MÆDICA - a Journal of Clinical Medicine

ORIGINAL PAPER

MAEDICA – a Journal of Clinical Medicine
2021; 16(2): 216-222
https://doi.org/10.26574/maedica.2021.16.2.216

Wellens Sign: Monography and Single Center Experience

Anamaria AVRAM[a, b], Valentin CHIONCEL[a, b], Alexandru IANCU[b], Suzana GUBERNA[b], Irina CUCIUREANU[a, b], Catalina ANDREI[a, b], Crina SINESCU[a, b]

[a]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[b]Emergency Clinical Hospital Bagdasar-Arseni, Bucharest, Romania

ABSTRACT

Objectives: *Objectives: Wellens syndrome has been described as a clinical and electrocardiographic complex that identifies a subset of patients with unstable angina (UA) at an impending risk of myocardial infarction (MI) and death in studies published almost four decades ago, before the wide use of cardiac biomarkers such as troponins. The clinical implications of Wellens sign in a contemporary cohort of patients with non-ST elevation acute coronary syndromes (NSTEACS) is yet to be defined.*

Materials and methods: We performed a prospective analysis of patients with acute coronary syndrome (ACS) and Wellens sign who underwent coronary angiography between January 2018 and December 2019. Patients follow-up visits were at one month and at six months. Clinical, electrocardiographic, biological and echocardiographic data were recorded at both follow-up visits.

Results: A total of 79 patients were included in the statistical analysis, of whom 16 (20.25%) had pure Wellens syndrome (normal myocardial necrosis biomarkers). The prevalence of type A Wellens sign was higher than previously reported (45.6%). The culprit coronary artery was most frequently LAD (49 pts, 62.03%), followed by LM (10 patients, 12.66%), right coronary artery (RCA) (eight pts, 10.13%), in-stent restenosis (three pts, 3.8%), left circumflex artery (LCX) (two pts, 2.53%) and bypass graft (one pt, 1.27%). Ischaemic reccurence rate within six months was 18,99%. The rate of reccurent percutaneous revascularization procedures was 11.54% and the rate of repeat target vessel revascularization (TVR) was 5.77% at six months. All-cause mortality rate at six months was 7.59%, with 5.06% cardiovascular deaths.

Conclusions: Early recognition of subtle ECG changes resembling Wellens sign in patients with chest pain is crucial as it reflects a large area of myocardium at risk. In our study, the culprit coronary artery was most frequently LAD (62.03%), with 36.7% proximal LAD culprit lesion, followed by LM (12.66%). Wellens syndrome should be considered a high risk condition that makes the conventional methods for risk assesment using risk scores unnecessary, useless and potentially deleterious. In our study, according to GRACE 1.0 risk score, 70.89% of patients were in the low risk group (1-108 points, estimated in-hospital death risk < 1%). No patient died during the initial hospitalization. All-cause mortality rate at six months was 7.59%, with 5.06% cardiovascular deaths.

Keywords: Wellens sign, NSTEACS, culprit vessel.

Address for correspondence:
Anamaria Avram
Work address: Şoseaua Berceni, Nr 10-12, Sector 4, Mail code 041915, Bucharest, Romania
Home address: Strada Braşov, Nr 13, Pantelimon, Judeţul Ilfov, Cod poştal 077145, Bucharest, Romania
Tel.: 0040724547835, email: anamaria.g.avram@gmail.com

Article received on the 28th of February 2021 and accepted for publication on the 29th of June 2021

INTRODUCTION

Wellens syndrome monograph

Prompt and adequate electrocardiogram (ECG) interpretation is essential for rapid institution of therapeutic interventions in order to save the myocardium at risk or limit the infarcted area in patients with acute coronary syndromes (ACS). The concept "time is muscle" dates for almost 50 years and has been issued by Eugene Braunwald, who postulated that the longer the myocardial ischaemia time, the more heart muscle is lost (1).

History

In 1982, de Zwaan with Wellens and collaborators have described in patients with unstable angina (UA) an eponymous ECG pattern, who identifies a subgroup with unfavorable outcome on conservative management (2). These pioneer studies have been made before the wide use of cardiac biomarkers such as troponins, that have been available in the '90s. Thus, we can speculate that some of UA patients included in the studies of Wellens and de Zwaan would have had troponin rise and would have been diagnosed with non-ST elevation myocardial infarction (NSTEMI) if troponin tests would had been available. Prevalence and clinical implications of Wellens sign in a contemporary cohort of patients with non-ST elevation acute coronary syndromes (NSTEACS) have not been established yet. In a study published in 2019, Wellens sign was seen in 8.8% of patients with NSTEMI (3).

