Research Square

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Managing 5-fluorouracil cardiotoxicity worldwide: do cardio-oncologists practice differently?

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Abstract

Aim: Fluoropyrimidines (5-fluorouracil and capecitabine) are cornerstones of cancer therapies but are associated with significant cardiotoxicity. This study aimed to compare pre- and post-cardiovascular event management practices between cardio-oncologists and other cardiologists during fluoropyrimidine treatment.

Methods: An academic web-based survey, designed by cardio-oncologists and oncologists, assessed practices.

Results: 253 cardiologists answer to the survey **(**75% European, 30% cardio-oncologists). Before fluoropyrimidine treatment, cardio-oncologists performed fewer routine echocardiograms and ischemia screenings tests in asymptomatic patients, with no differences for those with previous coronary artery disease. Temporary 5-fluorouracil contraindication was frequent in cases of suspected coronary disease (70 to 73%), with preventive strategies favoring calcium channel blockers and nitrates over beta-blockers. Up to 46% contraindicated 5-fluorouracil for asymptomatic significant coronary stenosis, with non-specialists being more likely to do so (p=0.004). Cardio-oncologists were more likely to recommend 5-fluorouracil rechallenge after acute coronary syndrome (93.3% vs. 78.0%), vasospasm (98.3% vs. 72.4%), heart failure (96.0% vs. 81.0%) or Takotsubo syndrome (100% vs. 93.9%) ($p < 0.05$ for all comparison), but not after atrial fibrillation (96.0% vs. 98.4%, p=0.137). Rechallenge timing varied: less than one month for vasospasm/atrial fibrillation, and 1–3 months for other events with significantly shorter delays among cardio-oncologists ($p<0.05$). Intensive care units were preferred for severe events, whereas conventional wards were considered sufficient for atrial fibrillation or heart failure.

Conclusion: Practices differ significantly according to the level of expertise in cardio-oncology, with specialists favoring earlier and more nuanced rechallenge strategies. The findings underscore the need for standardized protocols for 5-fluorouracil reintroduction.

Lay summary

The study highlights the following key findings:

- Before fluoropyrimidine administration, cardio-oncologists were more selective than general cardiologists in ordering cardiac investigations (such as echocardiograms or stress tests) for asymptomatic patients, focusing only on those at higher risk. This suggests a more targeted approach to avoid unnecessary tests.

- Calcium channel blockers and nitrates were preferred over beta-blockers for preventing cardiac complications, reflecting the role of coronary vasospasm as the most common form of cardiac toxicity (reported by 74% of physicians).

- Cardio-oncologists were more likely to recommend restarting 5-FU after events such as acute coronary syndrome, vasospasm, heart failure or Takotsubo syndrome.

- Cardio-oncologists tended to an earlier reintroduction of 5-FU (within a month) after vasospasm or atrial fibrillation, whereas a delay of 1–3 months was suggested for more severe events like acute coronary syndrome or heart failure.

- Reintroducing 5-FU was most often performed in intensive care units for severe events, while milder cases were managed in standard hospital wards.

Introduction

Fluoropyrimidines, including 5-fluorouracil (5-FU) and its oral prodrug capecitabine, are cornerstones of chemotherapy regimens for a wide range of cancers.[1] While generally well tolerated, these agents are associated with a well-documented spectrum of cardiotoxicity, ranging from myocardial ischemia (including coronary vasospasm) and atrial fibrillation (AF) to heart failure (HF), myocarditis, and Takotsubo syndrome.[2,3] Fluoropyrimidines are considered one of the most cardiotoxic chemotherapeutic agents.[2] Despite these risks, recent studies—particularly in patients with gastrointestinal cancers—have demonstrated a significant overall survival benefit associated with fluoropyrimidine-based chemotherapy, which outweighs the potential cardiac complications.[4–7] Efforts to identify predictors of fluoropyrimidine cardiotoxicity have not yet yielded a validated risk stratification tool. Several studies have found no association between traditional cardiovascular risk factors and higher rates of fluoropyrimidine-induced cardiotoxicities.[8–10] **In particular, Lyhne et al. found that subclinical coronary artery disease (CAD), as assessed by coronary artery calcium score, does not predict the risk of cardiotoxicity in cancer patients receiving fluoropyrimidine treatment**.[11] Current European guidelines recommend at baseline cardiovascular risk assessment using SCORE2 and advocate for CAD screening in high-risk patients, although the level of supporting evidence remains low.[2] Moreover, no cardiovascular preventive strategy has yet demonstrated efficacy in reducing cardiotoxicity in randomized controlled trials. The reported recurrence rate of cardiac complications is highly variable, ranging from 10 to 50% of patients following re-exposure to fluoropyrimidines, even among those receiving anti-anginal therapy.[8,12] One of the most pressing unanswered questions concerns the optimal management of fluoropyrimidine therapy following a cardiac event, particularly regarding the optimal medical treatment, the appropriate setting (intensive care unit, conventional ward, etc.), and the timing of fluoropyrimidine reintroduction. This study aimed to evaluate the practices of cardiologists (cardio-oncologists vs. other cardiologists) both before fluoropyrimidine administration and after a cardiovascular event during this treatment, using a survey.

