# Cardiovascular Outcomes of Patients With Pulmonary Hypertension Undergoing Noncardiac Surgery

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**Pulmonary hypertension (PH), defined by a mean pulmonary artery pressure of >25mm Hg at rest, is strongly associated with morbidity and mortality in the perioperative period. The prevalence and outcomes of PH among patients referred for major noncardiac surgery in the United States are unknown. Patients ≥18 years of age hospitalized for noncardiac surgery were identified from Healthcare Cost and Utilization Project's National Inpatient Sample data from 2004 to 2014. Pulmonary hypertension was defined by *International Classification of Diseases, Ninth Revision* diagnosis codes. The primary outcome was perioperative major adverse cardiovascular events (MACCE), defined as in-hospital death, myocardial infarction, or ischemic stroke. Among 17,853,194 hospitalizations for major noncardiac surgery, 143,846 (0.81%) had PH. MACCE occurred in 8.3% of hospitalizations with any diagnosis of PH in comparison to 2.0% of those without PH (p <0.001), driven by an increased frequency of death (4.4% vs 1.1%, p <0.001) and nonfatal myocardial infarction (3.2% vs 0.6%, p <0.001). After adjusting for demographics, clinical covariates, and surgery type, PH remained independently associated with MACCE (aOR 1.43, 95% CI 1.40 to 1.46). In conclusion, PH is associated with perioperative major adverse cardiovascular events. Careful patient selection, recognition of perioperative risks, and appropriate intraoperative hemodynamic monitoring may improve perioperative cardiovascular outcomes. Published by Elsevier Inc. (Am J Cardiol 2019;123:1532−1537)**

Pulmonary hypertension (PH), defined as a mean pulmonary artery pressure ≥25 mm Hg at rest,[1] can be identified by echocardiography in ~0.7% of patients referred for noncardiac surgery.[2] Patients with PH are at an increased risk of adverse events in the perioperative period,[3−5] with cardiovascular risks that may vary based on the severity of the hemodynamic abnormality, underlying mechanism of disease, the presence of cardiovascular risk factors and cormorbidities, and the type of noncardiac surgery to be performed. Unfortunately, few studies have identified large cohorts of patients with PH undergoing noncardiac surgery in the contemporary era. In the present study, we sought to evaluate the incidence of perioperative adverse cardiovascular events after noncardiac surgery in patients with and without PH using a large administrative database of hospital admissions from the United States.

## Methods

Patients ≥18 years of age undergoing noncardiac surgery from 2004 to 2014 were identified from the Healthcare Cost and Utilization Project's National Inpatient Sample (NIS).[6] The NIS is a national administrative database that contains discharge-level data for a 20% stratified sample of patients admitted to United States hospitals.[7] Patients were eligible for inclusion if the principal *International Classification of Diseases, Ninth Revision* (ICD-9) procedure code during hospital admission was a major therapeutic operating room procedure (Healthcare Cost and Utilization Project's Procedure class IV).[6] Patients who underwent cardiac transplantation, bone marrow transplantation, cardiac surgery, minimally invasive cardiac procedures, ophthalmologic surgery, dental surgery, radiation therapy, and nonoperating room procedures were excluded from all analyses. Pulmonary hypertension was identified by the ICD-9 diagnosis codes for primary pulmonary arterial hypertension (416.0) and all other nonprimary PH (416.8, 416.9), as previously defined.[8,9]

The primary outcome was MACCE, defined as in-hospital death, myocardial infarction (MI), or ischemic stroke. Perioperative MI was identified using ICD-9 diagnosis codes for acute ST-segment elevation myocardial infarction (410.01 to 410.61, 410.81, and 410.91) and non-ST-segment elevation myocardial infarction (410.71).[10] Acute ischemic stroke was identified using ICD-9 diagnosis codes 433.x1, 434.x1, 436, and 437.1.13. Other cardiovascular outcomes evaluated were acute pulmonary embolism (ICD-9 diagnosis codes 415.1x), cardiogenic shock (785.51) and cardiac arrest (427.5).

