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Research Article

Adenosine vs Regadenoson Pharmacologic Stress Differs in Women with Suspected Coronary Microvascular Dysfunction: A Report from the Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction (WISE-CVD) Study

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ABSTRACT

Background: Stress cardiac magnetic resonance (CMR) imaging with myocardial perfusion reserve index (MPRI) measurement has emerged as a noninvasive method for assessing coronary microvascular dysfunction (CMD) in the absence of obstructive coronary artery disease (CAD). Pharmacologic stress with adenosine or regadenoson is typically used with comparable coronary vasodilation, but higher unadjusted MPRI has been reported with regadenoson in healthy men. This difference has not been assessed in symptomatic or healthy women.

Methods: In a prospective cohort study, 139 symptomatic women with suspected CMD and no obstructive CAD underwent stress CMR and invasive coronary flow reserve (CFR) testing. Adenosine was the default vasodilator (n=99), while regadenoson was used if history of asthma or prior adenosine intolerance (n=40). Stress CMR was also performed in 40 age-matched healthy controls using adenosine (n=20) and regadenoson (n=20). Unpaired t-tests and analysis of covariance were performed to compare MPRI with adenosine and regadenoson in the symptomatic women and healthy controls.

Results: Compared to regadenoson cases, adenosine cases had lower invasive CFR (2.64±0.62 vs 2.94±0.68, p=0.01) and pharmacologic heart rate change (28±16 vs 38±15 bpm, p=0.0008). Unadjusted MPRI was lower in the adenosine compared to regadenoson cases (1.73±0.38 vs 2.27±0.59, $p<0.0001$). When adjusted for heart rate, rate-pressure-product, and invasive CFR, MPRI remained lower in the adenosine cases ($p<0.0001$). Invasive CFR to adenosine correlated with adenosine MPRI (r 0.17, p=0.02) but not regadenoson MPRI (r -0.14, p=0.19). There was no significant difference in MPRI in the controls who received adenosine vs regadenoson (2.27±0.33 vs 2.38±0.44, p=0.36).

Conclusion: In women undergoing stress CMR for suspected CMD, those who received adenosine had lower MPRI than those who received regadenoson. However, there were no differences in MPRI in the healthy controls. These findings suggest there may be physiologic differences in adenosine and regadenoson response in the coronary microcirculation of symptomatic women.

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Introduction

Perfusion cardiac magnetic resonance (CMR) is a well-accepted modality for detecting ischemia in patients with suspected obstructive coronary artery disease (CAD). Semi-quantitative evaluation of CMR first-pass perfusion time-intensity curve upslopes can be used to calculate a myocardial perfusion reserve index (MPRI) in response to vasodilator stress [1]. MPRI has emerged as a promising noninvasive method of diagnosing coronary microvascular dysfunction (CMD) in the absence of obstructive CAD [2]. MPRI is reproducible and predicts prognosis in women with signs and symptoms of ischemia and no obstructive CAD [3, 4]. With respect to pharmacological stressor agents, both regadenoson and adenosine are FDA-approved vasodilators for myocardial perfusion imaging. SPECT perfusion studies have shown that regadenoson is not inferior to adenosine in the assessment of perfusion defects in patients with CAD, and regadenoson may be preferred over adenosine due to bolus injection and fewer side effects [5, 6].

However, regadenoson has previously been shown to produce a higher MPRI than adenosine in healthy male volunteers, although no differences were noted after adjusting for heart rate (HR) [7]. It is unknown whether regadenoson and adenosine produce similar MPRI in women with suspected CMD and no obstructive CAD. Given the potential utility for MPRI to allow comparison of the extent of ischemia in different patients with CMD, it is important to identify any possible differences in regadenoson and adenosine stress for semi-quantitative myocardial perfusion analysis. We evaluated MPRI in 139 symptomatic women and 40 asymptomatic healthy women undergoing stress CMR with adenosine or regadenoson.

Methods

This study was approved by the Cedars-Sinai Medical Center and University of Florida institutional review boards, and written informed consent was obtained for all participants. We identified 139 women from the in the National, Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation – Coronary Vascular Dysfunction (WISE-CVD) study who underwent both research CMR and clinically indicated invasive coronary reactivity testing at Cedars-Sinai Medical Center, Los Angeles, or at the University of Florida, Gainesville.