Methods

Survey Design and Validation

This investigator-initiated survey was initially designed and drafted in English by the Cardio-Oncology Working Group of the French Society of Cardiology. The survey was developed, optimized, revised, and

approved by a panel of cardiologists, including board members of the Cardio-Oncology Working Group and French oncologists (see Supplementary Material). E.H. and P.Y.C. performed the final editing and implemented the survey on SurveyMonkey® (Momentive, Waterford, NY, USA). It comprised 27 questions, divided into sections for cardiologists and oncologists; this article focuses exclusively on the responses from cardiologists. The cardiologist survey is available in the Supplementary Material. The human ethics and consent to participate declarations are not applicable in the present study in accordance with the Declaration of Helsinki.

Survey Distribution

After validation, the survey was published on the SurveyMonkey platform and distributed via email to the mailing lists of the Cardio-Oncology Working Group of the French Society of Cardiology and the French Young Cardiologists in Training group. The survey link was also shared on several social media platforms and during the national French congress of cardio-oncology. Data collection occurred over a two-month period, from October 18, 2025, to December 18, 2025.

Statistical Analysis

Continuous variables with a normal distribution were summarized as mean ± standard deviation (SD), while skewed distributions were presented as median and interquartile range [IQR]. Categorical variables were expressed as percentages. Subgroup comparisons were performed using analysis of variance (ANOVA) for normally distributed continuous variables and appropriate non-parametric tests for non-normally distributed variables. A pre-specified subgroup analysis was conducted to compare self-declared cardio-oncology specialists with non-specialists. All analyses were performed using SPSS software, version 20.0.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as a two-sided P-value <0.05.

Results

Participant Characteristics

A total of 253 cardiologists from 20 countries completed the survey between October 18, 2025, and December 18, 2025. Participant characteristics are presented in Table 1. The median age was 39 years [IQR: 32–47], and 50.6% (n=128) were female. Most participants were based in Europe (n=189, 75.0%), with 48.4% (n=122) practicing in university hospitals. Self-declared cardio-oncology specialists accounted for 30.0% (n=76) of respondents, and 42.3% (n=85) had an academic background. The majority (55.7%, n=112) reported managing at least one cardio-oncology case per week, while 78.6% (n=158) encountered fewer than four 5-fluorouracil (5-FU)-related cardiovascular events annually. Cardio-oncologists were generally older, more often female, and more frequently specialized in heart failure or cardiovascular imaging. In contrast, other cardiologists were more likely to work in private practice and perform interventional cardiology procedures. Cardio-oncologists also reported receiving more theoretical training and managing more 5-FU-related cardiovascular events (Table 1).

Pretherapeutic Management Before 5-FU Administration

According to respondents, coronary vasospasm was the most commonly reported manifestation of 5-FU–related cardiotoxicity (74.1%, n=149), followed by atherothrombotic acute coronary syndrome (18.9%, n=59), heart failure (4.5%, n=9), atrial fibrillation (1.5%, n=3), and myocarditis (1.0%, n=2). The pretherapeutic workup proposed for asymptomatic patients—stratified by cardiovascular risk profile (no risk factors, known risk factors, or established CAD)—is summarized in Supplementary Table S1 (all cardiologists) and Table 2 (comparison between cardio-oncologists and other cardiologists). Cardio-oncologists performed significantly fewer transthoracic echocardiograms in asymptomatic patients in primary prevention and less frequently screened for myocardial ischemia in those with cardiovascular risk factors. No differences were observed in the workup for asymptomatic patients with a history of CAD (Table 2, Figure 1).

