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ORIGINAL RESEARCH

Outcomes by sex in the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial

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ABSTRACT

BACKGROUND: In the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial, among participants with stable coronary artery disease, the risk of cardiac events was similar between an invasive (INV) strategy of angiography and coronary revascularisation and a conservative (CON) strategy of initial medical therapy alone. Outcomes according to participant sex were not reported.

AIMS: We aimed to analyse the outcomes of ISCHEMIA by participant sex.

METHODS: We evaluated 1) the association between participant sex and the likelihood of undergoing revascularisation for participants randomised to the INV arm; 2) the risk of the ISCHEMIA primary composite outcome (cardiovascular death, any myocardial infarction [MI] or rehospitalisation for unstable angina, heart failure or resuscitated cardiac arrest) by participant sex; and 3) the contribution of the individual primary outcome components to the composite outcome by participant sex.

RESULTS: Of 5,179 randomised participants, 1,168 (22.6%) were women. Female sex was independently associated with a lower likelihood of revascularisation when assigned to the INV arm (adjusted odds ratio 0.75, 95% confidence interval [CI]: 0.57-0.99; p=0.04). The INV versus CON effect on the primary composite outcome was similar between sexes (women: hazard ratio [HR] 0.96, 95% CI: 0.70-1.33; men: HR 0.90, 95% CI: 0.76-1.07; $p_{interaction}$=0.71). The contribution of the individual components to the composite outcome was similar between sexes except for procedural MI, which was significantly lower in women (9/151 [5.9%]) than men (67/519 [12.9%]; p=0.01).

CONCLUSIONS: In ISCHEMIA, women assigned to the INV arm were less likely to undergo revascularisation than men. The effect of an INV versus CON strategy was consistent by sex, but women had a significantly lower contribution of procedural MI to the primary outcome.

KEYWORDS: clinical research; sex-based differences; stable angina

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In the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial, among participants with chronic coronary artery disease and moderate to severe myocardial ischaemia, there was no difference in the incidence of ischaemic cardiac events over a period of 3.2 years between an initial invasive (INV) strategy (coronary angiography followed by revascularisation via percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG] surgery when indicated) and an initial conservative (CON) strategy; the effect of an INV versus a CON strategy by participant sex was not reported in the original publication.

The pathophysiology of coronary artery disease and its clinical presentation are known to be different between sexes[1-8], and the efficacy, safety, and adoption of coronary interventions (both percutaneous and surgical) and of medical therapy varies significantly by sex[1,9-12]. It is thus unclear if the overall results of the ISCHEMIA trial hold true in both women and men.

In addition, in the ISCHEMIA trial, the individual components contributed differently to the primary composite outcome[13,14]. Due to the described differences in the adoption and outcomes of the different treatment strategies for coronary artery disease between sexes[13], the contribution to the individual components of the primary outcome in the INV and CON arms of the ISCHEMIA trial may be different by sex.

A better understanding of ISCHEMIA data by participant sex may inform the interpretation of the trial. Therefore, we conducted a *post hoc* analysis of the ISCHEMIA trial data by participant sex. The aims of this analysis were to compare 1) the association between participant sex and the likelihood and modality of revascularisation in the INV arm, 2) the effect of assignment to the INV and CON arms on the primary outcome by participant sex, and 3) the contribution of the individual components to the primary outcome among women and men.

Editorial, see page 515

Impact on daily practice

Women with stable coronary artery disease were less likely to undergo revascularisation than men. The effect of an invasive or conservative management strategy on cardiovascular death and myocardial infarction as well as rehospitalisation for unstable angina, heart failure or resuscitated cardiac arrest was overall similar for both sexes, but women had less procedural myocardial infarction.

Methods

DATA SOURCE

Data were obtained through the National Heart, Lung and Blood Institute (NHLBI) Biologic Specimen and Data Repositories Information Coordinating Center (BioLINCC). The need for an institutional review board (IRB) review was waived by the Weill Cornell Medicine IRB.

ISCHEMIA TRIAL DESIGN

The ISCHEMIA trial design and results have been previously published[13,15]. In brief, ISCHEMIA was a multicentre, randomised, controlled, open-label trial that assigned participants with moderate to severe ischaemia on non-invasive testing and acceptable levels of angina to either an initial INV strategy (coronary angiography and coronary revascularisation if appropriate) plus medical therapy or to an initial CON strategy with medical therapy alone, with angiography/revascularisation reserved for medical therapy failure (refractory angina or a primary outcome event). In the INV arm, the mode of revascularisation (CABG or PCI) was at the discretion of treating physicians. In the CON arm, 544/2,591 (20.9%) participants (of whom 108 were women) underwent unplanned revascularisation due to worsening clinical status.

The primary outcome was the composite of death from cardiovascular causes, myocardial infarction (MI), and hospitalisation for unstable angina, heart failure, or resuscitated cardiac arrest. Outcome definitions in the ISCHEMIA trial are included in **Supplementary Table 1**. The definition of non-procedural (spontaneous) MI was based on the Third Universal Definition of Myocardial Infarction (UDMI) types 1, 2, 4b and 4c. Procedural MI (PMI) required higher biomarker thresholds for confirmation than the 3rd UDMI[13,15]. An alternative, secondary definition used the same biomarker thresholds as the 3rd UDMI for defining PMI.

REVASCULARISATION BY SEX

To evaluate participant sex differences in revascularisation rates and modality, we examined the unadjusted and adjusted association between participant sex and the likelihood of undergoing revascularisation as well as the revascularisation modality (PCI or CABG) using logistic regression and multinomial logistic regression, respectively.

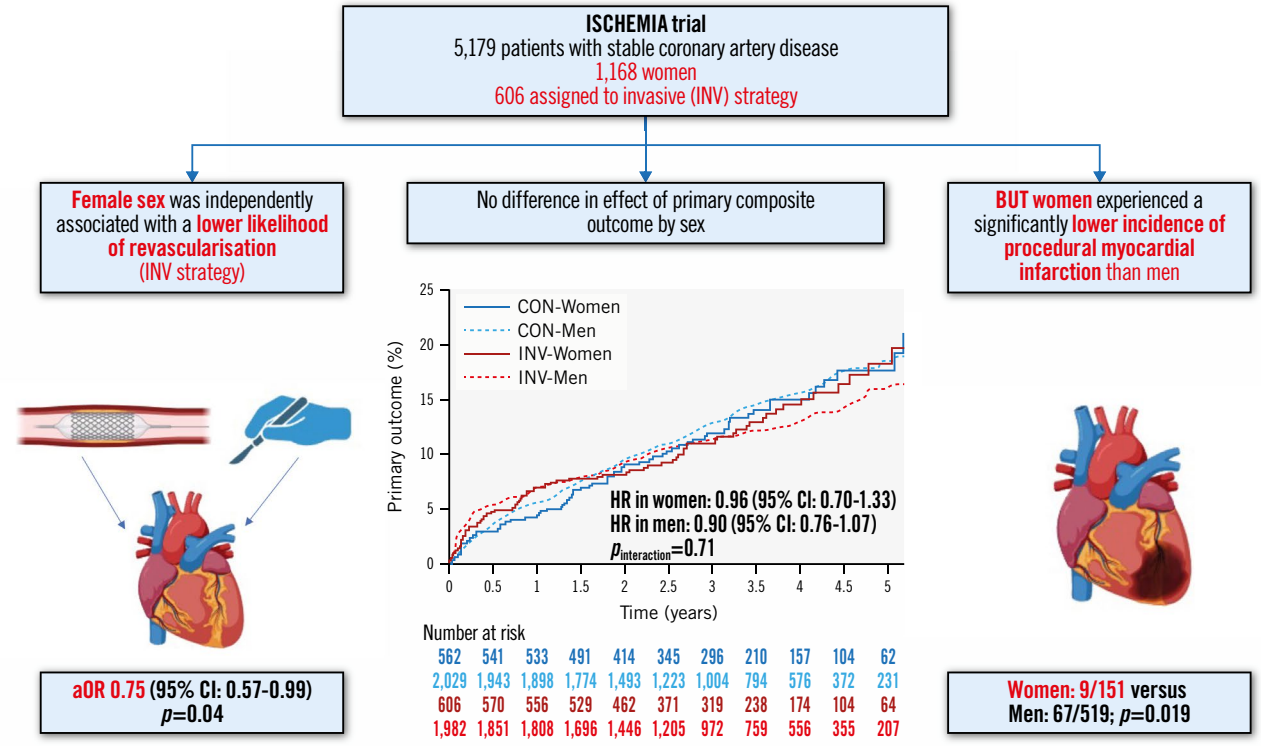
For these analyses, women and men in the INV arm who were revascularised without a preceding primary outcome event were categorised according to their first revascularisation procedure into the PCI or CABG group (INV-PCI and INV-CABG, respectively). Participants who did not undergo revascularisation or underwent revascularisation after having had a primary outcome event were the reference group. Participants in the CON arm who underwent unplanned revascularisation were not included in this analysis due to confounders related to key differences in clinical status and modality of revascularisation compared to participants who underwent planned revascularisation **(Central illustration)**.

Abbreviations

CABG coronary artery bypass grafting
CON conservative
INV invasive
ISCHEMIA International Study of Comparative Health Effectiveness With Medical and Invasive Approaches
MI myocardial infarction
PCI percutaneous coronary intervention
PMI procedural myocardial infarction
UDMI Universal Definition of Myocardial Infarction

EuroIntervention — Central Illustration

Outcome by sex in the ISCHEMIA trial.



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aOR: adjusted odds ratio; CI: confidence interval; CON: conservative; HR: hazard ratio; INV: invasive

EFFECT OF AN INVASIVE VERSUS A CONSERVATIVE STRATEGY BY PARTICIPANT SEX

To examine whether the effect of the two trial interventions (INV vs CON) were consistent among women and men, we compared the risk of the primary composite outcome and its components according to randomised treatment arm by participant sex.

The contribution of each individual component to the primary outcome was defined as the proportion of participants who met the primary outcome in whom that specific component was the only primary outcome event, i.e., participants who would not have met the primary outcome definition had they not had that specific event. MI was evaluated both overall (any MI) and stratified by the timing of its occurrence (PMI or spontaneous MI).

REVASCULARISATION OUTCOMES BY MODALITY AND PARTICIPANT SEX

We examined the risk of ISCHEMIA's primary outcome and its components after each revascularisation modality by participant sex; for this analysis, women and men in the INV arm who underwent revascularisation without a preceding primary outcome event were categorised at the time of their first revascularisation procedure as INV-PCI or INV-CABG, as appropriate. Even in this analysis, participants in the CON arm who underwent unplanned revascularisation were not included because of the potential confounders described above. Time-to-first-event analyses (from the time of revascularisation) were then performed to examine the cumulative risk of the primary outcome and its components after revascularisation by PCI and CABG by participant sex.

STATISTICAL ANALYSIS

Continuous data are reported as mean±standard deviation for variables with a normal distribution or median (1st quartile [Q1], 3rd quartile [Q3]) for variables with a skewed distribution. Categorical data are reported as frequency (percentage). Kaplan-Meier cumulative event rates were calculated for women and men in the INV and CON arms, and Cox proportional hazards regression, which included an interaction test between female versus male sex and randomised group allocation, was used to derive hazard ratios (HRs) for the INV versus CON strategy in women and men and test for heterogeneity of the treatment effect across sex. The following covariate set was included in the multivariable logistic and multinomial logistic regression models examining the association between female versus male sex and the revascularisation modality used: age, sex, prior MI, current smoker,

diabetes, left ventricular ejection fraction <45%, prior CABG, prior heart failure hospitalisation, chronic lung disease, prior stroke, known peripheral vascular disease, White versus non-White race, estimated glomerular filtration rate lower versus higher than 60 ml/min, and the number of diseased vessels (diameter stenosis ≥50%) as assessed by the coronary angiography core lab. Kaplan-Meier cumulative event rates were calculated for women and men in the INV-CABG and INV-PCI groups, censoring participants at the time of a first event or if lost to follow-up. Logistic regression was used to examine the association between female sex and the risk of PMI after revascularisation. These models were adjusted for the revascularisation modality (CABG vs PCI), randomised arm, and the covariates listed above.

All statistical analyses were performed with SAS software, version 9.3 (SAS Institute).

Results

STUDY POPULATION

Of 5,179 randomised participants in the ISCHEMIA trial, 1,168 (22.6%) were women. Baseline characteristics for women versus men are presented in **Table 1**. Compared with men, women were older and more likely to have hypertension and diabetes. The usage of guideline-directed medical therapy in men and women is presented in **Supplementary Table 2** and **Supplementary Table 3**.

REVASCULARISATION BY PARTICIPANT SEX IN THE INVASIVE ARM

Among participants who were randomised to the INV arm, 2,406/2,588 (93%) underwent coronary angiography without a preceding primary endpoint event (1,842/1,982 [93%] men and 564/606 [93%] women); of whom 518/2,400 (22%) had either intravascular imaging or coronary physiology performed (399/1,838 [22%] men and 119/562 [21%] women). A total of 2,012/2,588 (78%) participants randomised to the INV arm underwent revascularisation without a preceding primary outcome event (435/606 [72%] women and 1,577/1,982 [80%] men). Female participant sex was independently associated with a lower likelihood of undergoing revascularisation even after adjustment for age and clinical risk factors, as well as after adjustment for angiographic findings **(Table 2)**.

Among participants in the INV arm who were revascularised, PCI rather than CABG was used in 345/435 (79.3%) women versus 1,155/1,577 (73.2%) men (p=0.01). After adjustment for age and other clinical risk factors, as well as

Table 1. Baseline characteristics of patients.

Baseline characteristics	Women (N=1,168)	Men (N=4,011)	*p*-value
Age, years	65.0 [59.0-71.0]	64.0 [57.0-70.0]	0.002
Race			<0.001
Black or African American	57/1,154 (4.9)	147/3,975 (3.7)	
Other	289/1,154 (25)	1,233/3,975 (31)	
White	808/1,154 (70)	2,595/3,975 (65)	
Hispanic or Latino ethnicity	188/1,091 (17)	575/3,724 (15)	0.17
LVEF, %	62.0 [58.0-68.0]	60.0 [55.0-64.0]	<0.001
eGFR, ml/min/1.73 m^2	76.9 [61.7-92.9]	83.2 [70.2-99.0]	<0.001
Hypertension	922/1,164 (79)	2,867/3,997 (72)	<0.001
Diabetes	522/1,168 (45)	1,642/4,011 (41)	0.02
Insulin-treated	159/1,168 (14)	333/4,011 (8.3)	<0.001
Smoking status			<0.001
Current smoker	110/1,167 (9.4)	530/4,007 (13)	
Former smoker	301/1,167 (26)	2,025/4,007 (51)	
Never smoked	756/1,167 (65)	1,452/4,007 (36)	
Family history of premature CAD	297/1,016 (29)	873/3,474 (25)	0.01
Prior MI	184/1,165 (16)	807/3,997 (20)	0.001
Prior PCI	189/1,167 (16)	861/4,008 (21)	<0.001
Prior CABG	32/1,168 (2.7)	171/4,011 (4.3)	0.02
Prior HF	61/1,168 (5.2)	145/4,011 (3.6)	0.14
Atrial fibrillation/atrial flutter	46/1,166 (3.9)	175/4,007 (4.4)	0.59
Prior stroke	40/1,168 (3.4)	111/4,010 (2.8)	0.28
Prior cerebrovascular disease	89/1,166 (7.6)	288/3,999 (7.2)	0.66
Prior peripheral arterial disease	43/1,165 (3.7)	161/4,003 (4.0)	0.67
History of angina	1,068/1,168 (91)	3,573/4,011 (89)	0.02
Multivessel disease by CCTA			
Two-vessel disease	184/816 (23)	754/3,093 (24)	0.28
Three-vessel disease	205/816 (25)	1,142/3,093 (37)	<0.001

Data are presented as median [IQR] or n/N (%). CABG: coronary artery bypass grafting; CAD: coronary artery disease; CCTA: coronary computed tomography angiography; eGFR: estimated glomerular filtration rate; HF: heart failure; IQR: interquartile range; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention

Table 2. Association between sex and the likelihood of undergoing revascularisation for patients randomised to an invasive strategy.

