

A blurred, long-exposure photograph of a hospital hallway, showing a perspective view down the corridor with lights and doors on the right side. The image has a strong blue and teal color cast.

Fluorouracil Induced Vasospasm: An often-unrecognized complication

David Reeves, PharmD, BCOP
Associate Professor & Clinical Pharmacy Specialist
Butler University & Franciscan Health



Medication Event

68-year-old male with colon cancer, receiving 46 hour 5-fluorouracil (5FU) continuous infusion CADD pump presented to the Franciscan Health Indianapolis Emergency Department complaining of chest pain.

No prior cardiac history

Triage nurse documented chemo being administered

ECG: hyperacute T waves with diffuse ST elevation and new onset atrial fibrillation with rapid ventricular response

Cardiac catheterization: moderate calcific proximal mid LAD disease not requiring intervention; cause of chest pain likely coronary artery vasospasm

5FU infusion went unnoticed and continued in the ED, Cath Lab, and throughout his transition to the CCU.

Patient called oncology clinic the next morning to notify of admission and to obtain guidance regarding his soon to finish CADD pump. Clinic nurse promptly went to CCU to discontinue pump.

5-Fluorouracil Therapeutics



Fluorouracil (5-FU) and its oral prodrug, capecitabine, are essential components of therapy for multiple malignancies

- Mainstay of therapy for gastrointestinal malignancies
- May be used in combination with radiation

Mechanism of action

- Prevent DNA replication by inhibiting thymidylate synthetase

5-FU may be given as a bolus infusion or as a continuous infusion over 2+ days

- Typical adverse effects: myelosuppression/cytopenia, mucositis, diarrhea, palmar plantar erythrodysesthesia

Capecitabine given twice daily continuously for 14 days of each 21-day cycle

- Adverse effect profile similar to 5-FU infusions (mucositis, diarrhea, palmar plantar erythrodysesthesia)

Trifluridine/Tipiracil

- Oral nucleoside analog and thymidine phosphorylase inhibitor
- Typical adverse effects: myelosuppression, diarrhea

5-FU Induced Cardiotoxicity



Cardiac toxicities - less acknowledged/recognized adverse effects of 5-FU/capecitabine

- Chest pain, acute coronary syndromes (including myocardial infarction)
- Other less common toxicities: atrial fibrillation, myocarditis, pericarditis, heart failure, sudden cardiac death