Cardiologists were asked to evaluate four predefined clinical scenarios: chest pain suspicious for CAD, silent myocardial ischemia, symptomatic significant coronary stenosis, and asymptomatic significant coronary stenosis. The most common reasons for temporarily contraindicating 5-FU administration were suspicious chest pain (73.1%), silent myocardial ischemia (71.5%), and symptomatic significant coronary stenosis (70.0%), with no significant differences between cardio-oncologists and non-specialists. For asymptomatic significant coronary stenosis, 46.2% of respondents temporarily contraindicated 5-FU, with non-specialists more likely to do so (p=0.004). Calcium channel blockers and nitrates were preferred as preventive strategies over beta-blockers across all scenarios, particularly among cardio-oncologists with a statistically significant difference ($p \leq 0.001$ for all comparisons).

Coronary angiography was immediately recommended in 50.3% of cases with suspicious chest pain and 83.5% of cases with silent myocardial ischemia. Coronary revascularization, lipid-lowering therapy, and aspirin were widely endorsed. Percutaneous coronary intervention was more frequently indicated by non-specialists in symptomatic and asymptomatic significant coronary artery disease stenosis (p=0.0012 and $p<0.001$ respectively). All these data are summarized in Table 3 and Figure 2.

Cardiovascular Management After a Cardiovascular Event During 5-FU Administration Most cardiologists (69.5%, n = 137) reported being unaware of the existence of a 5-FU antidote, among those aware of the antidote (30.5%, n = 60), only two (1.0%) reported having ever used it. According to respondents, the estimated risk of cardiovascular event recurrence after a 5-FU-related cardiotoxic event was reported as <10% by 27.4% (n=54), 10–25% by 51.8% (n=102), 26–50% by 15.2% (n=30), and >50% by 5.6% (n=11). Reported modalities for 5-FU rechallenge post-event are detailed in Table 4. Respondents most frequently cited coronary vasospasm as a contraindication to 5-FU reintroduction (16.8%), compared with 2.5% for atrial fibrillation. Cardio-oncologists were more likely to recommend 5-FU rechallenge after acute coronary syndrome (p=0.005), coronary vasospasm ($p<0.001$), Takotsubo syndrome (p=0.037), and heart failure (p=0.003), whereas no difference was observed for atrial fibrillation (p=0.302; Figure 3 and Supplementary Table S2). Rechallenge was most often proposed in intensive care units in case of coronary vasospasm (47.0%), acute coronary syndrome (39.8%), and

Takotsubo syndrome (39.8%). Following acute heart failure, rechallenge was typically proposed in conventional cardiology wards (34.2%), and for atrial fibrillation, in conventional oncology wards (25.3%) (Table 4). Rechallenge location did not differ significantly, except for coronary vasospasm, which was more frequently managed in intensive care units by non-specialists (Figure 3 and Supplementary Table S2).

When 5-FU was reintroduced, cardiologists most commonly recommended a delay of less than one month after atrial fibrillation (79.3%) or coronary vasospasm (38.8%), and one to three months for Takotsubo syndrome (54.6%), acute coronary syndrome (54.5%), and heart failure (44.9%) (Table 4). Cardio-oncologists suggested earlier 5-FU reintroduction than non-specialists across all cardiovascular events ($p<0.05$ for all cardiovascular events, Figure 4 and Supplementary Table S3). Reported criteria for 5-FU reinitiation included restoration of sinus rhythm for atrial fibrillation (5.6%, n=11) and full recovery of left ventricular ejection fraction (LVEF) after Takotsubo syndrome (85.5%, n=147). For acute coronary syndrome, the following factors as reported by respondents influenced rechallenge decisions (in order of frequency): persistent myocardial ischemia (83.2%, n=164), complete coronary revascularization (77.7%, n=153), persistent heart failure (60.9%, n=120), post-infarction LVEF (56.9%, n=112), ventricular arrhythmias (45.2%, n=89), infarction type (STEMI vs. NSTEMI, 32.0%, n=63), and Killip class >2 (18.3%, n=36).