Model	OR for women vs men (95% CI)
Unadjusted	0.65 (0.53-0.80); p<0.001
Adjusted for age	0.66 (0.53-0.81); p<0.001
Adjusted for clinical risk factors*	0.62 (0.49-0.78); p<0.001
Adjusted for clinical and angiographic risk factors†	0.75 (0.57-0.99); p=0.04
Adjusted for clinical and angiographic risk factors¶	0.69 (0.52-0.90); p=0.006

*Adjusted for the following covariate set: age, sex, prior MI, current smoker, diabetes, left ventricular ejection fraction <45%, prior CABG, prior heart failure hospitalisation, chronic lung disease, prior stroke, known peripheral vascular disease, White versus non-White race, and eGFR <60 ml/min. †Fully adjusted to prior variables in addition to the number of diseased vessels (>50% diameter stenosis per angiographic core lab analysis). ¶Fully adjusted to prior variables in addition to the number of diseased vessels (>70% diameter stenosis per angiographic core lab analysis). CABG: coronary artery bypass grafting; CI: confidence interval; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; OR: odds ratio

Table 3. Association between sex and the likelihood of undergoing PCI and CABG for patients randomised to an invasive strategy.

Model	OR for women vs men (95% CI)	
	OR for PCI	OR for CABG
Unadjusted	0.71 (0.57-0.88); p=0.001	0.51 (0.38-0.67); p<0.001
Adjusted for age	0.71 (0.58-0.89); p=0.003	0.51 (0.38-0.68); p<0.001
Adjusted for clinical risk factors*	0.67 (0.53-0.86); p=0.001	0.48 (0.35-0.66); p<0.001
Adjusted for clinical and angiographic risk factors†	0.76 (0.58-1.01); p=0.06	0.64 (0.44-0.94); p=0.02
Adjusted for clinical and angiographic risk factors¶	0.70 (0.54-0.93); p=0.01	0.58 (0.40-0.83); p=0.003

*Adjusted for the following covariate set: age, sex, prior MI, current smoker, diabetes, left ventricular ejection fraction <45%, prior CABG, prior heart failure hospitalisation, chronic lung disease, prior stroke, known peripheral vascular disease, White versus non-White race, and eGFR <60 ml/min. †Fully adjusted to prior variables in addition to the number of diseased vessels (>50% diameter stenosis per angiographic core lab analysis). ¶Fully adjusted to prior variables in addition to the number of diseased vessels (>70% diameter stenosis per angiographic core lab analysis). CABG: coronary artery bypass grafting; CI: confidence interval; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; OR: odds ratio; PCI: percutaneous coronary intervention

after adjustment for angiographic findings, women were less likely than men to undergo PCI as well as CABG, but there was a stronger negative association between female participant sex and the likelihood of undergoing surgery **(Table 3)**.

CROSSOVER BY PARTICIPANT SEX IN THE CONSERVATIVE ARM

Among participants who were randomised to the CON arm, 487/2,591 (19%) underwent coronary angiography without a preceding primary endpoint event (375/2,029 [18%] men and 112/562 [20%] women); and 382/2,591 (15%) underwent revascularisation without a preceding primary outcome event (79/562 [14%] women and 303/2,029 [15%] men).

EFFECT OF AN INVASIVE VERSUS A CONSERVATIVE STRATEGY BY PARTICIPANT SEX AND CLINICAL OUTCOMES BY REVASCULARISATION MODALITY AND PARTICIPANT SEX

The risk of the primary composite outcome was similar between the INV and CON trial arms for both women and men **(Figure 1)**. There was no statistically significant interaction between participant sex and the risk of the primary outcome or any of its components including death, any MI, stroke, or rehospitalisation for unstable angina, heart failure, or resuscitated cardiac arrest **(Figure 1, Supplementary Figure 1)**. In the analysis of MI stratified by the timing of the event, however, women experienced significantly less PMI than men, while there were no differences in spontaneous MI **(Table 4)**.

The association between female participant sex and PMI was not statistically significant after adjustment for the revascularisation modality (CABG vs PCI; odds ratio [OR] 0.52, 95% confidence interval [CI]: 0.23-1.05; p=0.058) or after adjustment for the revascularisation modality, randomised arm, and clinical risk factors (OR 0.62, 95% CI: 0.26-1.30; p=0.236); these results were consistent when using the alternative PMI definition **(Supplementary Table 4)**.

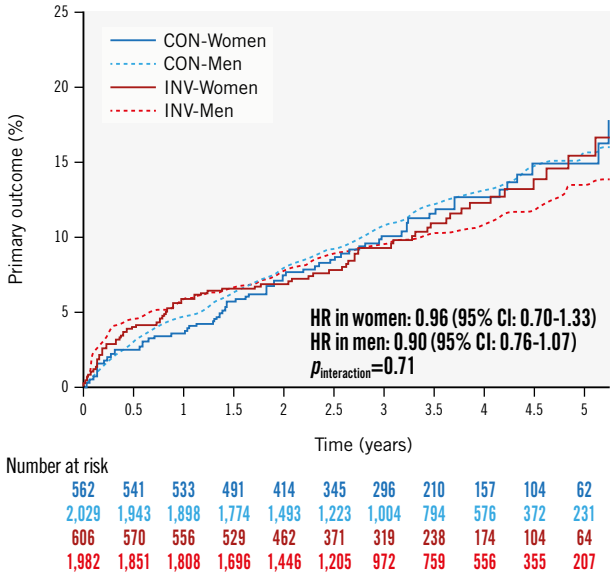

Figure 1. *Cumulative incidence of the primary outcome according to randomised group assignment for female and male participants. CI: confidence interval; CON: conservative; HR: hazard ratio; INV: invasive*

Among patients in the INV arm who underwent revascularisation, there was no statistical interaction between female participant sex and revascularisation modality (CABG vs PCI) for the risk of the primary outcome or its individual components **(Figure 2, Supplementary Figure 2)**.

Among patients who met the primary outcome, women were more likely than men to experience more than one type of primary outcome event. The proportion of participants

Table 4. Cumulative incidence of primary outcome components by participant sex.

	CON			INV			All		
	Women (N=562)	Men (N=2,029)	*p*-value	Women (N=606)	Men (N=1,982)	*p*-value	Women (N=1,168)	Men (N=4,011)	*p*-value*
Cardiovascular death	8.9% (30)	5.8% (77)	0.19	7.2% (28)	4.7% (60)	0.07	8.1% (58)	5.3% (137)	0.03
Any MI	11.2% (43)	12.4% (185)	0.46	10.5% (44)	10.5% (163)	0.32	10.8% (87)	11.5% (348)	0.21
PMI	0.6% (3)	1.2% (21)	0.27	1.3% (8)	3.3% (62)	0.02	1.0% (11)	2.2% (83)	0.01
Spontaneous MI	10.6% (40)	11.4% (168)	0.59	9.1% (36)	7.4% (105)	0.74	9.8% (76)	9.5% (273)	0.79
Hospitalisation	3.4% (13)	3.6% (47)	0.93	6.1% (22)	3.4% (45)	0.08	4.8% (35)	3.5% (92)	0.21

*log-rank. Kaplan-Meier rates are provided for each event. CON: conservative; INV: invasive; MI: myocardial infarction; PMI: procedural myocardial infarction

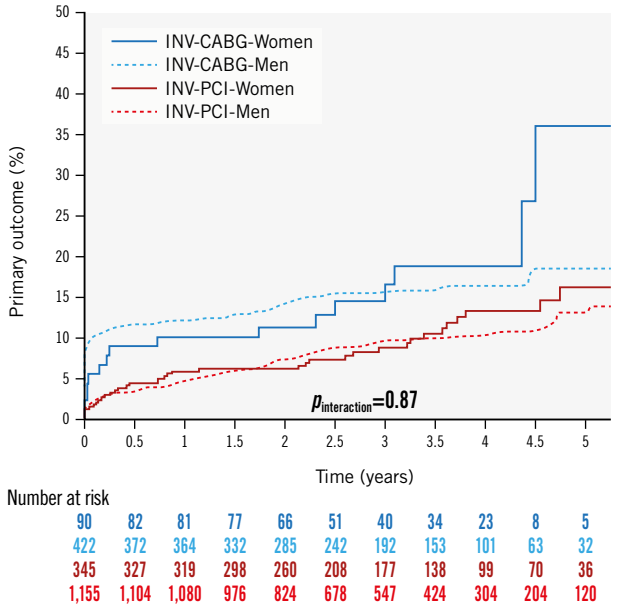

Figure 2. *Cumulative incidence of the primary outcome after revascularisation by CABG or PCI (median follow-up after revascularisation 2.09 years [0.17, 3.66]) for women and men randomised to an invasive strategy. CABG: coronary artery bypass grafting; CON: conservative; INV: invasive; PCI: percutaneous coronary intervention*

who had MI as the only primary outcome event (i.e., the contribution of MI to the primary outcome) was significantly lower in women compared with men **(Table 5)**. Specifically, women were less likely than men to have PMI as their only primary outcome event.

Similarly, when restricting the analysis to patients in the INV arm who met the primary outcome after undergoing revascularisation, MI was less commonly the only primary outcome event for women than for men **(Table 6)**, a difference that was predominantly driven by the rates of PMI.

Discussion

The key findings of this sex-stratified analysis of the ISCHEMIA trial are as follows: 1) female participant sex was independently associated with a lower likelihood of revascularisation among participants randomised to an INV treatment strategy even after adjustment for angiographic and clinical risk factors, and this negative association was stronger for CABG than for PCI; 2) at the median follow-up of 3.2 years, the incidence of the primary composite outcome of cardiovascular death, MI, or hospitalisation for unstable angina, heart failure, or resuscitated cardiac arrest was similar in the INV and CON arms in both sexes; 3) PMI contributed significantly less to the primary composite outcome in women than in men.

A lower likelihood of women compared with men to be referred for coronary revascularisation is consistent with the results of large registry studies[16-18], but it is unclear if the lower referral rates of women for revascularisation is due to physician bias or sex differences in baseline clinical status or the extent of coronary artery disease. The ISCHEMIA trial authors have previously reported that among enrolled trial participants, the extent of coronary disease was lower in women compared with men, but the prevalence of left anterior descending artery disease (one of the key drivers in the decision to revascularise) was similar between sexes[4]. In our analysis, the difference in revascularisation rates between sexes persisted even after adjustment for clinical and angiographic covariates, suggesting that referral bias may have played an important role.

The confirmation that randomisation to an INV versus CON strategy resulted in a similar risk of the primary composite outcome for both women and men contributes to a more complete understanding of the ISCHEMIA trial, since the results of the primary analysis were driven predominantly by the results in men. The relative effect of an INV versus CON strategy could have differed between women and men due to known sex differences in the efficacy and utilisation of medical therapy[1,19,20] and several key prevention strategies (including the use of antiplatelet and lipid-lowering therapy[21-24]) that were confirmed among participants enrolled in the ISCHEMIA trial[4]. In addition, the procedural risk of coronary revascularisation by both PCI and CABG has been shown to be higher in women, who also have a higher risk of cardiovascular events during the years after a coronary intervention compared with men[1,9,10].

As regards the individual components of the primary composite outcome, we found that women had significantly lower rates of PMI compared with men. We have previously reported that in ISCHEMIA the incidence of PMI was dependent on the revascularisation modality and significantly higher for CABG than for PCI[25], and in the present study the lower incidence of PMI among women was likely explained, at least in part, by the lower adoption of surgery as the coronary revascularisation modality in women.

Table 5. Contribution of individual components to primary outcome components by participant sex by intention-to-treat.

	CON			INV			All		
	Women (N of events =74/562)	Men (N of events =278/2,029)	*p*-value 0.11	Women (N of events =77/606)	Men (N of events =241/1,982)	*p*-value 0.07	Women (N of events =151/1,168)	Men (N of events =519/4,011)	*p*-value 0.02
Cardiovascular death only	20 (27.0)	53 (19.1)	0.14	15 (19.5)	42 (17.4)	0.73	35 (23.2)	95 (18.3)	0.20
Any MI only	34 (46.0)	155 (55.8)	0.15	32 (41.6)	138 (57.3)	0.018	66 (43.7)	293 (56.5)	0.007
PMI only	2 (2.7)	16 (5.8)	0.38	7 (9.1)	51 (21.2)	0.017	9 (5.9)	67 (12.9)	0.019
Spontaneous MI only	31 (41.9)	137 (49.3)	0.30	25 (32.5)	81 (33.6)	0.89	56 (37.1)	218 (42.0)	0.30
Hospitalisation only	5 (6.8)	33 (11.9)	0.29	13 (16.9)	29 (12.0)	0.33	18 (11.9)	62 (11.9)	0.99
More than one type of primary outcome event	15 (20.3)	37 (13.3)	0.14	17 (22.1)	32 (13.3)	0.07	32 (21.2)	69 (13.3)	0.02

Data are presented as N (%). CON: conservative; INV: invasive; MI: myocardial infarction; N: number; PMI: procedural myocardial infarction

Table 6. Contribution of individual components to primary outcome components by participant sex and revascularisation modality in the INV arm and by revascularisation modality.

