Sleep apnea in total joint arthroplasty patients and the role for cardiac biomarkers for risk stratification: an exploration of feasibility

Obstructive sleep apnea (OSA) is highly prevalent in patients undergoing total joint arthroplasty (TJA) and is a major risk factor for postoperative cardiovascular complications and death. Recognizing this, the American Society of Anesthesiologists urges clinicians to implement special considerations in the perioperative care of OSA patients. However, as the volume of patients presenting for TJA increases, resources to implement these recommendations are limited. This necessitates mechanisms to efficiently risk stratify patients having OSA who may be susceptible to post-TJA cardiovascular complications. We explore the role of perioperative measurement of cardiac troponins (cTns) and brain natriuretic peptides (BNPs) in helping determine which OSA patients are at increased risk for post-TJA cardiovascular-related morbidity.

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Over 1 million total hip and knee joint arthroplasty (total joint arthroplasty [TJA]) surgeries were performed in the USA in 2012, with costs exceeding \$25 billion [1,2]. Projection models predict a profound increase in the number of TJAs that will be performed by 2030, estimating a twofold and sixfold increase in total hip and knee arthroplasties, respectively [2]. The average patient presenting for TJA is older and obese [2]. Importantly, this demographic is also at increased risk for the common medical disorder of obstructive sleep apnea (OSA) [3–7]. Recent studies have identified the growing role of OSA as a major risk factor for adverse post-TJA cardiovascular complications, including death [8–16].

OSA is defined by recurring episodes of airway collapse during sleep, which terminate in a burst of sympathetic activity and a resulting arousal from sleep [17]. These events result in cyclic, intermittent hypoxemia and sleep fragmentation, that lead to daytime sleepi-

ness, multi-system physiologic perturbations and a host of adverse clinical conditions, that most commonly include cardiovascular complications [17–20]. Importantly, routine post-TJA clinical conditions (including noise [leading to sleep fragmentation], use of narcotics for pain control and supine positioning) exacerbate OSA symptoms and confer greater risk for post-TJA cardiovascular complications [9,10]. However, there is little information available that can be used to stratify which patients with OSA are especially at risk for post-TJA cardiovascular complications.

Given the expected increase in patients undergoing TJA, information that can be used for accurate and efficient cardiovascular-related risk stratification will be critical for effective post-TJA management of a patient with OSA. In this regard, the blood biomarkers cardiac troponins (cTns [cTnT or cTnI]) and brain natriuretic peptides (BNPs [BNP or N-terminal proBNP]) have shown promise for predicting risk of adverse cardiovascu-

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Table 1. Troponins as a marker of cardiovascular risk in noncardiac surgery.

Study (year)	Study design; biomarker(s)	Surgical procedure	n	Age [†] (years)	cTn measurement	Significant findings	Ref.
VISION writing group (2014)	Prospective; International – 8 countries; Hs-cTnT (fourth generation)	Elective and emergent low-risk surgeries: orthopedic, general, urology and gynecology, neurosurgery, vascular, thoracic	15,065	Distribution: 45–≥75	6–12 h after surgery and during the first 3 postoperative days	Increase in hs-cTnT independently predicted 30-day mortality and was the highest population attributable risk (34%) for perioperative complications, primarily cardiovascular (at high risk for nonfatal cardiac arrest). 8% of patients suffered myocardial injury within the first 2 days, out of which 58% did not meet criteria for the standard definition for an MI, and only 15.8% had ischemic symptoms	[30]
Nagele et al. (2014)	Prospective; cTnI, Hs-cTnT	Vascular, orthopedic, ENT, gynecology, urology, and neurosurgery. *All patients had several known CAD risk factors	n per group: Hs-cTnT: 608; cTnI: 618	65.2 ± 10.7	5 time-points: preoperative (baseline), end of surgery, and mornings of postoperative days 1, 2, and 3	98.5% of patients had detectable preoperative levels of hs-cTnT with 41% ≥14 ng/l (99th percentile). 13% of patients had detectable preoperative levels of cTnI with 4% ≥0.07 μg/l (99th percentile). 82% of patients had a postoperative increase in hs-cTnT. Only 13% of patients showed postoperative increases in cTnI. 8.6% of patients with preoperative hs-cTnT >14 ng/l had an MI compared with only 2.5% of patients with preoperative hs-cTnT <14 ng/l. 3-year mortality rate for patients with preoperative hs-cTnT >14 ng/l was 25% compared with only 11% for patients with hs-cTnT <14 ng/l	[21]
Borges et al. (2013)	Prospective; cTnI	Any elective noncardiac surgery with 1 RCRI risk factor	145	65.7 ± 9.8	Postoperative days 1 and 2 and those with symptoms of myocardial ischemia or surgical complications	32.4% of patients showed postoperative increase in cTnI. 16 (34%) of these patients had major adverse cardiac events. RCRI was an independent predictor for postoperative increases in cTnI	[36]

