**Effect of primary percutaneous coronary intervention on in-hospital outcomes among active cancer patients presenting with ST-elevation myocardial infarction: A propensity score matching analysis**

Short Title: pPCI in STEMI patients with current cancer

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# Abbreviations

MACCE Major Adverse Cardiovascular and Cerebrovascular Events

NIS National Inpatient Sample

OR Odds Ratio

PCI Percutaneous coronary intervention

PSM Propensity Score Matching

STEMI ST-Elevation Myocardial Infarction

Disclosures

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**Abstract**

**Introduction:** Primary percutaneous coronary intervention (pPCI) is the gold standard, guideline recommended revascularization strategy in patients presenting with ST-elevation myocardial infarction (STEMI). However, there are limited data on its use and effectiveness among patients with active cancer presenting with STEMI.

**Methods and Results:** All STEMI hospitalizations between 2004 and 2015 from the National Inpatient Sample were retrospectively analysed, stratified by cancer type. Propensity score matching was performed to estimate the average treatment effect of pPCI in each cancer on in-hospital adverse events, including major adverse cardiovascular and cerebrovascular events (MACCE) and its individual components, and compare treatment effect between cancer and non-cancer patients. Out of 1,870,815 patients with STEMI, 38,932 (2.1%) had a current cancer diagnosis (haematological: 11,251 [28.9% of all cancers]; breast: 4,675 [12.0%]; lung: 9,538 [24.5%]; colon: 3,749 [9.6%]; prostate: 9,719 [25.0%]). Patients with cancer received pPCI less commonly than those without cancer (from 54.2% for lung cancer to 70.6% for haematological vs. 82.3% in no cancer). Performance of pPCI was strongly associated with lower adjusted probabilities of MACCE and all-cause mortality in the cancer groups compared with the no cancer group. There was no significant difference in estimated average pPCI treatment effect between the cancer groups and non-cancer group.

**Conclusion:** pPCI is underutilized in STEMI patients with current cancer despite its significantly lower associated rates of in-hospital all-cause mortality and MACCE that is comparable to patients without cancer. Further work is required to assess the long-term benefit and safety of pPCI in this high-risk group.

**Key Words:** cancer, STEMI, percutaneous coronary intervention, management, outcomes

**Introduction**

Despite advances in multimodality oncology treatments including chemotherapy, targeted cancer therapeutics and radiotherapy, cancer remains the second leading cause of death globally.1 Cancer patients are at increased risk of cardiovascular disease, including coronary heart disease and heart failure, with causes attributed to patient-factors, malignancy itself, as well as its associated therapies. 2-9

ST-elevation myocardial infarction (STEMI) is the most acute manifestation of coronary heart disease and a leading cause of mortality globally.10 The management of STEMI has been transformed over the past two decades due to the wider availability of primary percutaneous coronary intervention (pPCI) and the timely provision of coronary revascularization, leading to a decline in STEMI-associated morbidity and mortality. 11, 12 Although pPCI has become the standard of care for STEMI presentations, there are limited data on whether cancer patients are as likely to be offered the intervention as those without cancer. Furthermore, it is unclear whether pPCI has comparable effectiveness in those with and without cancer presenting with STEMI.

We performed a propensity-score matched analysis of a nationwide sample of United States (US) hospitalizations between 2004 and 2015 to estimate the average treatment effect of pPCI in STEMI on in-hospital clinical outcomes among patients with different cancers and compare it to patients without active cancers.

**Methods**

*Data Source*

The National Inpatient Sample (NIS) is the largest publicly available all-payer database of hospitalized patients in the United States and is sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project (HCUP).13 It includes anonymized data on primary and secondary discharge diagnoses and procedures from more than 7 million hospitalizations annually. The NIS dataset was designed to approximate 20% stratified sample of United States hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population.14