	INV-REVASC			INV-CABG			INV-PCI		
	Women (N of events =52/445)	Men (N of events =179/1,609)	*p*-value 0.027	Women (N of events =16/93)	Men (N of events =68/437)	*p*-value 0.018	Women (N of events =36/352)	Men (N of events =111/1,172)	*p*-value 0.41
Cardiovascular death only	10 (19.2)	28 (15.6)	0.53	3 (18.8)	8 (11.8)	0.43	7 (19.4)	20 (18.0)	0.81
MI (any) only	21 (62.0)	111 (62.0)	0.007	5 (31.3)	47 (69.1)	0.009	16 (44.4)	64 (57.7)	0.18
PMI only	7 (13.5)	51 (28.5)	0.030	3 (18.8)	31 (45.6)	0.087	4 (11.1)	20 (18.0)	0.44
Spontaneous MI only	14 (26.9)	55 (30.7)	0.73	2 (12.5)	14 (20.6)	0.73	12 (33.3)	41 (36.9)	0.84
Hospitalisation only	9 (11.2)	20 (11.2)	0.24	4 (25.0)	7 (10.3)	0.21	5 (13.9)	13 (11.7)	0.77
More than one type of primary outcome event	12 (23.1)	20 (11.2)	0.039	4 (25.0)	6 (8.9)	0.09	8 (22.2)	14 (12.6)	0.18

Data are presented as N (%). CABG: coronary artery bypass grafting; INV: invasive; MI: myocardial infarction; N: number; PCI: percutaneous coronary intervention; PMI: procedural myocardial infarction; REVASC: revascularisation

The negative association of female participant sex with PMI did not remain statistically significant after adjustment for revascularisation modality and clinical and procedural risk factors; our study therefore does not directly support an independent association between participant sex and PMI. However, we cannot rule out the possibility that other participant sex-related factors contributed to the observed lower incidence of PMI in women versus men. For example, troponin levels are known to be lower in women[26] compared to men[12,27-29], and since the PMI definitions used in ISCHEMIA rely on biomarker criteria that are not sex specific, it is possible that PMI rates were artificially reduced in women.

In any case, the observation of a significant difference in PMI contribution to the primary outcomes by participant sex in ISCHEMIA is important because of the unclear clinical and prognostic relevance of PMI compared with the other clinical events included in the primary outcome[14,30].

Lastly, it must be noted that the crude rate of cardiovascular death in the overall, INV, and CON cohorts was significantly higher in women than in men in the present analysis. This observation is consistent with previous studies[10,31-33], but this finding may be due to multiplicity in testing and low statistical power rather than a truly significant difference between the sexes[34,35].

Limitations

This *post hoc* analysis has important limitations. While our adjustment models were based on all available clinical and angiographic data and the initial participant cohort was relatively homogeneous (as all participants met the ISCHEMIA inclusion criteria), it is likely that there are unaccounted confounders in the reported comparisons. As in many cardiovascular trials, the number of women enrolled in ISCHEMIA was relatively low, and lower than anticipated (actual: 23% vs anticipated: 35%), hence, the reported comparisons may be underpowered. Any nominal differences in event rates should therefore be interpreted with caution. In addition, the comparisons between revascularisation modalities suffer from

an intrinsic treatment allocation bias and must only be seen as hypothesis-generating.

Conclusions

In conclusion, in the ISCHEMIA trial, women were significantly less likely to undergo revascularisation when assigned to the INV treatment arm. The similarity in cardiac outcomes between an INV versus a CON strategy seen in the overall population was confirmed in both women and men, but women had a significantly lower incidence of PMI than men.

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Conflict of interest statement

D.L. 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Supplementary data

Supplementary Table 1. Event definitions in the ISCHEMIA trial.

Supplementary Table 2. Medication usage and medication goals met in the conservative treatment (CON) cohort.

Supplementary Table 3. Medication usage and medication goals met in the invasive treatment (INV) cohort.

Supplementary Table 4. Association between sex and the risk of procedural myocardial infarction as defined per the alternative (secondary) definition.

Supplementary Figure 1. Cumulative incidence of the adverse ischaemic events according to randomised group assignment for women and men.

Supplementary Figure 2. Cumulative incidence of the adverse ischaemic events after revascularisation by CABG or PCI (median follow-up after revascularisation: 2.09 years [0.17, 3.66]) for women and men randomised to an invasive strategy.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00011

Supplementary data

Supplementary Table 1. Event definitions in the ISCHEMIA trial.

Outcome	Definition
Death due to cardiovascular causes	All deaths excluding those for which the principal and underlying cause is solely non-cardiovascular. Any death for which a cardiovascular contributing cause is suspected will also be considered a cardiovascular death.
Myocardial Infarction	The Primary Definition is based upon the Universal Definition of MI, but relies upon sitere ported MI decision limits for troponin (which may or may not be the same as the manufacturer 99%URL), and has selected unique marker criteria for MI after PCI or CABG (Type 4a, 5). The Secondary Definition is also based upon the Universal Definition of Myocardial Infarction, but specifically uses the 99%URL from the assay manufacturer's package insert (which may or may not be the site's MI decision limit) and uses the same supporting criteria (eg. angiographic and ECG) as the UMI definition. All MI events will be classified based on the Universal MI classification system as follows: o Type 1: Spontaneous MI o Type 2: Secondary MI o Type 3: Sudden Death MI o Type 4a: MI related to PCI o Type 4b: MI related to stent thrombosis o Type 4c: MI related to stent restenosis o Type 5: MI related to CABG o Silent MI ***Spontaneous MI (Types 1, 2, 4b, 4c)*** Diagnosis of spontaneous MI was satisfied by a clinical setting consistent with acute myocardial ischemia and any one or more of the following criteria: Marker elevation, as outlined below and at least 1 of the following:

	○ Symptoms of ischemia, usually lasting > 20 minutes in duration ○ New ischemic ST and/or T wave and/or Q-wave ECG changes, or new LBBB, as described below ○ Imaging evidence of new loss of viable myocardium in comparison to the baseline imaging test ○ Angiographic evidence of intracoronary thrombus, stent thrombosis (4b) or high grade in-stent restenosis (≥50%) (4c) Marker data not available and at least 2 of the following: -New ischemic ST and/or T wave and/or Q-wave ECG changes, or new LBBB, as described below -Imaging evidence of new loss of viable myocardium in comparison to the baseline imaging test -Angiographic evidence of intracoronary thrombus. *Autopsy evidence of a fresh myocardial infarction as stand-alone criterion. **Spontaneous MI Marker Criteria** Troponin, including high-sensitivity troponin, is the preferred biomarker and takes precedence over CK-MB for both definitions. <u>Primary Definition:</u> Preferentially uses a troponin threshold value reported as MI Decision Limit or the Upper Limit of Normal (ULN). Marker elevation is defined as troponin > ULN/MI decision limit. If troponin is not done or not available, then CK-MB > ULN will qualify. If both troponin and CK-MB are not done or not available, then CK > 2 x ULN will qualify. <u>Secondary Definition:</u> Preferentially uses a troponin threshold reported by the manufacturer, namely, the manufacturer 99th percentile. Marker elevation is defined as troponin > 99th percentile. If the troponin 99th percentile is not reported, then troponin > ULN will qualify. If troponin is not done or not available, then CK-MB > ULN will qualify. If both troponin and CK-MB are not done or not available, then CK > 2 x ULN will qualify. **Spontaneous MI ECG Criteria** ECG criterion is considered to be met if any of the following:

	ST elevation: New ST elevation at the J-point in two contiguous leads with the cutpoints: ≥ 0.2 mV in men >age 40 and ≥ 0.25mV in men <40 years or ≥ 0.15 mV in women in leads V2–V3 and/or ≥ 0.1 mV in other leads, or new LBBB. Any new Q-wave in leads V2–V3 ≥ 0.02 seconds or QS complex in leads V2 and V3 or Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4– V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4–V6; II, III, and aVF) or R-wave ≥ 0.04 seconds in V1–V2 and R/S ≥ 1 with a concordant positive T- wave in the absence of a conduction defect. ST depression and/or T-wave changes, new horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T-wave inversion ≥ 0.1 mV in two contiguous leads. The ST-T wave criteria only apply in the absence of findings that would preclude ECG analysis such as LBBB, LVH with repolarization abnormalities, pre-excitation and pacemakers. **Silent MI** This event includes evidence of new silent Q-wave MI detected during routine protocol or clinically obtained ECG follow-up. Silent MI events will be classified as a type 1 MI. ***Sudden death MI (Type 3)*** MI events in which a presentation consistent with infarction is present but the patient dies before the biomarkers are drawn or within the first few hours of the event before the biomarkers become positive. Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST-segment elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. ***PCI-Related MI (Type 4a)***

	Primary Definition CK-MB is the preferred biomarker and takes precedence over troponin. For subjects with normal baseline biomarker level pre-PCI, peri-PCI MI requires a rise in CK-MB to >5-fold the ULN (or a rise in troponin to >35 times the MI Decision Limit/ULN, when CK- MB is unavailable) within 48 hours post-PCI. If pre-PCI cardiac markers (CKMB or cTn) are elevated, they must be stable or falling as indicated by two samples at least 6 h apart. The post-PCI CKMB level should reflect a rise of >20% over pre-PCI levels. In addition to biomarker criteria, peri-PCI MI requires at least one of the following: · Post- procedure angiographic TIMI 0/1 flow in a major coronary artery or a side branch with reference vessel diameter ≥2.0 mm which had TIMI 2-3 flow at baseline, or TIMI 2 flow in a major coronary artery or a side branch with reference vessel diameter ≥3.0 mm which had TIMI 3 flow at baseline or Type C dissection (NHLBI classification) or greater in the target vessel. · New ECG changes (ST segment elevation or depression >0.1mV in 2 contiguous leads), new pathologic Q-waves in ≥2 contiguous leads, or new persistent LBBB present on a post-PCI ECG obtained at least 30 minutes and up to 48 hours post procedure in the absence of any intervening coronary event between the time of the PCI procedure and the ECG showing changes. NOTE: A type 4a MI will be diagnosed with a rise in CK-MB to >10-fold the ULN (or when CK-MB is unavailable, a rise in troponin to >70 times the MI Decision Limit/ULN) as a stand-alone criterion. If biomarkers are missing, a type 4a MI will be diagnosed if BOTH ECG criteria (new ST elevation or depression, Q-wave criteria, or new and persistent LBBB) AND angiographic criteria above are present. If pre-PCI cardiac markers are missing, they will be assumed to be normal in those without a preceding event. **Secondary Definition** Elevation of troponin values >5 X 99th percentile URL within 48 hours post-PCI in patients with normal baseline troponin values pre-PCI AND a rise of troponin values >20% if the baseline values are elevated pre-PCI and are stable or falling.

	If the troponin 99th percentile is not available, the MI Decision Limit / ULN may be used. If troponins are not available, CKMB elevation >5 X ULN will be used. In addition to biomarker criteria, peri-PCI MI requires at least one of the following: -Symptoms suggestive of myocardial ischemia (≥20 min) New ischemic ST changes or new pathological Q waves. (see "ECG Criteria" above) Note the UMI definition uses ≥0.05 mV of STD whereas the ISCHEMIA definition uses ≥ 0.1mV for PCI related ECG criteria -Angiographic evidence of a flow limiting complication, such as loss of patency of a side branch, persistent slow-flow or no re-flow, embolization, or Type C dissection (NHLBI classification) or greater in the target vessel. -Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. NOTE: A type 4a MI will be diagnosed with a rise in troponin to >70 times the 99th percentile URL (or, when troponin is unavailable, a rise in CK-MB to >10 times the ULN) as a stand-alone criterion. If biomarkers are missing, a type 4a MI will be diagnosed if BOTH ECG criteria (new ST elevation or depression, Q-wave criteria, or new and persistent LBBB) AND angiographic criteria above are present. If pre- PCI cardiac markers are missing, they will be assumed to be normal in those without a preceding event. ***CABG-Related MI (Type 5)*** **Primary Definition** CK-MB is the preferred serum biomarker and takes precedence over cardiac troponin. For subjects with normal baseline biomarker level pre-CABG, peri-CABG MI requires a rise in CK-MB to >10-fold the ULN (or a rise in troponin to >70 times MI Decision Limit/ULN when CK-MB is unavailable) within 48 hrs post-CABG. In addition to biomarker criteria, peri- CABG MI requires at least one of the following: -A new substantial wall motion abnormality by cardiac imaging (CEC assessed), except new septal and apical abnormalities. The CEC will have latitude in determining whether a new wall motion abnormality is "substantial" in the context of the clinical event.

	-New pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB is present on post CABG ECG obtained day 3 post CABG, or hospital discharge, whichever comes earlier in the absence of any intervening coronary event between the time of the CABG procedure and the ECG showing changes. NOTE: A type 5 MI will be diagnosed with a rise in CK-MB to >15-fold the ULN (or when CK-MB is unavailable a rise in troponin to >100 times the MI Decision Limit/ULN) as a stand-alone criterion. If biomarkers are missing, an MI will be diagnosed if the ECG criteria (New pathologic Q waves or new persistent LBBB) AND new substantial wall motion abnormality are BOTH present. If pre-CABG cardiac markers are missing, they will be assumed to be normal in those without a preceding event. **Secondary Definition** Elevation of troponin values >10 X 99th percentile URL within 48 hrs post-CABG in patients with normal baseline troponin values (≤ 99th percentile URL). If the troponin 99th percentile is not available, the ULN may be used. If troponins are not available, CKMB elevation >10 X ULN will be used. In addition to biomarker criteria, peri-CABG MI requires at least one of the following: -New pathologic Q waves or new LBBB -Angiographic evidence of new graft or new native coronary artery occlusion. -Imaging evidence of new loss of viable myocardium. NOTE: A type 5 MI will be diagnosed with a rise in troponin to >100 times the 99th percentile URL (or when troponin is unavailable a rise in CK-MB to >15 times the ULN) as a stand-alone criterion. If biomarkers are missing, an MI will be diagnosed if the ECG criteria (New pathologic Q waves or new persistent LBBB) AND new substantial wall motion abnormality are BOTH present. If pre-CABG cardiac markers are missing, they will be assumed to be normal in those without a preceding event. ***Complicated MI and Large MI*** *Complicated MI:* Prognostically important MIs may also be identified as those with complications such as hemodynamic instability, cardiogenic shock, drop in