Etiology

According to the initial description made by Wellens and de Zwaan, Wellens syndrome is caused by coronary atherosclerosis, resulting from temporary left descendent coronary artery (LAD) occlusion because of atherosclerotic plaque rupture, with subsequent repermeabilisation due to spontaneous clot lysis before the development of myocardial infarction (MI) (4).

After the initial description, cases of Wellens syndrome caused by a variety of atherosclerothic causes have been reported as well as cases with other electrocardiographic or angiographic localisations (Table 1).

Pathophysiology

The pathophysiologic substrate of the Wellens pattern due to coronary artery atherosclerosis is not completely understood. The hypothesis of myocardial reperfusion lesion is the most widely accepted mechanism: a brief episode of myocardial ischaemia because of atherosclerothic plaque rupture results in acute thrombotic occlusion of the culprit artery, followed by spontaneous or pharmacologically facilitated reperfusion before MI development (5). This sequence of events determines initially a minimal ST segment elevation, then ST segment resolution and T wave inversion (biphasic or negative) once the blod flow is restored and symptoms disappear. The electrocardiographic and angiographic picture of Wellens syndrome suggests an "abortive" form of ST segment elevation myocardial infarction (STEMI).

The electrophysiologic explanation consists in the fact that, in the absence of transmural necrosis, the onset of epicardial depolarization is delayed as a result of decreased transmural velocity form the endocardium towards the epicardium. As a consequence, epicardial repolarization completes after endocardial repolarization, a phenomenon called repolarization dispersion which determines localised T wave inversion (6). In case of coronary reocclusion the first ECG sign is T wave pseudonormalization, accompanied by reccurence of chest pain. If the artery remains occluded, the patient develops STEMI. If the evolution

Atherosclerotic causes	Wellens phenocopies
Native coronary artery atherosclerosis	Non-critical plaque coronary artery vasospasm
Intrastent neoatherosclerosis	Coronary vasospasm due to illicit drugs use
Coronary artery bypass graft atherosclerosis	Spontaneous coronary artery dissection
Non-obstructive coronary artery disease	Coronary fistulae
	Myocardial bridging
	Stress cardiomyopathy
	Status postelectrical cardioversion for supraventricular rhythm disturbances

TABLE 1. Wellens syndrome etiology

is stuttering, with repetitive episodes of reperfusion and intermitent occlusion, the ECG will alternate the Wellens pattern with T wave pseudonormalization (7).

Electrocardiogram

According to the initial description, the typical ECG changes include isoelectric or minimally elevated (1 mm) takeoff of the ST segment, a concave or horizontal ST segment passing into a symmetricaly inverted T wave (2). The authors recognised two distinct morphologicall patterns:

- type A, less frequent (Figure 1): represents 25% of cases and is characterised by isoelectric or minimally elevated (1 mm) takeoff of the ST segment (subsequently called J point elevation), a concave or horizontal ST segment followed by an initial positive T wave at an angle of 135° and a terminal negative T wave (biphasic T waves, +/-);
- type B, the common type (Figure 2): represents 75% of cases and is characterised by takeoff of the ST segment from the QRS complex below the isoelectric line (subsequently called J point depression) and a convex ST segment followed by negative, deep and symmetrical T wave at an angle of 120° (2).

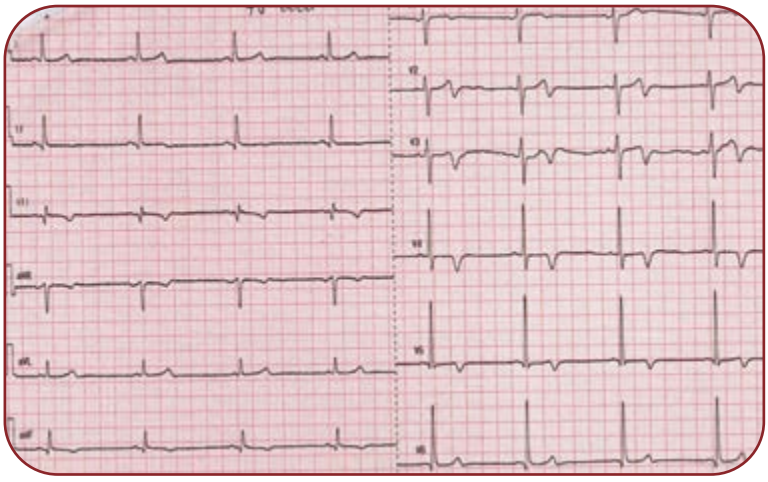

FIGURE 1. Type A Wellens electrocardiographic pattern (see text for further explanations).