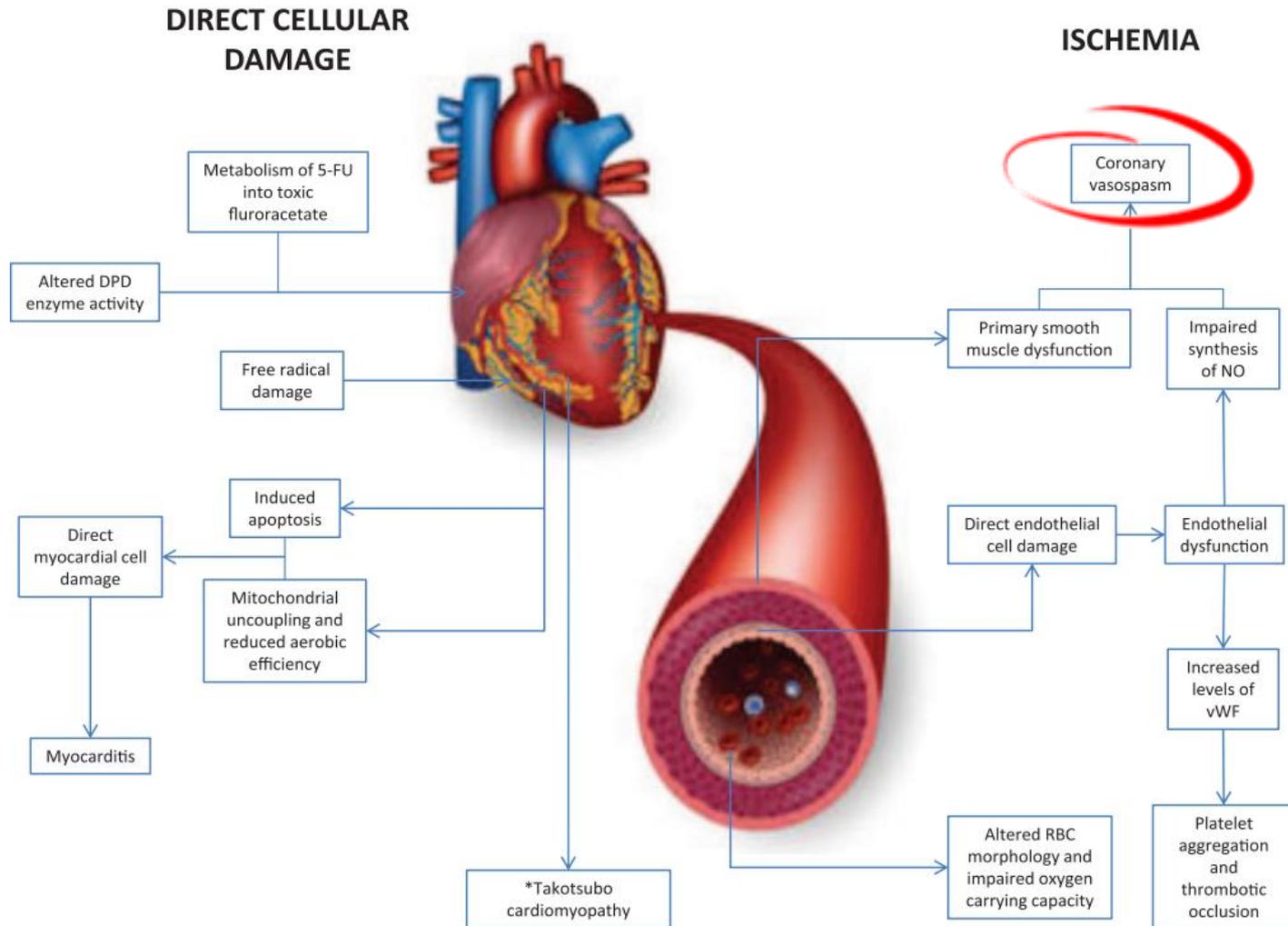
Coronary Vasospasm

- May have ECG findings (ST-segment elevation)
- May have biochemical evidence of myocardial injury (↑ troponin)
- Incidence:
 - 5-FU: 1-68%
 - Capecitabine: 3-35%
 - Trifluridine/tipiricil: Incidence unknown (one episode of cardiac ischemia among 800 patients in phase III trial)

Vasospasm Timing

- Typically, during first dose
- 12 hours following infusion initiation
- Could occur up to 1-2 days after infusion

Mechanism of 5-FU Induced Cardiotoxicity



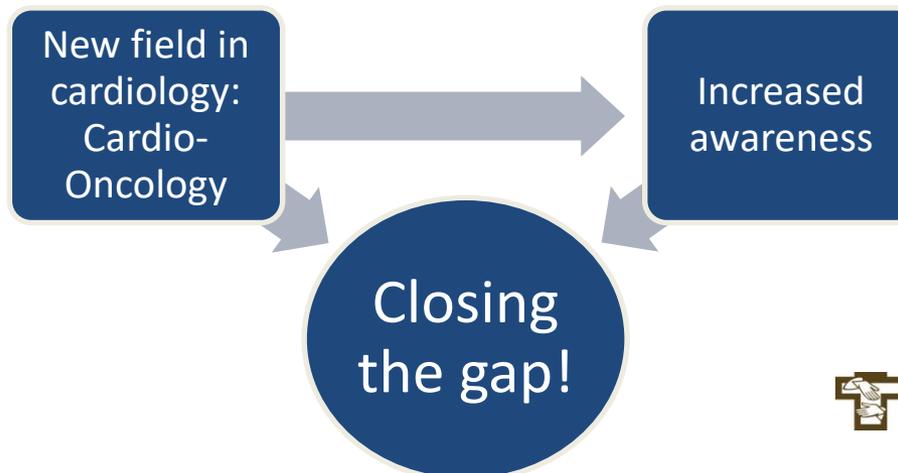
5-FU coronary vasospasm: often overlooked