	EF >10% from baseline, electrical instability with life-threatening VT or VF, or heart failure complicating MI. Complicated myocardial infarctions may typically require ICU care, invasive support (eg. intubation, IABP, PA catheters) and intravenous medications (eg. inotropes or antiarrhythmics.) CEC adjudicators will identify complicated MIs based upon the information available to them in the eCRF and source documents. -Hemodynamic instability: requiring fluids, inotropic or vasopressor support to maintain end-organ perfusion. May progress to shock if also accompanied by endorgan underperfusion. -Shock: Compromise of end-organ perfusion due to hemodynamic instability and sustained hypotension. Often manifested by hypotension, increased creatinine, shock liver, and decreased mentation. -Life-threatening VT or VF: Requiring antiarrhythmics or defibrillation to return sinus rhythm. Transient runs of VT (eg. during reperfusion) are not associated with hemodynamic instability are not usually considered life-threatening. -Decreased EF ≥ 10%: EF assessment during the event which indicates a drop from prior assessments (eg. EF 30% from previous EF 55%). -HF in the setting of an MI is defined on the basis of the physician's decision to treat HF with an intravenous (IV) diuretic, IV inotropic agent or IV vasodilator and at least 1 of the following: -Presence of pulmonary edema or pulmonary vascular congestion on chest radiograph believed to be of cardiac cause. -Rales greater than 1/3 up the lung fields believed to be due to HF. -Pulmonary Capillary Wedge Pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) greater than 18 mmHg. -Dyspnea, with documented paO2 less than 80 mmHg on room air or O2 saturation less than 90% on room air, without significant lung disease *Large MI*: The size of MI will be assessed by examining peak levels of cardiac biomarkers as a continuous function.
Resuscitated Cardiac Arrest	Successful resuscitation for documented cardiac arrest out-of-hospital (or ER) in a patient subsequently admitted to hospital, and then discharged. A patient who is successfully resuscitated but dies before hospital discharge of complications related to the cardiac arrest (e.g., anoxic encephalopathy, septic shock), will be

	classified as a coronary heart disease death. An uncomplicated procedure-related cardiac arrest with prompt resuscitation and without adverse sequelae will not be counted as an event. Events that meet the MI criteria will be categorized as MI
Hospitalization for Heart Failure	While patients may have multiple simultaneous disease processes, for the outcome event of heart failure requiring hospitalization, the diagnosis of congestive heart failure would need to be the primary process. Heart failure (HF) requiring hospitalization is defined as an event that meets the following criteria: a. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that result in at least a 24 hour stay (or a date change if the time of admission/discharge is not available). AND b. Clinical symptoms of heart failure, including at least one of the following: New or worsening Dyspnea, Orthopnea, Paroxysmal nocturnal dyspnea or increasing fatigue/worsening exercise tolerance AND c. Physical signs of heart failure, including at least two of the following: 1. Edema (> 2+ lower extremity) 2. Pulmonary rales (pulmonary edema not occurring as the consequence of an arrhythmia in the absence of worsening heart failure. If pulmonary edema complicates acute MI event should be coded as MI) 3. Jugular venous distension 4. Tachypnea (respiratory rate > 20 breaths/minute) 5. Rapid weight gain 6. S3 gallop 7. Increasing abdominal distension or ascites 8. Hepatojugular reflux 9. Radiological evidence of worsening heart failure 10. A right heart catheterization within 24 hours of admission showing apulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mm Hg and/or a cardiac output < 2.2 L/min/m2 NOTE: Biomarker results (e.g., brain natriuretic peptide (BNP)> 500 or Pro-NT BNP > 2500) consistent with congestive heart failure will be supportive of this diagnosis, but the elevation in BNP cannot be due to other conditions such as cor

	pulmonale, pulmonary embolus, primary pulmonary hypertension, or congenital heart disease. Increasing levels of BNP, although not exceeding the ULN, may also be supportive of the diagnosis of congestive heart failure in selected cases (e.g. morbid obesity). AND d. Need for additional/increased therapy Initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure and including at least one of the following: 1. Initiation of or a significant augmentation in oral therapy for the treatment of congestive heart failure 2. Initiation of intravenous diuretic, inotrope, or vasodilator therapy 3. Uptitration of intravenous therapy, if already on therapy 4. Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure. AND e. No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms are identified.
Stroke	The rapid onset of a new neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (eg. trauma, infection, or tumor). Neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Classification: o Transient Ischemic Attack o Ischemic Stroke o Hemorrhagic Stroke o Undetermined- or Uncertain type- of Stroke

Supplementary Table 2. Medication usage and medication goals met in the conservative treatment (CON) cohort.

A. Medication usage in conservative treatment cohort

Characteristic	Female, N = 562*	Male, N = 2,029*
ACEi/ARB		
Baseline	392/562 (70%)	1,339/2,027 (66%)
Month 1	386/544 (71%)	1,324/1,968 (67%)
Month 3	385/539 (71%)	1,325/1,963 (67%)
Month 6	388/542 (72%)	1,355/1,966 (69%)
Month 12	386/533 (72%)	1,354/1,932 (70%)
Month 18	380/521 (73%)	1,321/1,902 (69%)
Month 24	314/445 (71%)	1,151/1,666 (69%)
Month 30	277/372 (74%)	924/1,326 (70%)
Month 36	254/330 (77%)	781/1,115 (70%)
Month 42	185/250 (74%)	629/885 (71%)
Month 48	133/185 (72%)	474/675 (70%)
Month 54	86/124 (69%)	312/452 (69%)
Month 60	60/84 (71%)	210/311 (68%)
Beta-Blockers		
Baseline	470/562 (84%)	1,634/2,027 (81%)
Month 1	467/544 (86%)	1,649/1,968 (84%)
Month 3	460/539 (85%)	1,649/1,964 (84%)
Month 6	465/542 (86%)	1,648/1,966 (84%)
Month 12	462/533 (87%)	1,584/1,932 (82%)
Month 18	440/521 (84%)	1,558/1,902 (82%)
Month 24	377/445 (85%)	1,327/1,667 (80%)
Month 30	319/372 (86%)	1,065/1,326 (80%)
Month 36	291/330 (88%)	876/1,115 (79%)
Month 42	221/250 (88%)	713/885 (81%)
Month 48	162/185 (88%)	546/675 (81%)
Month 54	105/124 (85%)	350/452 (77%)
Month 60	69/84 (82%)	233/311 (75%)
Calcium Channel Blockers		
Baseline	189/562 (34%)	618/2,027 (30%)
Month 1	199/545 (37%)	635/1,968 (32%)
Month 3	202/539 (37%)	666/1,965 (34%)
Month 6	204/542 (38%)	662/1,967 (34%)
Month 12	210/533 (39%)	667/1,934 (34%)
Month 18	208/521 (40%)	687/1,904 (36%)
Month 24	174/446 (39%)	624/1,667 (37%)
Month 30	152/372 (41%)	487/1,326 (37%)
Month 36	151/330 (46%)	401/1,117 (36%)
Month 42	106/250 (42%)	325/885 (37%)

Month 48	82/185 (44%)	252/675 (37%)
Month 54	49/124 (40%)	165/452 (37%)
Month 60	34/84 (40%)	114/311 (37%)
Dual Anti-Platelet Therapy		
Baseline	110/562 (20%)	433/2,027 (21%)
Month 1	111/544 (20%)	420/1,966 (21%)
Month 3	121/539 (22%)	469/1,964 (24%)
Month 6	128/541 (24%)	501/1,965 (25%)
Month 12	125/530 (24%)	501/1,926 (26%)
Month 18	108/521 (21%)	470/1,900 (25%)
Month 24	89/445 (20%)	392/1,664 (24%)
Month 30	71/371 (19%)	295/1,324 (22%)
Month 36	57/328 (17%)	244/1,113 (22%)
Month 42	39/249 (16%)	172/883 (19%)
Month 48	25/184 (14%)	128/672 (19%)
Month 54	10/123 (8.1%)	62/451 (14%)
Month 60	7/83 (8.4%)	44/307 (14%)
Anti-Anginal Medications		
Baseline	229/562 (41%)	803/2,027 (40%)
Month 1	253/545 (46%)	837/1,968 (43%)
Month 3	244/539 (45%)	859/1,965 (44%)
Month 6	247/542 (46%)	826/1,967 (42%)
Month 12	233/533 (44%)	780/1,934 (40%)
Month 18	218/521 (42%)	730/1,904 (38%)
Month 24	194/446 (43%)	631/1,667 (38%)
Month 30	156/372 (42%)	479/1,326 (36%)
Month 36	129/330 (39%)	402/1,117 (36%)
Month 42	98/250 (39%)	297/885 (34%)
Month 48	72/185 (39%)	221/675 (33%)
Month 54	45/124 (36%)	139/452 (31%)
Month 60	24/84 (29%)	96/311 (31%)
Long-acting Nitrates		
Baseline	191/562 (34%)	671/2,027 (33%)
Month 1	207/545 (38%)	690/1,968 (35%)
Month 3	197/539 (37%)	713/1,965 (36%)
Month 6	198/542 (37%)	666/1,967 (34%)
Month 12	184/533 (35%)	619/1,934 (32%)
Month 18	169/521 (32%)	569/1,904 (30%)
Month 24	153/446 (34%)	495/1,667 (30%)
Month 30	127/372 (34%)	377/1,326 (28%)
Month 36	104/330 (32%)	318/1,117 (28%)
Month 42	75/250 (30%)	233/885 (26%)
Month 48	58/185 (31%)	168/675 (25%)
Month 54	35/124 (28%)	101/452 (22%)
Month 60	19/84 (23%)	70/311 (23%)

Anticoagulants		
Baseline	17/558 (3.0%)	72/2,006 (3.6%)
Month 1	16/538 (3.0%)	73/1,949 (3.7%)
Month 3	18/533 (3.4%)	74/1,940 (3.8%)
Month 6	18/533 (3.4%)	74/1,937 (3.8%)
Month 12	20/525 (3.8%)	84/1,895 (4.4%)
Month 18	20/512 (3.9%)	82/1,878 (4.4%)
Month 24	20/441 (4.5%)	94/1,648 (5.7%)
Month 30	23/367 (6.3%)	72/1,307 (5.5%)
Month 36	20/323 (6.2%)	66/1,100 (6.0%)
Month 42	16/246 (6.5%)	52/875 (5.9%)
Month 48	14/178 (7.9%)	41/663 (6.2%)
Month 54	9/122 (7.4%)	39/443 (8.8%)
Month 60	9/82 (11%)	29/308 (9.4%)
P2Y12 Inhibitors		
Baseline	130/562 (23%)	517/2,029 (25%)
Month 1	134/562 (24%)	501/2,029 (25%)
Month 3	138/560 (25%)	544/2,026 (27%)
Month 6	154/559 (28%)	584/2,021 (29%)
Month 12	147/557 (26%)	598/2,009 (30%)
Month 18	141/550 (26%)	564/1,991 (28%)
Month 24	121/473 (26%)	476/1,757 (27%)
Month 30	92/405 (23%)	361/1,412 (26%)
Month 36	75/355 (21%)	295/1,190 (25%)
Month 42	53/267 (20%)	208/964 (22%)
Month 48	36/204 (18%)	161/730 (22%)
Month 54	21/143 (15%)	83/488 (17%)
Month 60	13/89 (15%)	52/325 (16%)

[*] *n/N (%)*

ACEi/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker

B. Medication goals being met in conservative treatment cohort.

Characteristic	Female, N = 562*	Male, N = 2,029*
ACEi/ARB†		
Baseline	370/497 (74%)	1,206/1,644 (73%)
Month 1	363/480 (76%)	1,181/1,591 (74%)
Month 3	366/475 (77%)	1,179/1,588 (74%)
Month 6	368/478 (77%)	1,215/1,591 (76%)
Month 12	362/471 (77%)	1,209/1,565 (77%)
Month 18	356/458 (78%)	1,177/1,539 (76%)
Month 24	289/387 (75%)	1,022/1,353 (76%)
Month 30	256/322 (80%)	819/1,073 (76%)
Month 36	237/289 (82%)	690/902 (76%)

Month 42	171/213 (80%)	547/706 (77%)
Month 48	123/156 (79%)	418/540 (77%)
Month 54	80/104 (77%)	276/369 (75%)
Month 60	54/70 (77%)	190/261 (73%)
Beta-Blocker†		
Baseline	87/94 (93%)	379/423 (90%)
Month 1	83/90 (92%)	382/413 (92%)
Month 3	77/87 (89%)	373/409 (91%)
Month 6	81/87 (93%)	367/411 (89%)
Month 12	82/89 (92%)	350/406 (86%)
Month 18	77/85 (91%)	347/401 (87%)
Month 24	64/73 (88%)	302/361 (84%)
Month 30	58/65 (89%)	267/307 (87%)
Month 36	51/58 (88%)	224/263 (85%)
Month 42	40/46 (87%)	182/212 (86%)
Month 48	27/33 (82%)	152/178 (85%)
Month 54	14/19 (74%)	97/121 (80%)
Month 60	9/12 (75%)	67/89 (75%)
Aspirin/Anti-Platelet‡		
Baseline	528/561 (94%)	1,951/2,027 (96%)
Month 1	526/544 (97%)	1,919/1,965 (98%)
Month 3	524/539 (97%)	1,926/1,965 (98%)
Month 6	532/541 (98%)	1,927/1,964 (98%)
Month 12	515/531 (97%)	1,888/1,927 (98%)
Month 18	499/520 (96%)	1,848/1,898 (97%)
Month 24	433/445 (97%)	1,629/1,665 (98%)
Month 30	361/371 (97%)	1,296/1,324 (98%)
Month 36	320/328 (98%)	1,080/1,114 (97%)
Month 42	243/250 (97%)	863/883 (98%)
Month 48	178/184 (97%)	661/672 (98%)
Month 54	117/123 (95%)	437/450 (97%)
Month 60	81/83 (98%)	303/308 (98%)
High-Intensity Statin#		
Baseline	183/521 (35%)	795/1,946 (41%)
Month 1	230/511 (45%)	875/1,895 (46%)
Month 3	250/511 (49%)	963/1,904 (51%)
Month 6	273/525 (52%)	1,054/1,926 (55%)
Month 12	290/529 (55%)	1,114/1,921 (58%)
Month 18	302/520 (58%)	1,126/1,901 (59%)
Month 24	253/442 (57%)	1,018/1,665 (61%)
Month 30	219/370 (59%)	812/1,325 (61%)
Month 36	201/328 (61%)	692/1,114 (62%)
Month 42	156/249 (63%)	550/883 (62%)
Month 48	109/185 (59%)	414/675 (61%)
Month 54	72/124 (58%)	263/451 (58%)

Month 60	44/84 (52%)	186/311 (60%)
LDL and Statin$		
Baseline	139/542 (26%)	664/1,933 (34%)
Month 1	130/327 (40%)	529/1,168 (45%)
Month 3	166/397 (42%)	743/1,522 (49%)
Month 6	190/437 (43%)	824/1,600 (52%)
Month 12	191/484 (39%)	924/1,743 (53%)
Month 18	206/443 (47%)	883/1,641 (54%)
Month 24	181/393 (46%)	829/1,477 (56%)
Month 30	135/303 (45%)	638/1,140 (56%)
Month 36	147/283 (52%)	572/970 (59%)
Month 42	99/204 (49%)	456/737 (62%)
Month 48	77/156 (49%)	361/590 (61%)
Month 54	47/96 (49%)	210/367 (57%)
Month 60	33/63 (52%)	171/265 (65%)

[*] *n/N (%). †If the participant is not indicated to be on an Beta Blocker (or ACE inhibitor or an angiotensin receptor blocker), then this variable is missing for all visits corresponding to the participant. ‡This variable indicates whether or not the participant met the OMT goal of being on either an anti-platelet or an anticoagulant medication at the corresponding visit. #This variable indicates whether or not the participant met the OMT goal of being on a high-intensity dose of either rosuvastatin or atorvastatin at the corresponding visit. $This variable indicates whether or not the participant met the OMT goal of having their low-density lipoprotein cholesterol less than 70 mg/dL (or the equivalent of 1.9 mmol/L) and being on a statin medication at the corresponding visit.*

ACEi/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; LDL: low-desnity lipoprotein; NA: not applicable

Supplementary Table 3. Medication usage and medication goals met in the invasive treatment (INV) cohort.

