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Variation in the use of stress testing and outcomes in patients with non-ST-elevation acute coronary syndromes: insights from GUSTO IIb

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Aims Non-invasive risk stratification of low- and intermediate-risk non-ST-elevation acute coronary syndromes (NSTE ACS) patients has been recommended, but limited data exist about the variation in clinical practice of stress testing in these patients and the impact of such testing on their outcomes.

Methods and results Patients with NSTE ACS enrolled in the GUSTO IIb (Global Use of Strategies To Open occluded coronary arteries in acute coronary syndromes-IIb) trial ($n = 8011$) were analysed to evaluate patterns of stress testing in US and non-US patients and to further evaluate the clinical characteristics, procedure use, and outcomes of patients who underwent stress testing compared with those who did not. Stress testing was performed in 1878 (24%) patients. Compared with patients not undergoing stress testing, those undergoing stress testing had low-risk characteristics and significantly lower death (0.6% vs. 4.8%), and death or myocardial infarction (MI, 3.9% vs. 11%) rates at 30 days. Stress testing was performed as often after as before coronary angiography. Importantly, stress testing was helpful in stratifying patients into low (equivocal or negative test) or high (positive test) risk groups (30 day death 3.1% vs. 5%). Stress testing was performed more often in non-US than US patients, and US patients were 3.5 times more likely to undergo imaging as part of stress testing. However, the risks of 30-day death or MI; 6-month death, MI or revascularization; and 1-year death did not differ between US and non-US patients.

Conclusion Stress testing is commonly performed in low-risk NSTE ACS patients and provides modest additional prognostic information in this cohort. Significant geographical variation exists in the use of stress testing. Therefore, in the current practice environment where cardiac catheterization is often the first diagnostic modality used in patients with NSTE ACS, the role of non-invasive testing both before and after invasive procedure is in need of further study.

Keywords Acute coronary syndromes • Stress test • Myocardial infarction • Outcomes

Introduction

The practice guideline issued by the American College of Cardiology and the American Heart Association (ACC/AHA) on the management of non-ST-elevation acute coronary syndromes (NSTE ACS) recommends stress testing for risk stratification in low- and intermediate-risk patients who have been clinically stable for at least 48 h.[1] The long-term follow-up of the ICTUS

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(Invasive vs. Conservative Treatment in Unstable Coronary Syndromes) trial suggests that a selective invasive approach, including the use of stress testing in the higher-risk population with positive troponin to guide who gets coronary angiography, may be a reasonable approach.[2] The standard exercise electrocardiogram (ECG) stress test is recommended as the most reasonable test in most patients, with addition of an imaging modality for patients with uninterpretable ST-segments on the baseline ECG. The rationale is that functional status and the presence or absence of ischaemia guide invasive procedure referrals and ascertain prognosis.[1] However, despite strong endorsement by the ACC/AHA guidelines for the use of stress testing in the risk stratification of patients with NSTE ACS, less is known about the practice variation in the use of this strategy.[3–6]

A substantial proportion of patients enrolled in the international GUSTO IIb (Global Use of Strategies To Open occluded coronary arteries in acute coronary syndromes-IIb) trial underwent non-invasive testing and had related data captured prospectively.[7] Thus, this database affords an opportunity to perform a descriptive analysis of international and clinical differences, as well as procedure use and outcomes, among patients undergoing various modalities of risk stratification. In addition, it allows for an examination of the impact of stress testing on clinical decision making and the relationship with outcomes.

Methods

Patient population

The GUSTO IIb trial was a multicentre international trial comparing hirudin with unfractionated heparin in the management of acute coronary syndromes. The methods of this trial have been published elsewhere.[7] Briefly, 12 142 patients at 373 hospitals in 13 countries with chest discomfort within the previous 12 h associated with either transient or persistent ST-segment elevation or depression of more than 0.5 mm or with persistent, definite T-wave inversion of more than 1 mm were randomly assigned to 72 h of therapy with either intravenous heparin or hirudin between May 19, 1994 and October 17, 1995. Exclusions included warfarin therapy at the time of enrolment, active bleeding, history of stroke, contraindication to heparin therapy, serum creatinine > 2.0 mg per decilitre, systolic blood pressure > 200 mm Hg or diastolic blood pressure > 110 mm Hg, or women of childbearing potential. Patients were stratified according to the presence or absence of ST-segment elevation on the baseline ECG. Of the total number enrolled, 8011 patients did not have persistent ST-segment elevation on the baseline ECG and were considered to have NSTE ACS. This cohort formed the basis of the current retrospective analysis.

