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Application of the VIRGO taxonomy to differentiate acute myocardial infarction in young women

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ABSTRACT

Background: A sex-specific taxonomy was developed from the Variation in Recovery: Role of Gender Outcomes of Young AMI patients (VIRGO) study to better classify young women with AMI who received cardiac catheterization. We aim to determine whether this taxonomy is advantageous to the Universal Definition.

Methods: We conducted a single-center retrospective chart review of consecutive women aged ≤55 years presenting with AMI between 1/1/2013 to 9/1/2016 who underwent cardiac catheterization during the index admission. The proportion of women classified using the Universal Definition of MI and VIRGO classification systems were compared.

Results: Among women with AMI who underwent cardiac catheterization (n = 177), using the Universal Definition of MI, 68.4% were classified as Type 1, 11.9% as Type 2, and 2.3% as Type 4b; 17.5% were unclassified. Using the VIRGO taxonomy, most (68.4%) were classified as Class I (thrombosis/critical stenosis). The remaining patients were stratified by the presence of obstructive coronary artery disease (CAD) with demand (Class IIa: 4.0%) and without demand (Class IIb: 2.3%) versus non-obstructive CAD with demand (Class IIIa: 6.8%) and without demand (Class IIIb: 10.2%). Alternative discreet mechanisms (Class IV) were seen in 7.3%. Only 1.1% was unclassified.

Conclusions: In a cohort of young women with AMI, 1 in 3 patients who underwent cardiac catheterization did not exhibit the classic mechanism of plaque disruption/thrombosis. By comparison, the VIRGO taxonomy classified more young women and further distinguished presentations within categories of the Universal Definition of MI. Application of this nuanced taxonomy may support the development of individualized diagnostic and treatment strategies in young women with AMI.

1. Introduction

Acute myocardial infarction (AMI) in young women is a heterogeneous disease, with a range of mechanisms that do not fit into traditional classification systems for AMI. Specifically, a significant proportion of women ≤55 years of age do not fall into the classic categories of plaque rupture and myocardial oxygen supply-demand mismatch, the distinguishing characteristics between Types 1 and 2 AMI by the Fourth Universal Definition of MI [1,2]. Many young women have non-obstructive coronary artery disease (CAD) without an obvious trigger for ischemia [3]. Classification systems that account for this heterogeneity can lead to more targeted research and care management, expose areas of diagnostic and therapeutic uncertainty, and reveal variation in outcomes. Yet they are infrequently applied in real-world clinical settings [4]. With over 40,000 hospitalizations each year for young women with AMI, as well as evidence that this population experiences greater morbidity and mortality compared with other groups [5–11]; a more nuanced taxonomy of the phenotypic presentations common in young women may lead to new insights about clinical management, the effectiveness of standard AMI therapies, and prognosis.

Previously, a taxonomy for young women with AMI was empirically developed using data from the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study. In this study, women with AMI were more likely than men to exhibit non-classic features of AMI and as many as 1 in 8 women were unclassified by the Universal Definition of MI [2]. The taxonomy differs from the Universal definition

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in that it is not only based on disease presentation, but also cardiac catheterization findings, revealing 4 distinct phenotypes, and several sub-types of AMI. The investigators observed different treatment patterns between the various VIRGO classes, with possible implications for prognosis. However, this taxonomy has yet to be applied in populations outside of the VIRGO study cohort. Application of the VIRGO taxonomy in a hospital population can inform whether using the VIRGO taxonomy provides an advantage over the Universal Definition in classifying sub-types of AMI in young women, by differentiating unique pathophysiologic entities, and by classifying women without a defined mechanism but with common clinical findings on presentation. We aimed to determine whether the VIRGO taxonomy is advantageous to the Universal Definition of MI in classifying young women with AMI who received cardiac catheterization by capturing heterogeneous disease mechanisms. We also sought to compare patient characteristics between the VIRGO classes to better understand the unique phenotypes.

2. Methods

2.1. Data sources

We conducted a retrospective medical chart review of 306 consecutive women aged ≤55 years with a primary or secondary discharge diagnosis of AMI (ICD9 code = 410.xx), presenting between 1/01/2013 and 9/01/2016 at a large tertiary care hospital. After a detailed chart review, a total of 228 were included with a confirmed diagnosis of AMI (defined as elevation of cardiac biomarkers and either symptoms of acute ischemia or ECG findings such as new ST-T changes, new/presumably new left bundle branch block or Q-waves). For individual patients with multiple admissions, we only included the first recorded hospitalization for AMI within this time period.