A. Medication usage in invasive treatment cohort

Characteristic	Female, N = 606*	Male, N = 1,982*
ACEi/ARB		
Baseline	396/606 (65%)	1,289/1,978 (65%)
Month 1	404/587 (69%)	1,275/1,891 (67%)
Month 3	385/566 (68%)	1,272/1,891 (67%)
Month 6	397/573 (69%)	1,311/1,906 (69%)
Month 12	394/568 (69%)	1,306/1,876 (70%)
Month 18	398/561 (71%)	1,283/1,834 (70%)
Month 24	357/506 (71%)	1,114/1,586 (70%)
Month 30	280/398 (70%)	924/1,300 (71%)
Month 36	253/351 (72%)	771/1,087 (71%)
Month 42	197/267 (74%)	631/867 (73%)
Month 48	141/200 (70%)	466/662 (70%)
Month 54	92/131 (70%)	303/440 (69%)
Month 60	59/78 (76%)	191/271 (70%)
Beta-Blockers		
Baseline	470/606 (78%)	1,587/1,978 (80%)
Month 1	476/587 (81%)	1,601/1,891 (85%)
Month 3	452/566 (80%)	1,606/1,891 (85%)
Month 6	466/573 (81%)	1,604/1,906 (84%)
Month 12	447/568 (79%)	1,583/1,876 (84%)
Month 18	438/561 (78%)	1,517/1,834 (83%)
Month 24	401/506 (79%)	1,308/1,586 (82%)
Month 30	317/398 (80%)	1,067/1,300 (82%)
Month 36	272/351 (77%)	890/1,087 (82%)
Month 42	204/267 (76%)	702/867 (81%)
Month 48	157/200 (78%)	540/662 (82%)
Month 54	97/131 (74%)	358/440 (81%)
Month 60	58/78 (74%)	221/271 (82%)
Calcium Channel Blockers		
Baseline	193/606 (32%)	578/1,980 (29%)
Month 1	183/587 (31%)	574/1,892 (30%)
Month 3	174/567 (31%)	550/1,891 (29%)
Month 6	180/573 (31%)	572/1,906 (30%)
Month 12	178/568 (31%)	583/1,877 (31%)
Month 18	171/562 (30%)	577/1,835 (31%)
Month 24	169/506 (33%)	485/1,587 (31%)
Month 30	144/398 (36%)	429/1,300 (33%)
Month 36	128/351 (36%)	357/1,087 (33%)
Month 42	91/267 (34%)	290/868 (33%)

Month 48	65/200 (32%)	223/662 (34%)
Month 54	48/131 (37%)	151/440 (34%)
Month 60	29/78 (37%)	94/271 (35%)
Dual Anti-Platelet Therapy		
Baseline	152/606 (25%)	531/1,980 (27%)
Month 1	324/585 (55%)	1,123/1,891 (59%)
Month 3	327/567 (58%)	1,189/1,888 (63%)
Month 6	332/573 (58%)	1,201/1,906 (63%)
Month 12	290/568 (51%)	1,045/1,873 (56%)
Month 18	179/560 (32%)	660/1,831 (36%)
Month 24	152/504 (30%)	494/1,581 (31%)
Month 30	109/396 (28%)	362/1,297 (28%)
Month 36	90/348 (26%)	288/1,083 (27%)
Month 42	65/267 (24%)	215/862 (25%)
Month 48	46/199 (23%)	154/658 (23%)
Month 54	21/131 (16%)	82/437 (19%)
Month 60	13/77 (17%)	44/268 (16%)
Anti-Anginal Medications		
Baseline	238/606 (39%)	735/1,980 (37%)
Month 1	159/587 (27%)	555/1,892 (29%)
Month 3	130/567 (23%)	470/1,891 (25%)
Month 6	129/573 (23%)	420/1,906 (22%)
Month 12	129/568 (23%)	366/1,877 (19%)
Month 18	134/562 (24%)	322/1,835 (18%)
Month 24	112/506 (22%)	270/1,587 (17%)
Month 30	85/398 (21%)	232/1,300 (18%)
Month 36	71/351 (20%)	210/1,087 (19%)
Month 42	59/267 (22%)	166/868 (19%)
Month 48	45/200 (22%)	128/662 (19%)
Month 54	28/131 (21%)	72/440 (16%)
Month 60	14/78 (18%)	51/271 (19%)
Long-Acting Nitrates		
Baseline	199/606 (33%)	614/1,980 (31%)
Month 1	131/587 (22%)	441/1,892 (23%)
Month 3	110/567 (19%)	374/1,891 (20%)
Month 6	104/573 (18%)	330/1,906 (17%)
Month 12	103/568 (18%)	291/1,877 (16%)
Month 18	102/562 (18%)	243/1,835 (13%)
Month 24	83/506 (16%)	198/1,587 (12%)
Month 30	63/398 (16%)	171/1,300 (13%)
Month 36	54/351 (15%)	151/1,087 (14%)
Month 42	42/267 (16%)	119/868 (14%)
Month 48	28/200 (14%)	93/662 (14%)
Month 54	18/131 (14%)	57/440 (13%)
Month 60	11/78 (14%)	36/271 (13%)

Anticoagulants		
Baseline	22/600 (3.7%)	92/1,967 (4.7%)
Month 1	27/579 (4.7%)	107/1,872 (5.7%)
Month 3	27/559 (4.8%)	107/1,870 (5.7%)
Month 6	22/566 (3.9%)	113/1,882 (6.0%)
Month 12	22/561 (3.9%)	109/1,847 (5.9%)
Month 18	30/550 (5.5%)	106/1,818 (5.8%)
Month 24	28/501 (5.6%)	104/1,569 (6.6%)
Month 30	23/387 (5.9%)	87/1,285 (6.8%)
Month 36	20/343 (5.8%)	71/1,072 (6.6%)
Month 42	17/261 (6.5%)	62/850 (7.3%)
Month 48	14/198 (7.1%)	53/646 (8.2%)
Month 54	9/129 (7.0%)	42/430 (9.8%)
Month 60	7/76 (9.2%)	32/265 (12%)
P2Y12 Inhibitors		
Baseline	178/606 (29%)	615/1,982 (31%)
Month 1	345/606 (57%)	1,195/1,982 (60%)
Month 3	353/604 (58%)	1,271/1,973 (64%)
Month 6	358/599 (60%)	1,275/1,964 (65%)
Month 12	315/595 (53%)	1,130/1,959 (58%)
Month 18	206/591 (35%)	732/1,936 (38%)
Month 24	175/534 (33%)	565/1,676 (34%)
Month 30	126/425 (30%)	425/1,379 (31%)
Month 36	105/373 (28%)	339/1,160 (29%)
Month 42	80/287 (28%)	263/931 (28%)
Month 48	53/215 (25%)	185/708 (26%)
Month 54	27/140 (19%)	107/468 (23%)
Month 60	18/85 (21%)	59/292 (20%)

[*] *n/N (%)*

ACEi/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker

B. Medication goals being met in invasive treatment cohort.

Characteristic	**Female, N = 606***	**Male, N = 1,982***
ACEi/ARB†		
Baseline	372/525 (71%)	1,170/1,622 (72%)
Month 1	372/507 (73%)	1,141/1,554 (73%)
Month 3	354/489 (72%)	1,132/1,554 (73%)
Month 6	364/496 (73%)	1,169/1,566 (75%)
Month 12	356/490 (73%)	1,153/1,539 (75%)
Month 18	360/485 (74%)	1,128/1,496 (75%)
Month 24	326/439 (74%)	976/1,291 (76%)
Month 30	255/346 (74%)	808/1,060 (76%)
Month 36	227/303 (75%)	674/884 (76%)

Month 42	177/230 (77%)	552/712 (78%)
Month 48	126/173 (73%)	409/547 (75%)
Month 54	83/115 (72%)	268/360 (74%)
Month 60	52/67 (78%)	167/222 (75%)
Beta-Blocker†		
Baseline	83/95 (87%)	359/411 (87%)
Month 1	86/93 (92%)	356/395 (90%)
Month 3	77/86 (90%)	360/400 (90%)
Month 6	80/91 (88%)	361/405 (89%)
Month 12	80/91 (88%)	355/397 (89%)
Month 18	80/90 (89%)	335/384 (87%)
Month 24	74/82 (90%)	295/341 (87%)
Month 30	72/76 (95%)	248/290 (86%)
Month 36	64/70 (91%)	210/249 (84%)
Month 42	44/52 (85%)	170/203 (84%)
Month 48	32/39 (82%)	136/156 (87%)
Month 54	18/23 (78%)	99/117 (85%)
Month 60	11/13 (85%)	66/77 (86%)
Aspirin/Anti-Platelet‡		
Baseline	578/606 (95%)	1,921/1,980 (97%)
Month 1	573/585 (98%)	1,872/1,890 (99%)
Month 3	556/567 (98%)	1,874/1,887 (99%)
Month 6	564/573 (98%)	1,886/1,905 (99%)
Month 12	557/568 (98%)	1,849/1,875 (99%)
Month 18	539/560 (96%)	1,797/1,832 (98%)
Month 24	484/503 (96%)	1,549/1,582 (98%)
Month 30	379/396 (96%)	1,272/1,298 (98%)
Month 36	330/348 (95%)	1,063/1,083 (98%)
Month 42	260/267 (97%)	843/862 (98%)
Month 48	198/200 (99%)	641/658 (97%)
Month 54	130/131 (99%)	426/436 (98%)
Month 60	77/78 (99%)	264/270 (98%)
High-Intensity Statin#		
Baseline	194/585 (33%)	739/1,888 (39%)
Month 1	253/566 (45%)	891/1,811 (49%)
Month 3	258/552 (47%)	945/1,817 (52%)
Month 6	289/566 (51%)	1,047/1,859 (56%)
Month 12	291/566 (51%)	1,109/1,868 (59%)
Month 18	299/560 (53%)	1,113/1,832 (61%)
Month 24	272/506 (54%)	979/1,576 (62%)
Month 30	228/396 (58%)	816/1,296 (63%)
Month 36	215/351 (61%)	688/1,086 (63%)
Month 42	156/268 (58%)	531/867 (61%)
Month 48	112/200 (56%)	409/660 (62%)
Month 54	72/131 (55%)	253/439 (58%)

Month 60	37/78 (47%)	145/271 (54%)
LDL and Statin$		
Baseline	142/574 (25%)	654/1,889 (35%)
Month 1	132/345 (38%)	535/1,128 (47%)
Month 3	153/411 (37%)	743/1,399 (53%)
Month 6	174/458 (38%)	822/1,568 (52%)
Month 12	211/518 (41%)	925/1,703 (54%)
Month 18	206/452 (46%)	877/1,557 (56%)
Month 24	186/441 (42%)	819/1,425 (57%)
Month 30	147/322 (46%)	613/1,100 (56%)
Month 36	146/310 (47%)	559/945 (59%)
Month 42	106/224 (47%)	428/714 (60%)
Month 48	77/167 (46%)	346/567 (61%)
Month 54	53/103 (51%)	220/353 (62%)
Month 60	35/67 (52%)	151/244 (62%)

**n/N (%). †If the participant is not indicated to be on an Beta Blocker (or ACE inhibitor or an angiotensin receptor blocker), then this variable is missing for all visits corresponding to the participant. ‡This variable indicates whether or not the participant met the OMT goal of being on either an anti-platelet or an anticoagulant medication at the corresponding visit. #This variable indicates whether or not the participant met the OMT goal of being on a high-intensity dose of either rosuvastatin or atorvastatin at the corresponding visit. $This variable indicates whether or not the participant met the OMT goal of having their low-density lipoprotein cholesterol less than 70 mg/dL (or the equivalent of 1.9 mmol/L) and being on a statin medication at the corresponding visit.*

ACEi/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; LDL: low-desnity lipoprotein; NA: not applicable

Supplementary Table 4. Association between sex and the risk of procedural myocardial infarction as defined per the alternative (secondary) definition.

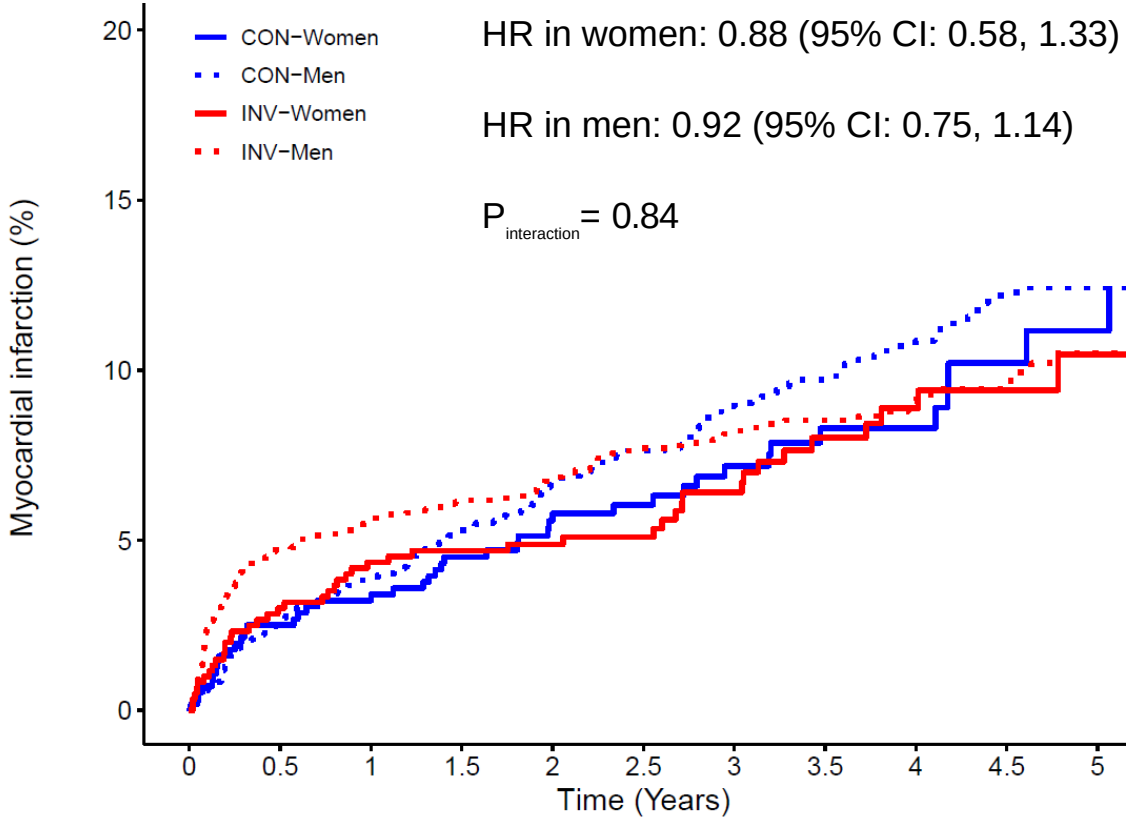
Incidence among revascularized patients		Odds ratio for women vs. men (95% confidence interval)	
Women	**Men**	**Adjusted for revascularization modality**	**Fully adjusted***
54/553 (9.8%)	201/2,045 (9.8%)	1.09 (0.78-1.50, p=0.59)	1.19 (0.83-1.67, p=0.33)

*Adjusted for the following covariate set: revascularization modality (CABG versus PCI), randomized arm, age, sex, prior MI, current smoking, diabetes, left ventricular ejection fraction less than 45%, prior CABG, prior heart failure hospitalization, chronic lung disease, prior stroke, known peripheral vascular disease, white versus non-white race, and eGFR lower than 60 ml/min.