Discussion

This international survey provides critical insights into the real-world management of fluoropyrimidine-induced cardiotoxicity by cardiologists, revealing significant variations in clinical practice between cardio-oncologists and other cardiologists (Central Figure). Before initiating 5-FU therapy, cardio-oncologists adopted a more selective approach, performing fewer routine echocardiograms and myocardial ischemia screenings in asymptomatic patients—regardless of cardiovascular risk profile—while maintaining similar practices for patients with established coronary artery disease. This suggests a more targeted, risk-stratified pretherapeutic assessment among specialists, likely reflecting greater familiarity with the specific challenges of cardio-oncology. According to current European guidelines, systematic baseline cardiovascular risk assessment (Class I, level C) is recommended for all patients, including blood pressure measurement, ECG, lipid profile, HbA1c, and SCORE2 (or equivalent) evaluation.[2] Over 80% of surveyed cardiologists reported performing these assessments in patients undergoing primary prevention. A recent meta-analysis demonstrated that hypertension and smoking significantly increase the risk of fluoropyrimidine-induced cardiotoxicity, with relative risks of 1.52 and 2.22, respectively.[13] However, no randomized trials to date have shown that better control of cardiovascular risk factors reduces this risk. Notably, the risk of myocardial ischemia including coronary vasospasm does not appear to be associated with traditional cardiovascular risk factors.[9] In secondary prevention, the survey revealed that more than 90% of cardiologists recommended a comprehensive cardiovascular risk assessment and ECG for patients. Evidence indicates that the risk of coronary events doubles after six months of 5-FU or capecitabine treatment and patients with established coronary

artery disease face a substantially higher risk of coronary events during fluoropyrimidine therapy compared to non-coronary patients.[14,15] Therefore, optimizing cardiovascular risk factor control prior to treatment initiation appears crucial. Current guidelines recommend performing pretherapeutic transthoracic echocardiography only in patients with symptomatic cardiovascular disease and coronary artery disease screening tests only in high- or very-high-risk patients. The survey reveals that non-specialist cardiologists tend to perform these investigations more frequently than cardio-oncologists in patients without history of CAD, likely reflecting a cautious approach. However, this practice may incur unnecessary costs, delay cancer treatment and potentially limit access to care for other clinical scenarios.

Fluoropyrimidine-induced cardiotoxicity is a well-documented adverse effect with highly variable presentation reflecting a complex and multifactorial pathophysiology. Coronary vasospasm and acute coronary syndromes are most commonly reported, representing half of cases.[16] Several mechanisms have been proposed, including vascular endothelial damage followed by coagulation, ischemia secondary to coronary artery spasm, direct toxicity on the myocardium and thrombogenicity.[17] The management of patients presenting with symptoms of angina, symptomatic or asymptomatic significant coronary stenosis prior to fluoropyrimidine treatment remains unclear due to a lack of scientific evidence. Temporary contraindication of 5-FU was commonly reported in case of suspected coronary events (70–73% of cases), with calcium channel blockers and nitrates favored over beta-blockers as preventive strategies, aligning with the pathophysiological role of vasospasm as the predominant mechanism of 5-FU cardiotoxicity, as reported by 74.1% of respondents. Notably, only 46% of cardiologists contraindicated 5-FU for asymptomatic significant coronary stenosis, a decision more frequently made by non-specialists, underscoring divergent risk tolerance between the two groups. Coronary revascularization via angioplasty was more frequently proposed by non-cardio-oncologists, particularly in cases of asymptomatic significant coronary stenosis. This decision warrants individualized discussion, especially given the increased risk of gastrointestinal bleeding in patients with colorectal cancer.[18] While shortening the duration of dual antiplatelet therapy may help mitigate bleeding risk, it is important to note that patients with advanced-stage cancer also face a threefold higher risk of acute coronary events 6 months after the diagnosis[19] and have a higher risk of stent thrombosis.[20]

Following a cardiovascular event, the estimated recurrence risk was most commonly reported as 10–25%, consistent with prior literature.[8,21] Rechallenging after an acute cardiovascular event is proposed by the current guidelines after multidisciplinary team discussion, optimization of cardioprotective drugs and in the absence of an equivalent alternative anticancer drugs.[2] Cardio-oncologists were significantly more likely to recommend 5-FU rechallenge after acute coronary syndrome, vasospasm, heart failure or Takotsubo syndrome ($p < 0.05$), but similarly for atrial fibrillation, highlighting a nuanced event-specific approach to treatment reinitiation. The optimal timing of fluoropyrimidine rechallenge remains unclear in the absence of robust scientific evidence. In this survey, cardio-oncologists proposed earlier reintroduction across all event types ($p < 0.05$), particularly for vasospasm and atrial fibrillation (less than one month), compared to 1–3 months for other events. Criteria for rechallenge—such as absence of

persistent ischemia, complete revascularization, or recovered LVEF—were rigorously applied, with 85.5% of respondents prioritizing full LVEF recovery post-Takotsubo syndrome as mentioned in the guidelines.[2] The optimal clinical setting for fluoropyrimidine rechallenge remains undefined due to the lack of scientific evidence and should enable the secure resumption of fluoropyrimidine treatment under conditions deemed optimal by the physician, given the risk of recurrence. Intensive care units were preferentially chosen for severe events (e.g., vasospasm, acute coronary syndrome), while conventional wards were deemed sufficient for atrial fibrillation or heart failure. These findings illustrate the complexity of balancing oncologic efficacy with cardiac safety and emphasize the need for standardized, evidence-based protocols to guide 5-FU rechallenge and monitoring strategies. This consideration is particularly important in cases of coronary vasospasm, where specific protocols involving calcium channel blockers and nitrates—administered under cardiological supervision—have successfully enabled the continuation of fluoropyrimidine therapy.[21–24]

