



Original Research

Progression of coronary atherosclerosis in patients without standard modifiable risk factors

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ABSTRACT

Background and aims: The outcome of patients with clinical coronary artery disease despite traditional risk factors is poorly understood.**Methods:** Clinical characteristics and plaque burden on serial intravascular ultrasonography were compared in patients without ($n = 165$) and with ($n = 492$) standard modifiable risk factors after matching on age, sex and use of statins from a database of 5823 patients participating in clinical trials of anti-atherosclerotic therapies.**Results:** Patients without standard modifiable risk factors had lower baseline systolic blood pressure (118 ± 12 vs. 129 ± 17 mmHg, $p < 0.001$), low-density lipoprotein cholesterol (87 ± 21 vs. 104 ± 34 mg/dl, $p < 0.001$), triglycerides [106 vs. 136 mg/dl, $p < 0.001$] and C-reactive protein [1.5 vs. 2.1 mg/l, $p = 0.001$]. At baseline, patients without modifiable risk factors had a lower percent atheroma volume (35.7 ± 8.6 vs. $38 \pm 8.8\%$, $p = 0.004$) and total atheroma volume (174.7 ± 80 vs. 190.9 ± 84 mm³, $p = 0.03$) and less images with calcification (22.2 vs. 26.5% , $p = 0.025$). The use of aspirin and statin prior to and during the trials was similar. The use of ACE inhibitors and beta blockers was lower in the no risk factor group prior to and during the trials. The change in percent atheroma volume (-0.2 ± 2.8 vs. $-0.1 \pm 3.6\%$, $p = 0.71$), total atheroma volume (-5.5 ± 23.4 vs. -3.8 ± 22.7 mm³, $p = 0.42$), and the percentage of patients demonstrating any degree of progression (50.9% vs. 45.1% , $p = 0.20$) were similar in those without and with standard modifiable risk factors, respectively.**Conclusion:** Patients who develop clinical coronary atherosclerosis without standard modifiable risk factors have similar rates of plaque progression to those with traditional risk factors.

1. Introduction

Despite the common perception that coronary artery disease (CAD) is well understood and managed, it remains the leading cause of mortality in adults worldwide [1]. Major advances have been made in the identification and treatment of standard modifiable risk factors for CAD - particularly hypercholesterolemia, hypertension, diabetes mellitus and smoking [2,3]. However, at an individual level, it is not uncommon for a patient to present with extensive atherosclerosis and acute coronary syndrome that is not clearly explained by such risk factors. We have previously reported an increase in prevalence of myocardial infarction patients presenting with no standard modifiable cardiovascular risk factors from 13% to 27% over a 10 year period [4], confirmed by findings

of a large, nation-wide cohort [5].

Despite the perceived low risk of CAD in patients with no standard modifiable risk factors, large observational studies have shown that these patients have higher in-hospital and 30 day mortality rates after myocardial infarction compared to patients with at least one of the major 4 modifiable risk factors [5–8]. Data from the National Registry of Myocardial infarction demonstrated this relationship, even after adjusting for age and other clinical factors, and identified an inverse association between the number of standard modifiable risk factors and the risk for in-hospital mortality [7]. The reasons for these apparently paradoxical differences in the mortality rates following myocardial infarction are not well understood.

Intravascular ultrasound (IVUS) permits quantitation of coronary

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atheroma burden and on serial imaging has been employed to evaluate the impact of medical therapies on disease progression [9–16]. We utilised serial IVUS data from a pooled cohort of 5823 patients enrolled in ten clinical trials [10–19] to examine rates of plaque progression in patients who had no standard modifiable risk factors versus individuals with risk factors who were matched on age, sex and use of statins.

2. Materials & methods

The current analysis investigated a pooled cohort of 5823 patients with angiographic CAD who underwent serial IVUS imaging in ten clinical trials evaluating the impact of medical therapies on plaque progression, the details of which have been discussed previously [10–16]. Of the 5823 patients, we identified 214 to have no standard modifiable risk factors (3.7%), including smoking, hypertension, diabetes and hypercholesterolemia, recorded on the basis of self-reporting. On review of the baseline systolic blood pressure and lipids of the patients in the no risk factor group, it was noted that these were elevated in some patients. Out of the 214 patients, 49 were noted to have either systolic blood pressure of >140 mmHg or total cholesterol >213 mg/dl or LDL >135 mg/dl at baseline. These patients were excluded. For the purpose of this analysis, patients with no standard modifiable risk factors ($n = 165$) were compared with patients with at least one such risk factor after matching (3:1) on age, sex and use of statins during the trials ($n = 492$).