Supplementary Figure 1. Cumulative incidence of the adverse ischaemic events according to randomised group assignment for women and men.

CON=conservative; INV= invasive; MI=myocardial infarction

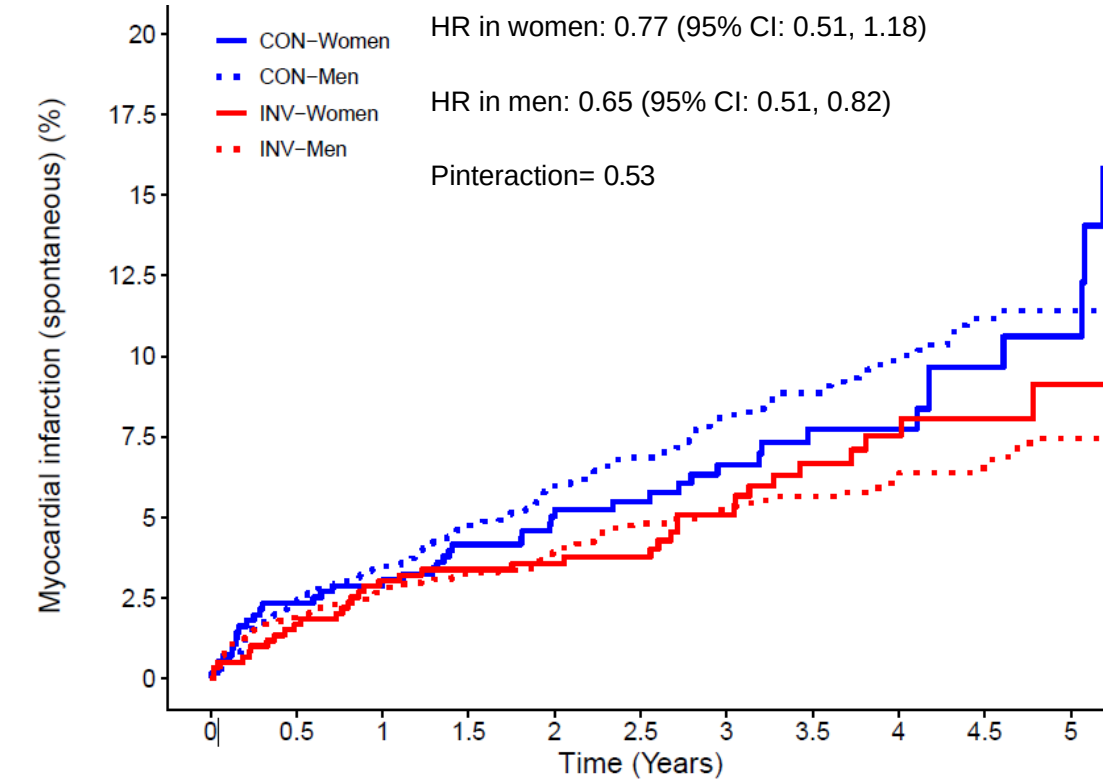
A. Myocardial infarction.



Number at risk

CON−Women	562	542	535	497	422	353	301	214	160	106	63
CON−Men	2029	1953	1917	1793	1509	1238	1020	810	587	379	235
INV−Women	606	574	562	537	470	380	327	241	176	106	67
INV-Men	1982	1859	1817	1707	1461	1219	986	771	566	365	216

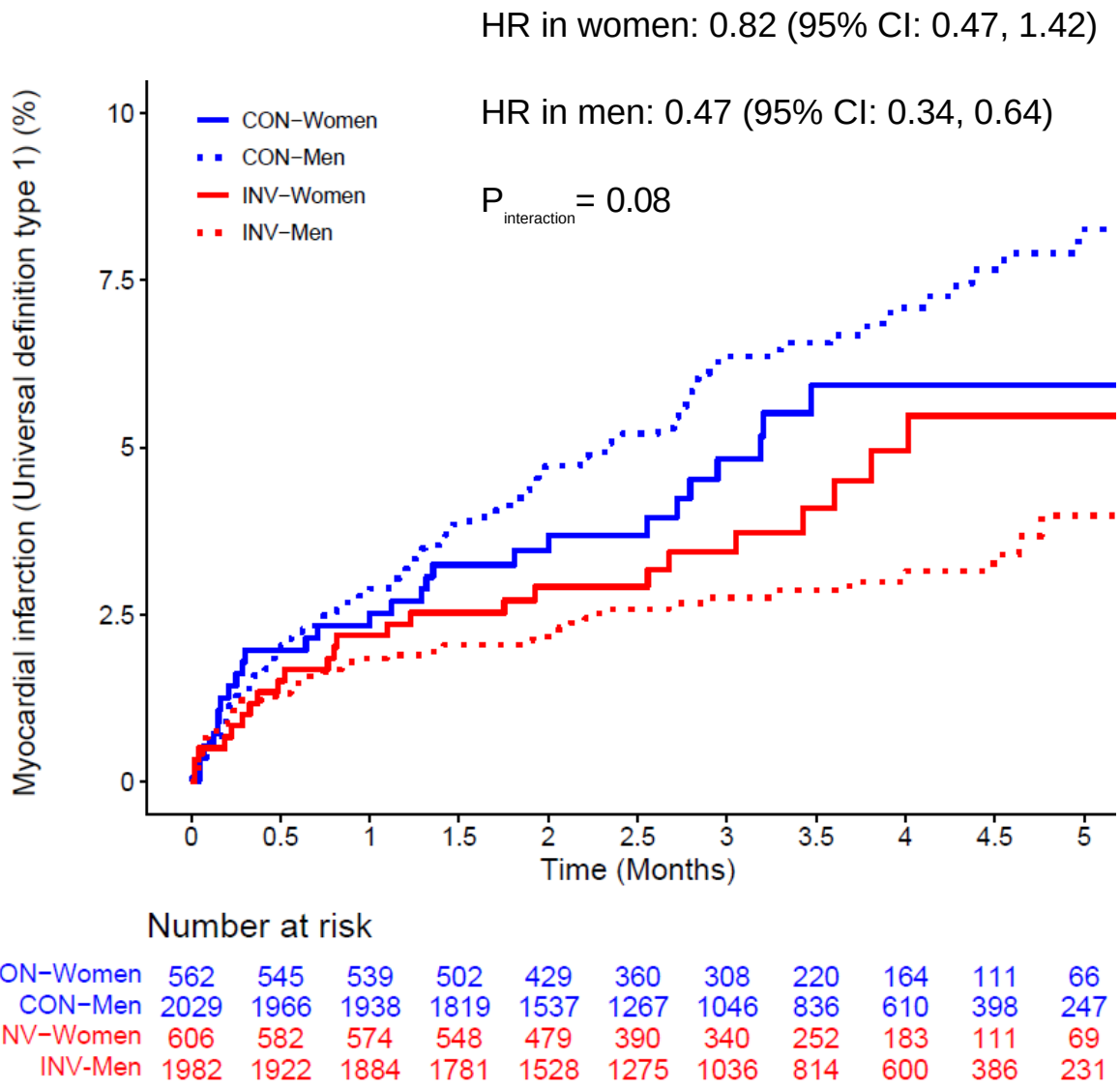
B. Spontaneous myocardial infarction.



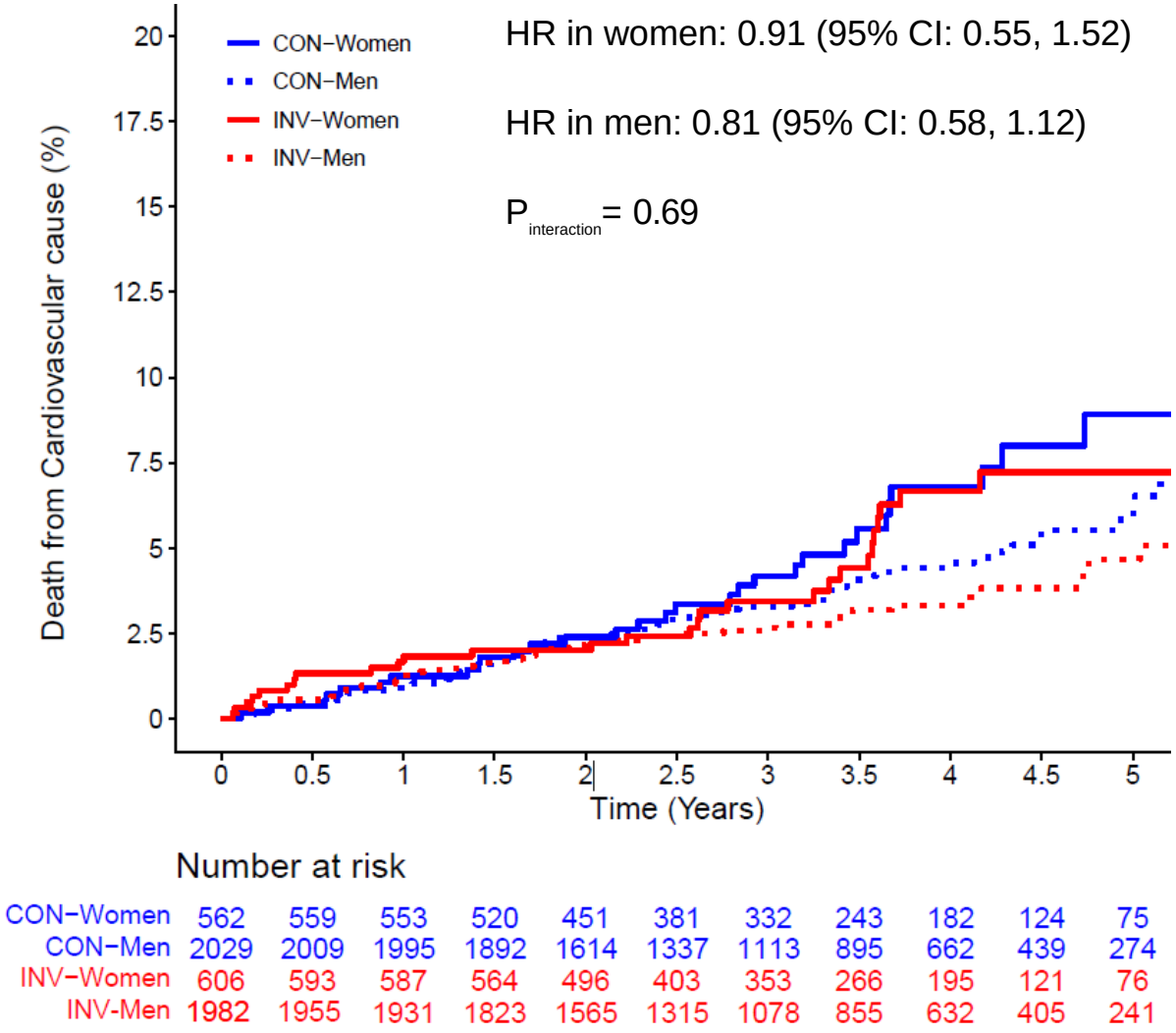
Number at risk

CON−Women	562	543	536	497	423	354	302	215	161	107	64
CON−Men	2029	1958	1926	1804	1521	1250	1030	820	594	385	238
INV−Women	606	581	569	544	477	387	334	246	180	109	68
INV-Men	1982	1911	1869	1759	1503	1252	1014	795	585	379	223

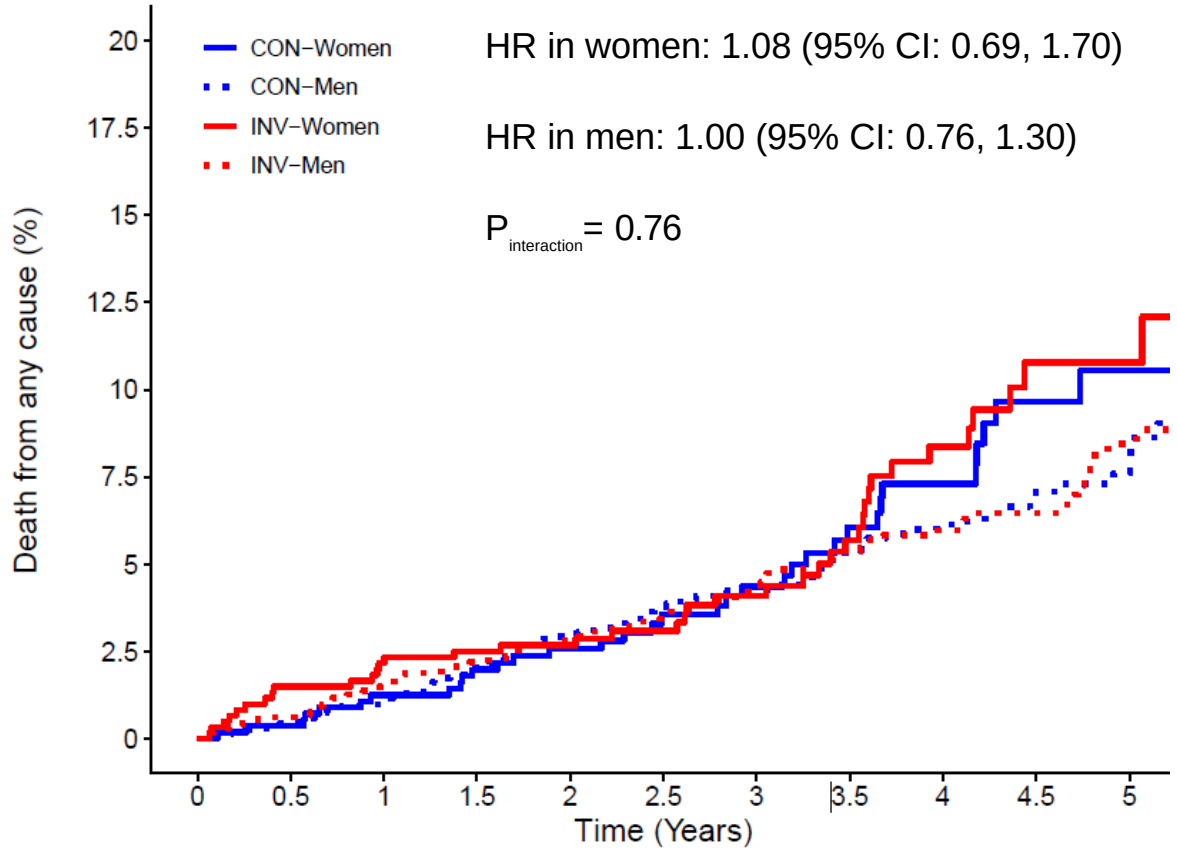
C. Myocardial infarction – Universal definition type 1.