Procedures

The occurrence of transvenous pacemaker insertion, Swan-Ganz catheter insertion, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), intra-aortic balloon pump insertion, and stress testing was recorded for each patient. For each procedure, the date of first occurrence was recorded. For stress testing, the type of provocation (exercise or other, including dobutamine, adenosine, and dipyridamole) as well as the type of imaging (ECG alone, echo, sestamibi, thallium, and radionuclide angiography) were recorded. The maximal heart rate experienced by the patient and the results of stress test categorized as positive, negative or equivocal were also recorded. The decision to perform procedures, including stress testing and the type of stress test, was not dictated by the study protocol but was left to the discretion of the treating physician.

Endpoints

The primary outcome of GUSTO IIB trial was the composite of death or non-fatal myocardial infarction (MI) (or reinfarction) in the first 30 days of follow-up. Definitions of MI and reinfarction have been previously published[7] and were classified by members of the clinical events committee, who were blinded to the patients' treatment assignment. Additional end-points of interests for current investigations included, death at 30 days and 1 year, and MI (or reinfarction) at 30 days.

Statistical analysis

Summary statistics are presented as frequencies and percentages or as medians and interquartile ranges (IQR) as appropriate. Comparisons between groups were made using the two-tailed Wilcoxon's rank sum test for continuous variables and the χ^2 or Fisher's exact test (when expected frequency count in the cell < 5) for categorical variables as appropriate. In all cases, missing data were not defaulted to negative and denominators reflect cases reported. Kaplan–Meier method was used to generate an estimate of unadjusted event-free survival at follow-up.

Previously published multivariable Cox Proportional Hazard model for 30-day death,[8] with countries categorized as US and non-US and the additional adjustment using a propensity score for stress testing (vs. no stress testing), was used to account for confounding and an inherent bias in the performance of stress testing. We also tested the effect of the interaction term between countries categorized as above with the use of stress testing on this event. The proportional hazards assumption was tested by modelling the factor of interest plus the interaction of the factor with the log of time. When the hazards assumption was violated, graphical representations were made. After visual inspection, if it was felt that applying the assumption lead to conservative estimates, then the factor was included as is, recognizing this limitation. The linearity assumption for continuous measures was evaluated using restricted cubic spline transformations. Models with the factor of interest included as a linear term only were compared with those in which the restricted cubic transformation was included. If the addition of the transformations was statistically significant, then the plot of the transformation vs. the log of the hazard ratio helped identify appropriate transformations to apply.

Variables used in the propensity model included: age, gender, race, weight, US vs. non-US sites, history of hypertension, history of diabetes, history of hypercholesterolemia, family history of premature coronary disease, history of MI, history of angina, history of PCI, history of coronary artery bypass surgery, history of smoking, history of congestive heart failure, history of cerebrovascular disease, history of severe lung disease, cancer in last 5 years, history of chronic renal insufficiency, peripheral vascular disease, systolic/diastolic blood pressure at randomization, heart rate at randomization, and rales at randomization. Summary statistics (mean, standard deviation, median and quartiles, and proportions) of those variables by stress groups within each quintile of the propensity scores were examined. We observed that balances in these covariates were well achieved. The propensity score was included as a linear term in the final multivariable model. Furthermore, we studied the effect of potential unmeasured confounders in the propensity analysis by performing a sensitivity analysis.

Similar method was used to derive independent clinical correlate of other adverse events at follow-up. Additionally, as the relationship between stress testing and outcome would be likely to be confounded in patients who had cardiac catheterization, MI, recurrent ischaemia, congestive heart failure or death in the first 48 h (for example, stress testing would be a marker for patients who survived long enough to get it), patients with these early events were excluded and multivariable modelling repeated as above using previously published model with propensity score as a covariate. Patients were censored at the point of the first occurrence of any of the above events. Stress test was entered in all models as a time-dependent covariate. Hazard ratios (HR) and 95% confidence intervals (CI) were constructed to provide point estimates of risk posed by individual clinical variables on events. A *P*-value of <0.05 was considered to denote a statistically significant difference between comparison groups. SAS 8.0 (SAS Institute, Cary, NC, USA) was utilized for all analyses.