Chest pain may be misinterpreted by patient

- Anxiety
- Gastrointestinal distress

Patients may not be asked during clinic appointment

Limited awareness among practitioners



5-FU Coronary Vasospasm Risk Factors

Age > 55?

Pre-existing renal disease?

Pre-existing cardiovascular disease?

- Ischemic heart disease
- Myocardial infarction
- Structural disease

Prior radiation therapy

Hypertension

Hyperlipidemia

History of smoking

Infusion regimen

- Infusional regimens (≥5 days) incidence: 2-18%
- Short term infusion regimens (i.e., 46 hours) incidence: 8.5%
- Bolus regimens incidence: 3%

DPD Deficiency?

5-FU Coronary Vasospasm Management

Immediate
cessation of 5-FU
or capecitabine

Symptomatic
management

Coronary
angiogram?

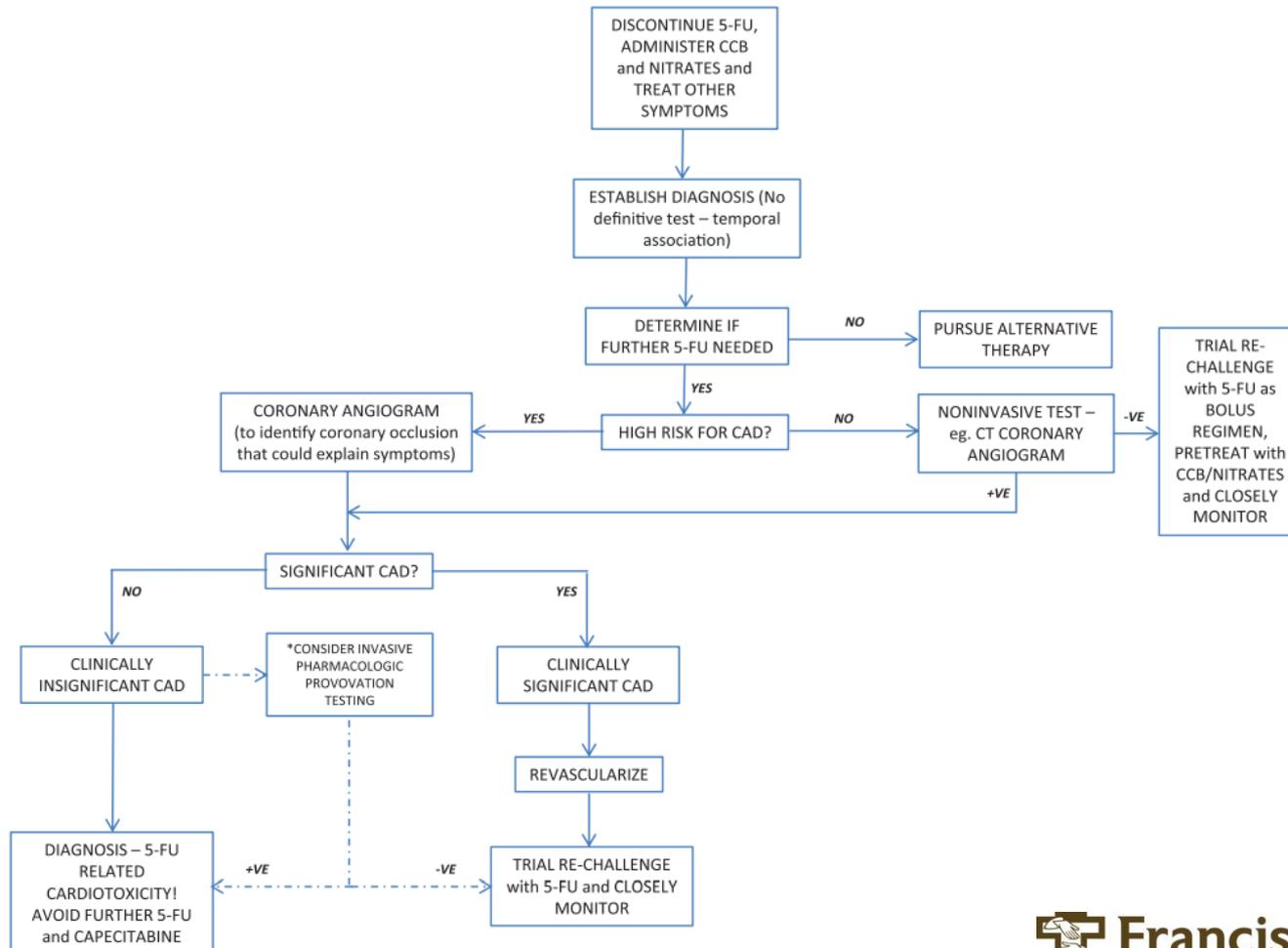
Prophylactic
nitrates and
calcium channel
blockers