3. Acquisition of IVUS images

Patients were imaged with either a 40 MHz Atlantis SR Pro (Boston Scientific Scimed, Inc., Maple Grove, MN, USA) or a 45 MHz Revolution (Volcano Corporation, San Diego, CA, USA) catheter. The target vessel for imaging was required to have at least 20% but not more than 50% stenosis on the coronary angiogram, at least 30 mm in length, with no prior revascularization and not planned for revascularization. After appropriate anticoagulation and intra-coronary nitrate, the IVUS imaging catheter was advanced beyond the lesion into the distal segment of the coronary artery. A pullback was performed at a constant speed of 0.5 mm/s and a continuous image of the coronary artery was acquired at 30 frames per second. IVUS images were matched with the coronary angiogram by identifying the proximal and distal side branches. Follow up IVUS imaging, after 18–24 months, was performed in the same coronary segment by using these side branches as landmarks. Images were stored and sent to a core lab for analysis.

4. Analysis of IVUS images

For each pull back, cross sectional images spaced 1 mm apart were selected for measurement. For each selected cross-sectional image, the leading edge of the lumen and the external elastic membrane (EEM) were manually traced to measure the lumen area and EEM area. IVUS images were analysed in a core laboratory by personnel blinded to all patient characteristics and treatment status. A number of plaque measures were derived from this analysis.

Percent atheroma volume (PAV) was determined as the proportion of the whole vessel wall occupied by plaque throughout the entire length of artery studied [11].

$$PAV = \frac{\sum(EEM \text{ area} - \text{lumen area})}{\sum(EEM \text{ area})} \times 100$$

Total atheroma volume (TAV) was determined by summation of atheroma area in all evaluable cross-sectional images [11].

$$TAV = \sum(EEM \text{ area} - \text{lumen area})$$

To account for potential differences in segment length between patients, TAV was subsequently normalized, by multiplying the average plaque area in a segment by the median number of evaluable images for

all patients in the study.

$$\text{Normalised TAV} = \frac{\sum(EEM \text{ area} - \text{lumen area})}{n} \times \text{Median number of images in cohort}$$

The quantitation of plaque calcium has been described previously [20]. The presence of calcium in each measured image was assigned a grade from 0 to 2. Grade 0 representing no calcium, grade 1 representing calcium with acoustic shadowing <90°, grade 2 representing calcium with shadowing >90°. In images that contained multiple calcium deposits, the grade represented the summation of all angles of acoustic shadows present. The degree of calcification is expressed as the percentage of images containing ≥ 1 grade of calcium. From serial imaging, changes in PAV and TAV were calculated as the difference from baseline to follow up and the percentage of images containing ≥ 1 grade of calcium at each time point were directly compared. The percentage of patients demonstrating any degree of progression or regression of either PAV or TAV were also determined.

5. Statistical analysis

Patients were identified with no standard modifiable risk factors ($n = 165$) and then those with at least one such risk factor were matched in a 3:1 fashion based on age, sex and use of statins during the trials ($n = 492$). These two groups were then compared on baseline clinical characteristics, use of secondary prevention medications, blood pressure, serum lipids, CRP, IVUS measurements, proportion of patients with >1 grade of calcium, and proportion of patients showing progression or regression. Continuous variables were compared between groups using Student's *t*-test or Wilcoxon rank-sum test, depending on if normally or non-normally distributed, respectively. Mean \pm standard deviation or median (interquartile range) are reported. Changes from baseline were assessed to see if significantly different than zero using the paired *t*-test or Wilcoxon signed-rank test, as appropriate. Categorical variables were compared between the two risk factor groups using Pearson's chi-squared or Fisher's exact test. Percentages are reported. Annualized changes in IVUS measurements were compared between the two groups using mixed models adjusting for baseline counterparts and with trial set as a random factor to control for heterogeneity across the ten studies. Least-squares means \pm standard error are reported. Given that each trial's duration varied from 18 to 24 months, annualized change in PAV is the interpolated value of change in PAV at 1 year. All tests were two-tailed with a significance level of 0.05. Analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