Among the 228 women with confirmed AMI, 177 underwent cardiac catheterization during the index admission. In the 51 patients who did not undergo cardiac catheterization, we identified reasons that these individuals did not receive the procedure based on documentation from the primary medical team. These included death prior to cardiac catheterization (n = 4), alternative diagnoses to explain troponin elevation (n = 31), cocaine use (n = 7), and other reasons outlined in Supplemental Table 1.

2.2. Medical chart review

Among the cohort of 177 women with AMI who underwent cardiac catheterization, we assessed the demographic (age, race/ethnicity) and clinical characteristics [cardiovascular risk factors; family history of premature CAD, prior percutaneous coronary intervention (PCI), MI or stroke], and symptoms on presentation. The type of AMI was also recorded [ST-Elevation Myocardial Infarction (STEMI) or Non-ST Elevation Myocardial Infarction (NSTEMI), documented by the clinical care team and confirmed by clinical review]. In-hospital clinical therapies were recorded, including revascularization [PCI, coronary artery bypass grafting (CABG), or no revascularization] and guideline-concordant discharge medications [aspirin, P2Y12 inhibitors, ACE inhibitors/ARBs, beta-blockers, and statins].

Patients were subsequently classified using the Universal Definition of AMI and the VIRGO taxonomy for AMI, using both clinical data and cardiac catheterization findings. Vital signs, laboratory data, emergency department notes, medical admission notes, cardiac catheterization reports, and discharge summaries to confirm the diagnoses and ascertain the necessary information to classify patients.

2.3. Classification using the Universal Definition of MI

Patients were classified using the Universal Definition of AMI based on clinical features and angiographic findings. Type 1 was defined as MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries. Type 2 was defined myocardial injury due to an imbalance between myocardial oxygen supply and demand (including coronary endothelial dysfunction, coronary artery spasm, coronary embolism). Charts were also reviewed for Type 3 (MI resulting in death when biomarker values are unavailable), Type 4a (MI related to PCI), Type 4b (MI related to in-stent thrombosis), and Type 5 (MI related to coronary artery bypass grafting).

2.4. Classification using the VIRGO taxonomy

The VIRGO taxonomy distinguishes four phenotypic classes and a fifth class for cases that are indeterminate. Class I denotes "Critical stenosis/thrombosis" (>70% stenosis, Fractional Flow Reserve (FFR) < 0.8 or thrombosis on angiogram). Class II denotes ≥50% stenosis in at least one epicardial vessel but without a critical stenosis/thrombosis. Class III indicates <50% stenosis in the epicardial vessels. Classes II and III were further divided into: subtype A (evidence of supply-demand mismatch) and subtype B (no evidence of supply-demand mismatch). Class IV denotes a specific alternate mechanism other than plaque rupture, diagnosed during angiography, including spontaneous coronary artery dissection (SCAD), vasospasm, coronary embolism, or possible stress induced cardiomyopathy. Since a final diagnosis of takotsubo cannot typically be confirmed until weeks to months after discharge when left ventricular function has recovered, and there may remain some clinical uncertainty about etiology at the time of presentation, "possible" takotsubo cardiomyopathy was assigned based on the treating team's clinical impression.

Patients were initially categorized by one physician (C.T.S.). For patients in whom the class designation was uncertain, their medical charts were re-reviewed by a cardiologist (E.S.S.) to determine classification. In some patients a distinct class could not be determined (i.e., patients with disease mechanisms that could fit into more than one class); these patients were classified as indeterminate (Class V), as was done in the original VIRGO taxonomy.

Evidence for supply-demand mismatch in both the Universal Definition and VIRGO Classification included systolic blood pressure ≥ 180 mmHg or < 90 mmHg; diastolic blood pressure ≥ 100 mmHg; heart rate > 120 bpm; atrial fibrillation/flutter; ventricular tachycardia/fibrillation; severe illness (pneumonia; exacerbation of chronic obstructive pulmonary disease (COPD); trauma; acute renal failure; stroke; severe gastrointestinal bleed; anemia; sepsis; surgical complication; any fracture; hyperosmolar hyperglycemic state; diabetic ketoacidosis); and other (surgery; hypoglycemia; seizure; acute liver failure; *Clostridium difficile* colitis; pyelonephritis).

2.5. Statistical analysis

We assessed the proportion of patients classified by the Universal Definition of AMI compared with the VIRGO taxonomy and examined differences between the two taxonomies in differentiating biological mechanisms and common phenotypic patterns. Among the VIRGO classes, we compared demographic characteristics, clinical presentation and in-patient management. This study was approved by the Yale Institutional Review Board of the Human Research Protection Program.