I Inclusion and Exclusion Criteria

WISE-CVD inclusion criteria included women with symptoms of chest pain or anginal equivalent and no obstructive CAD (< 50% luminal obstruction in one or more epicardial coronary arteries) by invasive coronary angiogram. Exclusion criteria included prior or planned percutaneous coronary intervention or coronary artery bypass grafting, acute myocardial infarction within 30 days, primary valvular heart disease, cardiogenic shock or intra-aortic balloon pump, inability to withdraw medications such as nitrates, calcium channel blockers, alpha-blockers, beta-blockers 24-48 hours prior to testing, New York Heart Association Class III or IV heart failure, ejection fraction <40%, hypertrophic obstructive cardiomyopathy or other preexisting cardiomyopathy, contraindications to CMR (including estimated glomerular filtration rate <45 ml/min), and contraindications to adenosine or regadenoson (including severe reactive airway disease, advanced heart block or sinus node dysfunction). Reference controls were 40 age-matched and hormone-status matched women without symptoms or cardiac risk factors who had a normal maximal Bruce-protocol exercise treadmill test.

II Coronary Reactivity Testing Protocol

All WISE-CVD participants underwent clinically indicated invasive coronary reactivity testing (CRT), which was performed per a standardized protocol(8) and within 30 days of the research CMR. Four CRT measures were assessed: 1) abnormal microvascular nonendothelial-dependent function, defined as CFR<2.5 in response to intracoronary adenosine, 2) abnormal microvascular endothelial function, defined as an increase in coronary blood flow (CBF)≤50% in response to acetylcholine (ΔCBF); 3) abnormal macrovascular endothelial function defined as a change in epicardial coronary artery diameter ≤ 0% in response to acetylcholine (ΔACH); 4) abnormal macrovascular non-endothelial function defined as a change in epicardial coronary artery diameter≤20% in response to nitroglycerin (ΔNTG). An abnormal CRT was defined as one or more abnormal measures. Reference controls did not undergo invasive testing.

III CMR Protocol

Both WISE-CVD participants and reference controls underwent standardized pharmacologic stress perfusion CMR with a 1.5T system (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany). First-pass perfusion imaging was performed using gadolinium contrast of 0.05 mM/kg (Gadodiamide, Omniscan, Amersham, Piscataway, NJ) infused at 4 ml/sec, followed by 20 ml saline at 4 ml/sec. Adenosine (140 mcg/kg/min) was infused for two minutes into the arm contralateral to the contrast injection prior to first-pass perfusion imaging and was continued until completion of the perfusion data acquisition. Resting perfusion imaging was performed 10 minutes later. Regadenoson was employed as the coronary vasodilator if patients had a history of mild-moderate asthma or had prior intolerance to adenosine. For the regadenoson protocol, resting perfusion imaging was performed first. Ten minutes after the resting scan, regadenoson (Lexiscan, Astellas Pharma) was administered as a 0.4mg/5 mL intravenous bolus, and perfusion images were acquired approximately 60 seconds after the administration of regadenoson.

Perfusion images were obtained in end-expiration in three left ventricular (LV) short-axis imaging slices (basal, mid and distal LV slice positions) with the following parameters: Gradient echo–EPI hybrid sequence, TR per slice: 148 ms, TE: 1.1 ms, BW: 1420 Hz/pixel, echo train length: 4, readout flip angle: 20°, slice thickness: 8 mm, image matrix: 160 x 70 pixels, in-plane resolution: 2.7 x 2.2 mm^2, parallel imaging (GRAPPA) factor: 2, imaging 3 slices every heartbeat. In the event of a peak stress heart rate of >120 bpm, two slices were obtained during stress first-pass imaging with exclusion of the distal LV slice position. For LV mass and function, resting breath-hold cine imaging using balanced-steady-state free precession was acquired covering the LV with a stack of 10 to 12 short-axis slices from base to apex, as well

as one 4-chamber long axis and one 2-chamber long axis image [field of view = 350 mm, temporal resolution = 44.4 ms, echo spacing = 3.2 ms, echo time = 1.3 ms, flip angle 80°, slice thickness 8.0 mm, 2 mm gap, 25 cardiac phases, parallel imaging (GRAPPA) factor: 2. HR and blood pressure were recorded at rest and peak stress. Rate-pressure product (RPP) was recorded as a product of HR and blood pressure at rest and at peak stress.

