortality (OR 1.03, 95% CI 0.87-1.22), major adverse cardiovascular events (MACE, OR 1.18, 95% CI 0.89-1.58), heart failure (OR 1.32, 95% CI 0.57-3.03), stroke (OR 1.13, 95% CI 0.56-2.26), or recurrent MI (OR 1.04, 95% CI 0.29-3.76) over a median follow-up of 3.5 years [6]. Women did, however, carry a significantly higher risk of in-hospital MACE than men (OR 1.33, 95% CI 1.16-1.53), while in-hospital mortality did not differ significantly by sex (OR 0.90, 95% CI 0.64-1.28) [6]. Table 1 summarizes all six sources reviewed here, and Table 2 sets the full range of MINOCA outcome comparisons out together.

Source	Years	N (sex)	Domain	Direction of sex gap
Symptom review [1]	-2019	27 studies pooled	Symptoms	Real, overlapping
GWTG-CAD [2]	'03-'08	104,817 (ACS)	PCI delay	Unchanged, 5 yrs
DTB review [3]	-2021	Pooled literature	PCI delay	Persists to 2022
SWEDHEHEART W. Sweden [4]	'95-'14	48,118 (35.4% W)	GDMT	Unchanged, 20 yrs
SWEDHEHEART national [5]	'03-'13	National cohort	Mortality	Narrows w/ GDMT adj.
MINOCA meta-analysis [6]	-2023	30,281 (59.7% W)	Outcome	No sig. difference

Table 1: Summary of the six sources reviewed, by study years, population, care-pathway domain, and the direction of the reported sex gap [1-6].

Outcome	Timing	OR (95% CI), women vs men
All-cause mortality	Long-term (median 3.5 yr)	1.03 (0.87-1.22)
MACE	Long-term	1.18 (0.89-1.58)
Heart failure	Long-term	1.32 (0.57-3.03)
Stroke	Long-term	1.13 (0.56-2.26)
Reinfarction	Long-term	1.04 (0.29-3.76)
MACE	In-hospital	1.33 (1.16-1.53)
All-cause mortality	In-hospital	0.90 (0.64-1.28)

Table 2: Pooled sex-comparison odds ratios across MINOCA outcomes, long-term versus in-hospital, meta-analysis of 30,281 patients [6].

MINOCA: more common in women, but long-term outcomes converge once past the index admission [6]

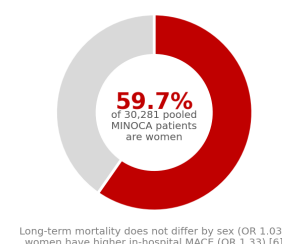


Figure 6: Sex composition of 30,281 pooled MINOCA patients and summary of key long-term versus in-hospital outcome comparisons [6].

Discussion

Read together, these six sources do not support a single answer to 'has the sex gap in ACS narrowed.' They support three different answers for three different domains. Symptom presentation shows a real but stable and overlapping sex difference that predates this review's earliest source and has not materially shifted since [1] -- there is nothing here to narrow, because the finding was never a treatment failure to begin with. Reperfusion delay and discharge prescribing show the opposite: a measurable, adjusted, statistically significant sex gap that has now been documented at both ends of a roughly twenty-year window -- 2003-2008 for door-to-balloon time in the GWTG-CAD registry, 2022 for the same finding in a contemporary systematic review, and explicitly tested for time trend across 1995-2014 for discharge prescribing in SWEDHEHEART -- without narrowing in either case [2,3,4]. That persistence, in domains where the fix (faster triage to the catheterization lab, writing the same four discharge prescriptions for a woman that a man would receive) requires no new science, is the least defensible finding in this review.

Long-term outcome is the one domain where the picture is more reassuring than a purely additive reading of 'women get less treatment' would predict. The SWEDHEHEART national cohort's own adjustment for guideline-indicated treatment use collapsed most of the excess mortality gap for NSTEMI and substantially reduced it for STEMI [5], and the MINOCA meta-analysis found no significant long-term outcome difference by sex at all, despite women's less favorable baseline risk-factor profile [6]. The most parsimonious reading of all six sources together is that the underlying biological difference in outcome, once it is actually measured net of unequal treatment, is smaller than the raw disparity literature of the early 2000s implied -- and that the treatment gap itself, not an intrinsic sex difference in prognosis, is now the more important remaining problem.

This reframes the twenty-year question usefully for clinicians: the persistence documented here is not evidence that sex differences in ACS biology are large and fixed. It is evidence that process-level inequities in how quickly and how completely women are treated have proven far more durable

than the underlying pathophysiology would justify.

Study limitations

This is a narrative review, not a systematic review with a single pre-registered search strategy, and it draws on six sources selected for topical relevance and data quality rather than through an exhaustive, reproducible search of every domain. The sources differ considerably in setting (Swedish national registry, US multicenter registry, international meta-analyses) and in era, which limits direct quantitative comparison across them even where the qualitative direction of a finding is consistent. The SWEDEHEART Western Sweden report's explicit test for narrowing over time [4] is a single-country finding and may not generalize to health systems with different structural incentives around guideline adherence. The MINOCA meta-analysis's reassuring long-term outcome finding [6] should not be over-read as showing sex parity in ACS overall: MINOCA is itself a minority presentation, women in that cohort had a worse baseline risk-factor profile than men, and the same meta-analysis found a significantly higher risk of in-hospital MACE in women, an important caveat this review has tried not to obscure. Finally, none of the sources reviewed here reports a single, harmonized time series spanning the full twenty years discussed in this article's title; the twenty-year framing is constructed by placing separately-conducted studies from different points in that window alongside one another, not by re-analyzing one continuous dataset.

Conclusion

Twenty years of literature on sex differences in acute coronary syndrome present a mixed and genuinely instructive picture rather than either a uniformly bleak or a reassuring one. Symptom presentation differs modestly and has not changed because it did not need to. Reperfusion delay and guideline-directed discharge prescribing remain measurably unequal across a span from 2003 through at least 2022, with no detectable narrowing despite being the domains most amenable to straightforward correction. Long-term outcome, once treatment differences are accounted for, looks considerably closer to sex parity than the disparity literature of two decades ago implied. The honest answer to what has actually narrowed, on the evidence assembled here, is: outcome, once treatment is equalized -- not treatment itself.

The practical implication for the clinician is narrow but concrete: a woman suspected of STEMI should not wait longer than a man for the catheterization lab, and the same four discharge medication classes under-prescribed to women in SWEDEHEART for twenty years [4] cost nothing extra to write for her too. Neither correction requires new trial evidence; both require only that an already-proven standard of care be applied without regard to sex, which is precisely what

the sources reviewed here show has not yet consistently happened.

The most useful outcome of revisiting this question every twenty years, rather than treating it as settled after the first wave of disparity studies in the early 2000s, is that it forces each domain to be re-tested on its own terms instead of inherited by assumption. Symptom overlap, reperfusion delay, prescribing, and long-term survival do not all move together, and the sources reviewed here suggest they will keep needing to be checked separately, not folded into one composite claim of progress or its absence.

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