Results

Baseline characteristics

Of the 8011 patients with NSTE ACS, data on the use of stress testing were obtained for 8005. Of these, 1878 patients (23.5%) underwent stress testing, and 6127 patients (76.5%) did not. *Table 1* show the baseline characteristics of patients who did and did not undergo stress testing. Patients who underwent stress testing had characteristics defining a lower risk NSTE ACS population than patients who did not undergo stress testing. These included younger age and male gender with lower incidences of diabetes, prior MI, and prior PCI. Overall, more than two-thirds of stress tests performed were ECG alone (*Table 2*). In decreasing order of frequency, the remainder used thallium, sestamibi, echo, and radionuclide angiography. Exercise testing was used in majority of patients (89%) with a small proportion (11%) receiving pharmacological provocation (*Table 3*).

The median time from enrolment to stress testing was 6 days. Of the 817 patients who underwent both stress testing and cardiac catheterization, more than one-half (52%) had the stress test after the catheterization (*Table 3*).

Table 1 Baseline characteristics

	Stress test	No stress test	*P*-value	US	Non-US	*P*-value
n	1878	6127		2250	5761	
Age (median, IQR)	63 (54–70)	67 (58–74)	<0.001	64 (54–73)	66 (58–73)	<0.001
Female	496 (26%)	2167 (35%)	<0.001	834 (37%)	1831 (22%)	<0.001
Hypertension	801 (43%)	3038 (50%)	<0.001	1335 (59%)	2506 (44%)	<0.001
Diabetes mellitus	267 (14%)	1238 (20%)	<0.001	537 (24%)	970 (17%)	<0.001
Current smoker	636 (50%)	1494 (40%)	<0.001	661 (45%)	1469 (41%)	0.006
History of smoking	628 (50%)	2273 (60%)	<0.001	797 (55%)	2108 (59%)	0.005
Prior MI	502 (27%)	2049 (33%)	<0.001	726 (32%)	1827 (32%)	0.622
Previous angina	1305 (70%)	4804 (78%)	<0.001	1896 (84%)	4218 (73%)	<0.001
Previous coronary angioplasty	156 (8%)	666 (11%)	<0.001	421 (19%)	401 (7%)	<0.001
Hyperlipidemia	776 (41%)	2492 (41%)	0.688	1045 (47%)	2223 (39%)	<0.001
Family history of coronary artery disease	712 (38%)	2499 (42%)	0.013	1200 (55%)	2011 (35%)	<0.001
Previous CABG	217 (12%)	752 (12%)	0.401	419 (19%)	552 (10%)	<0.001

IQR, interquartile range, CABG, coronary artery bypass graft surgery, MI, myocardial infarction, US, United States.

Table 2 Procedure use

	Stress test	No stress test	US	Non-US (combined)	Canada	Australia/ New Zealand	Europe
n	1878	6127	2250	5755	920	1025	3810
No stress test	0	6127 (100%)	1848 (82%)	4279 (74%)	663 (72%)	869 (85%)	2747 (72%)
Stress test	1878 (100%)	0	402 (18%)	1476 (26%)	257 (28%)	156 (15%)	1063 (28%)
No angiography	1061 (56%)	2413 (39%)	483 (21%)	2985 (52%)	514 (56%)	623 (61%)	1845 (48%)
Angiography	817 (44%)	3714 (61%)	1766 (79%)	2765 (48%)	399 (44%)	402 (39%)	1964 (52%)
Angiography and stress test	817 (44%)	0	230 (10%)	587 (10%)	110 (12%)	49 (5%)	428 (11%)
Angiography alone	0	3714 (61%)	1536 (68%)	2178 (38%)	289 (32%)	353 (34%)	1536 (40%)
Stress test alone	1061 (56%)	0	172 (8%)	889 (15%)	147 (16%)	107 (10%)	635 (17%)
Neither angiography nor stress test	0	2404 (39%)	311 (14%)	2093 (36%)	367 (40%)	516 (50%)	1210 (32%)

US, United States.

Table 3 Stress test modality

	Overall	US	Non-US (combined)	Canada	Australia/ New Zealand	Europe
Imaging modality						
n	1813	376	1437	220	156	1061
Electrocardiogram alone	1265 (70%)	63 (17%)	1202 (84%)	183 (83%)	129 (83%)	890 (84%)
Other (echo, sestamibi, radionuclide angiography, thallium)	548 (30%)	313 (83%)	235 (16%)	37 (17%)	27 (17%)	171 (16%)
Form of provocation						
n	1851	384	1467	250	156	1060
Exercise	1646 (89%)	285 (74%)	1361 (93%)	239 (96%)	134 (86%)	988 (93%)
Other (dobutamine, adenosine, dipyridamole)	200 (11%)	95 (25%)	105 (7%)	11 (4%)	22 (14%)	72 (7%)

US, United States.