Alternative
chemotherapies?

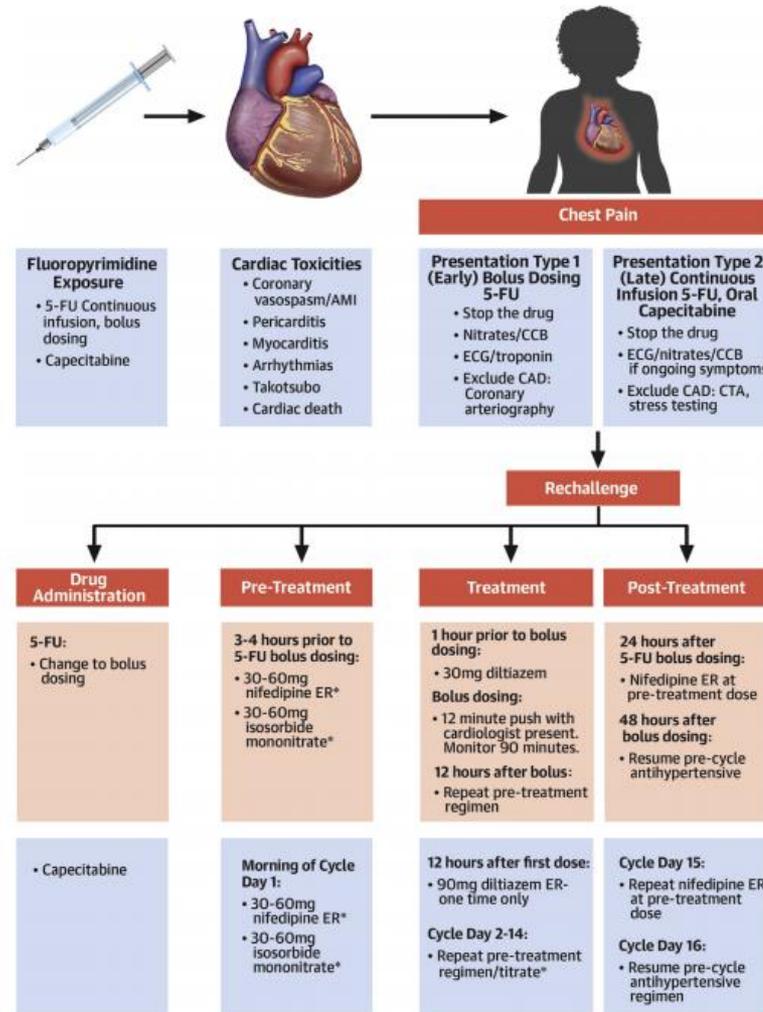
Inpatient
admission with
nitroglycerine drip

Antidote?

