

Sildenafil Serious Emergency Presentations; Starting with Angina, Myocardial Infarctions, Ventricular Fibrillation, and Ending with Death; Retrospective Observational Study (13-Report Cases)

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ABSTRACT

Background

Sildenafil is an approved first oral phosphodiesterase type-5 inhibitor pill by the Food and Drug Administration (FDA) in the treatment of the erectile dysfunction. Angina, coronary artery spasm, variant myocardial infarctions, ventricular fibrillation, and sudden cardiac death are reported a serious emergency and critical care cardiac presentations for sildenafil.

Method of Study and Patients

My case study was an observational retrospective thirteen case report series. The study was conducted in both Fraskour Central Hospital and physician outpatient. The author reported the thirteen cases of variant acute cardiac events through nearly three and a half years, started on December 27, 2015, ended on June 16, 2019.

Result

There are 30.77% presented with Unstable Angina (UA), 23.08% with anterior Myocardial Infarctions (MI), 7.69% with combined anterior and inferior MI, 7.69% inferior with RV MI, 7.69% with anterior MI with Right Bundle Branch Block (RBBB), 15.38% with inferior MI, and 7.69% with Ventricular Fibrillation (VF). The associated risk factors were smoking (38.46%), family history of Ischemic Heart Disease (IHD) (7.69%), marijuana with smoking; 23.08% hashish with smoking (23.08%), obesity with smoking (7.69%). Early sudden cardiac death occurred in 15.38% and lately in 7.69%. Congestive Heart Failure (CHF) had happened in 23.08%.

Conclusion

The unique advantages of the study were awareness for the critical side effects of sildenafil. Sildenafil may be a serious drug if concurrently taken in associated risk factors such as smoking and substance abuse.

Keywords: Angina, Death, Myocardial infarctions, Sildenafil, Serious Emergency Presentations, Ventricular fibrillation.

Abbreviations

CHF: congestive heart failure; CPR: cardiopulmonary resuscitation; DCC: Direct-Current Cardioversion; ECG: electrocardiogram; ED: erectile dysfunction; FDA: Food and Drug Administration; HIV: human immunodeficiency virus; ICU: intensive care unit; IHD: ischemic heart disease; LAD: left anterior descending artery; MI: myocardial infarctions; NO: nitric oxide; PDE-5 inhibitor: phosphodiesterase type-5 inhibitor; PTCA: Percutaneous; transluminal coronary angioplasty; RBBB: right bundle branch block; RV MI: right ventricular myocardial infarction; STDs: sexually transmitted diseases; STEMI: ST-Elevation Myocardial Infarction; UA: unstable angina.

INTRODUCTION

Historical Bit

On March 27, 1998, the FDA approved sildenafil as the first oral phosphodiesterase type-5 inhibitor (PDE-5 inhibitor) pill in the treatment of the Erectile Dysfunction (ED). The drug rapidly acquired publicity.[1-3] Nearly, it is estimated its using since the FDA approval, about 16 million men all over the world have used sildenafil.^{1,2} The initial US television announcements for sildenafil used by an aging Bob Dole (born 1923) as a spokesman, a 1996 Republican presidential candidate.⁴ Sildenafil already has been approved for commerce in more than 120 countries around the world.² Over the 7-years after its approval, more the 600 000-700 000 physicians worldwide have written more than 150 million sildenafil prescriptions for nearly 27 million men in the cases of erectile dysfunction.^{2,3,5} Sildenafil has become one of the most frequent displayed therapeutic agents in the press and on television.⁵

Sildenafil Abuse

Sildenafil citrate is one of the most commonly prescribed and abused pharmaceuticals at hand nowadays.^{2,5} It is a very communal drug for abuse.⁵ Sildenafil citrate is usually famous as Viagra which is a widespread recreational drug that is misused among teenage males.⁶ Sildenafil misusing is considered a leading factor to Sexually Transmitted Diseases (STDs), Human Immunodeficiency Virus (HIV) transmission, in pregnancy among teens.^{5,7,8} It may represent an increasing audience health problem everywhere in the United States.^{5,7,8}

