March 7, 2022

Dear Dr. Wang:

Please find attached our revised manuscript entitled “Day-to-Day Blood Pressure Variability Predicts Poor Outcomes Following Percutaneous Coronary Intervention: A Case Control Study” (manuscript # 72759) which we would like to resubmit for consideration for publication in the World Journal of Cardiology. Thank you for continued consideration and the opportunity to address the comments raised by the reviewers. We also would like to thank the reviewers for their valuable comments and consideration. Below, we address each of the comments made by the reviewers. We have revised the manuscript to reflect changes brought up in the concerns, each change will be highlighted.

Reviewer 1 comments:

1. What is the definition of readmission?
    - Our methods section (page 5, lines 15-16) now states: Readmission was defined as a recurrent admission to the hospital within 1 year of discharge after hospitalization from PCI procedure.
2. KM survival curve of MACE is needed of Systolic and Diastolic SD.
    - Our discussion section (page 19, lines 13-16) now states: While it would have been interesting to calculate a Kaplan-Meier survival curve for MACE, the specific dates for these key complications were unfortunately not included in the registry and so these data were unfortunately unavailable for analysis.

3. Data of LVEF, prior MI, prior PCI, CKD should be added.

- Data of LVEF, prior MI, prior PCI, CKD history have been added. With these new data, figure 1 was reconstructed as well as table 1. Our conclusions still held true after these additional variables were controlled for and there were only minimal shifts seen in figure 1. Our methods section (page 6, lines 2-6) now states: Logistic regressions of BPV predicting MACE, readmission, and MI outcomes after 1-year were done while controlling for age, sex, smoking status, diagnoses of hypertension or diabetes, prior CVD, prior MI, prior PCI, prior CABG, pre-procedure creatine level, prior PCI LVEF, anginal class (no symptoms as reference value, CCS I, II, III, or IV), on anti-anginal medications, and indication (staged PCI was used as the reference value).
- Our methods section (page 6, lines 6-9) now states: Although the registry data did not indicate which patients had pre-existing chronic kidney disease, we did analyze pre-procedural serum creatinine level. This was categorized as values of less than or equal to 2, 2-5, or greater than 5 mg/dL.
- To reflect the additional variables, figure 1 was revised and our results section (page 7, lines 1-6) now states: The risk of all-cause hospitalization was increased significantly by higher systolic BPV as calculated by both LC (OR=1.024, 95% CI 1.006 – 1.042) and SD (OR=1.049, 95% CI 1.000 – 1.099). The risk of MACE was also increased significantly by higher systolic BPV as calculated by LC (OR=1.024, 95% CI 1.007 – 1.042) and SD (OR=1.049, 95% CI 1.003 – 1.100). Although eight of the risks of these outcomes were not statistically significant, we noted a trend where patients with high BPV had increased risk of any outcome.
- Our discussion section (page 19, lines 11-13) now states: While considering kidney disease simply by pre-procedural serum creatinine levels is not ideal and represents a

limitation to this study, the diagnosis of chronic renal failure was not included in the data available for analysis.

4. Though the electronic medical record was queried and BP recordings (n=25,844) both from within and outside the hospital from patients. Details of blood pressure measurement were not mentioned. Where? How? Standard?

- Our discussion (page 19, lines 2-11) now states: Another potential concern is that the BP readings that were used in this study were derived from chart review after routine clinical practice rather than being measured by pre-designed specified protocols. Clinical trials often utilize very precise practices to measure BP precisely because without such practices BP measurement may differ from how it is routinely measured in the clinical setting. Our BP measurements do lack standardization, which thus could be interpreted as a weakness in that measurements were not taken at fixed intervals with fixed protocols. However, the BP measurements used here do reflect how physicians would routinely assess patients' BPV in the clinic. Thus, one might conversely propose that this apparent limitation actually makes our study results more relevant to the real world.

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Reviewer 2 comments:

It would be nice to add to the conclusion ways of reducing the blood pressure variability

Response:

- Our conclusion (page 20, lines 1-12) now states: Most percutaneous coronary interventions are relatively urgent and cannot be postponed for long periods of time for patients to attempt to modify risk factors prior to PCI. Furthermore, further research is

still required to identify changes or pharmacologic interventions that patients may undertake to usefully reduce their BPV. However, patients with higher BPV who are about to undergo PCI can and should be counselled that they are at a higher risk of post-procedural complications and that they should subsequently address any other modifiable risk factors that are also associated with poor post-operative outcomes to best optimize their individual post-procedural outcomes. Physicians performing PCI may also wish to consider BPV as they decide how aggressive to be in their procedures, while quality comparisons of PCI programs or research on future PCI interventions should consider as an additional risk factor in multivariate analyses of outcomes.