3. Results

3.1. Classification with the Fourth Universal Definition of MI

Within the overall population, the mean age was 48.0 ± 5.7 years and STEMI accounted for 41.2%. Using the Universal Definition of MI, 121 (68.4%) were classified as Type 1 (spontaneous MI; plaque rupture, ulceration, fissuring, erosion, or dissection), 21 (11.9%) as Type 2 (supply-demand mismatch including vasospasm, endothelial dysfunction or coronary embolism), and 4 (2.3%) as Type 4B (MI related to in-stent thrombosis). There were no patients with Type 3 AMI (MI resulting in death when biomarkers are unavailable) among those who underwent catheterization, however 4 patients with presumed AMI died prior to cardiac catheterization and were not included in the final cohort. In addition, Type 4A (MI related to PCI) and Type 5 (MI related to CABG) were not observed in this cohort. However, 31 (17.5%) women did not fit into any of the five classes of the Universal Definition (Fig. 1).

3.2. VIRGO classification

By comparison, the VIRGO taxonomy captured all but 2 women (considered indeterminate). Specifically, among 177 consecutive women presenting with AMI who had cardiac catheterization, 121 (68.4%) exhibited the classic mechanism of critical stenosis/thrombosis (including in-stent thrombosis, n = 4) (Class I; Table 1). Of the remaining patients with clinically confirmed AMI, there were 41 patients without a specific defined mechanism, classified as Class II and III. Among these patients, 11 (26.8%) had ≥50% stenosis in at least one epicardial vessel but without a critical stenosis/thrombosis (Class II) and 30 (73.2%) had <50% stenosis in the epicardial vessels (Class III). Within Class II and III, only 7 (17.1%; classified as IIa) and 12 (29.3%; classified as IIIa) had evidence of myocardial supply-demand mismatch, respectively. There were 13 women who had an identifiable discreet mechanism (Class IV; e.g., vasospasm, SCAD, coronary embolism, or possible takotsubo). In 2 women the class was considered indeterminate (Class V).