Tolerance and Efficaciousness

The primary clinical trials of sildenafil had been set in the US, the UK, and Europe.^{9,10} The secondary trials were done in Central and South America, Africa, Asia, and Australia.¹¹⁻¹⁸ the primary database of double-blind trials and open-label trials that done through a 10-year period (1993–2003) represents more than 13000 patient-years of experience with sildenafil as a therapy for erectile dysfunction.¹⁹ Sildenafil is typically well-tolerated and effective in the treatment of all types of ED; organic, psychogenic and mixed etiology⁹ and with various comorbidities.^{20,21}

Mechanism of Action

The pharmacological mechanism that inducing the erection of the penis involves the release of Nitric Oxide (NO) in the corpus cavernosum during sexual arousal. NO then stimulates the enzyme guanylate cyclase, which results in increased levels of Cyclic Guanosine Monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing blood flow. Sildenafil is a strong and selective inhibitor of cGMP specific PDE-5 in the corpus cavernosum, where PDE-5 is responsible for the degradation of cGMP.^{22,23}

Absorption

Sildenafil has rapid gastrointestinal absorption. The plasma concentrations are maximally reached within one-half to two-hours (median one-hour) of ingested oral dosing in the accelerated state. The mean absolute oral bioavailability is about 41 % (range 25-63 %).²²

Elimination

The sildenafil total body clearance is 41 L/h with a consequent terminal phase half-life of 3-5 h. After either oral or IV administration, sildenafil is excreted as metabolites mainly in the feces (about 80 % of given oral

dose) and to a marginal extent in the urine (about 13 % of given oral dose).²²

Dosage and Administration

Commonly, the recommended sildenafil dose is 50 mg taken, as needed, approximately one hour before sexual intercourse. However, sildenafil may be taken anywhere from four-hours to half-hour before sexual intercourse. Depend on efficiency and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended frequent dosing is once/day.²⁴

If the patient is older than age 65, or have serious hepatic or renal problems, your doctor may start you at the lowest dose (25 mg) of sildenafil. If the patient on protease inhibitors, such as for the treatment of human immunodeficiency virus, the recommend is a 25 mg dose and may limit you to a maximum single dose of 25 mg of sildenafil in a 48-hour period. If the patient has prostatic disorders or hypertension on alpha-blockers, the lower dose of sildenafil should be considered. If sildenafil is taken after a high-fat meal (e.g. a cheeseburger and French-fries), the drug may take a little longer to start working.²⁴

Contraindications

Indeed, the single absolutely contraindication for sildenafil is the synchronous use of nitrates.²⁵ The active IHD, CHF with hypovolemia or hypotension, and hypertensive patients on multiple antihypertensive regimens should avoid sildenafil.⁵ As soon as its FDA approval, a strict warning was attached to sildenafil and the other PDE-5 inhibitors: the drugs should not be used in conjunction with nitrate preparations because of the resultant marked lowering of blood pressure.⁵ Because sildenafil potentiates the hypotensive effects of organic nitrates, concomitant use of sildenafil with nitrates or nitric oxide donors is contraindicated.²⁶⁻²⁸ The patient should not take sildenafil if he: 1. take nitrates (such as nitroglycerin). 2. Use street drugs called “poppers” such as amyl nitrate or amyl nitrite, and butyl nitrate. 3. Take guanylate cyclase stimulators such as riociguat.²⁸ 4. The patient is allergic to sildenafil.²⁸ The PDE-5 inhibitors were eventually deemed safe for all but the most severely impaired heart patients.