IV CMR Semi-Quantitative Perfusion Analysis

CMR images were analyzed by experienced readers who were blinded to clinical data using CAAS MRV 3.3 software (Pie Medical Imaging B.V., Netherlands); all analyses were over-read by the same experienced investigator (LT)(2). The endocardial and epicardial contours were manually defined and adjusted to sample data from LV myocardium. Blood pool activity and any linear dark rim artifact at the LV cavity/endocardial border were excluded from the myocardial sample. The LV cavity region of interest was manually adjusted to include the region of maximal signal intensity within the cavity and to exclude papillary muscle. Time-intensity first-pass perfusion curves at rest and stress were generated by the software. The relative upslope was defined as the ratio between the maximal upslope of the time-intensity first-pass myocardial perfusion curve and the maximum upslope of the time-intensity LV cavity first-pass curve. MPRI was assessed as the ratio of the relative upslope during stress to the RU at rest. The AHA 16-segment model was used (true apex was not imaged), and the mean MPRI was the average of 16 segments. If only two-slice images were acquired due to high stress HR, data were recorded for 12 segments, and mean MPRI was the average of 12 segments. MPRI was calculated in the global (transmural), midventricular (6 segments), and the subendocardial and subepicardial halves of the myocardium(4). The WISE-CVD investigators have previously demonstrated that lower adenosine stress MPRI is predictive of having one or more abnormal CRT measures(2).

Table 1: Baseline Characteristics by Agent Received of Symptomatic Women with no Obstructive CAD.

Characteristics	**Adenosine (n=99)**	**Regadenoson (n=40)**	**p-value**
Age	54 ± 11	53 ± 11	0.52
Body mass index	29 ± 8	32 ± 7	0.01
Weight (kg)	72 ± 16	81 ± 19	0.01
Ethnicity (% Caucasian)	78 (79%)	31 (78%)	1
Diabetes	8 (8%)	6 (15%)	0.23
Hypertension	37 (37%)	17 (43%)	0.57
Current/former smokers	43 (43%)	19 (49%)	0.70
Dyslipidemia	8 (8%)	6 (15%)	0.23
Menopausal	32 (32%)	11 (28%)	0.69
Hormone replacement therapy	41 (41%)	21 (53%)	0.26
Ace-Inhibitor	19 (20%)	4 (11%)	0.31
Angiotensin Receptor Blocker	6 (6%)	2 (5%)	1
Beta-blocker	24 (26%)	11 (28%)	0.83
Diuretic	16 (16%)	8 (21%)	0.62
Birth Control Pill	74 (76%)	31 (82%)	0.65

mean ± standard deviation, or n (%)

Table 2: Cardiac Magnetic Resonance Imaging and Invasive Coronary Reactivity Testing of Symptomatic Women with no Obstructive CAD.

Variables	**Adenosine (n=99)**	**Regadenoson (n=40)**	**p-value**
Cardiac Magnetic Resonance Imaging			
LV mass (g)	93 ± 18	98 ± 14	0.03
Late Gadolinium Enhancement	3 (3.09%)	1 (2.63%)	1
LV end-diastolic volume (mL)	124 ± 25	128 ± 25	0.35
Mass/volume ratio	0.77 ± 0.14	0.79 ± 0.19	0.56
Ejection fraction (%)	68 ± 7	68 ± 7	0.83
Invasive Coronary Reactivity Testing			
CFR	2.64 ± 0.62	2.94 ± 0.68	0.01
ΔCBF (%)	83 ± 102	67 ± 72	0.71
ΔACH (%)	2.2 ± 13	-0.83 ± 15	0.49
ΔNTG (%)	17 ± 13	14 ± 14	0.17

mean ± standard deviation, or n (%)

LV= left ventricular, CFR= coronary flow reserve to intracoronary adenosine, ΔCBF= change in coronary blood flow in response to acetylcholine, ΔACH= change in epicardial diameter in response to acetylcholine, ΔNTG= change in epicardial diameter in response to nitroglycerin.