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Categorical variables were reported as percentages and compared by Chi-square tests. Continuous variables were reported as mean ± standard deviation (SD) and compared using the Student's *t* test. Multivariable logistic regression models were generated to estimate odds ratios for MACCE and its component end points, adjusted for age, gender, race/ethnicity, obesity, tobacco use, hypertension, hyperlipidemia, diabetes mellitus, end stage renal disease, coronary artery disease, prior revascularization with either PCI or CABG, peripheral vascular disease, valvular heart disease, prior venous thromboembolism, chronic lung disease, malignancy, anemia, alcohol abuse, elective/urgent hospitalization, surgery type, and year of hospitalization. A sensitivity analysis was performed evaluating patients with primary pulmonary arterial hypertension. A second sensitivity analysis was performed excluding patients with a diagnosis of venous thromboembolism, in whom PH may have developed acutely in the postoperative state. Venous thromboembolism diagnoses during the surgical hospitalization were identified using ICD-9 diagnosis codes for pulmonary embolism (415.1 ×) and lower extremity deep vein thrombosis (451.1 ×, 451.81, 453.2, 453.4 ×).[11] A sensitivity analysis was also performed excluding younger patients, restricting the analysis to adults age ≥45 years old. Sampling weights were applied to determine national incidence estimates when specified. Unweighted data were used in all other analyses. Statistical analyses were performed using SPSS 25 (IBM SPSS Statistics, Armonk, NY). Statistical tests are two-sided and p values <0.05 were considered to be statistically significant. The NIS is a publicly available, de-identified dataset, and the study was exempt from institutional board review.

## Results

A total of 17,853,194 hospitalizations for major noncardiac surgery were identified. Pulmonary hypertension was present in 143,846 hospitalizations (0.81%) for noncardiac surgery, corresponding to an estimated 693,819 surgical hospitalizations in the United States during this time period. Characteristics of patients with and without PH are shown in Table 1. Patients hospitalized for surgery with PH were older and less likely to be women than patients without PH. Smoking, obstructive sleep apnea, chronic pulmonary disease, and valvular heart disease were more common in patients with PH than those without PH. In both sexes, the frequency of PH diagnoses increased with age (Figure 1). The proportion of patients undergoing noncardiac surgery with a diagnosis of PH increased over time, from 0.4% in 2004 to 1.2% in 2014 (Figure 2).

Primary pulmonary arterial hypertension (WHO Group 1 PH) was identified in 3,500 cases, representing 2.4% of surgical hospitalizations with any diagnosis of PH and 0.02% of hospitalizations undergoing noncardiac surgery. This corresponds to an estimated 16,691 hospitalizations for surgery in the United States during this time period. Patients with WHO Group 1 PH tended to be younger (68.24 vs 71.66, p <0.001) and were more likely to be women (67.7% vs 63.2%, p <0.001). Characteristics of patients with WHO Group 1 PH in comparison to other types of PH are shown in Supplemental Table 2.

Among the 143,846 surgical hospitalizations with a diagnosis of PH, right-sided heart catheterization was performed during 2,961 (2.1%) hospitalizations. The proportion of patients who underwent right heart catheterization during the surgical hospitalization declined with increasing age, from 4.3% of patients age 18-39 years to 0.9% of patients older than 80 years of age. For all subtypes of noncardiac surgery, right-sided heart catheterization was performed in fewer than 5% of surgical hospitalizations with an associated diagnosis of PH. Among those with a diagnosis of pulmonary arterial hypertension (WHO Group 1 PH), right heart catheterization was performed in 4.3% (n = 149) of surgical hospital admissions.

Major adverse cardiovascular events were more common in surgical hospitalizations with PH in comparison those without PH (8.3% vs 2.0, p <0.001), driven by an increased frequency of death (4.4% vs 1.1%, p <0.001), nonfatal myocardial infarction (3.2% vs 0.6%, p <0.001) and stroke (1.5% vs 0.5%, p <0.001; Table 2). The rate of perioperative MACCE did not decline over time (Supplemental Figure 1). After adjusting for demographics, clinical covariates, and surgery type, a diagnosis of PH was independently associated with MACCE (aOR 1.43, 95% CI 1.40 to 1.46), in-hospital death (aOR 1.51, 95% 1.47 to 1.55) and MI (aOR 1.49, 95% 1.44 to 1.54; Table 2). Pulmonary hypertension was associated with a decreased risk of stroke after multivariable adjustment. Patients with PH were more likely to have pulmonary embolism, cardiogenic shock, and cardiac arrest in unadjusted and adjusted analyses.