[†]Age is given as mean and standard deviation unless otherwise specified.

BNP: Brain natriuretic peptide; CAD: Coronary artery disease; CHASE: Cardiac health after surgery; CK-MB: Creatinine kinase isoenzyme MB; cTn: Cardiac troponin I; cTnT: Cardiac troponin T; ENT: Ears, nose and throat; h: Hour or hours; hs-CRP: High-sensitivity C-reactive protein; Hs-cTnT: High-sensitivity cardiac Troponin T; l: Liter; μg: Micrograms; ml: Milliliter; MI: Myocardial infarction; ng: nanograms; ng/ml: Nanogram/milliliter; POISE: PeriOperative Ischemic Evaluation; RCRI: Revised Cardiac Risk Index; VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

Table 1. Troponins as a marker of cardiovascular risk in noncardiac surgery (cont.).

Study (year)	Study design; biomarker(s)	Surgical procedure	n	Age† (years)	cTn measurement	Significant findings	Ref.
van Waes et al.; CHASE investigators (2013)	Prospective observational; cTnI	General, neurological, vascular, ENT, dental, orthopedic, gynecological, urological, plastic	2216	cTnI measured: 71.0 ± 7.7; n = 1627. cTnI not measured: 70.2 ± 7.4; n = 589	First 3 postoperative days	19% patients with increased cTnI had myocardial injury (defined as levels >0.06 µg/l). The relative risk of an increase in troponin (0.07–0.59 µg/l) was 2.4. The relative risk of a 10–100-fold increase in troponin (≥0.60 µg/l) was 4.2. cTnI was an independent predictor of 30-day mortality	[28]
Simons et al. (2013)	Retrospective cohort; cTnI	Carotid revascularization, open AAA repair, endovascular AAA repair, infrainguinal lower extremity bypass	16,363	69.8 ± 10	Preoperation at time of surgery, and postoperation during hospital stay	1.3% of patients experienced a postoperative increase in cTnI. 1.6% of patients experienced a postoperative MI. cTnI elevation was most common following open AAA repair (3.9%), as was MI (5.1%). Postoperative increase in cTnI and postoperative MI were predictors of survival at 5 years (54% and 33%, respectively)	[34]
VISION writing group et al. (2012)	Prospective international – 8 countries; cTnT (fourth generation)	Elective and emergent surgery: low-risk, orthopedic, general, urology or gynecology, neurosurgery, vascular, thoracic	15,133	Distribution: 45–≥75	6–12 h after surgery and during the first 3 postoperative days	Increased (peak) cTnT levels were associated with 30-day mortality	[31]
Biccard et al. (2012)	Prospective observational; cTnI	Elective vascular surgery	788 (n varied per biomarker)	58.2 ± 14.2	BNP, C-reactive protein and cTnI drawn in the 24-h period before surgery; ST depression monitored in 318 patients who wore Holter monitors during 24-h period leading up to time of surgery	Elevated preoperative BNP and cTnI were associated, and predicted postoperative cardiac events. cTnI stratification reduced the correct risk classification of postoperative cardiac events, whereas BNP did not	[35]