Limitations

Despite some strengths including a large international sample with diverse practice settings and a focus on real-world practices with subgroup analysis (cardio-oncologists vs. other cardiologists), our study has some limitations. First, the study is based on an open-access, survey-based design, so we cannot affirm that all the responders were physicians; cardio-oncologist competency was also self-reported, which may introduce selection bias. based on a self-declaration. Thus, it could represent a bias selection. Second, around 20% of participants did not complete all the questions which may represent an additional selection bias by excluding physicians who reported the highest level of uncertainty about their management approach in this scenario. Additionally, we noted an underrepresentation of non-European practices.

Conclusion

This international survey reveals significant variability in managing fluoropyrimidine-induced cardiotoxicity, with cardio-oncologists favoring more selective assessments and earlier 5-FU rechallenge. The absence of standardized protocols for 5-FU reintroduction—including timing, setting, and patient selection—remains a critical gap. Global efforts to develop evidence-based, unified guidelines are urgently needed to balance oncologic efficacy, cardiac safety, and patient-centered care in cardio-oncology.

Declarations

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Generative Artificial Intelligence: The central figure has been generated with notebook LM then modified by the authors.

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Authors' Contributions: Emilie Hot and Pierre-Yves Courand conceived and designed the study, acquired and analyzed the data, and drafted the manuscript. All authors contributed to the interpretation of the data, critically revised the manuscript for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work.

Data availability statement: The datasets generated and/or analyzed during the current study are not publicly available due to but are available from the corresponding author on reasonable request for reviewing process.

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Tables

Tables are available in the Supplementary Files section.