Among the 3,500 patients with WHO Group 1 PH, MACCE occurred in 451 (12.9%) of patients undergoing noncardiac surgery. A total of 289 (8.3%) of patients died, 141 (4.3%) patients developed MI and 66 (1.9%) had an ischemic stroke. Pulmonary embolism occurred in 183 (5.3%) cases, cardiogenic shock occurred in 1.2% of patients and cardiac arrest occurred in 1.6% of cases. WHO Group 1 PH was also independently associated with MACCE after multivariable adjustment for demographics and clinical covariates (aOR 2.51, 95% CI 2.26 to 2.79; Supplemental Table 3).

The prevalence of PH varied by subgroup of noncardiac surgery. Among patients undergoing transplant, vascular, thoracic and orthopedic surgery, the proportion of patients with PH was 3.9%, 2.3%, 2.0%, and 1.0%, respectively. Among patients with PH who were hospitalized for surgery, the most common surgical subtypes were orthopedic (38.3%, n = 55,105), vascular (21.4%, n = 30,771), and general surgery (19.7%, n = 28,263).

Patients with PH had a higher risk of perioperative MACCE than those without PH, with the highest surgery-specific risks of MACCE for patients undergoing neurosurgery (13.0% vs 4.1, p <0.001), thoracic surgery (12.2% vs 5.6%, p <0.001), vascular surgery (11.2% vs 7.3%, p <0.001) and general surgery (9.3% vs 2.7%, p <0.001). Adjusted odds of MACCE associated with PH by surgical subtype are shown in Supplemental Figure 2. Surgical subtypes with low overall perioperative cardiovascular risk had the greatest increased odds of MACCE associated with PH.

In a sensitivity analysis excluding 12,211 PH patients with a diagnosis of pulmonary embolism or deep vein thrombosis, in whom PH may have developed acutely in

Table 1
Characteristics of patients age ≥ 18 years old hospitalized for non-cardiac surgery, with and without a pulmonary hypertension diagnosis.

| Variables | Pulmonary hypertension | | p value |
|---|---|---|---|
| | Yes | No | |
| | (n = 143,846) | (n = 17,709,348) | |
| Age (years) | 71.6 ± 14.6 | 53.5 ± 19.5 | <0.001 |
| Female sex | 91097 (63.3%) | 11447976 (64.8%) | <0.001 |
| Non-Hispanic White | 96685 (67.2%) | 10490933 (59.2%) | <0.001 |
| Non-Hispanic Black | 17352 (12.1%) | 1701974 (9.6%) | |
| Hispanic | 6915 (4.8%) | 1646805 (9.3%) | |
| Unknown race | 5207 (3.6%) | 886398 (5%) | |
| Other race | 17687 (12.3%) | 2983238 (16.8%) | |
| Tobacco use | 31034 (21.6%) | 3208943 (18.1%) | <0.001 |
| Obstructive sleep apnea | 18007 (12.5%) | 522743 (3%) | <0.001 |
| Hypertension | 98377 (68.4%) | 7203953 (40.7%) | <0.001 |
| Hyperlipidemia | 50002 (34.8%) | 3487250 (19.7%) | <0.001 |
| Diabetes Mellitus | 46724 (32.5%) | 2930582 (16.5%) | <0.001 |
| Coronary artery disease | 51335 (35.7%) | 2037382 (11.5%) | <0.001 |
| Prior percutaneous coronary intervention | 7728 (5.4%) | 431943 (2.4%) | <0.001 |
| Prior coronary bypass grafting | 10592 (7.4%) | 530568 (3%) | <0.001 |
| Peripheral vascular disease | 21267 (14.8%) | 847146 (4.8%) | <0.001 |
| Valvular heart disease | 45043 (31.3%) | 493374 (2.8%) | <0.001 |
| Malignancy | 8038 (5.6%) | 677157 (3.8%) | <0.001 |
| Anemia | 46003 (32%) | 2459097 (13.9%) | <0.001 |
| History of heart failure | 52791 (36.7%) | 734558 (4.1%) | <0.001 |
| Prior alcohol abuse | 3461 (2.4%) | 331264 (1.9%) | <0.001 |
| Prior drug abuse | 1972 (1.4%) | 253540 (1.4%) | 0.05 |
| Collagen vascular disease | 7623 (5.3%) | 367138 (2.1%) | <0.001 |
| HIV/AIDS | 227 (0.2%) | 20088 (0.1%) | <0.001 |
| Hypothyroidism | 23772 (16.5%) | 1498825 (8.5%) | <0.001 |
| Obesity | 24937 (17.3%) | 1730327 (9.8%) | <0.001 |
| Chronic kidney disease | 36649 (25.5%) | 980978 (5.5%) | <0.001 |
| Chronic pulmonary disease | 51285 (35.7%) | 2293988 (13%) | <0.001 |
| Prior venous thromboembolism | 7354 (5.1%) | 335226 (1.9%) | <0.001 |
| Atrial fibrillation | 49597 (34.5%) | 957789 (5.4%) | <0.001 |
| Elective admission for surgery | 50725 (35.4%) | 10154622 (57.5%) | <0.001 |
| Surgery type | | | <0.001 |
| General | 28263 (19.6%) | 3520784 (19.9%) | |
| Endocrine | 979 (0.7%) | 181206 (1%) | |
| Genitourinary | 5883 (4.1%) | 1038193 (5.9%) | |
| Neurosurgery | 4130 (2.9%) | 874500 (4.9%) | |
| Obestetrics/Gynecology | 3552 (2.5%) | 4254034 (24%) | |
| Orthopedics | 55105 (38.3%) | 5391446 (30.4%) | |
| Otolaryngology | 865 (0.6%) | 164638 (0.9%) | |
| Skin/Breast | 6361 (4.4%) | 654218 (3.7%) | |
| Thoracic | 5988 (4.2%) | 293127 (1.7%) | |
| Transplant | 1949 (1.4%) | 47788 (0.3%) | |
| Vascular | 30771 (21.4%) | 1289414 (7.3%) | |