Table 3: Hemodynamic Characteristics by Agent Received.

Characteristics	**Groups**	**Adenosine** (99 cases, 20 controls)	**Regadenoson** (40 cases, 20 controls)	**p-value**
Rest HR (bpm)	Cases	67 ± 10	69 ± 10	0.31
	Controls	63 ± 7	62 ± 11	0.84
Stress HR (bpm)	Cases	95 ± 18	107 ± 17	0.0002
	Controls	96 ± 13	108 ± 18	0.02
HR change from rest (bpm)	Cases	28 ± 16	38 ± 15	0.0008
	Controls	33 ± 12	46 ± 11	0.001
Rest SBP (mmHg)	Cases	129 ± 23	129 ± 16	0.98
	Controls	124 ± 22	125 ± 15	0.94
Stress SBP (mmHg)	Cases	134 ± 30	130 ± 18	0.28
	Controls	131 ± 18	124 ± 14	0.19
Rest RPP (bpm*mmHg)	Cases	8660 ± 1841	8970 ± 1862	0.37
	Controls	7782 ± 1681	7750 ± 1620	0.95
Stress RPP (bpm*mmHg)	Cases	12652 ± 3583	13892 ± 2801	0.0098
	Controls	12436 ±1734	13412 ± 2623	0.17

mean ± standard deviation

bpm= beats per minute, HR= heart rate, RPP= rate-pressure product, SBP= systolic blood pressure.

V Statistical Analysis

SAS version 9.3 software was used for statistical analysis. Unpaired t-tests were used to evaluate differences in adenosine and regadenoson scans, and analysis of covariance was performed to adjust the MPRI to RPP and CFR. The underlying assumptions of homoscedasticity and normality for the analysis of covariance were tested using the White test and Kolmogorov-Smirnov tests, respectively. Values were expressed as mean ± standard deviation or percentages as indicated. The critical significance level was set to 0.05.

Table 4: Myocardial Perfusion Reserve Index (MPRI) by Agent Received.

MPRI	**Groups**	**Adenosine (99 cases, 20 controls)**	**Regadenoson (40 cases, 20 controls)**	**p-value**
Unadjusted	Cases	1.73 ± 0.38	2.27 ± 0.59	<0.0001
	Controls	2.27 ± 0.33	2.38 ± 0.44	0.36
Adjusted for stress RPP*	Cases	1.73 ± 0.05	2.27 ± 0.07	<0.0001
Adjusted for invasive CFR*	Cases	1.74 ± 0.04	2.30 ± 0.07	<0.0001

*mean ± SE

CFR= coronary flow reserve to intracoronary adenosine, HR= heart rate, MPRI= myocardial perfusion reserve index, RPP= rate-pressure product.

Results

Of the symptomatic women, mean age was 54 ± 11 years with body mass index 30 ± 8, and there were significant differences in baseline demographics (Table 1). Baseline CMR characteristics were similar in the adenosine and regadenoson cases, except weight and left ventricular mass were lower in the adenosine cases (Table 2). The adenosine cases had lower invasive CFR to intracoronary adenosine compared to the regadenoson cases (2.64±0.62 vs 2.94±0.68, p=0.01). There were no statistically significant group differences in mean ΔCBF, ΔACH, or ΔNTG between the adenosine cases and the regadenoson cases, respectively (Table 2). There were significant differences in hemodynamic response after vasodilator infusion (Table 3). Peak HR was higher in the regadenoson group than the adenosine group. In addition, HR change from rest was greater in the regadenoson group than adenosine group, which translated to a higher stress RPP in the regadenoson group. There were no significant differences in rest HR, rest blood pressure, rest RPP, or peak blood pressure at stress. The regadenoson group had a significantly higher MPRI than the adenosine group (2.27 ± 0.59 vs 1.73 ± 0.38, p<0.0001) (Table 4). This difference persisted even after adjusting for stress RPP or invasive CFR.