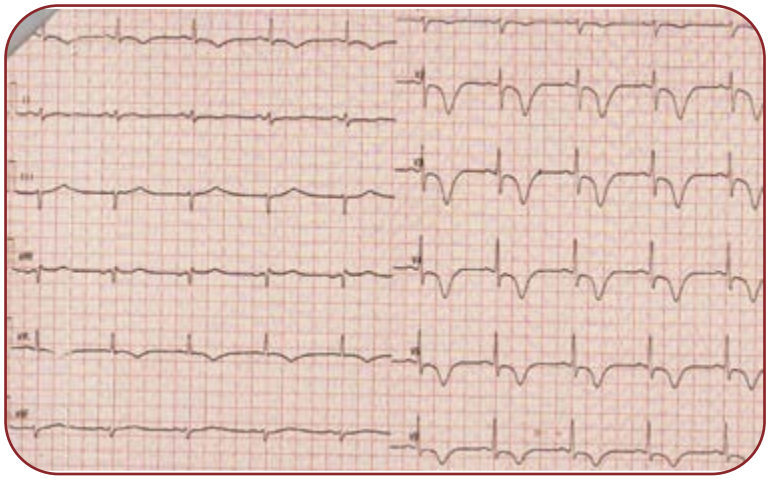

FIGURE 1. Type B Wellens electrocardiographic pattern (see text for further explanations).

The above abnormalities are most common in leads V2 and V3, but they may appear in V1 to V4 and, occasionally, in V5 and V6 (2, 8). The occlusion af the LAD before the second septal perforator determines T wave changes in V2-V3, but if the lesion is more proximal the changes will appear in more precordial leads (5).

T wave inversion is frequently accompanied by QT interval prolongation. According to de Zwan and Wellens observations, this is partly due to incorporation of a negative U wave in the terminal portion of the T wave (8).

Diagnosis

Wellens syndrome has been initially described as a clinical and electrocardiographic complex that identifies a subset of patients with UA at an impending risk of MI. The diagnostic criteria have been established in 2002 by Rhinehardt J and collaborators: negative, deep and symmetrical T waves in leads V2 and V3, ocasionally in leads V1, V4, V5 and V6, OR biphasic T waves in leads V2-V3, PLUS history of angina, characteristic ECG pattern present in pain-free state, absence or minimal ST segment elevation (< 1 mm), absence of precordial pathological Q waves, and normal or slightly elevated cardiac necrosis biomarkers (9).

These criteria are meant to exclude STEMI and myocardial necrosis sequelae, on one hand, and to differentiate Wellens syndrome from other causes of T wave inversion in precordial leads, on the other hand (Table 2).

Evolution and prognosis

Wellens syndrome is inherently linked to its prognostic significance. These patients are at increased risk for extensive anterior MI and, possibly, death. Considering the evolution of Wellens syndrome towards MI despite pharmacological treatment it is considered a premyocardial infarction state (10).

Normal variants: persistent juvenile pattern, athlete`s heart, hyperventilation
High voltage
Pericarditis and perimyocarditis
Pulmonary embolism and cor pulmonale
Right bundle branch block
Memory T waves
Cardiomyopathies: hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy
Channelopathies: Brugada syndrome
Drugs and alcohol: amiodarone, digitalis, alcoholism
Electrolyte disorders: hypokaliemia, hypomagnesemia
Central nervous system disorders
Generalised low voltage (flat) T waves: anasarca, mixedema

TABLE 2. Differential diagnosis of Wellens sign – adapted from (10)

Risk assesment is a crucial step in the management of patients with NSTEACS, as it determines the intensity and timing of therapeuthic interventions. Both ESC (11) and ACC/AHA guidelines (12) recommend the use of validated instrument for risk assesment such as GRACE or TIMI risk scores. None of the aforementioned risk scores considers the characteristics of Wellens syndrome. Moreover, they usually suggest a low risk profile in patients with Wellens syndrome. These limitations of the risk scores and the lack of large prospective observational studies or interventional studies make the current guidelines confusing in the management of Wellens syndrome (13). However, the few studies available so far clearly demonstrate the diagnostic accuracy of Wellens syndrome in identifying a critical LAD stenosis. In conclusion, Wellens syndrome should be considered a high risk condition that makes the conventional methods for risk assesment using risk scores unnecessary, useless and potentially deleterious. ❑