Hypertension was defined by Clinical Classificaitons Software (CCS) diagnosis codes 98 and 99. Hyperlipidemia was defined by CCS diagnosis code 53. Anemia was based on AHRQ co-morbidity measurement definitions for chronic blood loss and deficiency anemias. Obesity was based on the AHRQ co-morbidity measurement for obesity.

the perioperative period, MACCE occurred in 7.9% (n = 10,458), perioperative mortality was 4.2% (n = 5,522), and MI occurred in 3.0% (n = 3,989). After the exclusion of patients with acute VTE, PH remained independently associated with MACCE after multivariable adjustment (aOR of 1.47, 95% CI 1.44 to 1.50). Similar findings were observed in a sensitivity analysis of surgical patients older than age 45 years (n = 11,403,707), in whom PH was present in 1.2% of hospitalizations and was independently associated with an increased risk of MACCE (aOR 1.41 [95% CI 1.39 to 1.44]).

## Discussion

In a large cohort of 17,853,194 patients undergoing major noncardiac surgery, PH was identified in 1 of every 125 cases overall, and in 1 of every 84 patients who were age ≥45 years. Based on these data, more than 60,000 patients with PH are estimated to undergo noncardiac surgery in the United States each year. Pulmonary hypertension was most common in patients undergoing transplant, vascular, thoracic and orthopedic surgeries. Perioperative MACCE occurred more frequently among patients with PH