Adverse Effects

Sildenafil can cause several adverse effects.²⁴ The adverse effects are usually ranged from mild to moderate and mostly don't last longer than a few hours.²⁴ Some of these side effects commonly vary with higher doses. The most frequent sildenafil adverse effects are a headache, flushing of the face, and gastrointestinal upset.²⁴ Less recurrent adverse effects are transient color vision changes, photophobia, or blurred vision may occur. Rarely, men taking sildenafil reported a sudden diminution or blindness in one or both eyes.²⁴ Sudden loss or diminution in hearing, tinnitus, and dizziness, has been rarely reported in people taking PDE5 inhibitors, including sildenafil.²⁴ Myocardial infarction, Cerebrovascular Accident (CVA), irregular arrhythmias, and death have been reported rarely in men taking sildenafil.²⁴ Rare cardiovascular adverse effects (>1/10,000 and <1/1,000); sudden cardiac death, myocardial infarction, ventricular arrhythmia, atrial fibrillation, and unstable angina.²² Uncommon cardiovascular side effects (>1/1,000 and <1/100); arrhythmias, hypertension, and hypotension.²² The most serious sildenafil adverse events are left ventricular dysfunction in a dosing 20 mg and postural hypotension in a dosing 40 mg.⁴ Among the patients who used sildenafil, there was a worrisome 2-5.7-fold increased practice of unsafe sex compared with those patients who did not use sildenafil.⁵ Addition-

ally, the rate of STD was nearly 2-fold greater in the individuals who used sildenafil.⁵ Reports have raised concerns that sildenafil citrate may increase the risk of cardiovascular events, particularly fatal arrhythmias, in patients with cardiovascular disease. In the past few years, the cardiac electrophysiological effects of sildenafil citrate have been investigated extensively in both animal and clinical studies.²⁵ According to extensive data available to date, sildenafil citrate has been shown to pose minimal cardiovascular risks to healthy people taking this drug.²⁵ Initially, there was some anxiety about using these agents in patients with coronary heart disease or heart failure; however, controlled observations soon alleviated these anxieties.^{29,30}

CASE PRESENTATIONS

The author had reported thirteen-cases of serious acute cardiac presentations post-oral sildenafil. The study was conducted in both Fraskour Central Hospital and physician outpatient. The author reported thirteen cases of variant acute cardiac events through about 40-months, started on December 27, 2015, ended on June 16, 2019. All cases were male. There was a different diagnosis for all cases. Four cases of unstable angina, three cases of anterior MI, one case of anterior and inferior MI, one case of inferior and RV MI, one case of anterior MI with Right Bundle Branch Block (RBBB), two cases of inferior MI, one case of VF were the total diagnosis for the cases. Variable management and outcome for the cases were essential. Primary cardiovascular disorders implicated in differential diagnosis were excluded. Troponin test only was done for the eleven cases. All forms of nitrates or nitrites were never given. No reports for other workups. All eleven cases were received inhaled oxygen at 100%, 5 L/min, delivered by nasal cannula. More details see (Table 1).

Case No 1

A 50-year-old, carpenter, heavy smoker, marijuana abuse, Egyptian male patient presented in the emergency department with severe anginal chest pain, and hypotension. Cardiac arrest had happened on processing the ECG. DCC and CPR had failed but the death was the end. The printed ECG showed ventricular fibrillation (VF); mostly by myocardial infarction. The relatives gave a recent history of ingestion of 50 mg sildenafil tablet (Figure 1).

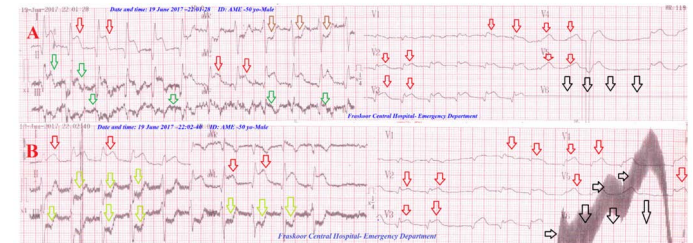
Figure 1. Case no 1; ECG tracing showing ventricular fibrillation



Case No 2

A 50-year-old, officer, Egyptian male patient presented in the emergency department with severe anginal chest pain, orthopnea, sweating, central cyanosis, and hypotension. Cardiac arrest had happened in the emergency room and after processing of the ECG. CPR was done but the death was the end. The ECG showed acute anterior and inferior STEMI with diverse change. Inhaled oxygen at 100%, 5 L/min, aspirin 75 mg 4 tablets, and clopidogrel 75 mg 4 tablets were immediately given. The relatives gave a recent history of ingestion of 25 mg sildenafil tablet (Figure 2).