*Study Design and Population*

This sample included adults (>=18 years) hospitalized for STEMI between January 2004 through September 2015. Data from October 2015 was recorded using a later version of the International Classification of Diseases (ICD) system, which has different definitions and classifications of diagnoses and procedures and was, therefore, not analysed. Retrospectively analyses were performed stratified by the presence or absence of current cancers in to 6 groups; no cancer, haematological malignancy, breast, lung, colon and prostate cancers. Haematological malignancies included lymphomas (Hodgkin’s and non-Hodgkin’s), leukaemias and multiple myeloma. Clinical and procedural characteristics, cancer diagnoses, and in-hospital clinical outcomes (other than mortality) were extracted from NIS using the International Classification of Diseases, ninth revision (ICD-9) procedure and diagnosis codes provided in the supplements (**Table S1**). Current cancer diagnoses were extracted using ICD-9 and Clinical Classification Software (CCS) diagnoses codes, respectively (**Table S2**). Primary PCI was identified as that performed on admission Day 1 using the ‘procedure day’ variables. Missing records (unweighted n=1,716, 0.4% of dataset) were excluded from the analysis, as were minors (age <18 years), cases undergoing other interventions such as fibrinolytic therapy (unweighted n=2,410), coronary artery bypass grafting (CABG) and cardiac implantable electronic device implantation (CIED) in order to isolate complications that could be attributed to PCI, and patients with multiple cancer sites. (Figure S1)

*Outcomes*

The primary outcome was major adverse cardiovascular and cerebrovascular events (MACCE), a composite of all-cause mortality, acute stroke or cardiac complications. Secondary outcomes included the components of MACCE as well as major bleeding, which was defined as any intracranial, gastrointestinal or post-procedural haemorrhage.

*Statistical Analysis (including propensity score matching)*

Statistical analysis was performed using Stata 15 (College Station, TX). For univariate comparison of characteristics between the groups, categorical variables were analysed using the chi-squared (X2) test and presented as percentages, while continuous variables were compared using the Kruskal-Wallis test and presented as medians with interquartile range (IQR).

Nearest neighbour propensity score matching (PSM) was performed in Stata within each of the study groups (no cancer, haematological, breast, lung, colon, and prostate) using the teffects psmatch command. This allowed us to estimate the average treatment effect of pPCI (vs. no PCI) on in-hospital outcomes within that group, which represents the difference in a subject’s outcomes with and without treatment. The teffects psmatch command runs logit models to generate estimate propensity scores for receipt of pPCI followed by PSM to estimate the average treatment effect of pPCI on in-hospital outcomes, expressed as coefficients with corresponding 95% confidence intervals (CI). The risk of pPCI complications and mortality was considered to be increased with positive coefficients and reduced with negative coefficients. PSM was also repeated with inclusion of patients who underwent diagnostic coronary angiography (CA) in the ‘no PCI’ group as a sensitivity analysis. Variables that each cohort was matched were selected a priori and included: age, sex (except in the breast and prostate cancer groups), hospital location/teaching status, weekend admission, smoking history, and the following comorbidities: atrial fibrillation (AF), heart failure, renal failure, hypertension, diabetes, anaemias, peripheral vascular disease (PVD), dyslipidaemia, chronic lung disease, dementia, thrombocytopenia, coagulopathies, anaemias (no cancer cohort only) and previous history of percutaneous coronary intervention or coronary artery bypass grafting, and year of admission. The following variables resulted in complete separation of data points and, therefore, were not included in PSM for cancer groups: anaemias (except in no cancer cohort), valve disease, previous MI and previous CVA. Comparison of average treatment effect coefficients between the no cancer and cancer groups was performed using the suest command in Stata.

To generate adjusted probabilities of primary and secondary outcomes in the pPCI and ‘no PCI’ groups, multivariable logistic regression models were performed in Stata with the inclusion of an interaction term between pPCI and study group (no cancer, haematological, breast, lung, colon, and prostate) followed by running the margins postestimation command, which reports adjusted probabilities for the outcome at different strata of interest.