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Study (year)	Study design; biomarker(s)	Surgical procedure	n	Age* (years)	cTn measurement	Significant findings	Ref.
Beattie <i>et al.</i> (2012)	Retrospective cohort; cTnI	All noncardiac and nontransplant surgeries requiring overnight admission	51,701	Troponin not ordered, n = 41,167, median 55. Troponin ordered, n = 10,534, median 66	Out of those with postoperative troponin measurements (n = 10,534), 74% were done within 72 h of surgery	Out of the 1173 patients who demonstrated postoperative increases in cTnI, 285 of these patients (24.3%) died. Out of the 880 patients with detectable cTnI levels below the threshold for MI, 142 (16.1%) died. Troponin was detected in 38.9% of the 1072 mortalities. Postoperative cTnI was associated with 30-day in-hospital mortality in a dose-dependent manner	[29]
Kouvelos <i>et al.</i> (2011)	Prospective; cTnI	Elective vascular surgery	295	71 (range: 41–89)	cTnI, CK-MB, and hs-CRP preoperation and at 24-h postoperation	3.8% of patients suffered cardiovascular related death, acute myocardial infarction, ischemic stroke and unstable angina over 12 months. Elevated postoperative cTnI was a strong predictor of cardiovascular events at 1 year. Postoperative cTnI was better at predicting cardiovascular events than both hs-CRP and CK-MB	[32]
Devereux <i>et al.</i> ; POISE investigators (2011)	Prospective; International from POISE trial subjects – 23 countries; cTn unspecified	Vascular, intraperitoneal, other (noncardiac surgeries)	8351	Median 75 (67–80)	cTn (or CK-MB if cTn testing was unavailable) measured 6–12 h after surgery as well as on days 1, 2, 3, postoperation. Patients/family contacted at 30 days after surgery	94.2% of patients with an MI showed increased cTn while 3.4% had increased CK-MB. Most cTn elevations occurred within 48 h of operation for both symptomatic and asymptomatic MI. 5% of patients had perioperative MI. 74.1% of MI occurred within 48 h of surgery; though, 65.3% did not experience ischemic symptoms. Perioperative MI was an independent predictor of death at 30 days. An increase in cTn or CK-MB to ≥ 3.6 -times the upper limit of normal (not defined with MI criteria) was an independent predictor of 30-day mortality	[27]

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Study (year)	Study design; biomarker(s)	Surgical procedure	n	Age [†] (years)	cTn measurement	Significant findings	Ref.
VISION writing group (2011)	Prospective; International – 5 countries; cTnT (fourth generation)	Orthopedics, intra-abdominal, neurosurgery, urology and gynecology, head and neck, thoracic, vascular, low-risk surgeries	432	63 ± 11	6–12 h after surgery, and on postoperative days 1–3	The observed perioperative cardiac event rate was 6 times of that predicted by RCRI. Out of the 18 patients who suffered MI, 12 (66.7%) showed no ischemic symptoms. Monitoring cTnT after surgery will help identify MI in postoperative patients	[76]
Cuthbertson et al. (2007)	Prospective; cTnI	Elective vascular, gastrointestinal, pelvic surgeries	204	66 (range: 57–74)	cTnI and BNP drawn preoperation; cTnI was also drawn at 24 and 72 h postoperation	During a median of 654 days: Increased cTnI at 24 h after surgery predicted medium-term mortality; however, cTnI at 72 h did not	[24]
Barbagallo et al. (2005)	Prospective, observational; cTnI	Elective major vascular surgery	75	72 ± 7.6	Before surgery and on days 1, 2, 3 postoperation	33% of patients had increased cTnI during the first 3 days after surgery from which 12% had an MI. Increased cTnI during the first 3 days after surgery was associated with major cardiac complications that occurred in the 6.6% of patients at 1 month	[26]
Bursi et al. (2005)	Prospective; cTnI	Elective major vascular surgery patients. Group 1: coronary revascularization within previous 5 years, Group 2: moderate cardiovascular risk predictors, Group 3: minor or no cardiovascular risk predictors	391	Group 1: 69.0 ± 9.4; Group 2: 70.4 ± 8.5; Group 3: 69.3 ± 8.6	Drawn on days 1, 2, 3 postoperation	Increased cTnI was associated with adverse outcomes (MI or death) even following multivariable adjustment at 30 days and 18.9 + 6.2 months	[23]
Martinez et al. (2005)	Prospective cohort; cTnI	Noncardiac surgery or major vascular surgery requiring minimum 24-h admission	467	69 ± 10	Immediately after surgery, 8-h postoperation and on postoperative days 1–3	cTnI (≥2.6 ng/ml) demonstrated greater specificity than absolute CK-MB in detecting myocardial injury	[25]

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Figure 1. Common postoperative complications in the patient with obstructive sleep apnea following total joint arthroplasty.