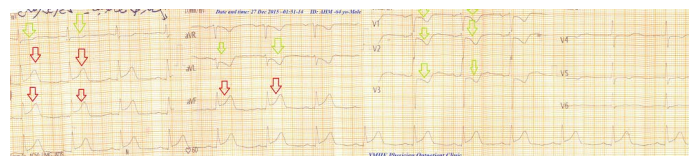
Figure 2. Case no 2: A-ECG tracing showing anterior (red arrows) and inferior MI (green arrows) with reciprocal ST-depression in aVR (brown arrows). Missed V6 lead mostly by sweating (black arrows), and sinus tachycardia. B-ECG tracing showing anterior (red arrows) and with inferior reciprocal ST-depression (lemon arrows). Missed V6 lead mostly by sweating (black arrows), and sinus tachycardia



Case No 3

A 64-year-old, farmer, heavy smoker, hashish abuse, Egyptian male patient presented to the physician outpatient clinic with vomiting, chest pain, sweating, dizziness, and hypotension. The ECG showed acute inferior and RV STEMI. Inhaled oxygen at 100%, 5 L/min, aspirin 75 mg 4 tablets, and clopidogrel 75 mg 4 tablets were urgently given and referred to ICU. The patient managed with streptokinase and anti-cardiogenic shock therapy. PTCA with stent was the interventional therapy two-week later. Early sinus bradycardia, first-degree heart block, and late recurrent angina were the main complications. The relatives gave a recent history of ingestion of 100 mg sildenafil tablet (Figure 3)

Figure 3. Case no 3: ECG tracing showing inferior anterior; II, III, aVF (red arrows) with reciprocal ST-depression in anterior leads; I, aVL, and V1-3 (lemon arrows), sinus bradycardia, and first-degree heart block



Case No 4

A 60-year-old, worker, heavy smoker, Egyptian male patient presented in the emergency department with dyspnea and hypertension. The ECG showed extensive acute anterior STEMI with RBBB. The patient was admitted in ICU. The patient managed with streptokinase, inhaled oxygen at 100%, 5 L/min, aspirin 75 mg 4 tablets, clopidogrel 75 mg 4 tablets, and other anti-ischemic measures. CHF was the main complications. The patient gave a recent history of ingestion of 50 mg sildenafil tablet (Figure 4).

Figure 4. Case no 4: ECG tracing showing RBBB (blue arrows), anterior MI; aVL, V1-6, and I: ST-elevation (red arrows), pathological Q (brown arrows) with inferior reciprocal ST-depressions in anterior leads; II, III, aVF (lemon arrows)



Case No 5

A 60-year-old, worker, heavy smoker, marijuana abuse, Egyptian male patient presented in the emergency department with severe anginal chest pain with hypertension. The ECG showed acute inferior STEMI.

The patient was admitted in ICU. The patient managed with inhaled oxygen at 100%, 5 L/min, aspirin 75 mg 4 tablets, clopidogrel 75 mg 4 tablets, and SL captopril 25 mg tablet were immediately given. The wife gave a recent history of ingestion of 100 mg sildenafil tablet with daily using the same dose. Unfortunately, the patient refused the ICU admission.