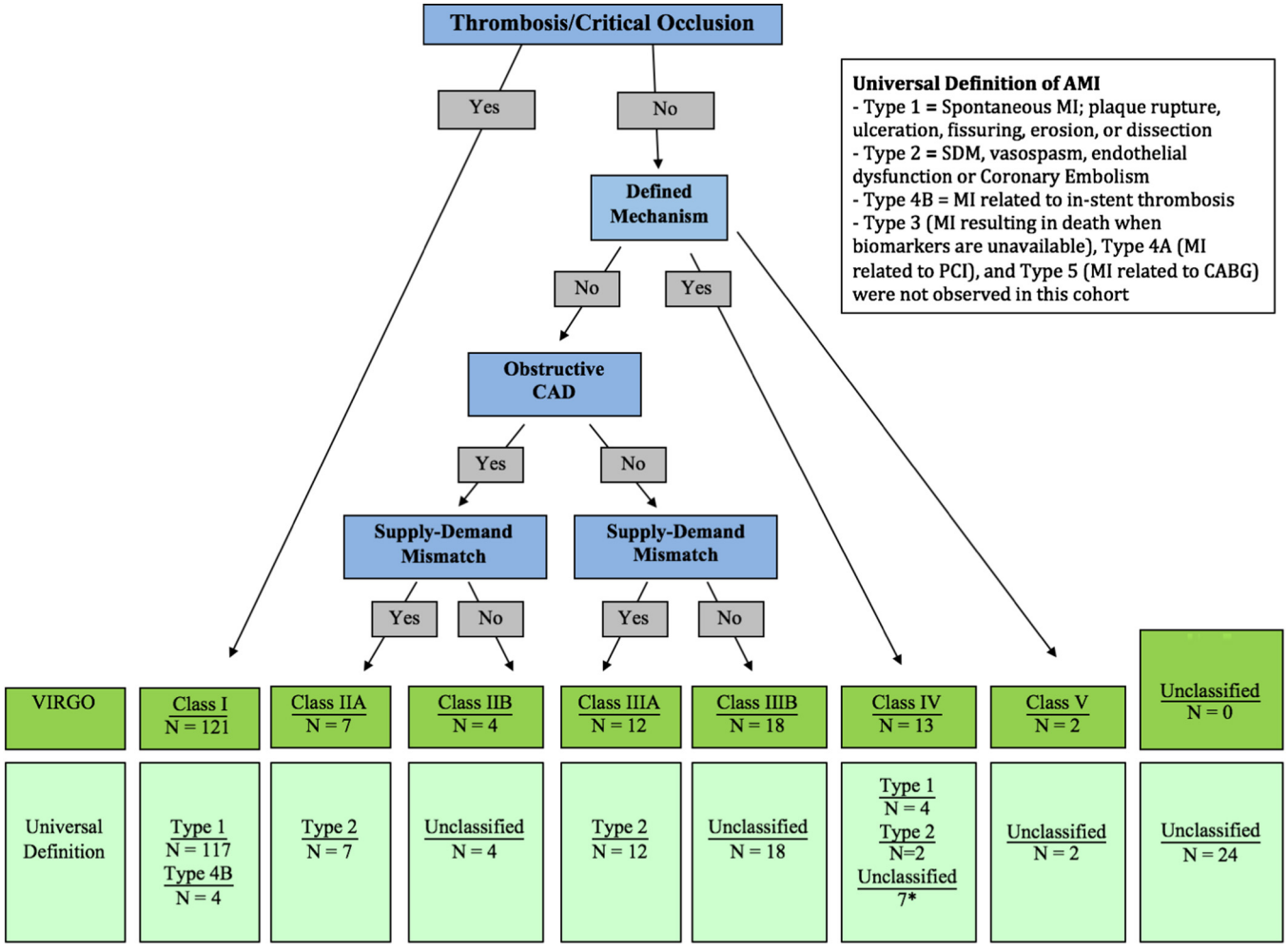

Fig. 1. Classification using VIRGO algorithm and the Universal Definition of AMI.
[Adapted from Spatz et al. Circulation. 2015 Nov 3;132 [18]:1710-8.]

3.3. Risk factors and presentation

Overall, 82.5% of the women with AMI had at least 1 traditional cardiac risk factor, which varied among classes. Previous coronary artery disease, hypertension, hyperlipidemia, smoking, and diabetes were observed in the majority of patients with Class I AMI. Women with Class II AMI (≥50% epicardial stenosis) generally did not have known coronary disease, but they tended to have traditional cardiovascular risk factors. Both patients in Class V AMI (indeterminate) had a known history of coronary disease. Fewer cardiovascular risk factors were seen in Class III AMI patients (<50% epicardial stenosis) and Class IV AMI patients (vasospasm, dissection, coronary embolism, or possible takotsubo) with smoking, diabetes, hypertension, and hyperlipidemia less prevalent than in Classes I and II (Table 1).

Among all classes there was a diversity of disease presentations (Table 2). Both STEMI and NSTEMI were observed among the different classes, with the highest proportion of STEMI in Class I (47.1%), Class IV (61.5%) and Class V (100%). Class IV patients with STEMI included 4 spontaneous coronary artery dissections, 1 vasospasm, 1 possible takotsubo, 1 coronary embolism and 1 patient with "spontaneous coronary artery dissection vs coronary embolism". Lower rates of STEMI were observed in Class II, (18.2%) and Class III (13.3%). Death before discharge occurred in 5 patients, all of whom were classified as Class I, but not other groups. Sources of supply-demand mismatch in Class II and III are outlined in Supplemental Table 2.

3.4. Treatment patterns among VIRGO classes

Treatment patterns varied among groups (Table 3). The vast majority of Class I patients (90.9%) received revascularization. Class I AMI patients tended to receive more standard post-AMI medications than the other groups, but there were still deficiencies in discharge prescription patterns. Specifically, out of the 116 patients who survived to discharge, 100% received aspirin, 91.4% received P2Y12 inhibitors, 84.5% received beta-blockers, 64.7% received ACE inhibitors/ARBs, and 93.1% received statins on discharge. Most patients in Class II and Class IV AMI patients received standard post-AMI medications. Among Class III and Class V AMI patients, discharge medications greatly varied.

4. Discussion

In a cohort of young women presenting to a large urban hospital with AMI, 1 out of 3 women did not have evidence of the classic mechanism of AMI - plaque rupture/erosion with critical stenosis/thrombosis. In this study, the Universal Definition of MI, which differentiates the most common presentations of AMI in older and male-dominated cohorts, only captured 82.5% of women with AMI who underwent cardiac catheterization, leaving 1 out of 6 women unclassified. By comparison, the VIRGO taxonomy distinguished phenotypes commonly observed in young women, including non-obstructive CAD (with or without demand ischemia) and SCAD.

Table 1
Baseline characteristics of young women (≤55 years) with AMI categorized with the VIRGO AMI taxonomy.