[†]Potential to be/or is lethal.

OSA: Obstructive sleep apnea; TJA: Total joint arthroplasty.

lar-related 30-day morbidity or mortality in patients undergoing noncardiac surgery [21–47], TJA [48–59] and to a certain degree in OSA patients [60–73]. While these biomarkers have been studied in surgical patients and OSA patients, none of these studies directly evaluated the perioperative patient with OSA undergoing noncardiac surgery or TJA.

In this review, we evaluate the feasibility of using cTns and BNP to risk stratify patients with OSA for cardiovascular complications post-TJA. We conclude that there is a logical link to be made in utilizing cTns and BNP for predicting risk of cardiovascular-related adverse events in OSA patients undergoing TJA. However, given the lack of studies directly evaluating the populations of interest, more research is needed.

Literature search

A literature search was conducted using the PubMed, Embase and Scopus electronic databases, and references of articles, limited to human studies, English language and primarily elective surgeries conducted within the past 10 years. Our findings are presented chronologically (see Tables 2–7), as more recent assays have been found to be more precise and sensitive, reducing S/N in sensing the biomarker within the assay [74]. Our search strategy included MeSH and exploratory keywords including ‘troponin’, ‘brain natriuretic peptide’, ‘perioperative or postoperative complication’, ‘noncardiac’ or ‘non-cardiac’ ‘surgery’, ‘total hip’ or ‘knee’ ‘joint arthroplasty’ and ‘obstructive sleep apnea’. Our review excluded studies evaluating cTns and BNP in cardiac

surgery, as levels of cTns and BNP are increased with cardiac instrumentation [75].

Total hip & knee joint arthroplasty (TJA)

Current trends show a growing prevalence in obesity [79] and an aging population [80], both of which increase the risk of joint disease, and cardiovascular disease [2]. Indeed, the group of patients undergoing TJA is unique as they typically have increased age, higher obesity levels and are also more likely to have pre-existing cardiovascular disease [2]. These trends of increasingly prevalent risk factors for TJA provide strong evidence that support projection models by the Task Force for Orthopedic Surgeons that the frequency of TJA procedures will continue to increase exponentially over the next decade [2]. The surgical procedure for TJA involves precise incisions through tissue of either the knee or hip, removal of eroded cartilage and bone, drilling into bone and compression of an artificial prosthesis into native bone structure [81, 82]. Recovery in the immediate postoperative period requires increased pain control, periods of immobilization in the supine position and/or periods of limited or passive range of motion [81,82]. The most common post-TJA cardiovascular complications include pulmonary embolism (PE) and acute myocardial ischemia or myocardial infarction (MI) [1,83]. Patients undergoing major orthopedic procedures such as TJA carry a moderate risk (1–5%) of developing postoperative cardiac complications [84,85]. However, pre-existing cardiovascular co-morbidities in the older and obese patient

presenting for TJA contributes to increased postoperative cardiac events that further complicate recovery [2]. Importantly, the existence of OSA in the TJA demographic further potentiates the manifestation and incidence of adverse postoperative cardiovascular complications [8–16].

Obstructive sleep apnea

The strongest risk factor for OSA is obesity [3–5,7]. Other major risk factors include advanced age [5], male gender and postmenopausal status in women [86]. Data from 2013, estimate that 34% of middle-aged men and 17% of middle-aged women suffer from at least mild OSA, and 13 and 6%, respectively, suffer from moderate-to-severe disease [5]. These estimates represent a clear increase in prevalence compared with the previous decade, reflecting the rising obesity levels in the population [5]. In-laboratory polysomnography (PSG) is the gold standard diagnostic tool for OSA, however, an unattended portable home sleep testing (HST) is accepted as a less expensive method of diagnosis for patients with a high pretest probability of OSA [87]. The primary measure of OSA severity is the apnea-hypopnea index (AHI) [87], the average number of apneas and/or hypopneas per hour of sleep (based on PSG) or recording time (when using