5-FU Coronary Vasospasm Management



Example of Re-challenge Protocol



* According to blood pressure

Role of Antidote in Vasospasm



Uridine triacetate (Vistogard)

- Approved in 2015 for patients with early-onset severe or life-threatening toxicities to 5-FU or capecitabine or for patients with an overdose
- Delivers high concentrations of uridine to compete with toxic 5FU metabolites
- Adult dose: 10g orally every 6 hours for 20 doses starting within 96 hours of the 5-FU or capecitabine administration

Open-label phase 2 clinical trial (n=142)

- 96% survived
- 2 patients presented with acute, life-threatening cardiotoxicity
- Rapid reversal of severe, acute cardiotoxicity (defined as cardiomyopathy)
- No mention of coronary vasospasm

Uridine triacetate average wholesale price: \$96,312/course of therapy

- Role in coronary vasospasm unknown at this time (especially given rapid resolution in majority of patients with vasodilator therapy)

Insights from a Community-Based Cardio-Oncology Cohort – The Franciscan Experience



Purpose

- Describe our experience with 5-FU-induced angina and coronary vasospasm at our community-based cardio-oncology practice and to highlight opportunities for improvement in the management of these patients

Methods

- Patients seen by the Franciscan Health Indianapolis cardio-oncology service for the management of 5-FU-induced coronary vasospasm between 01/2017 and 12/2019 were reviewed
- Data describing the presentation, work-up, management, and ability to tolerate re-challenge of 5-FU based chemotherapy was collected
- To determine the incidence of 5-FU-induced coronary vasospasm at our institution, a query of the electronic health record was completed to identify all patients receiving a 5-FU based chemotherapy regimen between 01/2017 and 12/2019

Franciscan Health's Experience: Results

15 out of a total of 437 patients (3.4%) receiving 5FU alone or in combination with other agents experienced angina or coronary vasospasm

Median time to onset of symptoms was cycle one (range: cycle 1 to cycle 4)

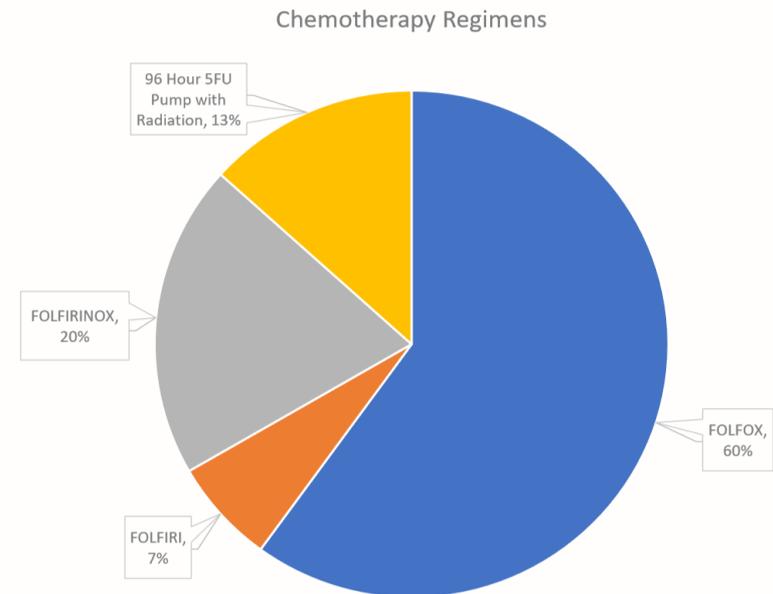
9 patients presented to emergency department (ED); 6 described angina during an office visit.