**Results**

**Whole cohort**

A total of 1,870,815 hospitalizations for STEMI between 2004 and 2015 were included in the final analysis, including 1,831,883 hospitalisations (97.9%) with no current cancer diagnosis, 11,251 (0.6%) with haematological malignancy, 4,675 (0.2%) with breast cancer, 9,538 (0.5%) with lung cancer, 3,749 (0.2%) with colon cancer, and 9,719 (0.5%) with prostate cancer. The majority of patients without cancer received pPCI for STEMI (82.3%) whereas the rates of pPCI were much lower in the current cancer groups (54.2%-70.6% vs. 82.3%), especially those with lung cancer (54.2%). (**Table S3**)

*Patient and procedural characteristics*

 Several differences in sociodemographic and clinical characteristics were observed between patients in the pPCI and no PCI subgroups within each study group. (**Table S3**) Patients who underwent pPCI were generally younger and more likely to be male (all patients were male in the prostate cancer cohort), privately insured or self-payers, and admitted to larger bed size and urban teaching hospitals. Patients who underwent pPCI in the no cancer and current cancer groups had a lower prevalence of AF, anaemia, heart or renal failure, chronic pulmonary disease, dementia and previous AMI (except lung cancer group), and a higher prevalence of certain risk factors such as dyslipidaemia, ventricular arrhythmias and previous PCI (except in breast cancer). Furthermore, those who underwent PCI in the cancer groups were more likely to have cardiogenic shock compared to those who did not undergo PCI. Amongst those who underwent pPCI, patients with cancer were more likely to have a single vessel intervention and receive bare metal (vs. drug eluting) stents compared to those without cancer.

*In-hospital outcomes*

 The crude rates of MACCE, all-cause mortality, acute stoke and major bleeding were significantly higher in the ‘no-PCI’ compared to the pPCI groups in patients without cancer as well as in patients with different cancer types. (**Table S4**) Two exceptions were major bleeding in breast cancer patients and acute stroke in those with colon cancer, both of which were higher in the pPCI subgroup of the respective cancer. Amongst the pPCI groups, the unadjusted rates of adverse events (MACCE, all-cause mortality and major bleeding) were significantly higher in the cancer groups compared to those without cancer, and highest in the lung and colon cancer groups. Cardiac complications were significantly higher in the pPCI subgroup compared to ‘no PCI’ subgroups in cancer and no cancer groups, primarily driven by coronary dissection in the pPCI subgroups.

**Propensity score matched cohort**

*Patient and procedural characteristics*

After propensity score matching, a total of 111,738 weighted hospitalization records for STEMI were included in the analysis, including 104,222 (93.3%) with no current cancer diagnosis, 1,891 (1.7%) haematological malignancy, 1,019 (0.9%) with breast cancer, 2,330 (2.1%) with lung cancer, 670 (0.6%) with colon cancer, and 1,606 (1.4%) with prostate cancer. (**Table 1A**) Overall, there was a good balance of baseline characteristics between the PCI and no PCI groups in each of the cancer types in the propensity matched cohort, as evidenced by the minimal standardised bias (<5%) as well as t-test p-values (tables for each study group in Appendix A). Furthermore, histograms illustrating propensity scores pre- and post-matching for each study groups are illustrated in Appendix A. In terms of procedural characteristics, patients undergoing pPCI were more likely to require circulatory support in the form of LV assist device or IABP compared to those in receipt of conservative management (i.e. no PCI). (**Table 1B**) Amongst those who underwent pPCI, patients with breast and lung cancer were more likely to have a single vessel intervention compared to those without cancer, whereas those with haematological, prostate and colon cancers were more likely to receive multivessel PCI. Patients with cancers were also more likely to receive bare metal (vs. drug eluting) stents compared to those without cancer. The patterns observed in patient and procedural characteristics were persistent even after the inclusion of patients undergoing diagnostic CA in the ‘no PCI’ group. (**Table S5**)

*Average treatment effects*

The estimated average treatm­­­­­­­­­­­­­­­­­­ent effects derived from PSM demonstrated a strongly negative (protective) association between pPCI and MACCE as well as mortality in the no cancer and cancer subgroups. (**Table 2**) The average treatment effect of pPCI on MACCE and mortality in the cancer groups was at least equal to, or in some cases greater, than the no cancer group. The average treatment effect of PCI on major bleeding and acute stroke was insignificant in the cancer groups, except in colon cancer where PCI had a positive treatment effect on acute stroke. These findings persisted even with the inclusion of patients who underwent diagnostic CA in the ‘no PCI’ (reference) subgroups. (**Table S6**)