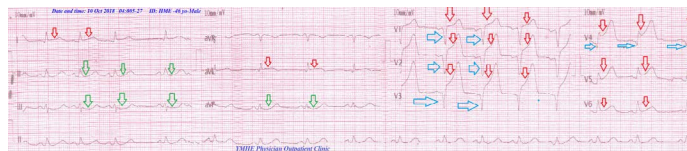
Case No 6

A 67-year-old, driver, heavy smoker, Egyptian male patient presented in the emergency department with severe anginal chest pain with hypertension. The ECG showed acute inferior STEMI. The patient was admitted in ICU. The patient managed with streptokinase, Inhaled oxygen at 100%, 5 L/min, aspirin 75 mg 4 tablets clopidogrel 75 mg 4 tablets, other anti-ischemic measures, and anti-hypertensive therapy. CHF was the main complications. The relatives gave a recent history of ingestion of 50 mg sildenafil tablet.

Case No 7

A 46-year-old, driver, heavy smoker, hashish abuse, Egyptian male patient presented to the physician outpatient clinic with severe anginal chest pain with hypotension. The ECG showed extensive acute anterior STEMI. The patient was referred to ICU. The patient managed with streptokinase, anti-ischemic measures, and anti-cardiogenic shock therapy. PTCA with stent was the interventional therapy on the same day. The patient gave a recent history of ingestion of 100 mg sildenafil tablet. Unfortunately, death had happened within 6-months after CHF (Figure 5).

Figure 5. Case no 7: ECG tracing showing extensive anterior MI (red arrows), pathological Q (blue arrows) with inferior reciprocal ST-depression (green arrows)



Case No 8

A 63-year-old, farmer, tobacco smoker, hashish abuse, Egyptian male patient presented to the physician outpatient clinic with severe anginal chest pain, irritability, and hypotension. The ECG showed extensive acute anterior STEMI. The patient was referred to ICU. The patient managed with streptokinase, inhaled oxygen at 100%, 5 L/min, aspirin 75 mg 4 tablets, clopidogrel 75 mg 4 tablets, other anti-ischemic measures, and anti-cardiogenic shock therapy. PTCA with stent was the interventional therapy two-days later. CHF was the main complications. The relatives' patient recent history of ingestion of 50 mg sildenafil tablet.

Case No 9

A 40-year-old, blacksmith worker, tobacco smoker, marijuana abuse, Egyptian male patient presented to the physician outpatient clinic with severe anginal chest pain, irritability, and hypertension. The ECG showed acute anteroseptal STEMI. The patient was referred to ICU. The patient managed with streptokinase, inhaled oxygen at 100%, 5 L/min, aspirin 75 mg 4 tablets, clopidogrel 75 mg 4 tablets, and other anti-ischemic measures. PTCA with recanalization of LAD was the interventional therapy two-days later. Recurrent angina was the main complications. The patient gave a recent history of ingestion of 50 mg sildenafil tablet.

Case No 10

A 50-year-old, benzene seller, smoker, Egyptian male patient presented to the physician outpatient clinic with severe anginal chest pain. The ECG showed no abnormality. The patient was referred to ICU as unstable angina. The patient managed with inhaled oxygen at 100%, 5 L/min, aspirin 75 mg 4 tablets, clopidogrel 75 mg 4 tablets, and other anti-ischemic measures. Recurrent angina was the main complication. The patient gave a recent history of ingestion of 25 mg sildenafil tablet.

Case No 11

A 50-year-old, carpenter, smoker, Egyptian male patient presented to the physician outpatient with severe anginal chest pain and near syncope. The ECG showed incomplete RBBB and S1Q3T3 pattern. The patient was referred to ICU as unstable angina with suspicion of pulmonary embolism. The patient managed with inhaled oxygen at 100%, 5 L/min, aspirin 75 mg 4 tablets, clopidogrel 75 mg 4 tablets, other anti-ischemic measures, and heparin. Recurrent angina was the main complications. The relatives gave a recent history of ingestion of 50 mg sildenafil tablet (Figure 6). Pulmonary embolism was excluded.