Of the reference controls, mean age was 53 ± 10 years with body mass index 26 ± 4, with no significant differences between those who received adenosine vs regadenoson. Despite a higher stress HR response in the regadenoson group, stress RPP was not different between groups (Table 3). MPRI was not significantly different between the two groups (adenosine 2.27 ± 0.33 vs regadenoson 2.38 ± 0.44, p=0.36). Since invasive CFR was not performed and stress RPP was not different in controls, further adjustment was not needed.

Discussion

We have identified a potential difference between adenosine and regadenoson in the semi-quantitative assessment of myocardial perfusion in women with angina and no obstructive CAD. MPRIs were unexpectedly higher in the cases who received regadenoson compared to adenosine even when adjusted for baseline invasive CFR to intracoronary adenosine, but not different in controls who received adenosine vs regadenoson. These differences are pertinent for the use of MPRI as a diagnostic tool for CMD in individual patients, as the

thresholds for abnormality are likely to be different for these two stress agents. These differences are also relevant to use of MPRI in the management of CMD, in which MPRI may be used as a prognostication tool in those with suspected myocardial ischemia but with non-obstructive coronary artery disease. In this setting, the degree to which the MPRI is abnormal may guide the use of aggressive treatment of patients at higher risk for cardiovascular events [3].

Adenosine and regadenoson differ in their mechanisms for causing coronary and systemic vasodilation. While adenosine is a nonselective adenosine A_2 receptor agonist, regadenoson is a selective adenosine A_{2A} receptor agonist. Regadenoson has a less severe side-effect profile [9]. Regadenoson also has the advantage of convenient administration as a single-dose intravenous bolus, compared to adenosine which requires weight-adjusted dosing and intravenous infusion, which is a technical hindrance when infusing remotely through tubing during imaging. Regadenoson is known to produce a higher HR than adenosine, primarily caused by sympathetic excitation [9, 10]. It has been reported in animal studies that regadenoson is a more potent vasodilator than adenosine with coronary circulatory predilection and produces a higher effective dose compared to adenosine, while having similar maximal increase in coronary blood flow, hemodynamic changes and radiotracer biodistribution [9, 11, 12].

Vasu et al. investigated differences in vasodilator efficacy using quantitative perfusion CMR and found that regadenoson and adenosine had similar vasodilator efficacy in healthy men [7]. In this study, 15 healthy normal volunteers (94% male, mean age 21 years) underwent rest-stress CMR with regadenoson and adenosine on different days. Similar to our study, regadenoson produced a higher HR response than adenosine (95 ± 11 vs 76 ± 13 bpm) and a higher MPRI (3.11 ± 0.63 vs 2.7 ± 0.61, p=0.02). However, when adjusted for HR, the MPRI were no longer significantly different between regadenoson and adenosine (2.04 ± 0.34 vs 2.12 ± 0.27, p= NS). However, the adenosine and regadenoson HR responses in our study were higher than the responses obtained in Vasu et al's study, and our HR and BP responses were similar to a previously published study of adenosine CMR that included women with chest pain and no obstructive CAD [13]. Thus, a sex-specific HR response to vasodilator stress may play a role the disparity in regadenoson and adenosine MPRI differences in our study that remained even after HR adjustment. In particular for women with ischemia and no obstructive CAD, there may be secondary factors that influence the hemodynamic response of adenosine and regadenoson, including heightened cardiac nociception and the cardiac autonomic dysfunction [14].

The ADVANCE-MPI trial also suggested some sex differences in adenosine vs regadenoson response. The investigators demonstrated that regadenoson was noninferior to adenosine for the detection of ischemia using SPECT, with better tolerance in both women and men [15]. However, during visual analysis of perfusion defects, the agreement rate between adenosine and regadenoson was lower in women versus men with moderate and large areas of ischemia. In addition, women are more likely to experience symptoms after receiving adenosine or regadenoson than men [15-17]. This supports the hypothesis that there may be some sex-specific differences in vasodilator stress response.