MATERIALS AND METHODS

We performed a prospective analysis on 79 patients with ACS and Wellens sign who underwent coronary angiography between January 2018 and December 2019, with follow-up visitis at one month and six months. Inclusion criteria were as follows: 1) chest pain (or equivalents); 2) ischaemic changes on ECG consisting of negative, deep and symmetrical T waves or biphasic T waves; 3) absence of ST segment elevation. Exclusion criteria were: 1) complete bundle branch block; 2) ventricular paced rhythm; and 3) pathological Q waves in precordial leads.

Data collection

Medical records were reviewed and the patients` demographic data were recorded. Laboratory data on admission and throughout hospital stay were recorded. High sensitive cardiac troponin I was measured using PATHFASTTM hs-cTnI assay (LSI Medience Corporation, Mitsubishi Chemical Europe GmbH). The overall upper limit of normal for high sensitive troponin I is 27.9 ng/L, which represented the 99th percentile reference value. Standard 12-lead electrocardiograms were obtained at presentation to the emergency department and were reviewed by two independent reviewers in a blind manner. Transthoracic echocardiography was performed within 48 hours from admission. Left ventricular ejection fraction was determined using biplane Simpson`s method. All patients underwent risk assesment using as a predictive model the GRACE 1.0 risk score. All patients underwent coronary angiography. All coronary angiographies have been reviewed by both the treating cardiologist and an interventional cardiologist blinded to the clinical data. Obstructive coronary artery disease was defined as stenosis ≥ 50% in the left main coronary artery and ≥ 70% in any other epicardial coronary arteries. The culprit lesion was determined based on electrocardiographic, echocardiographic and angiographic data. Treatment strategy was established by a heart team, including the treating cardiologist and two interventional cardiologists. Patients follow-up visits were at one month and at six months.

Clinical, electrocardiographic, biological and echocardiographic data were recorded at both follow-up visits. ❑

RESULTS

A total of 79 patients with ACS and Wellens sign were included, out of which 67.1% were men. The median age was 62.28 years (from 40 to 83 years). Baseline demographic and clinical characteristics are summarized in Table 3.

The ECG at presentation revealed an electrical sequelae of an old MI in seven (8.9%) patients, in all cases in the inferior territory. All patients had Wellens ECG pattern; 42 patients (53.2%) exhibited Wellens sign at presentation, and the rest developed it during hospital stay. Thirty-six patients (45.6%) had type A Wellens sign, and the rest type B Wellens sign. The most frequent ECG territory affected was the anterior territory (48 pts, 60.76%), followed by antero-septal (10 pts, 12.66%), anterior and inferior (nine pts, 11.39%), antero-lateral (seven pts, 8.86%), infero-lateral (three pts, 3.8%) and inferior (two pts, 2.5%).

Among the 79 patients, 16 (20.25%) had normal myocardial necrosis biomarkers and 64 (81.01%) normal myocardial necrosis enzymes with minimal rise of the troponins. Across the whole lot, the mean value of high sensitive troponin I at presentation was 900.14 ng/L, and the mean value of the maximum increase of troponin 2419.57 ng/L.

TABLE 3. Baseline demographic and clinical characteristics

	Number	Frequency (%)
Sex	53	67,1
History of angina	51	64,6
History of MI	20	25,3
History of PCI	10	12,7
History of CABG	2	2,5
Hypertension	68	86,1
Dyslipidemia	61	77,2
Diabetes mellitus or prediabetes	39	49,3
Current smoker	37	46,8
Antiagregant pretreatment	40	50,6
Betablocker pretreatment	44	55,7
Statin pretreatment	37	46,8

Echocardiographic evaluation revealed the presence of an inferior aneurysm in three patients (3.8%). Among the 79 patients, 21 (26.58%) had no wall motion anomalies. The mean value of the left ventricular wall motion score index (LVWMSi) was 1.34 (minimum 1, maximum 2.41, SD 0.37) and the mean left ventricular ejection fraction (LVEF) was 46.97%.