Figure 6. Case no 11: ECG tracing showing S1Q3T3 pattern (red arrows) incomplete RBBB (green arrows)



Case No 12

A 60-year-old, farmer, smoker, Egyptian male patient presented to the physician outpatient clinic with severe anginal chest pain and sweating. The ECG showed T-wave widening and sinus tachycardia. The patient was referred to ICU as unstable angina. The patient managed with inhaled oxygen at 100%, 5 L/min, aspirin 75 mg 4 tablets, clopidogrel 75 mg 4 tablets, other anti-ischemic measures, and heparin. CHF was the main complications. The patient gave a recent history of ingestion of 100 mg sildenafil tablet (Figure 7).

Figure 7. Case no 12: ECG tracing showing wide T-wave (red arrows) and sinus tachycardia



Case No 13

A 75-year-old, farmer, smoker, Egyptian male patient presented to the physician outpatient clinic with severe anginal chest pain and dizziness. The ECG showed no significant abnormality. The patient was initially diagnosed as unstable angina. Unfortunately, the patient refused the ICU admission. The patient managed with inhaled oxygen at 100%, 5 L/min, aspirin 75 mg 4 tablets, clopidogrel 75 mg 4 tablets, other anti-ischemic measures, and heparin. The patient gave a recent history of ingestion of 50 mg sildenafil tablet. The patient is psychiatric with there was a history of depression on clomipramine 50 mg tablet. For more details for all the study cases (Table 1).

Table 1. Summary of the History, Clinical, and Management Data for the Study Cases

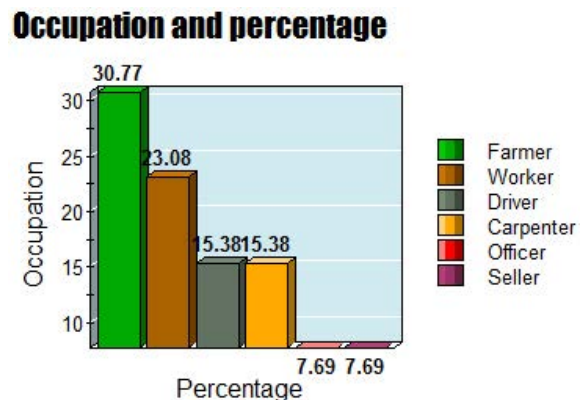
Case No.	Age	Sex	The main complaint	BP	Pulse	RR	O2 Sat. %	Associated RF	Final diagnosis	Outcome	Ingested dose/	Occupation
				mg Hg	bpm						mg	
1	50	M	Chest pain	80/50	Pulsless 120	30	78	Smoker, addict	VF+SCD	???MI+Death	50	Carpenter
2	50	M	Chest pain	90/70	60	42	84	Family history	Inf +Ant MI	CHF+Death	25	Officer Farmer
3	64	M	Vomiting	90/60	110	24	92	Smoker, addict	Inf +RV MI	Recur. angina	100	Worker
4	60	M	Dyspnea	150/90	86	18	98	Smoker	Ant MI +RBBB	CHF	50	Worker
5	60	M	Chest pain	160/110	104	20	95	Smoker, addict	Inf MI	Unknown	100	Driver
6	67	M	Chest pain	170/100	70	26	97	Smoker	Inf MI	CHF	50	Driver
7	46	M	Chest pain	90/60	78	28	91	Smoker, addict	Extensive ant	CHF+ death	100	Farmer
8	63	M	Chest pain	80/60	82	16	95	Smoker, addict	Ant MI	CHF	50	Worker
9	40	M	Chest pain	160/90	78	22	94	Smoker, addict	Ant MI	Recur. angina	50	Seller
10	50	M	Chest pain	140/80	62	18	96	Smoker , obese	UA	Recur. angina	25	Carpenter
11	50	M	Chest pain	110/80	140	24	96	Smoker	UA	Recur. angina	50	Farmer
12	60	M	Chest pain	140/70	80	20	96	Smoker	UA	CHF	100	Farmer
13	75	M	Chest pain	130/80		14	95	Smoker	UA	Unknown	50	Direct