VIRGO classification	I Thrombosis/ critical stenosis 121 (68.4%)	IIA ≥50% stenosis with SDM[a] 7 (4.0%)	IIB ≥50% stenosis without SDM[a] 4 (2.3%)	IIIA <50% stenosis with SDM[a] 12 (6.8%)	IIIB <50% stenosis without SDM[a] 18 (10.2%)	IV Discreet mechanism (e.g., SCAD) 13[b] (7.3%)	V Multiple classes or unclassified 2[c] (1.1%)	All classes 177
Clinical characteristics								
Age (mean)	48	49	49	48	44	49	42	48
Race/ethnicity								
White	74 (61.2%)	2 (28.6%)	4 (100%)	5 (41.7%)	10 (55.6%)	10 (76.9%)	2 (100%)	107 (60.5%)
Black	30 (24.8%)	2 (28.6%)	–	5 (41.7%)	3 (16.7%)	2 (15.4%)	–	42 (23.7%)
Hispanic	12 (10.0%)	3 (42.9%)	–	1 (8.3%)	4 (22.2%)	1 (7.7%)	–	21 (11.9%)
Asian	3 (2.5%)	–	–	1 (8.3%)	1 (5.6%)	–	–	5 (2.8%)
Other	2 (1.7%)	–	–	–	–	–	–	2 (1.1%)
≥1 CAD risk factor[d]	108 (89.3%)	7 (100%)	1 (25.0%)	10 (83.3%)	11 (61.1%)	7 (53.8%)	2 (100%)	146 (82.5%)
Smoking status								
Any smoking	96 (79.3%)	3 (42.9%)	2 (50.0%)	5 (41.7%)	12 (66.7%)	10 (76.9%)	2 (100%)	130 (73.4%)
Current (past month)	80 (66.1%)	2 (28.6%)	2 (50.0%)	2 (16.7%)	7 (38.8%)	3 (23.1%)	2 (100%)	98 (55.4%)
Past	16 (13.2%)	1 (14.3%)	–	3 (25.0%)	5 (27.8%)	7 (53.8%)	–	32 (18.1%)
Never	23 (19.0%)	4 (57.1%)	2 (50.0%)	7 (58.3%)	6 (33.3%)	3 (23.1%)	–	45 (25.4%)
Unknown	1 (1.0%)	–	–	–	–	–	–	1 (0.6%)
Family history of premature CAD	35 (28.9%)	2 (28.6%)	2 (50.0%)	3 (25.0%)	3 (16.7%)	–	1 (50.0%)	46 (26.0%)
Past medical history								
Hypertension	70 (57.9%)	5 (71.4%)	1 (25.0%)	9 (75.0%)	8 (44.4%)	4 (30.8%)	1 (50.0%)	98 (55.4%)
Hyperlipidemia	46 (38.0%)	4 (57.1%)	–	2 (16.7%)	5 (27.8%)	3 (23.1%)	–	60 (33.9%)
Diabetes	49 (40.5%)	4 (57.1%)	–	4 (33.3%)	2 (11.1%)	2 (15.4%)	1 (50.0%)	62 (35.0%)
Type 1	3 (2.5%)	–	–	–	–	–	–	3 (1.7%)
Type 2	46 (38.0%)	4 (57.1%)	–	4 (33.3%)	2 (11.1%)	2 (15.4%)	1 (50.0%)	59 (33.3%)
CAD or past MI	21 (17.4%)	3 (42.9%)	–	1 (8.3%)	1 (5.6%)	–	2 (100%)	28 (15.8%)
Stroke/transient ischemic attack	6 (5.0%)	1 (14.3%)	–	2 (16.7%)	–	2 (15.4%)	–	11 (6.2%)
Peripheral arterial disease	–	1 (14.3%)	–	–	–	–	1 (50.0%)	2 (1.1%)
Heart failure	4 (3.3%)	2 (28.6%)	–	3 (25.0%)	–	–	–	9 (5.1%)
Chronic kidney disease	10 (8.3%)	2 (28.6%)	–	3 (25.0%)	1 (5.6%)	–	–	16 (9.0%)
Dialysis	3 (2.5%)	1 (14.3%)	–	–	1 (5.6%)	–	–	5 (2.8%)
Transplant	1 (1.0%)	–	–	–	–	–	–	1 (0.6%)
COPD	8 (6.6%)	–	–	2 (16.7%)	–	1 (7.7%)	–	11 (6.2%)
Asthma	6 (5.0%)	3 (42.9%)	1 (25.0%)	–	3 (16.7%)	–	1 (50.0%)	14 (7.9%)
Sleep apnea	5 (4.1%)	2 (28.6%)	1 (25.0%)	2 (16.7%)	–	–	–	10 (5.6%)
Hypercoagulable disorder[e]	3 (2.5%)	–	–	1 (8.3%)	–	–	–	4 (2.3%)
Past venous thromboembolism	6 (5.0%)	–	–	1 (8.3%)	3 (16.7%)	–	–	10 (5.6%)
History of cancer	5 (4.1%)	–	1 (25.0%)	1 (8.3%)	2 (11.1%)	–	–	9 (5.1%)
Autoimmune disorder	18 (14.9%)	–	–	1 (8.3%)	–	1 (7.7%)	–	20 (11.3%)
Hypothyroidism	11 (9.1%)	–	–	2 (16.7%)	1 (5.6%)	1 (7.7%)	–	15 (8.5%)
Depression	29 (24.0%)	–	1 (25.0%)	–	3 (16.7%)	3 (23.1%)	–	36 (20.3%)
Anxiety	19 (15.7%)	–	–	2 (16.7%)	3 (16.7%)	4 (30.8%)	–	28 (15.8%)
Other psychiatric illness	2 (1.7%)	–	–	1 (8.3%)	–	–	1 (50.0%)	3 (1.7%)
Polycystic ovarian syndrome	–	–	–	1 (8.3%)	1 (5.6%)	–	–	2 (1.1%)
BMI (mean)	31.2	34.0	28.1	28.6	31.3	31.4	32.3	31.1