Figures

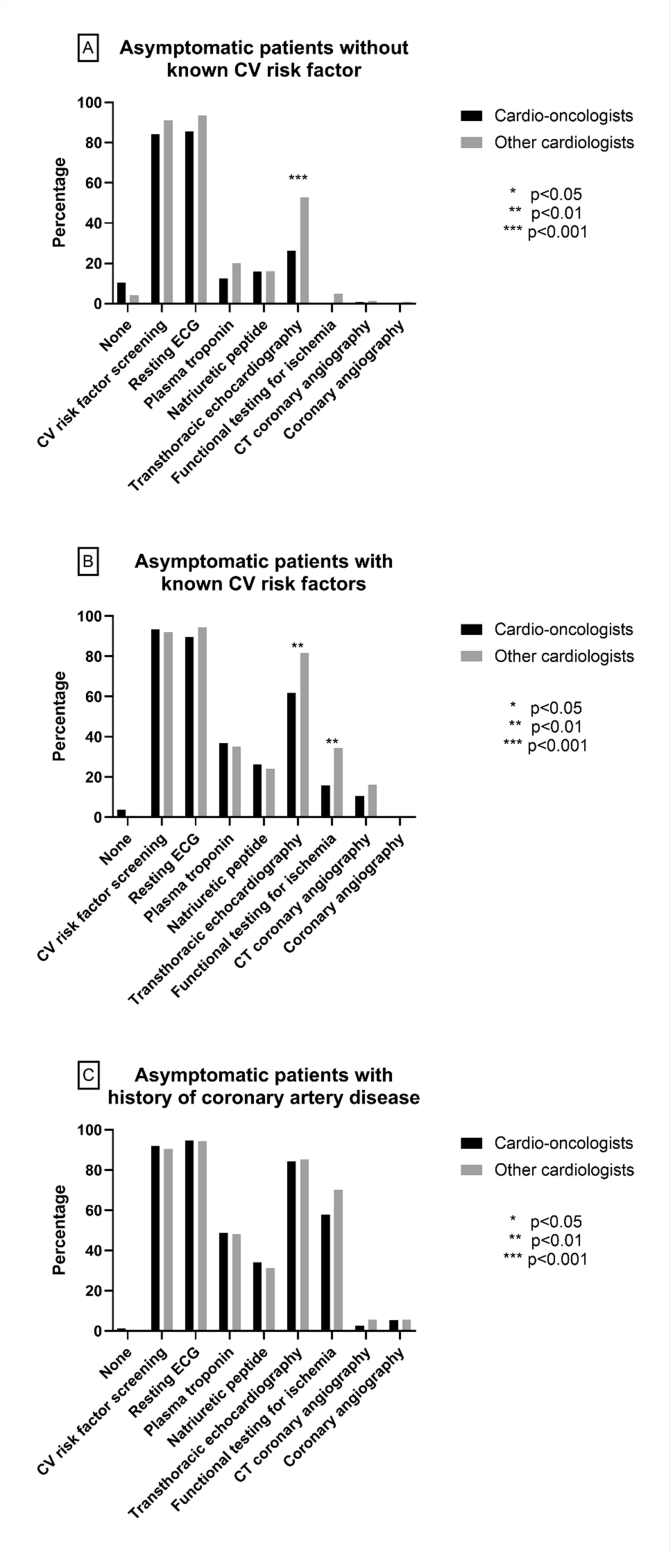


Figure 1

Pretherapeutic work-up before 5-FU administration in asymptomatic patients

CT: computed tomography, CV: cardiovascular

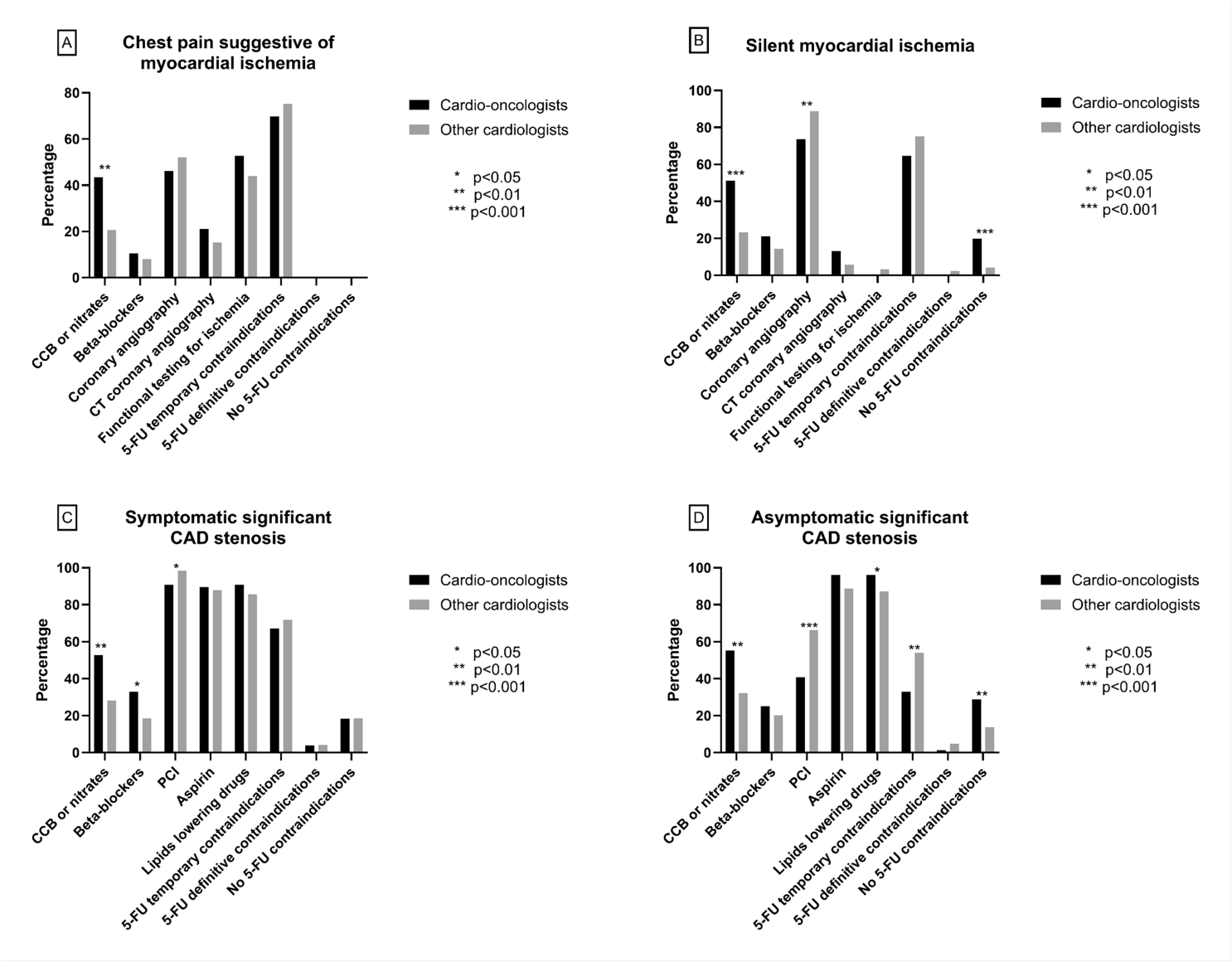


Figure 2

Pretherapeutic management before 5-FU administration in patients with suspected or confirmed coronary artery disease