HST). The AHI can be used to define disease severity as normal ($AHI < 5$), mild ($AHI \geq 5$ and < 15); moderate ($AHI \geq 15$ and ≤ 30) or severe ($AHI > 30$) [87]. The main treatment for OSA is positive airway pressure (PAP), which works as a pneumatic splint to maintain airway patency, reduce arousals and restore oxygenation [87]. OSA has been shown to contribute to a wide variety of cardiovascular manifestations (see **Figure 1**), including coronary ischemia [18,66], myocardial infarction [18,66], arrhythmias [19,88], heart failure [89], hypertension [90], venous thromboembolism [91–94] and stroke [95]. Complex pathophysiological mechanisms, some that remain unclear, contribute toward the pathogenesis of cardiovascular events among OSA patients. These include the development of severe negative intrathoracic pressure as a result of arduous respiratory efforts to overcome upper airway collapse, sympathetic activation during episodes of apnea, sleep fragmentation and increased rapid eye movement (REM) activity, intermittent hypoxemic stress, dysregulation in neurohumoral, carotid chemoreflex (augmented) and baroreflex (reduced) function, inflammation, endothelial dysfunction, metabolic dysregulation and thrombosis [17,20,96,97]. Over time, recurrent swings in negative intrathoracic pressure can lead to increased cardiac preload and left ventricular afterload, increased car-

Clinical conditions that exacerbate pathophysiology and symptoms in postoperative patients with obstructive sleep apnea.

Use of general anesthetics, opioids, hypnotics, benzodiazepines [10,13,107,112,114,,15,117,119,126]

- Increased critical airway pressure.
- Increased incidence of pharyngeal collapse from reduction in genioglossus muscle activity.
- Decreased hypoxemic and hypercapnia ventilatory response from effects on peripheral chemoreflex loop and peripheral chemoreceptors.
- Impaired arousal response.
- Decreased minute ventilation.

Patient positioning [126]

- Increased use of supine positioning following TJA.

Exposure to environmental factors (patient care activities, noise, light, pain, surgical stress) [10, 97, 119, 125]

Alterations in sleep architecture

- Increased sleep fragmentation.
- Decreased REM sleep (especially on postoperative nights one and two).
- Decreased slow wave sleep.
- Inverted or altered circadian rhythm cycle with peak surge in sympathetic activity between midnight and six in the morning.
- Increased REM sleep (rebound REM; postoperative days 3–5), a stage of sleep associated with increased propensity for sleep-disordered breathing and associated bursts of sympathetic activity.

Alternations in blood biomarkers (select)

- Increased cortisol.
- Increased pro-inflammatory response (release of $TNF-\alpha$, IL-1, IL-6, C-reactive protein).
- Increased secretion of leptin (induces sympathetic activity, functions as an immunomodulator, in addition to regulating body adiposity).
- Increased activation of transcription factor $NF-\kappa B$ and inflammatory pathways attributed to hypoxemia.
- Decreased anti-inflammatory response such as IL-10.

OSA: Obstructive sleep apnea; REM: Rapid eye movement; TJA: Total joint arthroplasty.

diac work load, ventricular wall stress, unmet myocardial oxygen demand in the presence of alveolar hypoxia and hypercapnia and ultimately myocardial stress, ischemia, injury or infarction [17,20,97]. Furthermore, increased cardiac work, altered cardiac stretch and cardiac mechanoreceptors, systemic hypoxemia, respiratory acidosis (from carbon dioxide retention) and sympathetic hyperactivity contribute to dysregulated cardiac automaticity and arrhythmias [17,20,97]. Increased sympathetic activity and REM activity also contribute to blood pressure surges, fluctuating vagal tone, decreased heart rate variability, disruption in cardiac automaticity and arrhythmias [17,65,96].