[a] Supply-demand mismatch.
[b] Comprised of 4 spontaneous coronary artery dissections, 1 vasospasm, 6 possible takotsubo, 1 coronary embolism and 1 patient with "spontaneous coronary artery dissection vs coronary embolism".
[c] Comprised of individuals with previous stents, but no lesions on angiogram.
[d] CAD risk factors included Hypertension, Hyperlipidemia, Diabetes, Current Smoking, CAD/past-MI or CAD equivalents (Stroke, PAD).
[e] Hypercoagulable Disorder included Anti-phospholipid syndrome; Factor V Leiden, or recurrent unprovoked Deep Vein Thrombosis.

In clinical practice, the 2 taxonomies can serve different purposes. The Universal Definition of MI classification system does not require angiography, and thus serves as an important initial tool in the stratification and management of patients with AMI. The VIRGO taxonomy, on the other hand, relies on cardiac catheterization findings, which was not performed in 20% of women presenting with AMI. Many of these women remain undiagnosed and more studies are needed to better identify clinical pathways to elucidate the underlying pathological mechanisms. Still, the VIRGO taxonomy provides important information about anatomy and mechanisms of disease for women undergoing cardiac catheterization. This is particularly important for advancing the management of young women presenting with AMI, many of whom do not exhibit angiographic findings consistent with the classic mechanism of plaque rupture/thrombosis, and thus fall outside of traditional guideline-based care.

Additionally, the VIRGO taxonomy highlights the residual uncertainty in mechanisms underlying AMI, and can serve as an important tool to guide research into new or obscured biological mechanisms that may inform diagnosis and treatment among the different classes. As more advanced imaging and other diagnostic techniques become a routine part of the clinical care of patients with AMI, the taxonomy should evolve to accommodate mechanisms uncovered by such modalities. Ultimately, the VIRGO taxonomy is intended as a starting point, when cardiac catheterization is utilized, which could lead to more precision-based approaches to diagnosis and treatment of AMI in young women.

Consistent with the original VIRGO study, women without evidence of coronary stenosis or thrombosis on angiogram comprised the second largest class, accounting for 16.9% of the cohort; the majority of whom had no evidence of supply-demand mismatch or another identifiable mechanism. One possible explanation is that these patients have severe microvascular dysfunction or embolization of a thrombus to the microvasculature, which is not visible on an angiogram of the epicardial vessels. Cardiac PET and cardiac magnetic resonance may be useful

Table 2
Clinical presentation of young women (≤55 years) with AMI categorized with the VIRGO AMI taxonomy.