3 of 9 patients presenting to ED had acute ST-elevation myocardial infarctions prompting emergent cardiac catheterizations

- 2 patients had no coronary disease and one had a 50% coronary lesion treated medically

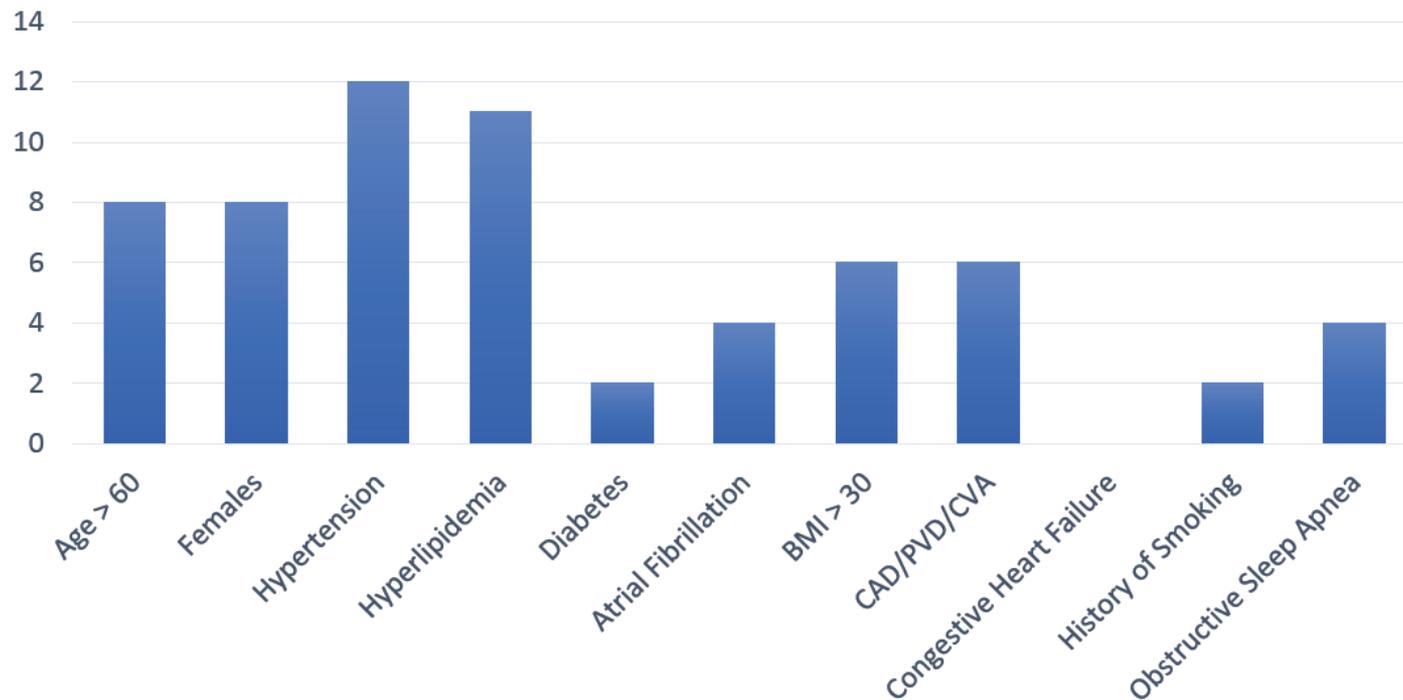
All three STEMI presentation patients did not have their 5FU continuous-infusion pumps discontinued until after their cardiac catheterization was complete

All patients experiencing angina were referred to the cardio-oncology service for further management