6. Results

6.1. Clinical characteristics

Baseline demographics and medications are shown in Table 1 for patients with no risk factors matched on age (mean 55.7 ± 9.4 years), sex (17% females) and use of statins during the trials (93.9 vs. 94.1%, $p = 0.78$). Patients with at least one standard modifiable risk factor were more likely to have a history of congestive heart failure (3.9 vs. 0.6%, $p = 0.035$) or to have undergone prior percutaneous coronary intervention (36 vs 22%, $p = 0.001$) compared to those with no identifiable risk factors. Baseline use of aspirin (94.5 vs 91.7%, $p = 0.23$) and statins (74.5 vs. 77.4%, $p = 0.45$) was similar between the two groups but use of baseline beta blockers (61.8 vs. 74.6%, $p = 0.002$) and ACE inhibitors (29.7% vs. 51.8%, $p < 0.001$) was lower in patients without standard modifiable risk factors. The use of aspirin (96.4 vs. 92.1%, $p = 0.06$) and statins (93.9 vs. 94.5%, $p = 0.78$) during the trials was similar in both groups. The use of beta blockers (57.6 vs. 76.6%, $p < 0.001$) and ACE inhibitors (34.5 vs. 55.7%, $p < 0.001$) was lower in patients without standard modifiable risk factors during the trials.

Table 1

Demographics and medications at baseline. Results expressed as mean \pm SD or percentage.

Parameter	No Risk Factors n = 165	Risk Factors n = 492	p-value
Age, years	55.7 \pm 9.4	55.7 \pm 9.4	0.99
Female, %	17.0	16.5	0.88
Caucasian, %	96.4	93.3	0.15
Current Smoker	0	31.0	<0.001
BMI, kg/m ²	28.6 \pm 4.7	30.6 \pm 5.7	<0.001
Hypertension, %	0	81.7	<0.001
Diabetes, %	0	28.5	<0.001
Hyperlipidemia, %	0	77.8	<0.001
Angina, %	31.5	45.7	0.002
History of CHF, %	0.6	3.9	0.035
History of MI, %	34.5	30.9	0.38
History of stroke, %	0	2.2	0.07
History of PCI, %	21.8	36.4	0.001
History of CABG, %	1.8	1.9	1.0
Medication use prior to study entry			
Aspirin, %	94.5	91.7	0.23
Statins, %	74.5	77.4	0.45
Beta Blockers, %	61.8	74.6	0.002
ACE Inhibitors, %	29.7	51.8	<0.001
Medication use during studies			
Aspirin, %	96.4	92.1	0.06
Statins, %	93.9	94.5	0.78
Beta Blockers, %	57.6	76.6	<0.001
ACE Inhibitors, %	34.5	55.7	<0.001

ACE inhibitors = Angiotensin converting enzyme inhibitors, CHF = Congestive heart failure, CABG = Coronary artery bypass graft, MI = Myocardial infarction, PCI = percutaneous coronary intervention, SD = standard deviation.

6.2. Metabolic and BP parameters

Risk factor control is summarized in Table 2. Patients without standard modifiable risk factors had lower baseline levels of LDL cholesterol (87.4 \pm 20.5 vs. 103.6 \pm 34.3 mg/dL, p < 0.001), triglycerides [106.2 (75.6, 150.5) vs. 136 (101, 197) mg/dL, (p < 0.001)], systolic (118 \pm 12 vs. 129 \pm 17 mmHg, p < 0.001) and diastolic (73.7 \pm 8.2 vs. 77.3 \pm 9.8 mmHg, p < 0.001) blood pressure, and a higher HDL cholesterol (44.9 \pm 11.9 vs. 42.8 \pm 11.6 mg/dL, p = 0.05). During the course of the studies, patients without risk factors had a greater increase in systolic blood pressure (2.9 \pm 12 vs. 0.3 \pm 15, p = 0.04) and HDL cholesterol (9.5 \pm 13.7 vs. 4.4 \pm 9.8 mg/dL, p < 0.001) and a lesser reduction in LDL cholesterol (−11.0 \pm 26.8 vs. −23.9 \pm 38.3 mg/dL, p < 0.001) compared to patients with risk factors. Patients with standard modifiable risk factors had higher hsCRP levels at baseline [2.1 (1.0, 4.8) vs. 1.5 (0.8, 3.2) mg/L, p = 0.001] however the change in hsCRP was similar in both groups during the studies [−0.2 (−1.4, 0.5) vs. −0.1 (−0.9, 0.4) mg/L, p = 0.38].