DISCUSSION AND RESULTS

Occupation

- Farmer; 30.77% (4 cases)
- Worker; 23.08% (3 cases)
- Driver; 15.38% (2 cases)
- Carpenter; 15.38% (2 cases)
- Officer; 7.69% (1 case)
- Seller; 7.69% (1 case) (Figure 8)

Figure 8. Showing the percentage of occupation for sildenafil



The Main Complaint

- Chest pain; 84.62%
- Vomiting; 7.69%
- Dyspnea; 7.69% (Figure 9)

Figure 9. Showing the main complaint post-using sildenafil

The Main Complaint and Sildenafil

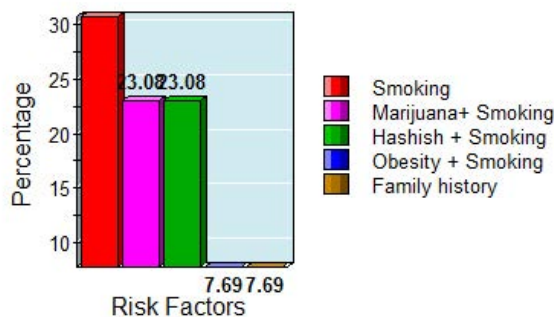


The Associated Risk Factors in the Study

- Male sex; 100% (13 cases)
- Age averages; Mean 56.53, Median: 60, Mode: 50
- Risk Factors (RF)
- Smoking; 38.46%
- Family history; 7.69%
 - And double RF
 - Addict + Smoking; 46.15%
 - Marijuana+ Smoking; 23.08%
 - Hashish + Smoking; 23.08%
 - Obesity + Smoking; 7.69% (Figure 10)

Figure 10. Showing the percentage of the associated risk factors on using sildenafil

Associated Risk Factors and Sildenafil



Averages of Ingested Dose/mg

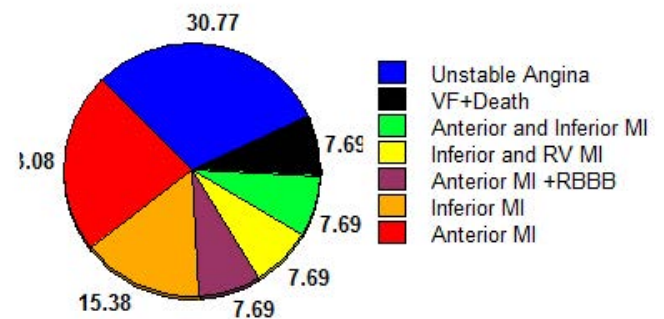
- Mean: 61.53, Median: 50, Mode: 50

The Final Diagnosis and Sildenafil

- Unstable Angina; 30.77% (4 case)
- VF and Death; 7.69% (1 case)
- Combined Anterior with Inferior MI; 7.69% (1 case)
- Inferior and RV MI; 7.69% (1 case)
- Anterior MI with RBBB; 7.69% (1 case)
- Inferior MI; 15.38% (2 cases)
- Anterior MI; 23.08% (3 cases) (Figure 11)

Figure 11. Showing the final diagnosis on using sildenafil

The Final diagnosis and Sildenafil



Outcome

- Death; 7.69% (1 cases)
- CHF; 30.77% (4 cases)
- CHF with Death 15.38% (2 cases)
- Recurrent angina; 30.77% (4 cases)
- Unknown outcome; 15.38% (2 cases) (Figure 12)

Figure 12. Showing the outcome on using sildenafil

Outcome and Sildenafil



CONCLUSION AND RECOMMENDATIONS

Sildenafil is one of the most serious drugs. Cardiovascular status of the patient should be taken into consideration before starting sildenafil drug in the treatment of erectile dysfunction. Awareness for the severe side effects of sildenafil is pivotal. Sildenafil may be a serious drug if

concurrently is taken in associated major risk factors such as smoking and substance abuse.

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CONFLICTS OF INTEREST

We hold that we have no conflicts of interest with any consistency.

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