All patients underwent risk assesment using as a predictive model the GRACE 1.0 risk score, with a mean value of 97.68 points (from 56 to 174 points); 70.89% of patients were in the low risk group (1-108 points, estimated in-hospital death risk < 1%), 21.52% in the intermediar risk group (109-140 points, estimated in-hospital death risk 1-3%) and 7.59% in the high risk group (>140 points, estimated in-hospital death risk > 3%).

The mean time frame until coronary angiography was 81.46 hours (minimum one hour, maximum 14 days). Thus, most of the patients (41.77%) underwent coronary angiography within 24 to 72 hours from admission, 29.11% within two to 24 hours from admission and 2.53% within two hours from presentation.

The inventory of atherosclerothic coronary disease showed the absence of significant coronary stenoses in four patients (5.06%), univascular disease in 34 patients (43.04%), bivascular disease in 18 patients (22.78%), trivascular disease in 11 patients (13.92%), left main (LM) disease plus one vessel in one patient (1.27%), LM disease plus two vessels in three patients (3.8%), LM disease plus three vessels in six patients (7.59%) and combined native coronary arteries and bypass grafts in two patients (2.53%). The culprit coronary artery was most frequently LAD (49 pts, 62.03%), followed by LM (10 patients, 12.66%), right coronary artery (RCA) (eight pts, 10.13%), in-stent restenosis (three pts, 3.8%), left circumflex artery (LCX) (two pts, 2.53%) and bypass graft (one pt, 1.27%). Among the 49 patients with LAD-related ACS, 29 (59.18%) had the culprit stenosis in segment I, 17 (34.69%) in segment II and the rest (three pts, 6.12%) in segment III. The mean severity of the LAD culprit stenoses was 88.88%. Thus, 31 patients (63.27%) had a 70-94% LAD stenosis, 13 patients (26.53%) had LAD subocclusion (95-99% stenosis) and five patients (10.2%) had LAD occlusion (two pts with acute thrombotic occlusion and three pts with chronic occlusion).

After coronary angiography, 52 patients (65.83%) have been treated ad hoc by coronary angioplasty, 13 patients (16.46%) have been adressed for surgical coronary revascularization, eight patients (10.13%) had no revascularization solution, two patients (2.5%) had been recommended a myocardial viability test and the rest of four patients (5.06%) had no indication for myocardial revascularization.

Among the 52 patients managed interventionally, one patient (1.92%) underwent pharmacoactive baloon angioplasty and the rest were treated with stent implantation. A total of 82 stents have been implanted during the initial procedure. Thus, complete single procedure interventional revascularization has beed achieved in 43 patients (92.69%).

During hospital stay, 15 patients (18,99%) presented in-hospital complications; among them, seven patients (8.86%) had contrast-induced nephropathy, six patients (7.59%) had vascular acces site bleeding, one patient (1.27%) had a stroke and one patient had a ventricular rhythm disturbance. None of the patients died during the initial hospital stay.

In the patients adressed for surgical myocardial revascularization, cardiac surgery risk assesment using EUROSCORE II revealed a mean value of 4.82% (minimum 0.7%, maximum 23%). Among the 13 patients adressed for surgical myocardial revascularization, only five (38.46%) underwent surgery.

At one month visit, two patients (2.53%) had died, one because of sudden death three weeks after the initial hospitalization and the other because of complications occured after coronary bypass artery grafting (postoperative myocardial infarction, septic shock). All-cause mortality rate at six months was 7.59% (six patients), with 5.06% cardiovascular deaths. The rate of rehospitalizations of any cause within six months was 30.11% (23 patients), with 24.05% cardiovascular hospitalizations.

Echocardiographic evaluation at six months revealed a mean LVEF of 50.49%. Ischaemic reccurence rate within six months was 18.99% (15 patients). Among the 79 patients, 11 patients needed interventional revascularization procedures, of which eight (10.13%) patients as an emergency. The rate of reccurent percutaneous revascularization procedures was 11.54% (six patiens) and the rate of repeat target vessel revascularization (TVR) 5.77% at six months. ❑