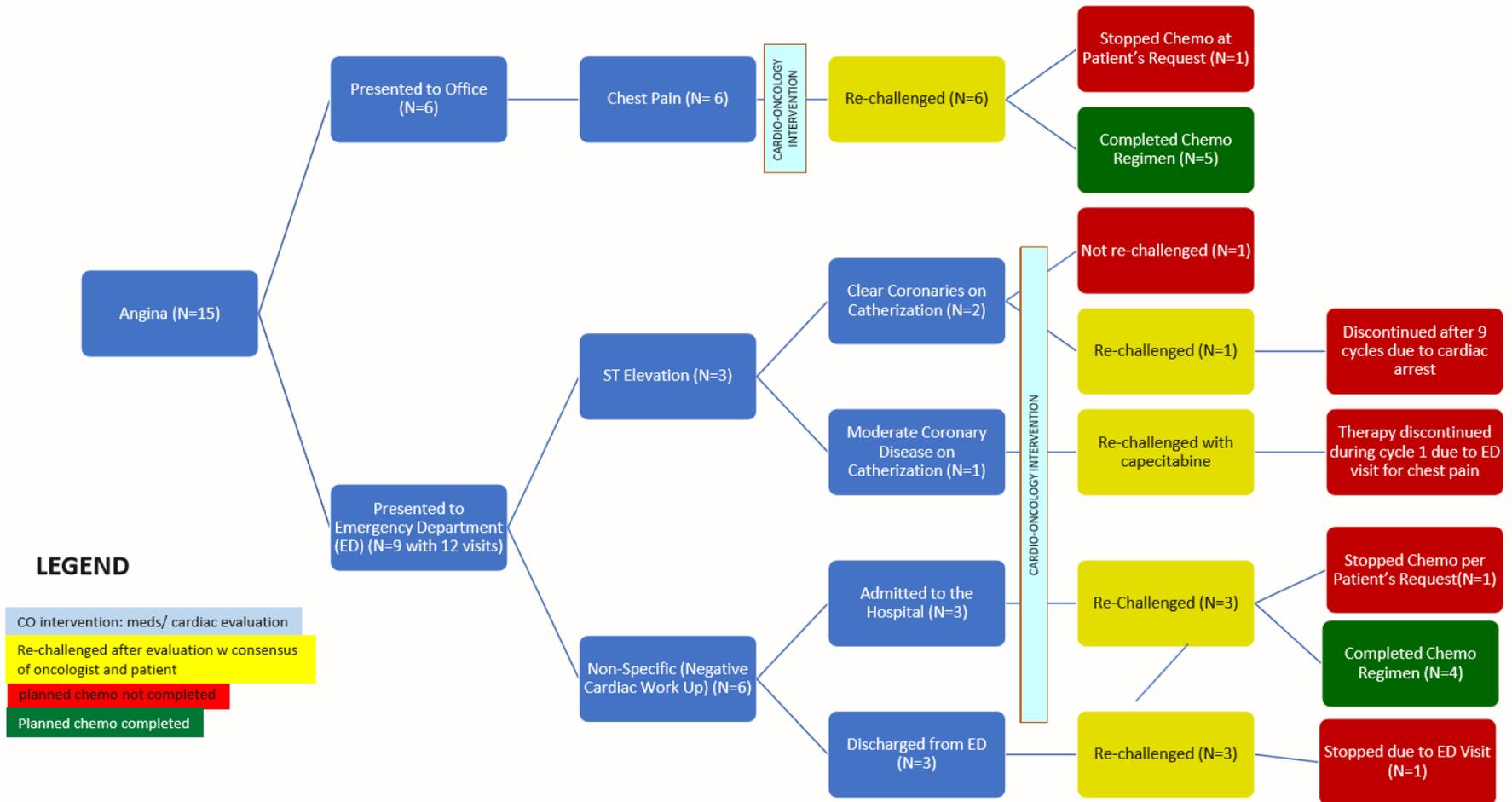


Franciscan Health's Experience: CV Risk Factors

Baseline Patient CV Risk Factors (N=15)