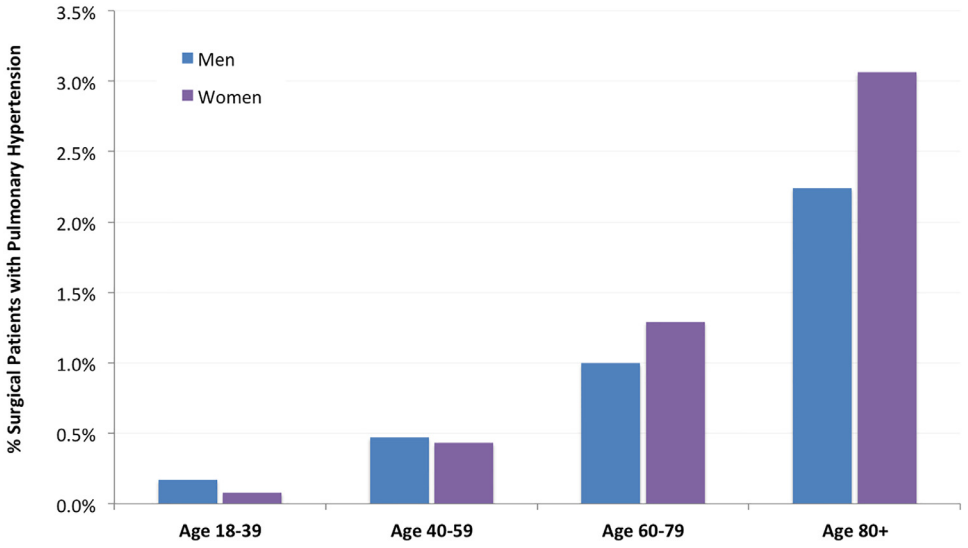


Figure 1. Frequency of pulmonary hypertension among patients undergoing for non-cardiac surgery, by age and sex.

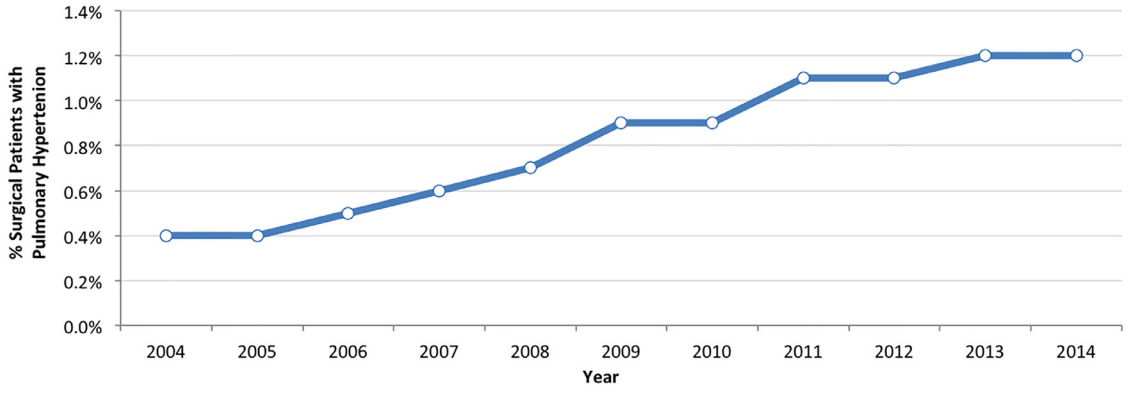


Figure 2. The proportion of patients undergoing non-cardiac surgery with a diagnosis of pulmonary hypertension over time.

in comparison to those without, driven by excess mortality, perioperative MI, and ischemic stroke. Among patients with PH, MACCE was diagnosed in 8.3% of cases and 4.4% of patients died in-hospital after surgery. The increased risks of MACCE associated with PH were observed across multiple major surgical subtypes. Pulmonary arterial hypertension, identified in 0.02% of patients undergoing noncardiac surgery, was a particularly high-risk subgroup with a significant burden of cardiovascular complications.

These findings are consistent with previous reports of patients with PH undergoing noncardiac surgery from small single center retrospective studies. In previous series,

Table 2
Perioperative outcomes of non-cardiac surgery, with and without a diagnosis of pulmonary hypertension.

| | Pulmonary hypertension | | | |
|---|---|---|---|---|
| | Yes (n = 143,846) | No (n = 17,709,348) | Unadjusted p value | Adjusted* OR (95% CI) |
| Major averse cardiovascular events | 11985 (8.3%) | 346110 (2%) | <0.001 | 1.43 (1.40 – 1.46) |
| Death | 6354 (4.4%) | 199234 (1.1%) | <0.001 | 1.51 (1.47 – 1.55) |
| Acute myocardial infarction | 4535 (3.2%) | 98026 (0.6%) | <0.001 | 1.49 (1.44 – 1.54) |
| Stroke | 2192 (1.5%) | 82046 (0.5%) | <0.001 | 0.93 (0.89 – 0.98) |
| Other cardiovascular complications | | | | |
| Pulmonary embolism | 8824 (6.1%) | 124266 (0.7%) | <0.001 | 3.35 (3.27 – 3.44) |
| Cardiogenic shock | 916 (0.6%) | 12100 (0.1%) | <0.001 | 2.37 (2.20 – 2.55) |
| Cardiac arrest | 1651 (1.1%) | 41834 (0.2%) | <0.001 | 1.72 (1.63 – 1.81) |