US patients vs. non-US patients

Table 1 shows the clinical characteristics of US patients vs. non-US patients. Patients in the US were 2 years younger but otherwise had higher risk profiles including more female gender, risk factors, and prior coronary revascularization. *Tables 2* and *3* show the pattern of use of stress testing and type of stress test modalities in US vs. non-US patients, and in patients enrolled in Canada, Australia and New Zealand, and Europe. The proportion of patients who were managed with a non-invasive approach (either stress testing or just medical treatment without stress testing or angiography), the use of invasive procedures, type of stress test and form of provocation were similar among the non-US sites. Fewer US patients underwent stress testing (adjusted odds ratio in propensity analysis 0.67, 95% CI 0.58–0.77 vs. non-US patients) and more underwent cardiac catheterization compared with non-US patients. Additionally, fewer US patients underwent stress testing alone, whereas the proportion of patients who underwent both coronary angiography and stress testing was similar in both US and non-US patients, US patients were 80% more likely to undergo coronary angiography alone. Data on type of stress test were obtained in 1813 patients, and type of provocation used in 1851 patients (*Table 3*). In the US, fewer than 20% of patients underwent exercise ECG stress testing, compared with over 80% of non-US patients. US patients were nearly 3.5 times more likely to have pharmacological provocation during their stress test.

Procedure use and outcomes

Information on 6-month events was available in 7836 (98%) and 1 year vital status was available in 7300 (91%) patients. *Table 4* shows the use of invasive procedures and outcomes of patients who did and did not undergo stress testing. Fewer patients who underwent stress testing also underwent catheterization and revascularization (PCI or CABG), and they had lower rates of death and death or MI at 30 days than patients who did not undergo stress testing. The composite of death, MI or revascularization at 6 months was lower in the stress test vs. the no-stress test group [Kaplan–Meier probability of event 0.19 (95% CI 0.18–0.20) and 0.24 (95% CI 0.23–0.25), respectively; log-rank $P < 0.001$]. Similarly, 1-year mortality was also lower in the stress test group [Kaplan–Meier probability of death 0.03 (95% CI 0.02–0.04) vs. 0.11 (95% CI 0.11–0.13) for no-stress test group, $P < 0.001$] The lower use of invasive procedures and lower rates of most adverse events in the stress test group were seen irrespective of whether patients were enrolled in US or not (*Table 5*). *Table 6* shows procedural use and outcomes according to various strategies of patient management. The lowest event rates were in patients who underwent stress testing either alone or in combination with coronary angiography, and the highest event rates were in those who had neither diagnostic test.

Table 7 shows the procedural use and outcomes based on the results of stress testing in 1875 patients. Significantly more patients with positive stress tests had cardiac catheterization, PCI, and CABG than patients with negative or equivocal stress tests.

Table 4 Procedure use and outcomes based on stress test vs. no stress test

	Stress test	No stress test	*P*-value
n	1878	6127	
Cardiac catheterization	817 (44%)	3714 (61%)	<0.001
PCI (30 days)	274 (15%)	1401 (23%)	<0.001
CABG (30 days)	132 (7%)	1150 (19%)	<0.001
MI (30 days)	65 (3.5%)	415 (6.8%)	<0.001
Death (30 days)	11 (0.6%)	295 (4.8%)	<0.001
Death or MI (30 days)	73 (3.9%)	624 (10%)	<0.001
Death (6 months)	34 (1.8%)	493 (8.2%)	<0.001
Death or MI (6 months)	110 (6%)	878 (15%)	<0.001
Death, MI or revascularization (6 months)	359 (20%)	1453 (24%)	<0.001
Death (1 year)	55 (3.2%)	589 (11%)	<0.001

CABG, coronary artery bypass graft surgery, MI, myocardial infarction, PCI, percutaneous coronary interventions.