In addition to these pathophysiological mechanisms, cycles of intermittent hypoxia that occur in OSA activate vascular inflammatory pathways, and produce pro-inflammatory cytokines, reactive oxygen species and increased expression of adhesion molecules, which in turn contribute to endothelial dysfunction and atherosclerosis [17,96]. Increased levels of pro-coagulant factors (such as plasminogen-activator inhibitor type-1, fibrinogen or platelet activity and aggregation) [91,93,94] are linked to OSA severity and circadian variation contributing to early morning fibrinolytic activity [98, 99] and cardiovascular events [100–104]. These same mechanisms associated with cardiac myocyte stress have been shown to be triggers for the release of cTns and BNP [75,105], making these biomarkers a potential indicator for OSA-related cardiovascular risk.

TJA, OSA & adverse outcomes

The co-existence of common clinical conditions in the perioperative treatment of TJA patients (see **Box 1**) further potentiates the effects of OSA [12–13,106–119]. The use of general anesthetics, opioid pain control, benzodiazepines and supine patient positioning during and post-TJA all act to promote and prolong airway closure, worsening desaturation and increasing the frequency of sympathetic bursts that accompany the termination of sleep-disordered breathing events [8–11,14,83,120–124]. Additionally, standard patient care activities, noise, light, pain and surgical stress [125] not only disrupt sleep architecture, but also increase sympathetic activity [10] and inflammation [125]. Taken together, this may render patients with OSA who undergo TJA at even greater risk for postoperative cardiovascular complications compared with patients without OSA. Several studies have found that most postoperative complications typically occurred within the first 24–72 h of surgery, a period of time during which disruptions from these clinical conditions are more prominent [10, 107–108,111,114,117,119].

In 2001, a pivotal study published by Gupta and colleagues observed that 39% of patients diagnosed with

OSA experienced post-TJA complications compared with only 19% of controls without OSA [10]. Patients having OSA were more likely to experience adverse postoperative events in general; however, given that both patients having OSA and controls without OSA experienced an adverse event, the event in the patient having OSA (approximately 22% compared with 9% in controls) was commonly cardiovascular related and included myocardial infarction, myocardial ischemia, arrhythmias and pulmonary embolus [10]. Other post-TJA complications experienced by both groups were not limited to acute hypercapnia or episodic hypoxemia, delirium, wound infections and nerve palsy [10]. Further, subanalyses revealed that patients with OSA developed 15% more serious post-TJA complications (including cardiac events requiring patient transfer to an intensive care unit [ICU]), had significantly longer length of stay (LOS), unplanned ICU days and total ICU days compared with patients without OSA [10]. Illustrating the efficacy of proper treatment, none of the 33 patients who used PAP therapy developed any complications in the first 24 h [10]. A larger, subsequent study in the US Nationwide Inpatient Sample database of 258,445 TJA patients showed that patients with OSA developed more hypoxia, had increased rates of pulmonary embolism and in-hospital mortality and higher postoperative hospital charges [9]. Other studies of post-TJA patients with OSA also observed increased adverse cardiovascular complications including development of pulmonary embolism [9,12,124], cardiac complications (nonmyocardial infarction) [13] and need for intubation/use of mechanical ventilation [12,13]. Additionally, the increased use of economic resources such as unplanned transfer to the ICU [11,13], longer hospital stays [8,13] and increased hospital costs [9] have been reported. Recognizing the growing impact that OSA has on adverse postoperative complications, the American Society of Anesthesiologists (ASA) [126] has urged providers to implement special considerations such as PAP therapy or enhanced monitoring in the postsurgical management of patients with OSA.

Given the evidence linking TJA, OSA and adverse postoperative cardiovascular outcomes, we review how the use of the blood biomarkers cTns and BNP could represent additional information that may augment current perioperative risk stratification for a cohort of at-risk TJA patients with OSA. The literature provides notable differences among various studies evaluating cTns and BNP in OSA patients. These differences from the studies generally relate to the clinical variability in biomarker measurement techniques as well as differences in study design. These are detailed in the 'Limitations and challenges' section.