DISCUSSION

Our study revealed that: 1) The prevalence of type A Wellens sign was higher than previously thought (45.6%). 2) One fifth of patients with Wellens sign had pure Welens syndrome (normal myocardial necrosis biomarkers) and 81% normal myocardial necrosis enzymes with minimal rise of the troponins. 3) According to GRACE 1.0 risk score, 70.89% of patients were in the low risk group (1-108 points, estimated in-hospital death risk < 1%). 4) The culprit coronary artery was most frequently LAD (62,03%), with 36.7% proximal LAD culprit lesion, followed by LM (12.66%). 5) Among patients with LAD-related ACS, the majority (63,27%) had a 70-94% stenosis. 6) After coronary angiography, 65.83% of patients have been treated *ad hoc* by coronary angioplasty and in 92.69% of cases complete single procedure interventional revascularization has beed achieved. 7) All-cause mortality rate at six months was 7.59%, with 5.06% cardiovascular deaths. 8) The rate of rehospitalizations of any cause within six months was 30.11%, with 24.05% cardiovascular hospitalizations. 9) Ischaemic reccurence rate within six months was 18.99%. 10) The rate of reccurent percutaneous revascularization procedures was 11.54% and the rate of repeat target vessel revascularization (TVR) 5.77% at six months. ❑

CONCLUSIONS

Wellens sign in patients with ACS can be caused by a variety of atherosclerothic and non-atherosclerothic causes. Early recognition of subtle ECG changes resembling Wellens sign in patients with chest pain is crucial as it reflects a large area of myocardium at risk. In our study, the culprit coronary artery was most frequently LAD (62,03%), with 36.7% proximal LAD culprit lesion, followed by LM (12.66%). Wellens syndrome should be considered a high risk condition that makes the conventional methods for risk assesment using risk scores unnecessary, useless and potentially deleterious. In our study, according to GRACE 1.0 risk score, 70.89% of the patients were in the low risk group

(1-108 points, estimated in-hospital death risk < 1%). No patient died during the initial hospitalization. All-cause mortality rate at six months was 7.59%, with 5.06% cardiovascular deaths.

Wellens syndrome represents a premyocardial infarction state and has a major diagnostic and prognostic significance. Due to frequent underdiagnostic and potentially fatal consequences, Wellens syndrome has been called "the widow-maker syndrome" (14). ❑

Conflicts of interest: none declared.
Financial support: none declared.

References

1. **Braunwald E.** Featuring: Eugene Braunwald**.** *Eur Cardiol* 2019;2:130-133.
2. **de Zwaan C, Bär FW, Wellens HJ.** Characteristic electrocardiographic pattern indicating a critical stenosis high in left anterior descending coronary artery in patients admitted because of impending myocardial infarction. *Am Heart J* 1982;4 Pt 2:730-736.
3. **Kobayashi A, Misumida N, Aoi S, et al.** Prevalence and Clinical Implication of Wellens' Sign in Patients With Non-ST-Segment Elevation Myocardial Infarction *Cardiol Res* 2019;3:135-141.
4. **Miner B, Hart EH.** Wellens Syndrome. [Updated 2019 Mar 9]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing, 2019 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482490/
5. **Marzlin KM.** Wellens Syndrome. *AACN Adv Crit Care* 2018;3:360-364.
6. **de Luna AB, Zareba W, Fiol M, et al.** Negative T wave in ischemic heart disease: a consensus article. *Ann Noninvasive Electrocardiol* 2014;5:426-441.
7. **Cadogan M.** Wellens syndrome. https://litfl.com/wellens-syndrome-ecg-library/
8. **de Zwaan C, Bär FW, Janssen JHA, et al.** Angiographic and clinical characteristics of patients with unstable angina showing an ECG pattern indicating critical narrowing of the proximal LAD coronary artery. *American Heart Journal* 1989;3:657-665.
9. **Rhinehardt J, Brady WJ, Perron AD, et al.** Electrocardiographic manifestations of Wellens' syndrome. *Am J Emerg Med* 2002;7:638-643.
10. **Minner B, Grigg WS, Hart EH.** Wellens syndrome. NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK482490/
11. **Roffi M, Patrono C, Collet JP, et al.** ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;3:267-315. doi: 10.1093/eurheartj/ehv320. Epub 2015 Aug 29.
12. **Amsterdam EA, Wenger NK, Brindis RG, et al.** 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;24:e139-e228.
13. **Celestini A, Paglia F.** The Wellens' Syndrome in the management of acute coronary syndromes. *Intern Emerg Med* 2012;7 Suppl 1:S19-S20.
14. **Yusuf Muharam M, Ahmad R, Harmy MY.** The 'widow maker': Electrocardiogram features that should not be missed. *Malaysian Family Physician* 2013; 1.