Table 5 Procedure use and outcomes based on stress test vs. no stress test stratified by region

	Stress test US	No stress test US	*P*-value	Stress test: non-US	No stress test: non-US	*P*-value
n	402	1848		1476	4279	
Cardiac Catheterization	230 (57%)	1536 (83%)	<0.001	587 (40%)	2178 (51%)	<0.001
PCI (30 days)	91 (23%)	614 (33%)	<0.001	183 (12%)	787 (18%)	<0.001
CABG (30 days)	39 (9.7%)	466 (25%)	<0.001	93 (6.3%)	684 (16%)	<0.001
MI (30 days)	17 (4.2%)	108 (5.8%)	0.200	48 (3.3%)	307 (7.2%)	<0.001
Death (30 days)	1 (0.2%)	77 (4.2%)	<0.001	10 (0.7%)	218 (5.1%)	<0.001
Death or MI (30 days)	17 (4.2%)	169 (9.1%)	0.001	56 (3.8%)	455 (11%)	<0.001
Death (6 months)	6 (1.5%)	135 (7.4%)	<0.001	28 (1.9%)	358 (8.5%)	<0.001
Death or MI (6 months)	28 (7.2%)	241 (13%)	<0.001	82 (5.7%)	637 (15%)	<0.001
Death, MI or revascularization (6 months)	87 (22%)	372 (21%)	0.441	272 (19%)	1081 (26%)	<0.001
Death (1 year)	10 (2.6%)	168 (9.5%)	<0.001	45 (3.4%)	421 (11%)	<0.001

CABG, coronary artery bypass graft surgery, MI, myocardial infarction, PCI, percutaneous coronary intervention, US, United States.

Table 6 Procedure use and outcomes among patients undergoing stress test alone, stress test after angiography, coronary angiography alone and no stress test

	Stress test only	Coronary angiography alone	Neither stress test nor angiography	Stress test before coronary angiography	Stress test after coronary angiography
n	1061	3714	2404	394	423
Cardiac catheterization-in hospital	0	3714 (100%)	0	394 (100%)	423 (100%)
PCI (30 days)	22 (2.1%)	1375 (37%)	26 (1.1%)	114 (29%)	138 (33%)
CABG (30 days)	27 (2.5%)	1012 (27%)	137 (5.7%)	73 (19%)	32 (7.6%)
MI (30 days)	19 (1.8%)	267 (7.2%)	147 (6.1%)	19 (4.8%)	27 (6.4%)
Death (30 days)	7 (0.7%)	98 (2.6%)	196 (8.2%)	2 (0.5%)	2 (0.5%)
Death or MI (30 days)	25 (2.4%)	342 (9.2%)	280 (11.6%)	20 (5.1%)	28 (6.6%)
Death (6 months)	21 (2.0%)	173 (4.7%)	318 (13.4%)	7 (1.8%)	6 (1.4%)
Death or MI (6 months)	45 (4.4%)	436 (12%)	439 (19%)	26 (6.7%)	39 (9.5%)
Death, MI or revascularization (6 months)	164 (16%)	804 (22%)	644 (27%)	91 (24%)	104 (25%)
Death (1 year)	36 (3.7%)	207 (6.1%)	380 (17.4)	10 (2.8%)	9 (2.4%)

CABG, coronary artery bypass graft surgery, MI, myocardial infarction, PCI, percutaneous coronary interventions.

There was trend for higher 30-day and 6-month events and 1-year death in patients with positive stress tests compared with those with negative or equivocal stress test.

Among patients with equivocal stress test results, more patients underwent cardiac catheterization compared with patients with negative stress tests. Fewer patients with equivocal test results underwent revascularization compared with those with negative tests. Although the rates of death and death or MI at 30-day were similar, the rates of these events at 6 months were higher in patients with equivocal test compared with negative test.

Finally, Cox proportional hazard modelling (including adjustment for propensity score) identified stress testing to be associated independently with the lower risk of 30-day death (HR 0.47, 95% CI 0.24–0.89, $P = 0.022$) and death or MI (HR 0.56, 95% CI 0.38–0.83, $P = 0.004$). Similarly, the stress test group showed a lower risk of 1 year (adjusted HR 0.58, 95% CI 0.42–0.81; $P = 0.001$) and 30-day to 1 year (adjusted HR 0.63, 95% CI 0.45–0.88; $P = 0.008$) mortality. This trend for the association of stress testing with better outcomes persisted even after exclusion of patients having cardiac catheterization, MI, recurrent ischaemia, congestive heart failure or death in the first 48 h [30-day death (HR 0.52, 95% CI 0.26–1.05, $P = 0.067$), 30-day death or MI (HR 0.61, 0.41–0.90, $P = 0.014$), 1-year death (HR 0.61, 95% CI 0.43–0.87, $P = 0.007$), and 30-day to 1 year death (HR 0.65, 95% CI 0.46–0.93; $P = 0.017$)]. The composite end-point of death, MI or revascularization at 6-month was similar in patients