Study (year)	Study design; biomarker(s)	Surgical procedure	n	Age [†] (years)	cTn measurement	Significant findings	Ref.
Ray et al. (2010)	Prospective; cTnI	Elective THA *Patients in this study had no minimal cardiac risk	62	73	Preoperative cTnI + 6 other biomarkers drawn postoperation. cTnI drawn on postoperative day 2 and day 4, ECG on postoperative day 2 and compared with preoperative ECG	cTnI was not associated with cardiac events. 9.7% of patients had a postoperative cardiac event (non-ST segment elevation MI, heart failure, arrhythmia)	[77]
Ausset et al. (2008)	Prospective observational; cTnI	Elective primary or re-operation THA, emergency hip fracture surgeries	88	72.1 ± 2.8	cTnI drawn at least once on either the mornings of postoperative days 1, 2, 3. 78% of patients had levels drawn on all 3 days. Telephone follow-up at 1-year postoperative (with the patient, family member or patient's physician)	Increased cTnI was observed in 12.5% of patients (72% of these patients were asymptomatic). At the 1-year follow-up, 45% of patients had a major cardiac event (chest pain, signs of cardiac failure) compared with 4% of patients who had a normal cTnI. All cause mortality rate was 36% in the increased levels of cTnI group compared with 7% in normal levels of cTnI group. Increased cTnI was an independent factor for all cause mortality (primarily in patients undergoing emergent and re-operation surgeries)	[56]
Mouzopoulos et al. (2007)	Prospective; cTnI	Hemiarthroplasty for hip fracture, intramedullary nailing for hip fracture, THA	90	75 ± 6.7	cTnI, CPK, CK-MB drawn immediately postoperation and at the 24-, 48-, 72-, 96- and 120-h time-points post operation	Increased cTnI was observed only in patients who had postoperative MI. False increase of CK-MB index was observed in 43.3% of patients who did not have an MI. Increased CPK and increased CK-MB with peak levels was observed on postoperative day 1 for all surgeries. Increased CPK and increased CK-MB were more pronounced following THA	[78]

[†]Age is given as mean and standard deviation unless otherwise specified.

CK-MB: Creatinine kinase isoenzyme MB; CPK: Creatinine phosphokinase; cTn: Cardiac troponin; cTnI: Cardiac troponin I; MI: Myocardial infarction; THA: Total hip arthroplasty; TKA: Total knee arthroplasty.

Cardiac troponins: a marker for cardiovascular risk

Troponin is a protein complex involved in muscle contraction that is comprised of three distinct subunits: troponin T (cTnT), troponin I (cTnI) and troponin C (cTnC) [105]. The troponin T (largest subunit; 37–39 kiloDalton) and troponin I (26 kiloDalton) isoforms are specifically involved in cardiac muscle contraction, while the troponin C isoform is involved in cardiac as well as skeletal muscle contraction. With myocardial injury, ischemia or necrosis, cardiac cell membrane integrity is interrupted and cardiac troponins T and I are released from myocytes into the blood stream. Elevation in either cTnT or cTnI is universally accepted as a highly sensitive laboratory measure in the diagnosis of myocardial infarction [105]. Cardiac troponins (cTnT or cTnI) can be detected in the blood within 2–4 h of myocardial damage and may persist for up to 21 days [75,105]. Increased serum and plasma levels of troponin can also be seen during open heart surgery, percutaneous coronary intervention, pulmonary embolism, end-stage renal disease, pericarditis, myocarditis, aortic dissection, acute heart failure, strenuous exercise, chest wall trauma, cardiac contusion, chemotherapy, malignancy, inflammation, stroke, sepsis, subarachnoid hemorrhage and rhabdomyolysis [105,127]. In addition to underlying disease states, the variability in sample processing, differences in manufacturing methods and variation in the generation of cTn product measured (e.g., fourth generation cTnT or high sensitivity cTnT [hs-cTnT]) may all affect interpretation of results [105,128].

Troponins as a marker of cardiovascular risk in noncardiac surgery

Most of the studies that have investigated the role of perioperative measurement of cTns evaluated patients undergoing noncardiac surgery, rather than solely on TJA, and were assessing for myocardial injury [23,26,28] and infarction [21–27] (see Table 1). These studies have a great deal of heterogeneity in the specific assays and timing of troponin measurement, as well as specific populations within the larger grouping of noncardiac surgery. Thus, this review focuses on several of the larger and more applicable studies. However, overall, several studies have shown that elevated cTn levels predicted or were associated with 30-day mortality [23,27, 29–31] and long-term (up to 5 years) morbidity [32] or mortality [21,24,33–34]. These studies share similarities in their limitations, strengths and weaknesses, and the majority of such findings are grouped under the ‘Limitations and challenges’ section unless as discussed below.