VIRGO classification	I Thrombosis/ critical stenosis 121 (68.4%)	IIA ≥50% stenosis with SDM[a] 7 (4.0%)	IIB ≥50% stenosis without SDM[a] 4 (2.3%)	IIIA <50% stenosis with SDM[a] 12 (6.8%)	IIIB <50% stenosis without SDM[a] 18 (10.2%)	IV Discreet mechanism (e.g., SCAD) 13[b] (7.3%)	V Multiple classes or unclassified 2[c] (1.1%)	All classes 177
Type of AMI								
STEMI	57 (47.1%)	–	2 (50.0%)	4 (33.3%)	–	8 (61.5%)[d]	2 (100%)	73 (41.2%)
NSTEMI	64 (52.9%)	7 (100%)	2 (50.0%)	8 (66.7%)	18 (100%)	5 (38.5%)	–	104 (58.8%)
Clinical symptoms								
Chest pain	105 (86.8%)	4 (57.1%)	3 (75.0%)	12 (100%)	18 (100%)	12 (92.3%)	2 (100%)	156 (88.1%)
Cardiac arrest	7 (5.8%)	–	1 (25.0%)	–	–	–	–	8 (4.5%)
Presenting rhythm								
Sinus rhythm	112 (93.0%)	6 (85.7%)	3 (75.0%)	11 (91.7%)	18 (100%)	12 (92.3%)	2 (100%)	164 (92.7%)
VT/VF	9 (7.4%)	–	1 (25.0%)	1 (8.3%)	–	1 (7.7%)	–	12 (6.8%)
Atrial fib/flutter	–	1 (14.3%)	–	–	–	–	–	1 (0.6%)
In-hospital mortality	5 (4.1%)	0	0	0	0	0	0	5

[a] Supply-demand mismatch.
[b] Comprised of 4 spontaneous coronary artery dissections, 1 vasospasm, 6 possible takotsubo, 1 coronary embolism and 1 patient with "spontaneous coronary artery dissection vs coronary embolism".
[c] Comprised of individuals with previous stents, but no lesions on angiogram.
[d] Class IV patients with STEMI included 4 spontaneous coronary artery dissections, 1 vasospasm, 1 possible takotsubo, 1 coronary embolism and 1 patient with "spontaneous coronary artery dissection vs coronary embolism".

in diagnosing microvascular disease [12,13]. Still, few studies have examined this approach in patients with AMI [14]. Another possible explanation, especially among women presenting with STEMI, is that there was an evolving plaque, with spontaneous resolution of thrombus or vasospasm that is no longer present at the time of the cardiac catheterization. One study showed that the use of intravascular ultrasound (IVUS) at the time of coronary angiography in patients without epicardial disease detected evidence of a recent plaque rupture in 38% of patients [15]. Such patients may have incomplete thrombosis, distal embolization of plaque debris, or endogenous thrombolysis mechanisms, such that the angiogram appears "normal" at the time of angiography. Still, the uncertainty of disease mechanism underscores the importance of distinguishing these patients at the time of diagnosis, to better characterize the disease.

Finally, more nuanced classification systems can hopefully advance precision-based treatment approaches for patients with non-classic types of AMI. At present, the treatment of patients with AMI but without evidence of coronary stenosis or plaque, is relatively unknown. Not surprisingly, in this study, we did not find consistent patterns in medication use by clinical phenotype. In the SWEDEHEART observational study of patients with confirmed AMI but without evidence of plaque rupture, the use of statins and ACE inhibitors/ARBs was associated with fewer subsequent major adverse cardiac events at one year, with a trend toward a positive effect with beta-blockers, but neutral effect with dual anti-platelet therapy [3]. ACE inhibitors have been shown to reduce angina in people with presumed microvascular disease and there is some evidence that statins may be beneficial in improving endothelial function and vasodilation [16]. Beta-blockers and calcium channel blockers have also been beneficial for symptom management in patients with microvascular dysfunction and angina [17–22]. If an undetected plaque rupture is indeed the mechanism of AMI in a portion of these patients, standard post-AMI medications, would likely be beneficial. Interestingly, a recent observational study comparing patients with Myocardial Infarction with Non-Obstructive Coronary Arteries

Table 3
Treatment patterns of young women (≤55 years) with AMI categorized with the VIRGO AMI taxonomy.