* Adjusted for demographics, clinical comorbidities, urgent/emergent hospitalization, and non-cardiac surgery type as described in the methods.

perioperative mortality ranged from 4% to 26%, with morbidity 6% to 42% associated with PH.[2,4,12–16] In a small case-control series of 173 patients, PH was associated with a higher incidence of decompensated heart failure, respiratory failure, hemodynamic instability, prolonged ventilatory support and longer ICU stays.[14] Prior pulmonary embolism, right axis deviation on ECG, right ventricular hypertrophy, elevated RV systolic pressures, vasopressor use, anesthesia without nitrous oxide have been independently associated with perioperative mortality in patients with PH.[4] The most recent guidelines recognize pulmonary arterial hypertension (WHO Group 1), high pulmonary artery systolic pressures (>70 mm Hg), right ventricular dilation, pulmonary vascular resistance >3 Wood units, and New York Heart Association class III or IV symptoms as high risk features of PH.

Patients with PH are particularly vulnerable during the perioperative period, since they tolerate hemodynamic and fluid shifts poorly. General anesthesia, unavoidable for most intermediate and high-risk surgeries, may lead to systemic vasodilatation and perioperative hypotension. Extubation may also be challenging with right ventricular dysfunction and post-operative hemodynamic optimization may lead to prolonged intubation. All of these factors may underlie the increased frequency of MACCE observed in the present analysis.

Despite the impact of PH on clinical outcomes, perioperative care guidelines provide limited recommendations for the evaluation and management of PH patients planned for noncardiac surgery. Patients with PH should undergo a comprehensive preoperative evaluation, with assessment of volume status, 12-lead electrocardiography, echocardiography, and appropriate chest imaging based on anticipated surgical risk. Right-sided heart catheterization may be useful for invasive confirmation of pulmonary artery pressures and to establish the etiology of PH. However, few patients with PH underwent perioperative right heart catheterization in the present analysis.[17] In addition, recent ACC/AHA guidelines provide a class IIa recommendation for preoperative evaluation by a PH specialist.[12] Whenever possible, noncardiac surgery should be performed in a center with PH expertise, and cardiac anesthesia involvement is indicated in patients with severe disease.[17] Finally, the ACC/AHA guidelines provide a class I recommendation to continue home pulmonary vasodilators in patients with PH who are already treated with these agents and are planned for noncardiac surgery.[12]

There are a few notable limitations of the present analysis. First, diagnoses recorded in the NIS reflect administrative coding data and are subject to reporting bias and/or errors. Pulmonary hypertension and perioperative major adverse cardiovascular events may be underdiagnosed. In particular, a recent study raises questions about the accuracy of administrative coding data to diagnose pulmonary arterial hypertension.[18] Second, the results of echocardiography were not recorded in the NIS, and left ventricular function and pulmonary artery pressures are unknown. World Health Organization (WHO) Group classifications were not available. Consequently, the severity and mechanism of PH could not be ascertained. The prognostic significance of PH independent of left ventricular function requires confirmation. Third, in-hospital use of diuretics, pulmonary vasodilators, and anticoagulants could not be determined. Fourth, the sequence of noncardiac surgery preceding nonfatal cardiovascular complications cannot be definitively established. However, high-risk noncardiac surgery is contraindicated early after stroke or AMI, and patients with PH presenting with MACCE would be unlikely to undergo noncardiac surgery during the same hospital admission. Fifth, data were analyzed as a simple random sample unless otherwise specified. Unweighted analyses may introduce empirical weighting that may not be reflective of the national population of patients undergoing surgery. Finally, long-term postoperative outcomes were not available from this in-hospital dataset.

In conclusion, this study is the largest to date to assess the outcomes of PH in noncardiac surgery. We found that PH is present in 1 of every 125 patients undergoing major noncardiac surgery and is an important risk factor for perioperative adverse cardiovascular events. Additional research is necessary to evaluate associations between the mechanism and severity of PH and perioperative outcomes. Meticulous preoperative assessment and planning, hemodynamic monitoring during the perioperative period, and appropriate postoperative care remain the cornerstones of care for patients with PH undergoing noncardiac surgery.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi:10.1016/j.amjcard.2019.02.006.


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