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Title	Relationship between initial treatment strategy in stable coronary artery disease and one-year costs: a population-based cohort study
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Reviewer 1	Dr. Sophia Papadakis
Institution	University of Ottawa Heart Institute, Division of Prevention and Rehabilitation, Ottawa, Ont.
General comments (author response in bold)	Comment #1: This paper reports on a large (n=39,126) chart review of administrative databases in Ontario to examine the relationship between type of therapy (medial vs revascularization) and hospital revascularization ratio in predicting 1 year cumulative health care costs when controlling for other patient level factor. The study was conducted by ICES investigators and offers important insights which may be useful in guiding future decision making regarding treatment strategy for patients with CAD. **We thank the reviewer for the kind comment.** Major: Comment #2: Medication costs – Authors report that the Ontario Drug database was used to obtain cost of medication for participants over the age of 65. Since inclusion criteria did not restrict participation to over 65 it would seem that this is a significant limitation of the study examining costs of medical treatment vs. revascularization in particular if there are any trends related to age in choice of treatment. Did the authors consider estimates to include in the costing. This should otherwise be more clearly highlighted in the study limitations. Given the overall direction of the findings would not change this would be a minimum strategy to address this point. **We thank the reviewer for pointing this out. In Ontario, medication data cannot be obtained for patients <65 years old because those costs rest on private insurance companies and/or patients, and is not paid for by the Ontario government. We agree that the societal costs are higher than our paper acknowledges. However, this costing paper is intended to be from the perspective of the third party payer of healthcare in Ontario, the Ministry of Health and Long Term Care. As such, the Ministry's prescription drug coverage is limited to patients >65 years old, which is why we did not provide estimates of medication cost for patients <65 years old. Selecting costs that are only relevant to the payer's perspective is consistent with the guidelines established by the Canadian Agency for Drugs and Technologies in Health.[1] Additionally, the mean age of patients is 66 years (see Table 1) and the percentage of patients in the cohort <65 years is moderate (43.7%). Also, the total cost for medications is a small percentage of the overall healthcare costs for this population (15.9%).** **We have added to our limitations section to highlight and address this issue.** **Page 12, paragraph 2, line 249** **"First, this study did not take on a societal perspective, but rather that of the 3rd party payer for the province. Therefore, we excluded some potential costs, such as patient out of pocket and lost productivity costs,[19] and medication costs for patients < 65 years old, as Ontario only provides comprehensive prescription drug coverage for patients ≥ 65 years old. As such, total costs are skewed toward older patients. However, given the majority of patients in our cohort were over 65 years of age and importantly the bulk of costs were non-medication related, this would not have made a qualitative difference in our conclusions."** **1. Guidelines for the Economic Evaluation of Health Technologies: Canada.** **3rd ed. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health; 2006.** Comment #3: Figure 1 - I was not able to locate figure 1 which was identified as inclusion criteria in the text. There is a figure listed as supplemental figure 1, which reports on variation in initial treatment strategy. **Our apologies. Our tables and figures were in excel spreadsheets that contained multiple tabs. The tabs did not appear to be viewable to the reviewers. We have corrected this issue by including each table and figure as a separate excel file.** Comment #4: Page 21 includes and unlabeled figure. This appears to be a continuation of table 2, but should be more clearly identified. Simple formatting of the page layout to make this figure fit on one page would be more appropriate. **We thank the reviewer for pointing this out. We are unsure if the reviewer is**

	referring to Table 2 or Figure 2, so we have made formatting changes to both. Comment #5: Data being reported was collected between 2008-2011 and is now 4-7 years old. Is there a reason more recent data was not used? Are there any time trends that may make data from this time period differ from more recent experience. Would recommend authors could address this in the limitation sections of the discussion. **We chose an older data collection time frame in order to provide adequate patient follow up time for each patient; however, we acknowledge that there is newer data available. The interventions studied here are well-established, and no large technological advances in these interventions have occurred in the last 4 years. Therefore, we do not expect more recent data would produce results that are significantly different than those of the time period we chose. We have addressed this comment in the limitations section of the discussion.