Science editor comments:

The authors predicted the adverse prognosis after percutaneous coronary intervention by observing the variability of daily blood pressure. The manuscript is well written and can be helpful for the readers to ameliorate the diagnostic and therapeutic approach for this scenario. However, I don't think novelty is enough. The format of the table adopts three line table.

Response:

- To address the question of novelty, our discussion (page 14) now states: While high BPV has been associated with worse post-operative outcomes after complex and highly invasive procedures such as CABG, colectomy, and total hip replacement (4,5), this is to our knowledge the first study investigating how BPV affects these outcomes after a much less invasive procedure such as PCI in patients who are known to have cardiac disease.

- The format of the tables has been changed and the changes to these tables and the new figure 1, redone to include the additional variables suggested by the reviewer, are shown below

T**able 1:** Descriptive statistics of variables in data set by adverse event for 471 patients with percutaneous coronary intervention.

	No MACE (N=324)			**Had MACE (N=147)**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
*Systolic SD	324	13.72	6.02	147	15.38	5.26
Diastolic SD	324	8.54	3.11	147	8.93	2.71
*Systolic LC	324	37.11	14.79	147	44.31	15.42
*Diastolic LC	324	23.60	7.78	147	26.37	9.09
Systolic Average	324	131.83	11.47	147	132.20	11.63
*Diastolic Average	324	74.82	7.75	147	71.33	7.64
*Number of BP Readings	324	40.19	35.86	147	62.81	52.85
*Mean Days Between Readings	324	59.07	37.04	147	42.19	30.70
*Age	322	67.87	11.21	147	70.69	11.86
* Pre PCI LVEF	252	56.44	11.73	122	53.06	13.63
* Pre Creatinine	307	1.15	0.98	138	1.50	1.19
		N	**%**		**N**	**%**
Sex	469					
Male		110	74.83		228	70.37
Female		37	25.17		94	29.01
Race	469					
White		142	96.60		312	96.30
Other		5	3.40		10	3.09
Hispanic		1	0.68		4	1.23
*Smokes	467	22	14.97		51	15.74
*Has Hypertension	469	135	91.84		266	82.10
Has Diabetes	469	67	45.58		122	37.65
Had Prior CVD	469	39	26.53		68	20.99
* Had Prior MI	470	106	32.72		63	42.86
Had Prior PCI	470	125	38.58		67	45.58
* Had Prior CABG	470	53	16.36		41	27.89
* Prior Creatinine	445					
0 to 2		296	91.36		118	80.27
>2 to 5		8	2.47		18	12.24
>5		3	0.93		2	1.36
*Anginal Class	469					
No Symptoms		33	22.45		24	7.41
CCS I		11	7.48		39	12.04
CCS II		27	18.37		87	26.85

CCS III		43	29.25	95	29.32
CCS IV		33	22.45	77	23.77
*On Anti-Anginal Medication	469	114	77.55	204	62.96
*Beta-Blockers		98	66.67	164	50.62
Calcium Channel Blockers		37	25.17	76	23.46
* Long-Acting Nitrates		33	22.45	41	12.65
Ranolazine		3	2.04	2	0.62
Indication	471				
Non-STEMI		82	55.78	167	51.54
STEMI		9	6.12	39	12.04
Other Stage		56	38.10	118	36.42
MACE within 1 Year	471				
Readmission				131	27.81
MI				47	9.98
Death				21	4.46
CVA				6	1.27

- * $p<.05$; independent t-tests for continuous variables, Chi-Square for categorical variables. Chi-Square for creatinine was values 0 to 2 compared to higher than 2 mg/dL. Adverse events were major adverse cardiac events, readmission, stroke, death, or cerebral vascular accident within one year of procedure. LC is largest change from one consecutive blood pressure reading to the next.

Table 2. Receiver operating characteristic analysis of cutoff values for four measures of blood pressure variability predicting adverse events.