*In-hospital outcomes*

In the propensity matched cohort, the adjusted probabilities of MACCE, mortality and acute stroke, in both the no cancer and cancer groups were significantly lower in the pPCI groups compared to the no PCI groups (**Table 3**, **Figure 1**). One exception was the probability of acute stroke in colon cancer patients, which was higher in patients who underwent pPCI (1.5% 95% CI 1.1-1.9% vs. 0.3% 95% CI 0.0-0.5%). Although the adjusted probability of major bleeding was lower in those treated with pPCI in the no cancer group, there was no difference in major bleeding probabilities between pPCI and no PCI subgroups across all cancer groups. This pattern persisted even with the inclusion of patients who underwent diagnostic CA in the no PCI subgroups. (**Table S7**)

**Discussion**

 This is the first study to compare rates of utilisation of pPCI in STEMI patients with and without diagnosis of current cancer and reports several important findings. First, we find that among patients presenting with STEMI, those with active cancer received pPCI less commonly than those without cancer. Second, we observe that those with cancer who underwent PCI were more critically ill compared to those who did not undergo PCI as evidenced by their high rates of cardiogenic shock and need for circulatory support. Finally, we demonstrate that, depending on cancer type, pPCI had a similar or stronger treatment effect in cancer as in no cancer, with associated reduction of all-cause mortality and MACCE in both groups, and no increase in associated risk of major bleeding and acute stroke. Notwithstanding, all-cause mortality was higher in cancer patients than those without cancer even after management with pPCI.

 Despite the high risk of mortality associated with STEMI, ranging from 2.5% to 10% at 30 days, the adoption of pPCI and secondary preventative therapies has led to a significant improvement in its short and long-term prognoses.11, 12, 15-17 In comparison to the general population, cancer patients are at an increased risk of cardiovascular mortality, which often exceeds the index-cancer related mortality in certain cancer types, as well as stent thrombosis after PCI.18 8, 19-21 Equally, cancer patients are also at a high risk of bleeding due to factors such as tumour angiogenesis, increased use of anticoagulation, cancer-associated coagulopathies due to liver metastases, and thrombocytopaenia from bone marrow suppression.22 23 Together, these factors may bias operators towards a more conservative (medical) approach to management in this high-risk group.

There are limited outcomes data on cancer patients undergoing PCI, especially STEMI, as they are frequently excluded from randomised and observational studies, as well as from established ischemic and bleeding risk assessment scores such as GRACE and CRUSADE, respectively.24 25, 26 Previous data suggests that compared to patients without cancer, those with cancer are less likely to receive pPCI in the context of AMI and have worse associated outcomes.27 To date, there is a paucity of evidence to establish whether the benefit of pPCI in STEMI applies to those with active cancer, or whether any benefit is outweighed by bleeding or other complications.

The present study is the first to examine the rates of invasive management strategy for STEMI in patients with and without cancer, and shows that patients with active cancers, including haematological, breast, lung, colon and prostate were less likely to undergo pPCI. This finding may reflect concerns about the often elevated bleeding risk among patients with cancer and challenges imposed by the need for commitment to dual antiplatelet therapy (DAPT) for 6-12 months in case of receipt of PCI.28 This duration may be even longer in patients on chemotherapy, which delays endothelialisation of stents.29 The Society of Cardiovascular Angiography and Interventions (SCAI) consensus statement on the management of cardio‐oncology patients in the cardiac catheterisation laboratory recommends the consideration of percutaneous revascularisation even in cancer patients with an expected survival of less than 1 year.8 SCAI also recommends specific strategies to address the risk of PCI-related complications in cardio-oncology patients, including the use of balloon angioplasty over stenting in patients with platelets <30,000/mL, BMS in patients with an urgent need for surgery or chemotherapy (within 4 weeks), radial approach and micro-puncture techniques for vascular access, as well as the use of coronary imaging (intravascular ultrasound (IVUS) or optical coherence tomography (OCT)) to ensure optimal stent opposition. Other strategies that may reduce the bleeding risk in cancer patients include the use of less potent antiplatelet therapy (e.g. clopidogrel), avoidance of glycoprotein 2b/3a inhibitors wherever possible, and the use of drug coated/drug-eluting stent platforms requiring a shorter DAPT duration (e.g. 1 month) such as Biofreedom ™ DCS1 and Resolute Onyx stents. 30, 31 32 33