Table 7 Outcomes based on result of stress test

	Positive	Negative	Equivocal	*P*-value
n	740	817	320	
Cardiac catheterization	438 (59%)	260 (32%)	117 (37%)	<0.001
PCI (30 days)	145 (20%)	93 (11%)	35 (11%)	<0.001
CABG (30 days)	101 (14%)	24 (2.9%)	7 (2.2%)	<0.001
MI (30 days)	33 (4.5%)	22 (2.7%)	9 (2.8%)	0.127
Death (30 days)	7 (0.9%)	3 (0.4%)	1 (0.3%)	0.256
Death or MI (30 days)	37 (5.0%)	25 (3.1%)	10 (3.1%)	0.105
Death (6 months)	19 (2.6%)	8 (1.0%)	7 (2.3%)	0.054
Death or MI (6 months)	54 (7.5%)	38 (4.8%)	17 (5.5%)	0.080
Death, MI or revascularization (6 months)	192 (27%)	111 (14%)	56 (18%)	<0.001
Death (1 year)	28 (4.1%)	16 (2.2%)	11 (3.9%)	0.088

CABG, coronary artery bypass graft surgery, MI, myocardial infarction, PCI, percutaneous coronary interventions.

who underwent stress test compared with those who did not (adjusted HR 0.99, 95% CI 0.86–1.14; $P = 0.851$). Additionally, the interaction term countries' (US vs. non-US) use of stress test was not significant for most events. Finally, sensitivity analysis to account for unmeasured confounders in propensity analysis demonstrated results consistent with above, i.e. stress testing was associated with better outcomes.

Discussion

Our study findings

Our data provide an important insight into the use of non-invasive stress testing in the management of patients with NSTE ACS in routine practice. This descriptive study from a large international trial indicates that substantial differences exist with regard to the use of non-invasive testing for these patients. In GUSTO-IIb, less than one quarter of patients underwent stress testing after NSTE ACS. Moreover, in almost half the patients who underwent both stress testing and cardiac catheterization, stress testing was performed only after cardiac catheterization. This is not surprising as a hierarchical approach to diagnosis and treatment where cardiac catheterization is performed only after ischaemia demonstrated on stress testing is reserved for patients with stable angina and most patients with non-STEMI ACS are managed with aggressive invasive approach.

These data indicate that the invasive strategy has been the preferred mode of patient management in NSTE ACS for over 10 years, as recently endorsed by ACC/AHA guidelines.[1] In contrast, stress testing was infrequently used and generally performed in a low-risk population. Additionally, stress test appeared to be as frequently used in patients with NSTE ACS to supplement information obtained on coronary angiography and/or determine the functional significance of coronary artery stenosis as to decide the need for an invasive procedure. Thus, it may not be surprising that the rates of coronary revascularization, non-fatal MI, death, and death or non-fatal MI were significantly lower among patients who underwent stress testing as opposed to those who did not.

Nonetheless, even among the low-risk group undergoing stress testing, the results were useful in distinguishing patient risk, at least at 6 months. Patients with a positive stress test were more likely to have revascularization, non-fatal MI, death and death or non-fatal MI than those without a positive stress test.

Important international differences in the use of stress testing were noted. Overall the non-US countries were similar in their use of stress testing, and type and modality of stress test. Fewer US patients underwent stress testing, and of those who did, pharmacological testing was employed more commonly with concurrent imaging modality in the majority. In contrast, not only was stress test performed more commonly in the non-US patients, but also the majority underwent just a regular exercise ECG stress test only. Perhaps the higher risk of US compared with non-US patient population enrolled in GUSTO IIB accounts for some of the differences in the use of type of stress test. Nonetheless, in US as well as outside US, physicians selected relatively low risk group for stress testing as reflected by the low outcome rates. Thus, even when patients were selected for stress test, US patients had greater likelihood of having a more expensive form of stress testing, i.e. that requiring additional imaging rather than just ECG stress test compared with non-US patients. The low-risk nature of patients undergoing stress testing in the US is highlighted by the finding that of 402 patients undergoing stress testing of any type, only one died by day 30. Patients who underwent neither stress test nor cardiac catheterization were the highest-risk cohort.