Prior invasive studies in predominantly male patients with intermediate coronary stenoses have compared intravenous adenosine and regadenoson and found no significant difference in fractional flow reserve [18-20]. Although semi-quantitative MPRI predicts presence of underlying CMD by invasive CRT measures, we found that invasively determined CFR to intracoronary adenosine only mildly correlated with adenosine MPRI and did not correlate with regadenoson MPRI in symptomatic women with no obstructive CAD (Figure) [2]. We recently demonstrated that lower CFR values are observed with intravenous adenosine compared to intracoronary adenosine, partially modulated by the systemic effect of adenosine given by the intravenous route, and we suspect this may also be true with intravenous regadenoson although no studies have evaluated regadenoson during invasive CFR [21]. In our current study, both adenosine and regadenoson MPRI values were lower than the invasively determined adenosine CFR values for the cases.

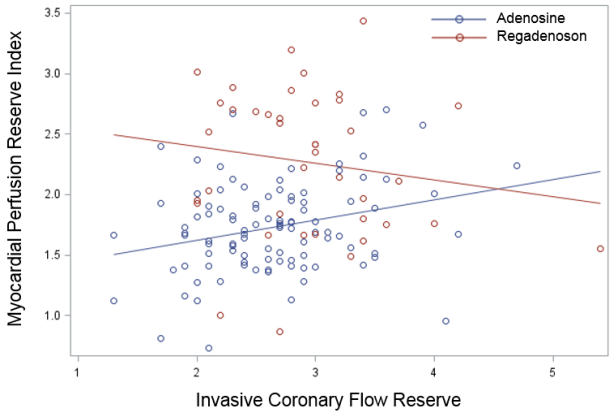

Figure 1: Relationship between MPRI (stratified by adenosine or regadenoson stress) and invasive CFR to intracoronary adenosine. MPRI with adenosine mildly correlated with invasive coronary flow reserve to intracoronary adenosine (r 0.17, p=0.02), but MPRI with regadenoson did not correlate with invasive CFR to intracoronary adenosine (r -0.14, p=0.19).

Additional limitations and possible explanations for perfusion differences in the regadenoson and adenosine groups are related to the protocol. First, the women in the adenosine group weighed less than the regadenoson group. Since regadenoson is administered as a bolus without consideration of the patient's weight while adenosine dosing is weight-based, lower-weight women receiving regadenoson may have higher effective hyperemia than they would have with adenosine, leading to higher MPRI. This is consistent with a prior study showing higher regadenoson MPRI than adenosine MPRI achieved in nonobese patients but no significant difference in obese patients [22]. Second, the order of stress perfusion in the two protocols was different between the two protocols: adenosine-rest vs rest-regadenoson. Stress-rest was the protocol used for adenosine, while rest-stress was selected for regadenoson, due to persistent heart rate elevation secondary to the longer half-life of regadenoson. Third, additional myocardial perfusion measurements such as myocardial peak signal intensity and time to max were not recorded, and full quantitative perfusion analysis was not available for these cohorts, thus limiting comprehensive understanding of potential group differences. Fourth, since there were women in the regadenoson group who were not given adenosine due to history of asthma or reactive airway disease, there may be differences in coronary

vasodilator response related to a subject's history of asthma or reactive airway disease.

Bronchial adenosine receptors are upregulated in asthmatics, and it is unknown whether adenosine receptors may be upregulated in the coronary vasculature in this population, thus potentially affecting response to vasodilator stress [23]. We hypothesize that women with asthma may have a stronger coronary vasodilator response to selective adenosine A2 receptor agonists, leading to higher MPRI in the regadenoson group. Finally, and most importantly, since we did not perform both adenosine and regadenoson stress in the same women, the presence and severity of CMD may be a confounder despite the adjustment for baseline CFR. The reference controls did not demonstrate a significant difference in MPRI by stress agent, which may indicate that underlying abnormalities in coronary vascular reactivity may play a role.

Conclusion

In women undergoing stress CMR for evaluation of persistent chest pain and no obstructive CAD, adjusted and unadjusted MPRIs were unexpectedly higher in the group who received regadenoson compared to adenosine, but not in healthy reference controls. These findings suggest there may be physiologic differences in adenosine and regadenoson response in the coronary microcirculation of symptomatic women.

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Competing Interests

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Data Analysis and Interpretation: JW, SJ, GCW, MM, XZ, JWP, BS, AR, CJP, DSB, LEJT, CNBM
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