Our propensity matched analysis demonstrates that PCI was associated with significantly lower adjusted probabilities of MACCE and all-cause mortality in STEMI patients of all cancer types, and that the estimated treatment effect of PCI on their outcomes was similar to, or greater than that of patients without cancer. The significant association between PCI and MACCE as well as mortality in the cancer groups, with similar safety endpoints during the in-hospital phase has significant clinical implications. The present findings add to the currently limited evidence on STEMI management in cancer patients and would support interventional cardiologists’ clinical decision making when managing this high-risk population. Our findings also emphasise the need to study long-term outcomes of intervention (vs. conservative management) in active cancer patients presenting with STEMI.

Although a limited number of studies have demonstrated worse outcomes in cancer patients after AMI, they were not designed to estimate the treatment effects of PCI on clinical outcomes in this population compared to those without cancer.27 34 35 Furthermore, the proportion of STEMI cases in previous studies did not exceed a third of all cases. Although the association between PCI and outcomes such as mortality and bleeding has not been previously evaluated in cancer patients presenting with STEMI, previous studies have either compared PCI complications or AMI complications, separately, between patients with and without cancer.34, 36 36 In an analysis of the Bern PCI registry, Ueki et al. reported increased hazard ratios (HR) of all-cause and cardiac mortalities (HR 2.03, 95% CI 1.55-2.65 and 1.64, 95% CI 1.17-2.31) as well as BARC (Bleeding Academic Research Consortium) 2 to 5 bleeding (HR 1.55, 95% CI 1.14-2.11) in 1,368 cancer patients compared to those without cancer.34 There was no difference in BARC 2 to 5 bleeding between cancer groups whereas the hazard of cardiac mortality was significantly higher in cancer groups. However, their findings were derived from a small and heterogenous cohort of both AMI and stable patients. Our previous analysis by Bharadwaj et al. reported increased odds of MACCE, mortality and bleeding in AMI patients with current cancer (breast, lung, colon and prostate), including those with STEMI, but did not compare outcomes between PCI and no PCI groups.27

*Limitations*

There are several limitations to the current study. First, the administrative nature of the NIS database is susceptible to coding errors, although the use of ICD-9 codes for cardiovascular outcomes research has been previously validated.37, 38 Second, despite propensity matching addressing the possibility of selection bias, 39 it does not address the possibility of residual confounders such as patient wishes and reasons for not performing PCI. Third, the NIS dataset does not provide information on pharmacotherapy, including chemotherapy medications and antithrombotic therapy, and staging of cancer, which may have an impact on outcomes. Fourth, the NIS does not capture specific information such as PCI procedural complexity, characteristics of coronary lesions and operator experience. Fifth, our study only reports in-hospital outcomes and it is possible that the difference in survival and complication rates between patients with and without cancer could become more pronounced on long term follow up. Finally, although we were able to capture major bleeding events as defined by ICD-9 codes, the lack of certain elements of standardised bleeding definitions such as BARC or thrombosis in myocardial infarction (TIMI) precluded their calculation.

# Conclusion

 In the present nationwide analysis, we demonstrate that PCI is underutilised in STEMI patients with current cancer compared to those without cancer. PCI was associated with significantly lower rates of in-hospital all-cause mortality and composite MACCE compared with conservative medical management, both in cancer and no cancer patients, with no increased risk of in-hospital complications, including major bleeding and stroke. Further work is required to assess long-term outcomes, including cardiac mortality and safety, between intervention and conservative management strategies in active cancer patients presenting with STEMI. 40

# Conflicts

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), Level Ex, MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald’s Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda.

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# Figure title and legend

**Figure 1. Adjusted odds ratios (OR) and 95% confidence intervals (CI) of adverse events in the PCI subgroups\***

**Caption:** \*‘No PCI’ excludes those undergoing diagnostic coronary angiography, \*\*MACCE: Composite of mortality, acute stroke and cardiac complications