VIRGO classification	I Thrombosis/ critical stenosis 121 (68.4%)	IIA ≥50% stenosis with SDM[a] 7 (4.0%)	IIB ≥50% stenosis without SDM[a] 4 (2.3%)	IIIA <50% stenosis with SDM[a] 12 (6.8%)	IIIB <50% stenosis without SDM[a] 18 (10.2%)	IV Discreet mechanism (e.g., SCAD) 13[b] (7.3%)	V Multiple classes or unclassified 2[c] (1.1%)	All classes 177
Revascularization								
PCI	110 (90.9%)	1 (14.3%)	–	–	–	3 (23.1%)[d]	–	114 (64.4%)
CABG	–	1 (14.3%)	–	–	–	1 (7.7%)[e]	–	2 (1.1%)
None	11 (9.1%)	5 (71.4%)	4 (100%)	12 (100%)	18 (100%)	9 (69.2%)	2 (100%)	61 (34.5%)
Discharge medications								
Aspirin	116 (95.9%)	7 (100%)	4 (100%)	8 (66.7%)	14 (77.8%)	10 (76.9%)	2 (100%)	161 (91.0%)
P2Y12 inhibitor	106 (87.6%)	5 (71.4%)	1 (25.0%)	2 (16.7%)	6 (33.3%)	7 (53.8%)	1 (50.0%)	128 (72.3%)
Beta-blocker	98 (81.0%)	5 (71.4%)	3 (75.0%)	9 (75.0%)	11 (61.1%)	7 (53.8%)	1 (50.0%)	134 (75.7%)
ACE inhibitor/ARB	75 (62.0%)	5 (71.4%)	2 (50.0%)	7	5 (27.8%)	4 (30.8%)	–	98 (55.4%)
Any statin	108 (89.3%)	7 (100%)	4 (100%)	4 (33.3%)	12 (66.7%)	9 (69.2%)	2 (100%)	146 (82.5%)
High intensity	89 (73.6%)	5 (71.4%)	2 (50.0%)	3 (25.0%)	6 (33.3%)	6 (46.2%)	2 (100%)	113 (63.8%)
Moderate intensity	18 (14.9%)	1 (14.3%)	2 (50.0%)	1 (8.3%)	6 (33.3%)	3 (23.1%)	–	31 (17.5%)
Low intensity	1 (0.8%)	1 (14.3%)	–	–	–	–	–	2 (1.1%)
None	8 (6.6%)	–	–	8 (66.7%)	6 (33.3%)	4 (30.8%)	–	26 (14.7%)

[a] Supply-demand mismatch.
[b] Comprised of 4 spontaneous coronary artery dissections, 1 vasospasm, 6 possible takotsubo, 1 coronary embolism and 1 patient with "spontaneous coronary artery dissection vs coronary embolism".
[c] Comprised of individuals with previous stents, but no lesions on angiogram.
[d] Stenting occurred in 2 patients with coronary dissection and 1 patient with coronary embolism.
[e] CABG was performed in a patient with coronary dissection.

(MINOCA) to patients with MI related to obstructive lesions showed that MINOCA patients tended to be women, younger and less likely to have traditional cardiac risk factors. At a median follow up of 14 months, MINOCA patients treated with dual anti-platelet therapy, statins, and ACE inhibitors tended to have fewer adverse cardiac events, while the use of beta-blockers showed no impact on outcomes [23].

There are several limitations to this study. First, if clinicians did not diagnose AMI in patients who presented with ischemic symptoms or ECG changes and biomarker elevation, but without evidence of coronary disease on cardiac catheterization, some Class III cases would have been missed. However, if no alternative diagnosis was found, we assume AMI would likely have been coded. Additionally, as a single center study, the distribution of VIRGO classes in this study may be driven by institutional diagnostic and treatment patterns. Institutions with varying use of modalities for diagnosing AMI (e.g., routine use of IVUS or MRI) may yield different patterns. However, the VIRGO taxonomy was empirically derived from women and men presenting to over 100 hospitals across the U.S., and our study parallels findings in young women from this study, with Class I being most common, followed by Class III. Although the VIRGO taxonomy also has a role in male patients presenting with AMI, in our prior research and others, we observed that women are more likely to present with unique phenotypes, supporting a greater utility of the VIRGO taxonomy among women. Finally, given the small sample size and single site nature of the findings, descriptions of the frequency of medication use and outcomes by VIRGO class are exploratory. Further prospective studies are needed to illuminate the association of the VIRGO taxonomy with prognosis and outcomes.

5. Conclusion

Among a clinical population of young women with AMI, we observed substantial heterogeneity in underlying disease mechanisms, though in many cases the biological mechanism was unknown. The Universal Definition of MI accounted for 82.5% of the cohort, and several distinct mechanisms of AMI were grouped together, potentially obscuring important phenotypes in young women. In comparison, the VIRGO taxonomy classified nearly all patients who had cardiac catheterization, distinguishing those with non-obstructive CAD, those with discreet AMI mechanisms (e.g., vasospasm; SCAD), and differentiating those with shared characteristics though unknown disease mechanisms. These data support the importance of adopting a more nuanced classification system into routine clinical practice, which may lead to new insights and promote research aimed to better illuminate disease mechanisms in young women, along with individualized treatment approaches to improve outcomes.

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Declaration of interests

None. No competing interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.03.054.

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