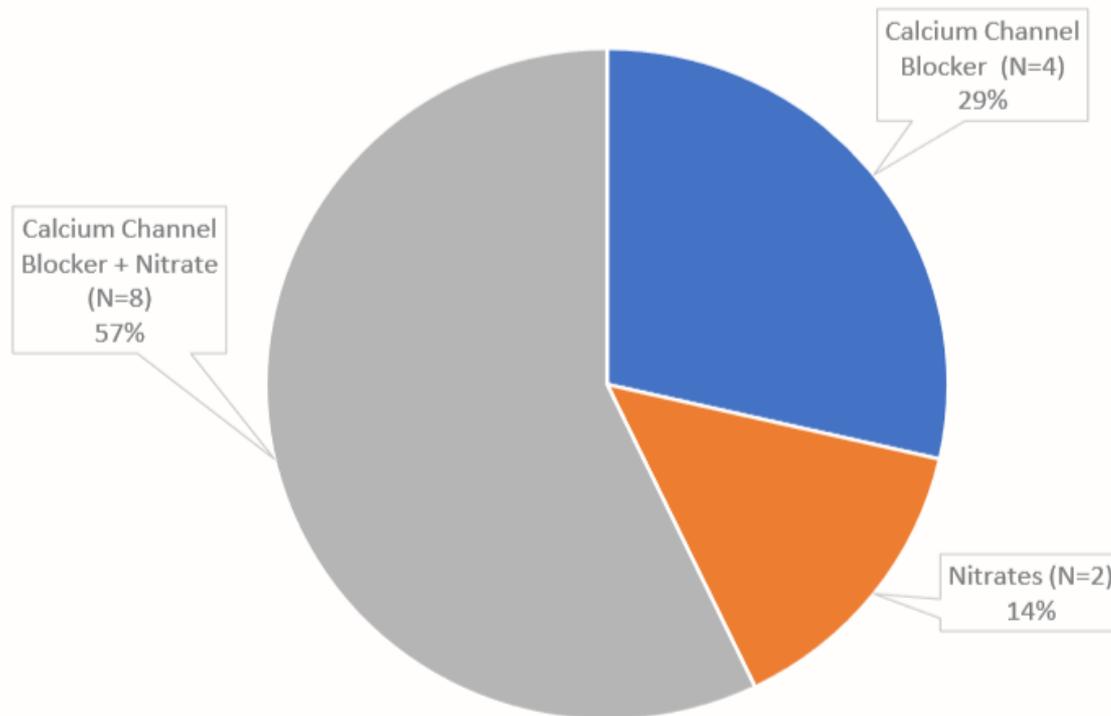


5FU Re-Challenge



Management of Patients Re-Challenged

Medical Management of Patients Re-challenged



Opportunities

Appropriate management relies on prompt identification of 5-FU as a potential cause of angina or coronary vasospasm



Increase awareness among cardiac, emergency care, and oncology providers



Ensure easy identification of patients receiving 5-FU infusions within the emergency care setting

Steps taken at Franciscan Health Indianapolis

- Implementation of a large, bright blue tag on continuous ambulatory delivery devices with instruction for emergency care providers (Franciscan Health Indianapolis Infusion Nurses Improvement Initiative)
- Implementation of a wallet card for each patient including information about their oncology treatment regimen
- Implementation of a pink warning sticker on infusion port dressing
- Education of providers within the following settings: emergency department, cath lab, and cardiac care unit



**IF CARDIAC ISSUES
STOP CHEMO PUMP**

ACKNOWLEDGEMENTS:

Kerry Skurka RN, BSN

Vijay Rao MD PhD

Meghana Raghavendra MD

***Franciscan Health Indianapolis
Cardio-Oncology Program***

Fluorouracil Induced Vasospasm: An often-unrecognized complication

David Reeves, PharmD, BCOP
Associate Professor & Clinical Pharmacy Specialist
Butler University & Franciscan Health

 **Franciscan** HEALTH