6.3. Plaque burden and progression

Measures of plaque burden and calcification at baseline and serial changes are summarized in Table 3. At baseline, patients without standard modifiable risk factors demonstrated a lower PAV (35.7 \pm 8.6 vs. 38.0 \pm 8.8%, p = 0.004) and TAV (174.7 \pm 80.2 vs. 190.9 \pm 84.2 mm³, p = 0.03) compared with those with at least one risk factor. Similar reductions in PAV (−0.2 \pm 2.8 vs. −0.1 \pm 3.6%, p = 0.71) and TAV (−5.5 \pm 23.4 vs. −3.8 \pm 22.7 mm³, p = 0.42), as well as the percentage of patients demonstrating any degree of regression of plaque (49.1 vs. 54.9%, p = 0.20) with study treatment were observed in patients without and with modifiable risk factors. Patients without standard modifiable risk factors had less plaque calcification [22.2 (5.1, 38.5) vs. 26.5 (10.9, 45.8) %, p = 0.025], however a similar change in plaque calcification [1.4 (0.0, 6.9) vs. 2.5 (0, 8.1)%, p = 0.51] was observed compared to patients with risk factors, respectively. Results were similarly non-significant in comparing the adjusted annualized changes between groups.

Table 2

Blood pressure, Lipids and CRP at baseline and follow up. Results expressed as mean \pm SD or median (interquartile range).

Parameter	No Risk Factors n = 165	Risk Factors n = 492	p-value
Systolic blood pressure (mmHg)			
Baseline	118 \pm 12	129 \pm 17	<0.001
Follow-up	121 \pm 11	129 \pm 13	<0.001
Absolute change	2.9 \pm 12	0.3 \pm 15	0.04
P value for change within group	0.003	0.69	
Diastolic blood pressure (mmHg)			
Baseline	73.7 \pm 8.2	77.3 \pm 9.8	<0.001
Follow-up	74.8 \pm 7.4	77.3 \pm 7.8	<0.001
Absolute change	1.2 \pm 8.1	0 \pm 9.4	0.15
P value for change within group	0.065	0.99	
LDL cholesterol (mg/dL)			
Baseline	87.4 \pm 20.5	103.6 \pm 34.3	<0.001
Follow-up	76.4 \pm 22.2	79.9 \pm 29.7	0.17
Absolute change	−11.0 \pm 26.8	−23.9 \pm 38.3	<0.001
P value for change within group	<0.001	<0.001	
HDL cholesterol (mg/dL)			
Baseline	44.9 \pm 11.9	42.8 \pm 11.6	0.052
Follow-up	54.3 \pm 19.0	47.3 \pm 14.3	<0.001
Absolute change	9.5 \pm 13.7	4.4 \pm 9.8	<0.001
P value for change within group	<0.001	<0.001	
Triglycerides (mg/dL)			
Baseline	106.2 (75.6, 150.5)	136 (101, 197)	<0.001
Follow-up	99.9 (73.7, 135.8)	131 (95.6, 175.7)	<0.001
Absolute change	−2.5 (−27.6, 13.0)	−6 (−37.2, 22.0)	0.42
P value for change within group	0.14	<0.001	
CRP (mg/L)			
Baseline	1.5 (0.8, 3.2)	2.1 (1.0, 4.8)	0.001
Follow-up	1.2 (0.6, 2.9)	1.7 (0.9, 3.7)	0.005
Absolute change	−0.1 (−0.9, 0.4)	−0.2 (−1.4, 0.5)	0.38
P value for change within group	0.10	<0.001	

BP = blood pressure, CRP = C-reactive protein, HDL = high density lipoprotein, LDL = low density lipoprotein, TG = Triglycerides.