** **Page 13, paragraph 1, line 264** **"Fourth, our cohort was accrued from 2008-2011 which was the most recent data available at the time of our study. We acknowledge the data are over 5 years old; however, the interventions and practice patterns studied here are well-established, and we do not expect more recent data would be significantly different than the time period we chose because care for these patients has not changed."** Comment #6: Patient level predictors – the patient level predictors examined are listed in table 3 but should also be referenced in main text briefly. Are there any patient level predictors that are hypothesized to influence outcomes that were not available via the administrative databases that should be reported in the study limitations? Are there any hospital level factors that should be identified? **Thank you for the suggestions on how to clarify our co-variates list. We have edited our methods section to provide more details regarding our co-variates. There are certainly co-variates that were not available, which may have been influencing the outcomes we see here. We have now added a section in the limitations to address this.** **Methods section** **Page 8, paragraph 1, line 149** **"Our models included 2 main co-variates of interest: 1) the treatment allocation (medical vs percutaneous coronary intervention vs coronary artery bypass grafting) and 2) the revascularization ratio (high vs medium vs low). In addition, the models included an interaction between treatment allocation and revascularization ratio. We adjusted the models for patient, physician and hospital factors, including patient demographics, cardiac morbidities, risk factors, diagnostic test results, coronary anatomy, referral physician specialization and hospital catheterization volume, as listed in Table 3."** **Limitations section** **Page 13, paragraph 1, line 260** **"Third, we were limited to evaluating co-variates that were captured in the databases available. Other factors may have been influencing patient costs. For example, aspects of physician and hospital culture may have influenced patients' treatment strategy, and therefore costs."** Comment #7: There were substantial differences in patients treated medically vs revascularized as described on page 10 - with medically treated patients being older, more likely to be female, having greater co-morbidity and less severe anginal symptoms based on Canadian Cardiovascular Society (CCS) class. These differences to me suggest that patients who are treated medically are more complex and more likely to be at higher risk of hospitalization and death. It is likely that clinicians/families/patients simply not choosing to revascularize patients who are older with greater co-morbidity and less angina? Does this simply suggest that clinicians are making the appropriate choices in terms of treatment strategy? This should be discussed in more detail in the discussion and implications to study findings examined more thoroughly. **We thank the reviewer for pointing this out. We agree that it is likely that sicker patients are not being revascularized. We cannot speculate from this costing paper as to whether clinicians are making the appropriate choices for treatment strategy, as we did not specifically examine clinical outcomes. However, we have studied this topic in a recent published study by our group, where we had examined variation in treatment strategy and its effects on clinical outcomes using the same cohort of stable angina patients. We found that patients treated at high revacularization ratio hospitals by PCI had greater mortality than patients treated at low revascularization ratio hospitals, and that the greater mortality was not due to differences in patient characteristics.[1] We have modified our limitations section in the discussion to incorporate the reviewer's comments.** **Page 12, paragraph 2, line 257**

	"Second, there were substantial differences in patients treated medically versus revascularized. Medically treated patients were older, more likely to be female and have greater co-morbidity. This may suggest that patients who are treated medically are more complex and more likely to be at higher risk of morbidity and mortality." **1. Bennell MC, Qiu F, Kingsbury KJ, Austin PC, Wijeysundera HC. Determinants of variations in initial treatment strategies for stable ischemic heart disease. CMAJ. 2015 July 14;187(10): E317-25.** Comment #8: Main findings – we know CABG is expensive. Authors report the largest single expense in the costing exercise was the cost of CABG. In order to offset these costs significant reductions in future hospitalization/intervention would be required. Is the 1-year time horizon sufficient. While this is noted in the limitations I think it warrants more attention in terms of study design so we do not misinterpret the findings of the study as suggesting medical management is more cost-effective. **We thank the reviewer for commenting on this important point. The reviewer is correct that a year time horizon may be insufficientbecause CABG costs decrease with longer-term follow up due to less frequent additional procedures being needed compared to other treatments.[1] However this limitation is mitigated becausefor longer term follow-up, costs are discounted annually. Best practice in costing analyses is to discount annually to reference that society has a positive time preference for costs – future costs are weighted less heavily than current costs.