D. Cardiovascular death.



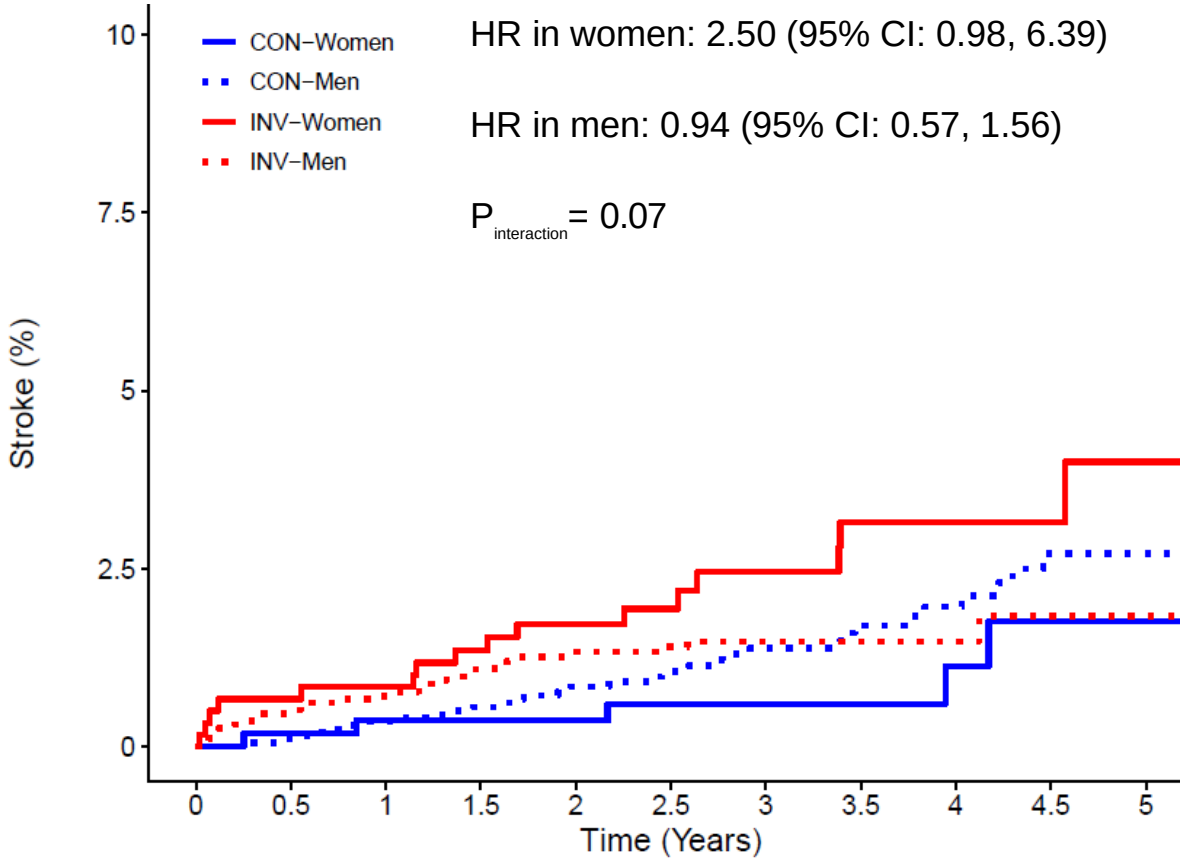
E. All-cause death.



Number at risk

CON−Women	562	559	553	520	451	381	332	243	182	124	75
CON−Men	2029	2009	1995	1892	1614	1337	1113	895	662	439	274
INV−Women	606	593	587	564	496	403	353	266	195	121	76
INV-Men	1982	1955	1931	1823	1565	1315	1078	855	632	405	241

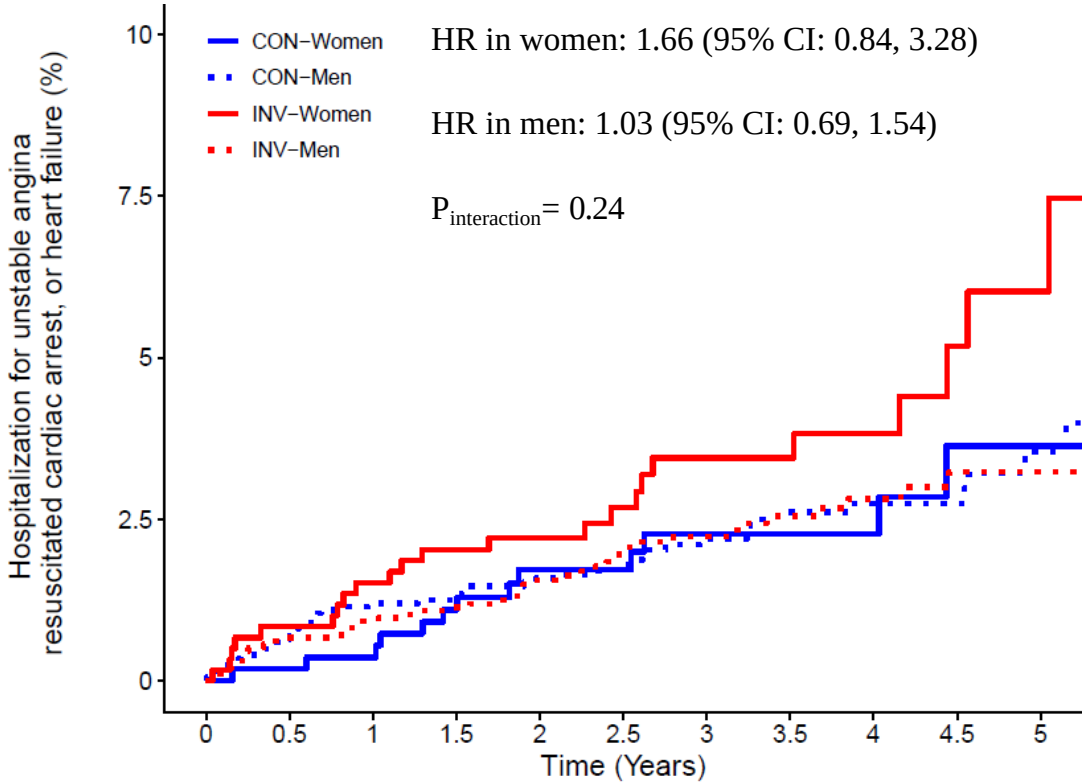
F. Stroke.



Number at risk

CON−Women	562	554	548	515	442	373	324	237	178	119	73
CON−Men	2029	2004	1985	1877	1596	1320	1092	880	653	427	268
INV−Women	606	587	582	555	488	396	344	258	192	119	73
INV−Men	1982	1939	1904	1794	1539	1290	1047	829	615	392	236

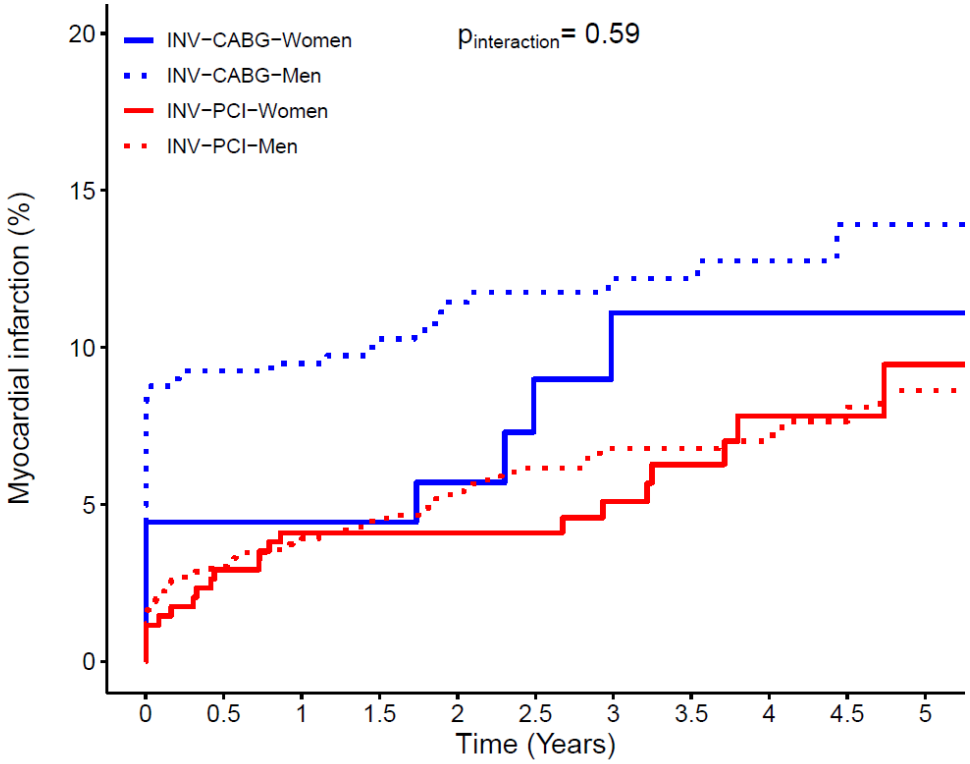
G. Hospitalisation for unstable angina, resuscitated cardiac arrest or heart failure.



Supplementary Figure 2. Cumulative incidence of the adverse ischaemic events after revascularisation by CABG or PCI (median follow-up after revascularisation: 2.09 years [0.17, 3.66]) for women and men randomised to an invasive strategy.

CABG=coronary artery bypass grafting; CON=conservative; INV= invasive; MI=myocardial infarction; PCI=percutaneous coronary intervention.

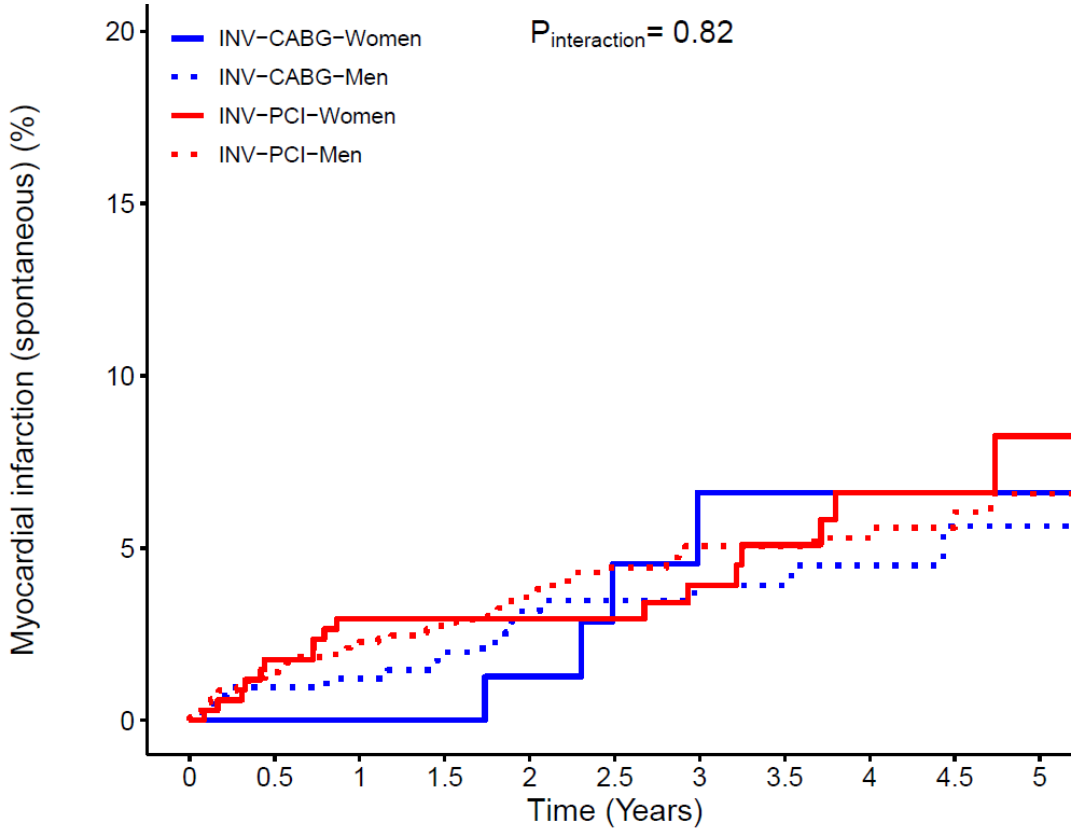
A. Myocardial infarction.



Number at risk

INV−CABG−Women	90	84	84	80	69	54	42	35	24	9	7
INV−CABG−Men	422	376	368	335	289	246	196	156	104	67	36
INV−PCI−Women	345	330	322	302	262	212	179	139	100	71	38
INV−PCI−Men	1155	1106	1082	981	831	685	554	427	305	205	120

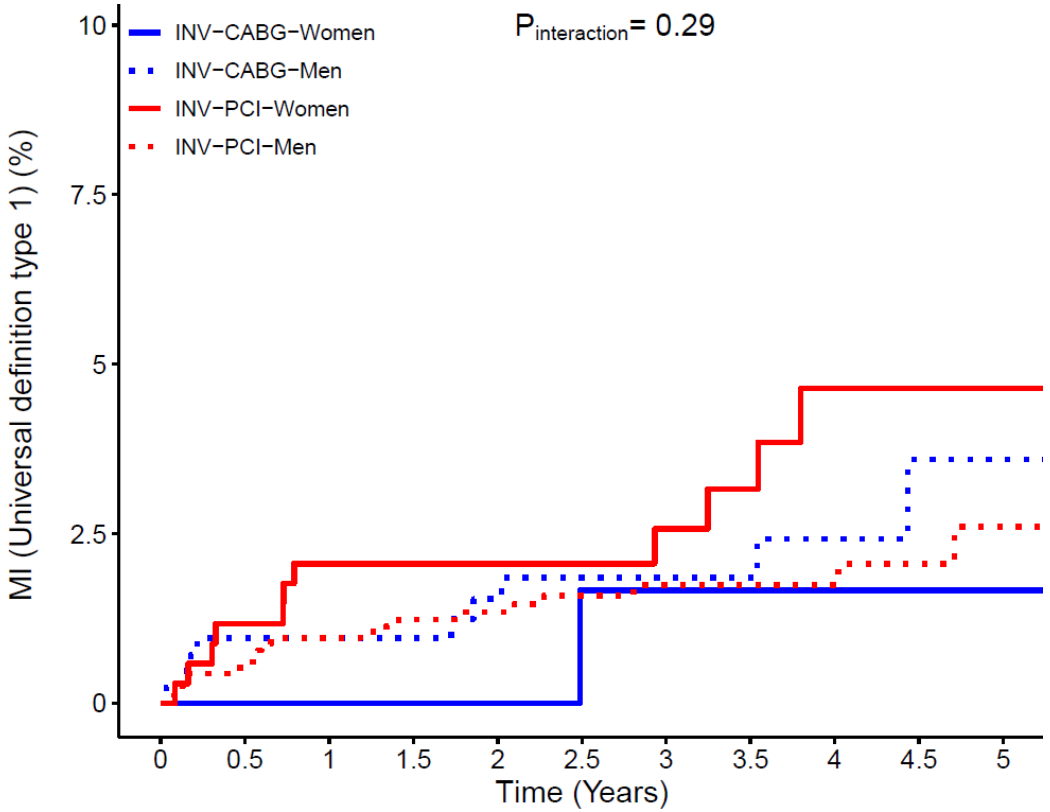
B. Spontaneous myocardial infarction.