7. Discussion

The underlying pathology and clinical progression of coronary atherosclerosis in patients whose disease cannot be attributed to the presence of traditional risk factors has not been well studied. This study compared coronary plaque burden and longitudinal changes, as assessed by serial IVUS, in patients presenting with angiographic coronary disease in the presence and absence of established risk factors. We observed that while patients without traditional risk factors demonstrated a lower degree of both plaque burden and calcification, they demonstrated a similar response to patients with such risk factors, in terms of plaque progression with medical therapy. This suggests the absence of traditional risk factors does not impact the potential modifiability of atherosclerotic plaque in these patients.

Patients without traditional risk factors have been reported to account for 10–30% of patients in large observational studies of acute coronary syndromes [4–8]. A study of 542,008 patients presenting with their first myocardial infarction reported that in-hospital mortality inversely associated with the number of risk factors, a finding which persisted after adjusting for clinical variables, including age and sex [7]. The presence of traditional risk factors may also potentially influence the clinical presentation of acute coronary syndromes, with reports that patients with fewer risk factors are more likely to present with STEMI and cardiac arrest [21]. While the mechanisms underlying these worse outcomes in the acute setting remain to be understood, the current analysis permitted examination of plaque progression.

The ability to image atherosclerotic plaque in a serial fashion has permitted the opportunity to study the potential impact of both risk

Table 3

IVUS parameters: plaque burden, vessel wall dimension, calcification and progression. Results expressed as mean \pm SD or median (interquartile range).

Parameter	No Risk Factors n = 165	Risk Factors n = 492	p-value
Percent atheroma volume (%)			
Baseline	35.7 \pm 8.6	38.0 \pm 8.8	0.004
Follow up	35.5 \pm 8.8	37.9 \pm 9.0	0.003
Absolute change	-0.2 \pm 2.8	-0.1 \pm 3.6	0.71
P value for change within groups	0.43	0.73	
Adjusted annualized change ^a	-0.08 \pm 0.17	-0.02 \pm 0.13	0.64
Total atheroma volume (mm ³)			
Baseline	174.7 \pm 80.2	190.9 \pm 84.2	0.03
Follow up	169.2 \pm 82.5	187.1 \pm 84.0	0.02
Absolute change	-5.5 \pm 23.4	-3.8 \pm 22.7	0.42
P value for change within groups	0.003	<0.001	
Adjusted annualized change ^a	-2.1 \pm 1.1	-2.0 \pm 0.8	0.90
EEM volume (mm ³)			
Baseline	483.2 \pm 169.6	500.1 \pm 181.7	0.30
Follow up	470.4 \pm 174.2	490.5 \pm 178.9	0.21
Absolute change	-12.8 \pm 49.9	-9.6 \pm 39.7	0.41
P value for change within groups	0.001	<0.001	
Adjusted annualized change ^a	-3.9 \pm 2.2	-5.0 \pm 1.5	0.63
Lumen volume (mm ³)			
Baseline	308.5 \pm 109.1	309.2 \pm 118.2	0.95
Follow up	301.2 \pm 111.1	303.4 \pm 116.5	0.83
Absolute change	-7.3 \pm 36.3	-5.8 \pm 33.2	0.63
P value for change within groups	0.01	<0.001	
Adjusted annualized change ^a	-2.1 \pm 1.8	-3.4 \pm 1.2	0.40
Percent of images with calcium ≥ 1			
Baseline	22.2 (5.1, 38.5)	26.5 (10.9, 45.8)	0.025
Follow up	26.4 (4.5, 44.4)	31.3 (13.4, 50.5)	0.03
Absolute change	1.4 (0.0, 6.9)	2.5 (0, 8.1)	0.51
P value for change within groups	<0.001	<0.001	
PAV			
Progressors (%)	50.9	45.1	0.20
Regressors (%)	49.1	54.9	

EEM = external elastic membrane, PAV = percent atheroma volume.