[2] Therefore, future costs are devalued at a constant proportional rate (5% annually in Canada). Discounting is consistent with the guidelines established by the Canadian Agency for Drugs and Technologies in Health.[3] We have modified the discussion to include this point.** **Page 13, paragraph 1, line 275** **"Finally, we limited our analyses to health care costs over a restricted 1 year time-horizon in a cohort of patients post coronary angiography. As such, our results cannot be generalized to stable patients who have not undergone angiography. The use of a short time horizon may bias results against coronary artery bypass grafting, as it is associated with fewer revascularizations in the long term. However, these long term costs would be discounted and therefore have a substantially lesser impact on overall costs."** **1. Weintraub, W. S., Mauldin, P. D., Becker, E., Kosinski, A. S., & King, S. B., 3rd. (1995). A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel coronary artery disease. Results from the Emory Angioplasty Versus Surgery Trial (EAST). *Circulation, 92*(10), 2831-2840.** **2. Krahn, M., & Gafni, A. (1993). Discounting in the economic evaluation of health care interventions. *Medical Care, 31*(5), 403-418.** **3. Guidelines for the Economic Evaluation of Health Technologies: Canada.** **3rd ed. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health; 2006.** Comment #9: Analysis – Models appear to have been adjusted for patient level factors. What about hospital level factors? **The models were adjusted for patient, physician, and hospital level factors. We have now clarified in the methods section what variables were included in the analysis.** **Page 8, paragraph 1, line 149** **"Our models included 2 main co-variates of interest: 1) the treatment allocation (medical vs percutaneous coronary intervention vs coronary artery bypass grafting) and 2) the revascularization ratio (high vs medium vs low). In addition, the models included an interaction between treatment allocation and revascularization ratio. We adjusted the models for patient, physician and hospital factors, including patient demographics, cardiac morbidities, risk factors, diagnostic test results, coronary anatomy, referral physician specialization and hospital catheterization volume, as listed in Table 3."** Comment #10: Interpretation, 1st para, 1st sentence – I am unclear on what "as did patients treated with either type of revascularization" means. Can authors please clarify. **We apologize for the confusion. We have edited the sentence.** **Page 11, paragraph 1, line 215** **"In this study we found significant variation in 1-year cumulative health care costs among stable coronary artery disease patients treated at different hospitals. Patients with greater co-morbidity and patients treated by**

	revascularization were associated with higher cost." Comment #11: Abstract, conclusion: The concluding sentence should be reworded to provide a clearly summary of study findings i.e. what is the main finding in terms of revascularization strategy. **We have modified the abstract conclusion for clarity.** **Page 3, paragraph 1, line 49** **"The majority of healthcare costs were due to acute care hospitalizations, and costs were higher for patients undergoing revascularization than medical therapy. This study suggests that treatment decision has a substantial impact on healthcare resources."** Minor: Comment #12: Abstract, results, 2nd last line - Should be "significantly" versus "significant" or "have a significant impact on costs" **Thank you for pointing out this typo. We have made this change in the text.** **Page 2, paragraph 3, line 46** **"Hospital revascularization ratio did not significantly impact costs. There was no significant interaction between treatment and revascularization ratio."** Comment #13: Introduction, 1st paragraph: Why use an American reference when reporting on a Canadian study? Please replace with the best available Canadian source. **We have replaced this reference with an estimate of the economic burden in Canada.** **Page 4, paragraph 1, line 56** **"The cost of cardiovascular disease and stroke is $7.6 billion in Canada for direct health care costs annually and $14.6 billion for indirect costs of disability or death [3]."** Comment #14: Table 3 – I would recommend grouping hospital level factors examined together – one appears at top and one a bottom at present. **We had grouped the hospital level variable 'hospital revascularization ratio' at the beginning of the table to highlight its importance as one of the two main co-variates of interest. However, we appreciate that its presence at the top may produce confusion. Therefore, we have moved it to be grouped with the other hospital level factor at the bottom of the table. We have added italics to the two main co-variates of interest to highlight their importance in the study.** Comment #15: Appendix Table 1 – I am afraid I am not clear on what the terms high, medium, low treatment represent. If I review the text analysis methods I believe this is the revascularization ratio. Please define in footnote in table and clarify in main text. **We thank the reviewer for pointing out the confusion in this table. We have modified the table so that the rows now read "high vs. low revascularization ratio", etc. so that the rows more clearly reflect the variable measured.**
Reviewer 2	Dr. Kevin Levitt
Institution	University of Toronto, Cardiology, Toronto, Ont.