					95% Confidence Interval	
	Cutoff	**Sensitivity**	**Specificity**	**AUC**	**LL**	**UL**
MACE						
Systolic SD	12.0	0.7755	0.4475	0.6300	0.5752	0.6792
Diastolic SD	8.0	0.6395	0.5216	0.5674	0.5102	0.6195
Systolic LC	33.0	0.7891	0.4414	0.6510	0.5957	0.7001
Diastolic LC	26.0	0.5102	0.6235	0.5837	0.5262	0.6359
Readmission						
Systolic SD	14.0	0.5573	0.6324	0.6348	0.5792	0.6846
Diastolic SD	8.0	0.6565	0.5206	0.5734	0.5149	0.6267
Systolic LC	33.0	0.8168	0.4412	0.6592	0.6039	0.7083
Diastolic LC	25.0	0.5573	0.6176	0.6018	0.5426	0.6549
MI						
Systolic SD	13.5	0.6596	0.5684	0.6234	0.5371	0.6967
Diastolic SD	9.0	0.4894	0.6604	0.5730	0.4800	0.6533
Systolic LC	48.0	0.4468	0.7665	0.6609	0.5649	0.7393
Diastolic LC	26.0	0.6170	0.6038	0.6255	0.5370	0.7004

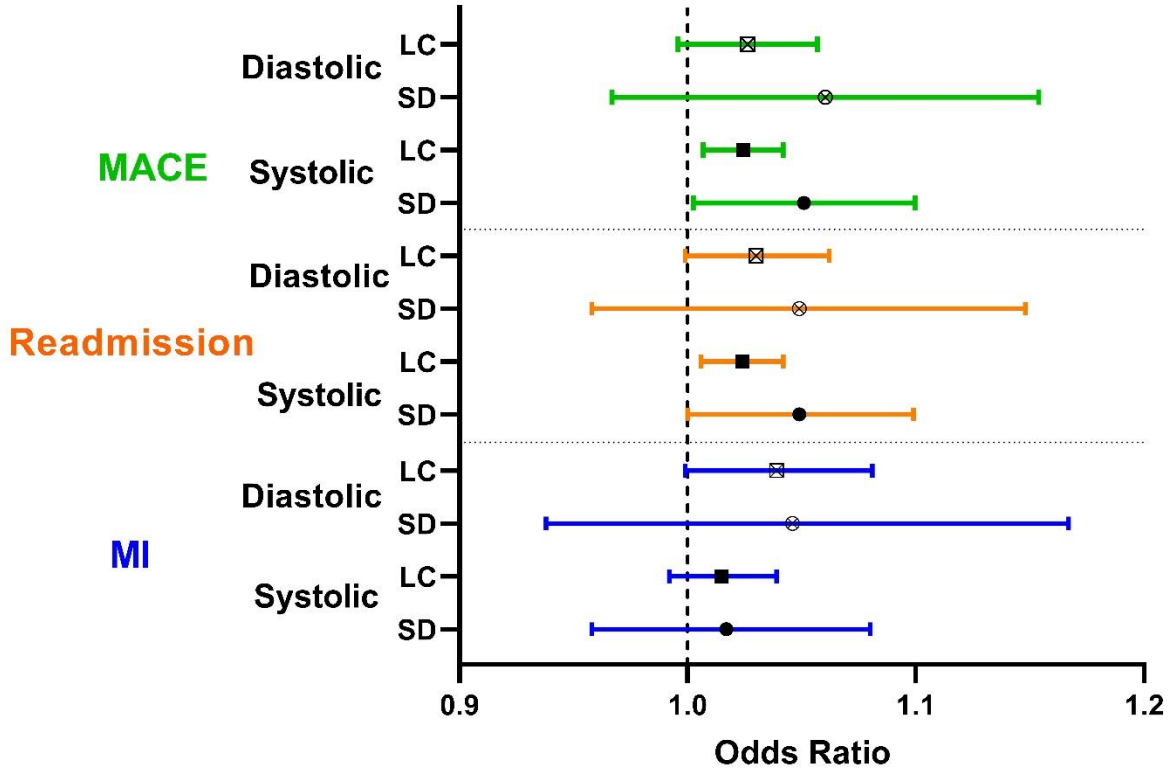

Figure 1: Adjusted odds ratios with 95% confidence intervals from logistic regressions of preoperative blood pressure variability predicting outcomes after percutaneous coronary intervention. Odds ratios were controlled for age, sex, smoking status, diagnoses of hypertension or diabetes, prior cardiovascular disease, prior myocardial infarction, prior coronary artery bypass graft, prior PCI LVEF, prior creatinine, anginal class, on anti-anginal medications, indication, and average systolic or diastolic blood pressure. Due to some missing values, myocardial infarction was not adjusted for PCI LVEF and creatinine.

We would again like to thank the reviewers and editors for their helpful suggestions, which we believe have substantially improved the manuscript. We hope that it may now be considered suitable for the World Journal of Cardiology.

Very truly yours,

Marc D. Basson, MD, PhD