CT: computed tomography, CCB: calcium channel blocker, CAD: coronary artery disease, PCI: percutaneous intervention, 5-FU: 5-fluorouracil

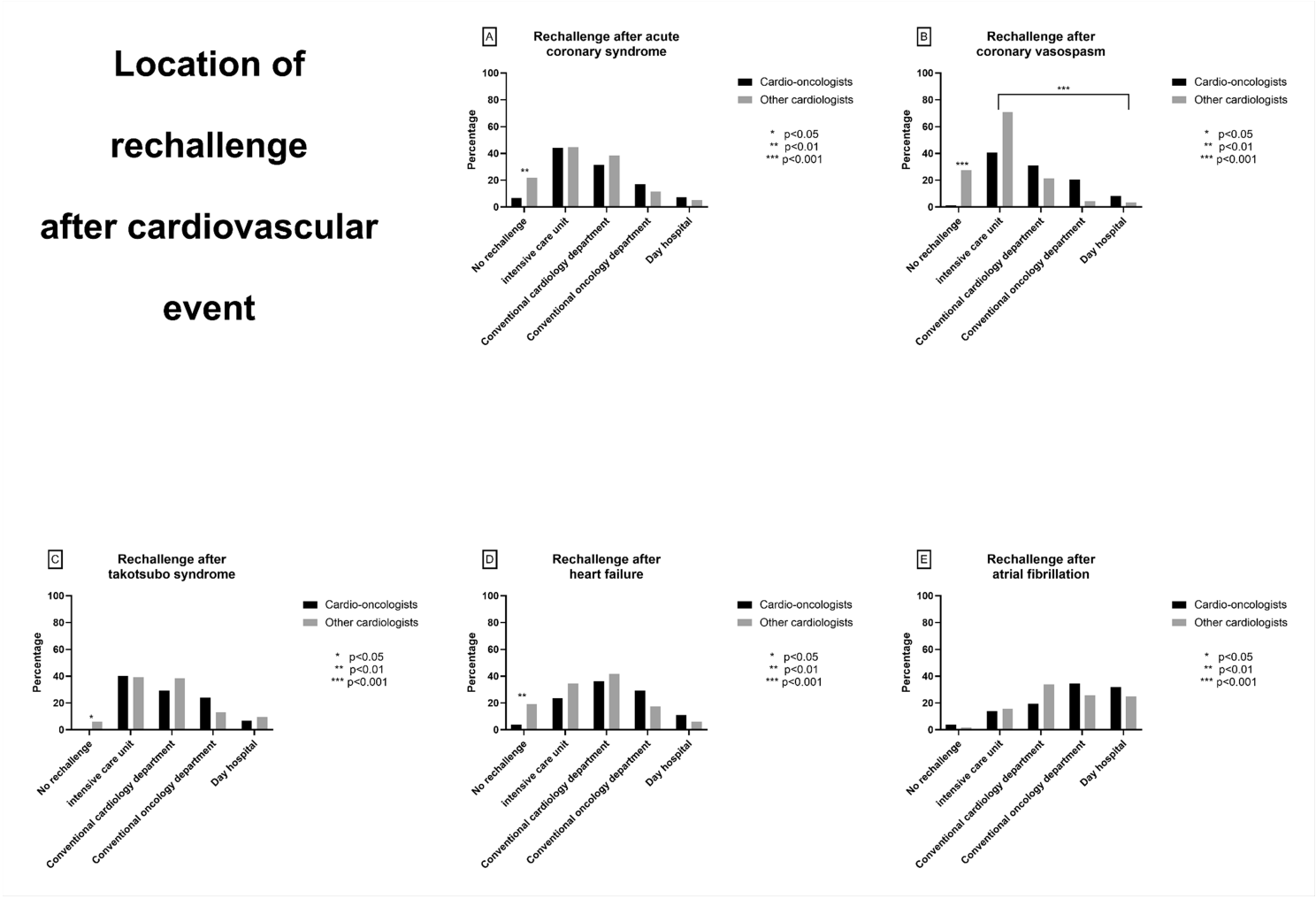


Figure 3

Location of rechallenge after cardiovascular events in patients treated with 5-fluorouracil