Comparison with other studies

The Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy (PURSUIT) trial examined variations in patients management and outcomes for ACS in Latin and North America. They found a non-significantly higher rate of stress testing in Latin American patients compared with North America (16% vs. 14%, $P = 0.2$). However, the proportion of patients with positive (44% vs. 43%), equivocal (16 vs. 13%) and negative (40% vs. 44%) stress results did not differ between these two geographical regions. Although patients randomized in Latin America had higher mortality after controlling for baseline risk,[9] the study did not directly examine the influence of a non-invasive risk stratification strategy on outcome.

A previous GUSTO IIB analysis found that Canadian patients were more likely to undergo stress testing than US patients.[10] Although there was no difference in 1-year mortality, significantly more Canadian patients had reinfarction and angina at 6 months. This study did not examine the relationship of stress testing with subsequent clinical outcome.

Similar to our results, the FRISC trial[11] categorized 766 stress tests as 'high,' 'intermediate,' or 'low' risk. The combination of stress testing and maximal troponin T level allowed better categorization into low, intermediate, and high-risk groups with death or MI rates of 1%, 7%, and 20%, respectively. Mortality was highest among patients unable to perform exercise stress testing. Thus, FRISC and our data suggest a unifying message, i.e. in contemporary management of NSTE ACS patients, low-risk patients undergo stress test and stress testing further defined risk even in this low-risk subgroup.[11]

Recent registry experience supports our findings. First, stress testing is utilized in between 20 and 25% of patients.[12–14] This has been a constant finding over time, since GUSTO IIb was completed over 10 years ago.[15] Secondly, the majority of stress testing continues to use only the ECG, without imaging, although the use of imaging has been steadily increasing.[12–14] Thirdly, recent data from the German Acute Coronary Syndrome registry also showed that high risk patients such as those with left ventricular ejection fraction $<40\%$, age >70 years and those with prior stroke were less likely to undergo stress testing.[16] All-cause 1 year mortality was 13.6% without stress testing vs. 5.1% with stress testing. Stress test allowed further separation into low- (negative study) vs. high- (positive study) risk with 1-year mortality rates of 4.4% vs. 6.5%. Fourth, the use of invasive procedure in itself did not preclude the use of stress testing with patients undergoing non-invasive evaluation before or even after coronary angiography.

The findings in our and other studies that results of non-invasive strategies correlates with outcomes in patients with unstable angina are consistent with that of other investigations published previously.[17,18] The Multicenter Myocardial Ischemia Research Group (MMIRG) studied 936 patients with stable CAD who underwent non-invasive testing within 6 months after a hospitalization for either MI or unstable angina. At 23 months of follow-up, ST depression on the resting ECG, and the combination of exercise ST depression and limited exercise duration were independent prognostic factors for the composite endpoint of death, non-fatal MI, or unstable angina.[17] Finally, the RISC study group reported that the extent of ischaemic ST depression and low maximal workload were independent predictors of 1-year infarct-free survival in 740 men hospitalized with unstable angina.[18]

Limitations of our study

Our study is retrospective and cannot be used to determine a causal relationship. Most importantly, our data should not be regarded as suggesting that a non-invasive strategy is associated with better outcomes than an invasive strategy or medical management without stress testing despite appropriate multivariable analysis. Randomized clinical trials have demonstrated that an early invasive approach in patients with NSTE ACS is generally associated with better outcomes.[19,20] We are unable to adjust for the influence of any unmeasured confounders (covariates), both during propensity analysis and during evaluation of adjusted outcomes. Our study is unable to determine whether the lower use of concurrent imaging outside the US is related to lack of widespread availability of the facility to perform such techniques, cost constraint, or more appropriate use of imaging in these patients compared with US patients.

Conclusions

Analysis of the GUSTO IIb trial reveals marked variation in the use of stress testing in patients with acute coronary syndromes, with US patients more likely to receive additional imaging testing. Overall, stress testing was done in very low risk NSTE ACS patients and appeared to provide modest additional prognostic information in these patients. Our data indicate equal likelihood of stress testing being done after (vs. before) diagnostic cardiac catheterization. Therefore, in the current practice environment where cardiac catheterization is often the first diagnostic modality used in patients with NSTE ACS, the role of non-invasive testing both before and after invasive procedure is in need of further study.

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