Number at risk

INV−CABG−Women	90	87	87	83	72	57	45	36	25	9	7
INV−CABG−Men	422	409	401	366	312	266	213	169	114	74	39
INV−PCI−Women	345	334	326	306	266	216	183	142	103	72	39
INV−PCI−Men	1155	1124	1100	998	846	696	563	436	312	210	124

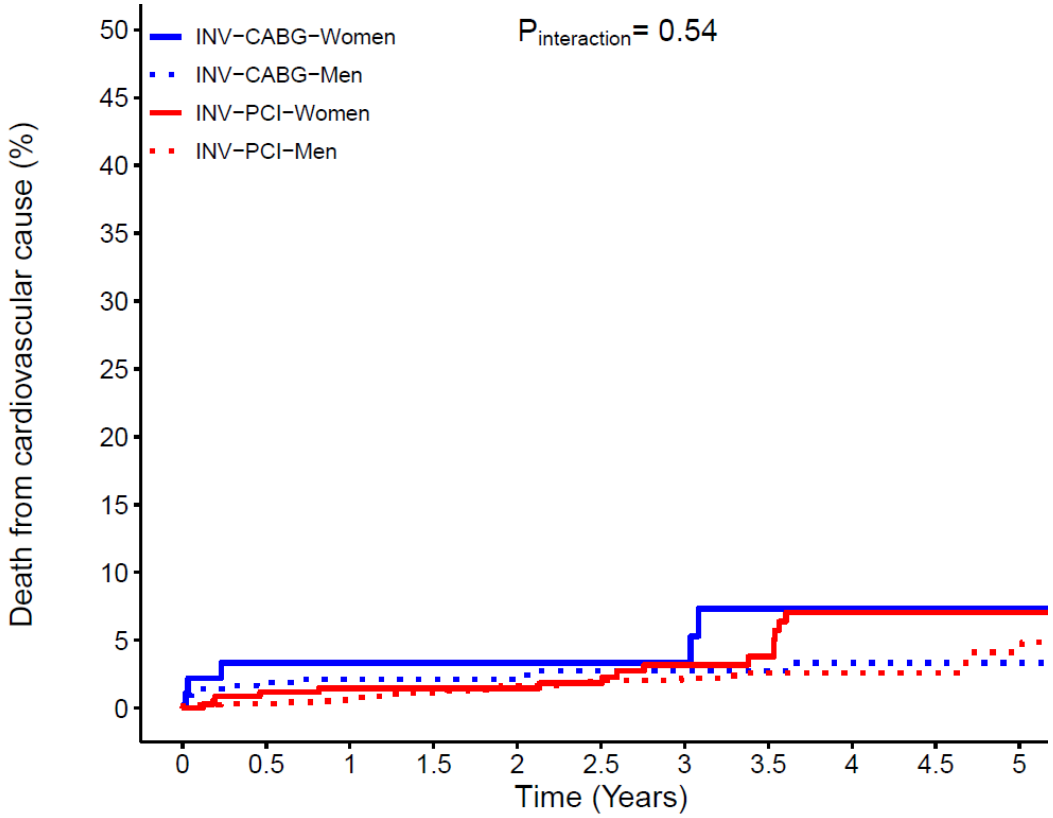
C. Myocardial infarction – Universal definition type 1.



Number at risk

INV−CABG−Women	90	87	87	83	73	59	48	37	25	9	7
INV−CABG−Men	422	409	402	370	317	270	218	174	117	74	39
INV−PCI−Women	345	335	328	308	267	217	185	144	104	73	40
INV−PCI−Men	1155	1133	1113	1014	862	709	577	445	318	213	127

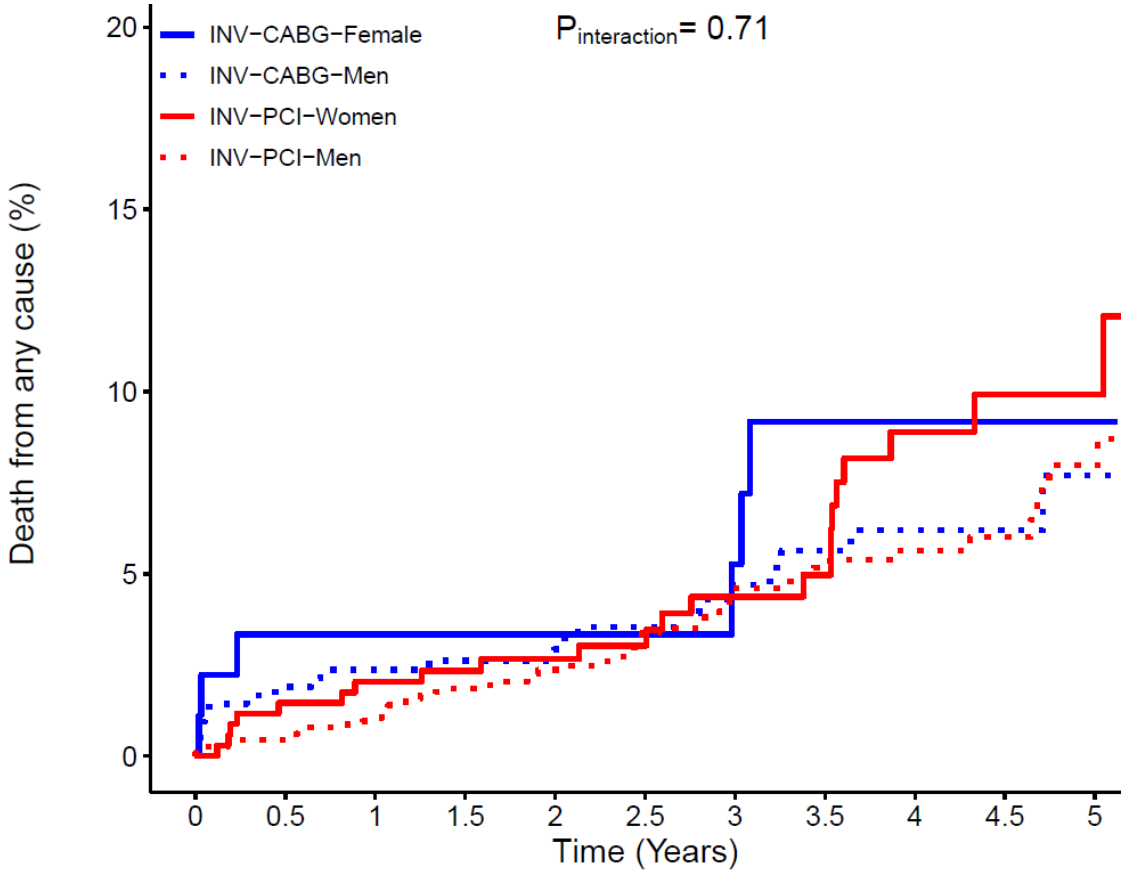
D. Cardiovascular death.



Number at risk

INV−CABG−Women	90	87	87	83	73	60	49	38	25	9	7
INV−CABG−Men	422	413	406	373	322	277	226	181	123	78	41
INV−PCI−Women	345	338	335	314	273	223	191	151	111	78	44
INV−PCI−Men	1155	1140	1128	1028	876	723	591	458	327	218	130

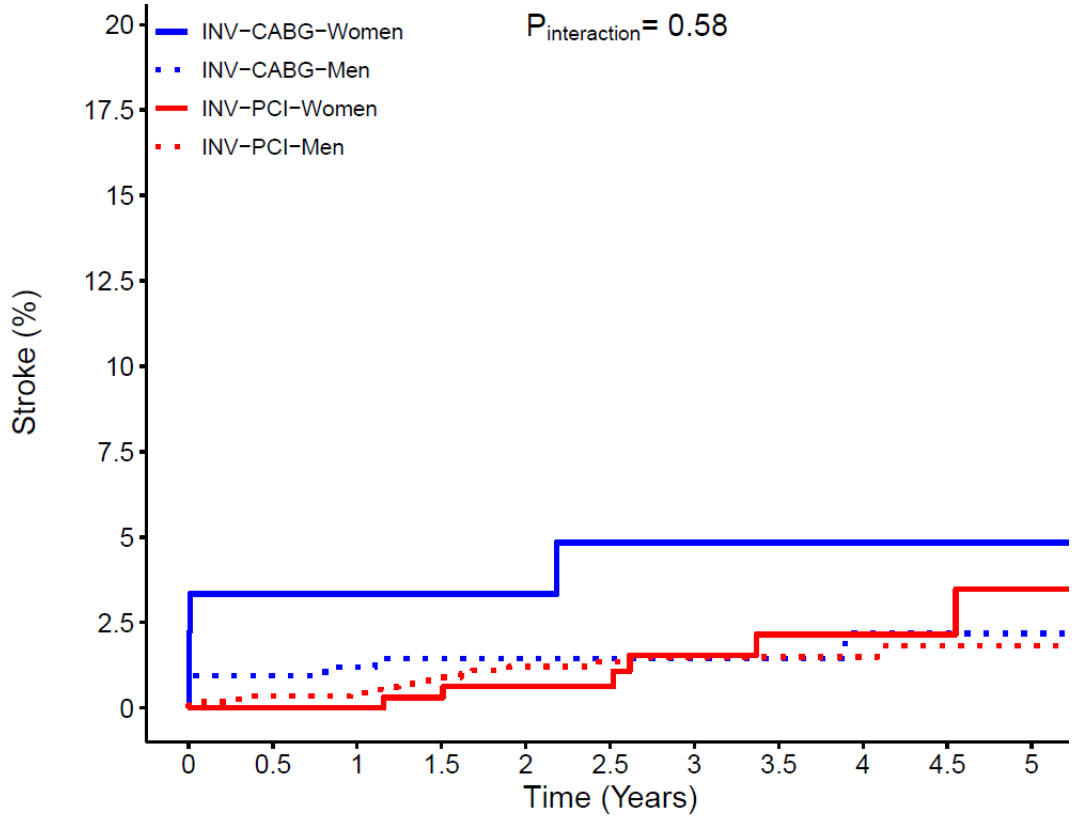
E. All-cause death.



Number at risk

INV−CABG−Women	90	87	87	83	73	60	49	38	25	9	7
INV−CABG−Men	422	413	406	373	322	277	226	181	123	78	41
INV−PCI−Women	345	338	335	314	273	223	191	151	111	78	44
INV−PCI−Men	1155	1140	1128	1028	876	723	591	458	327	218	130

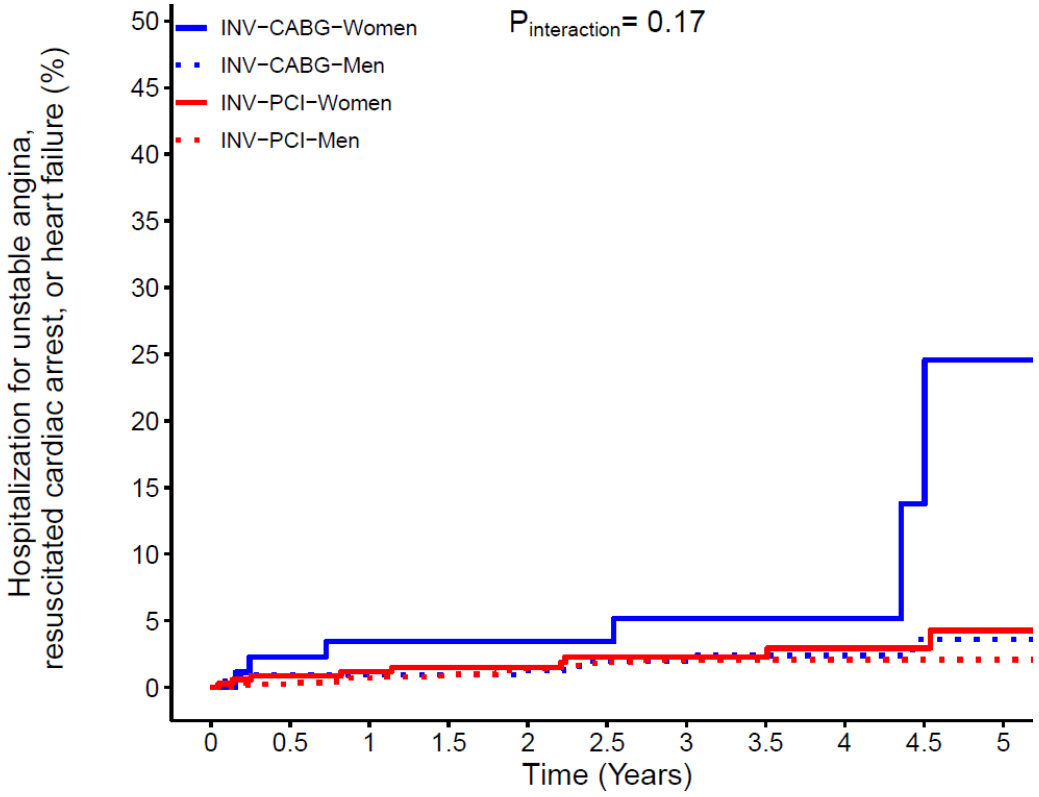
F. Stroke.



Number at risk

INV−CABG−Women	90	85	85	81	71	56	46	36	24	8	6
INV−CABG−Men	422	409	401	367	317	271	220	176	120	74	40
INV−PCI−Women	345	338	334	314	273	223	191	149	110	77	42
INV−PCI−Men	1154	1133	1117	1015	862	710	578	449	322	212	128

G. Hospitalisation for unstable angina, resuscitated cardiac arrest or heart failure.



Number at risk

INV−CABG−Women	90	85	84	80	70	57	46	36	24	8	5
INV−CABG−Men	422	409	402	370	318	271	219	174	117	71	36
INV−PCI−Women	344	335	331	310	271	219	189	148	109	76	41
INV−PCI−Men	1155	1135	1116	1016	862	708	577	450	323	214	128