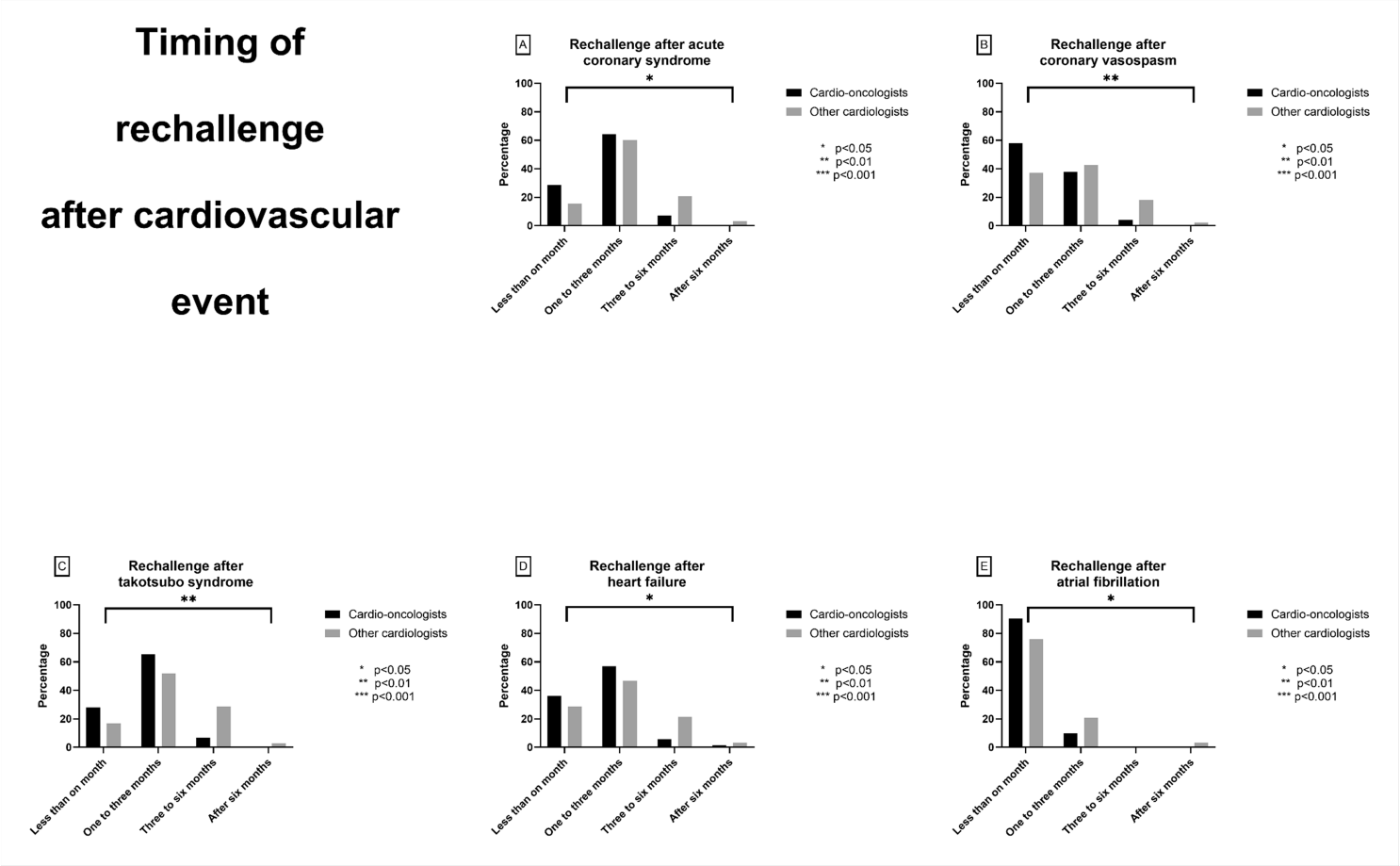


Figure 4

Timing of rechallenge after cardiovascular events in patients treated with 5-fluorouracil

Supplementary Files

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