^a Adjusting for trial and respective baseline measures. Least-squares means \pm standard error reported.

factors and medical therapies on disease progression [9]. These studies have largely confirmed the importance of traditional risk factors associating with both disease burden and progression over time. For example, multiple studies have demonstrated the beneficial effects of lowering LDL cholesterol, while trials have reported variable effects of infusing HDL and that modest increases in HDL cholesterol levels associate with the beneficial effects of statins [9]. Increasing levels of blood pressure, including those within the prehypertensive range, associate with greater disease progression [22]. Diabetes is associated with more diffuse and extensive atherosclerotic plaque, with evidence of less regression in response to use of lipid lowering therapy [23]. Atherogenic dyslipidemia, as evidenced by the triglyceride/HDL cholesterol ratio, closely associates with disease progression in patients with diabetes [24]. The contribution of multiple metabolic risk factors to cardiovascular risk in diabetes is further supported by evidence that more intensive targeting of these parameters results in an incremental benefit on coronary atherosclerosis [9,25]. These studies reinforce the importance of traditional risk factors underlying atherosclerotic disease in many patients.

However, the absence of these risk factors in some patients presenting with myocardial infarction has stimulated the search to identify additional factors that may potentially influence the underlying disease within the artery wall. While increasing attention has highlighted the

importance of inflammation in atherosclerosis, even in the absence of traditional risk factors [26], this was not an explanation for disease in those without risk factors, with lower levels of hsCRP in this group compared to patients with risk factors. Given that all patients in these studies had presented for a clinically indicated coronary angiogram, both the absence of traditional risk factors or the presence of less atherosclerotic plaque in this group did not prevent their clinical presentation. Further work will be required to determine what other factors may have driven the heightened susceptibility to atherosclerosis and clinical presentation in these individuals. For example, repetitive long term exposure to air pollution promotes atherosclerosis and increases the risk of myocardial infarction [27]. Genome wide association studies have identified more than 50 loci associated with risk of coronary artery disease and genetic risk score based on these alleles can identify individuals at high risk of coronary artery disease [28]. Interestingly, in subjects with high genetic risk, a favorable lifestyle can reduce the relative risk of coronary artery disease by 50% when compared with unfavorable lifestyle [28].

A number of caveats should be noted with regard to this analysis. Patients were selected from trials using different pharmacologic interventions which may have influenced the results, however, patients were taken from all 10 trials and this prevented any one therapy from predominating in the whole cohort. As the role of statins in lowering plaque progression is well established, therefore, both groups were matched for use of statins. Any further selection based on therapies was not possible as this would have significantly reduced the number of patients with no risk factors. All patients had undergone coronary angiography on the basis of a symptomatic presentation. It is uncertain whether the findings translate to the asymptomatic population. The studies employed IVUS imaging with measurements of plaque burden, the implications for measures of plaque composition are unknown. While several reports have demonstrated the association between disease burden and progression with cardiovascular events [29], the current analysis lacked power to directly compare clinical outcomes in the two groups. Differences in medication use were observed between the groups, which may reflect a potential clinical bias to undertreat patients without risk factors, despite the presence of clinically manifest coronary atherosclerosis. Importantly, these findings do suggest a similar degree of modifiability of disease when intensive risk factor targeted therapies are used. The distinction between patients with and without risk factors may not be binary but rather a graded continuous relationship. Sipahi et al. have demonstrated progression of coronary artery disease over a wide blood pressure range from 100 mmHg into the hypertensive range [22]. There may also be a variation in the degree of control of risk factors. Atheroma progression has been observed in patients with early diabetes even after achieving optimal glycemic control due to residual risk factors which emphasizes the need to control all risk factors [30]. Furthermore, studies with more intensive treatment of risk factors have demonstrated less progression of plaque and even regression [15,22].

In summary, the absence of traditional risk factors associates with less extensive atherosclerotic plaque in a cohort recruited with known clinically significant coronary disease. Whilst these patients were less likely to receive evidence-based therapies, the progression of their disease in serial IVUS evaluation appeared similar to the patients with risk factors. Increased use of evidence-based agents in these "low risk" patients may produce greater benefit, although this requires further investigation. This study highlights an ongoing need to better understand the factors that do influence the pathophysiology in these patients, in order to develop new strategies for cardiovascular disease prevention and treatments relevant to this group of patients and beyond.

Author contributions

JM, GF, KK, SV and SJN contributed to the conception of the work. JM and JC contributed to data analysis. JM, GF and SJN drafted the manuscript. SEN critically revised the manuscript. All gave final approval and

agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of interests

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