General comments (author response in bold)	Comment #1: Kang et al report a study evaluating the costs associated with cardiac care for patients with stable coronary artery disease. They examined the variation in costs among these patients in the province of Ontario. Revascularization was the largest driver for cost highlighting the need for appropriate utilization of invasive therapeutic options. This study is novel and attempts to fill the gap in knowledge with information regarding the costs associated with revascularization strategies. Ontario is Canada's largest province and provides a suitable location to study this issue. The manuscript is well written with clear explanation of concepts. **We thank the review for the kind assessment of our work.** Minor Revisions: Comment #2: The cohort includes drug costs only for patients over the age of 65. Is there any mechanism to capture to costs of individuals <65yrs? **This issue was also brought up by reviewer #1 comment #2 and by the editor comment #3. In Ontario, medication data cannot be obtained for patients <65 years old because those costs rest on private insurance companies and/or patients, and is not paid for by the Ontario government. We agree that the societal costs are higher than our paper acknowledges. However, this costing paper is intended to be from the perspective of the third party payer of healthcare in Ontario, the Ministry of Health and Long Term Care. As such, the Ministry's prescription drug coverage is limited to patients >65 years old, which is why we did not provide estimates of cost for patients <65 years old.**

	Selecting costs that are only relevant to the payer's perspective is consistent with the guidelines established by the Canadian Agency for Drugs and Technologies in Health.[1] Additionally, the mean age of patients is 66 years (see Table 1) and the percentage of patients in the cohort <65 years is moderate (43.7%). Also, the total cost for medications is a small percentage of the overall healthcare costs for this population (15.9%). **We have added to our limitations section to highlight and address this issue.** **Page 12, paragraph 2, line 249** **"First, this study did not take on a societal perspective, but rather that of the 3rd party payer for the province. Therefore, we excluded some potential costs, such as patient out of pocket and lost productivity costs,[19] and medication costs for patients < 65 years old, as Ontario only provides comprehensive prescription drug coverage for patients ≥ 65 years old. As such, total costs are skewed toward older patients. However, given the majority of patients in our cohort were over 65 years of age and importantly the bulk of costs were non-medication related, this would not have made a qualitative difference in our conclusions."** **1. Guidelines for the Economic Evaluation of Health Technologies: Canada.** **3rd ed. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health; 2006.** Comment #3: Are the costs of multiple angiograms on the same patient all included in the patients' cost if it occurred in the same year? **Yes, the costs of multiple angiograms on a single patient are included in the costs for that year. Our study tracked all costs per patient from the point of the first angiogram.** Comment #4: There was a tremendous variation in patient costs from $54 to 985,600. It is unclear how the angiogram and physician costs were captured in the patient with a cost of $54? **We thank the reviewer for making this important point. We agree that the patient cost of $54 is an unusual outlier. Upon examining our costs more closely, we have found that this patient was correctly included as a patient who underwent an angiography; however, the cost of the angiogram was not listed for this patient. The $54 was due to physician costs. We are unsure as to why the cost of the angiogram was not included for this patient. It may have been that the patient died during the angiogram. Given the skewed nature of costing data with the presence of both upper and lower outliers wehave decided to report the Q1-Q3 rather than the full range of our data, in order to more accurately reflect the central tendency of our costing data.** **Page 2, paragraph 2, line 42** **"The mean 1-year cost was $24,026 (Q1: $8,235, Q3: $30,511)."** **Page 9, paragraph 3, line 174** **"Individual patient 1-year cost varied substantially (Q1: $8,235, Q3: $30,511)."** Comment #5: What were the reasons for reduced costs of males as compared to females? If more female patients were treated medically shouldn't the costs be less? There should be should discussion regarding this in the interpretation section of the paper. **We can only speculate as to the reason why males had less reduced costs compared to females as our study design was not one that allows us to identify the underlying mechanism of these differences. We hypothesize that it may be related to less health seeking behavior on the part of males, resulting in the small difference in costs. We have modified the discussion to include this point.** **Page 12 Paragraph 1, line 240** **"We also identified a number of patient-level factors that were associated with increased health care costs, including gender and previous coronary artery bypass grafting. We can only hypothesize as to the reasons for these findings. For sex, males may have less health seeking behavior, which translated into a small difference in overall costs. For patients with previous coronary artery bypass grafting, we anticipate that these patients were more likely to be treated medically or by percutaneous coronary intervention rather than redoing surgery, resulting in lower overall costs."** Comment #6: Furthermore, what are the potential reasons for previous history of cardiac surgery demonstrating a significant and large reduction in mean cost? **Patients with a previous history of cardiac surgery are likely to have been treated by either medical therapy or PCI, rather than redo surgery. We have shown this in previous work (cite the Journal of general internal medicine). We have added this to the discussion section (please see response to Comment 5).**

	Comment #7: What percent of costs were related to medication use. What percentage of patients were less than 65? If this accounted for a significant %, then comment should be made in the limitations that total costs may be under-represented. **The total cost for medications is a small percentage of the overall healthcare costs for this population at 15.9%. We agree with the reviewer that this is an important issue and have added this to the limitations section, as outline in the response to comment 2.** Comment #8: Figure 2 has some formatting issues to ensure it fits on 1 page. **We thank the reviewer for pointing out this oversight on our part. We have made formatting changes to this figure.**