One of the largest studies to date, the Vascular Events in Noncardiac Surgery Patients Cohort Eval-

uation (VISION), evaluated levels of cTnT (using a fourth generation assay) drawn 6–12 h following surgery and during the first three postoperative days within 15,133 older adult patients (aged ≥ 45 years) undergoing noncardiac surgery [31]. The investigators found that higher peak levels of cTnT over the follow-up period were associated with increased risk of 30-day mortality [31]. Specifically, compared with the 1% of patients with cTnT levels ≤ 0.01 ng/ml, 4% of patients with cTnT levels of 0.02 ng/ml, 9.3% of patients cTnT levels between 0.03 and 0.29 ng/ml and 16.9% of patients with cTnT levels ≥ 0.30 ng/ml died within 30 days of surgery [31]. Forty five percent of these deaths were vascular in origin. Risk factors associated with increased 30-day mortality and increased cTnT levels included advanced age, the need for emergent surgery or major general surgery and the presence of recent coronary arterial disease. Neither OSA diagnosis (based on interviews and medical record review) nor major orthopedic surgery (20.4% of surgeries studied) was significantly associated with either 30-day mortality or increased cTnT. The authors concluded that given that the median time from elevation of cTnT at 0.02 ng/ml to death was 13.5 days, there could be sufficient time for the initiation of special considerations and potential interventions in the perioperative phase in order to minimize mortality [31]. Despite the large sample size of the study, several specific limitations include the lack of cTnT collected before surgery, the lack of association between cTnT to changes in renal function such as the estimated glomerular filtration rate in the perioperative period, and a record of any interventions that may have occurred with findings of a critical value of cTnT [31].

In a subsequent analysis of 15,065 patients in the same cohort, the VISION investigators found that 8% of patients met criteria for myocardial injury (evidenced with cTnT optimal discriminatory point levels > 0.03 ng/ml) within the first 2 days following surgery [30]. Myocardial injury was not only an independent predictor of 30-day mortality, but was also the population with the highest attributable risk toward primarily cardiovascular-related perioperative complications [30]. However, 58% of those patients who had evidence of myocardial injury did not meet criteria for the universal definition of myocardial infarction and only 15.8% of patients who met criteria for myocardial injury exhibited symptoms of cardiac ischemia [30]. A limitation in this study included the potential of missed cases of ischemic events as the study analyzed a higher optimal discriminatory threshold level of the cTnT assay (peak of 0.04 ng/ml compared with 0.03 ng/ml). Similarly, in a study of 8351 patients who underwent elective noncardiac surgery, the PeriOp-

erative ISchemic Evaluation (POISE) trial, increased cTn (unspecified generation) levels, drawn 6–12 h following surgery and during the first three postoperative days, were associated with myocardial ischemia in patients who suffered both symptomatic and asymptomatic postoperative MI [27]. Most events related to myocardial infarction or ischemia occurred within 48 h postsurgery [27].

Other studies have found increased levels of cTnI or cTnT (including hs-cTnT), drawn preoperation and/or for any of the first three mornings postoperation [21,23–24,26, 28, 32], or for at least two consecutive days postoperation [22,25,34] were helpful in identifying risk for postoperative cardiac complications for up to 1 month [23,25–26,28–29], 1 year [32] and up to 5 years [21,24, 34] following surgery. In addition to increased postoperative morbidity, both cTnI and cTnT or hs-cTnT have been associated with identifying increased risk of mortality. A systematic review and meta-analyses found that increased cTn levels following surgery were an independent predictor of mortality within 1 year [33]. Furthermore, increased postoperative cTnI [23–24,28–29] and cTnT or hs-cTnT [21,27,30–31,34] levels predicted or are associated with decreased 5-year [34], 1–3 year [21, 23–24] and 30-day survival [27,29–31].

Troponins as a marker of cardiovascular risk in TJA

The majority of the data in orthopedic surgery patients are from those undergoing emergency procedures, such as those necessitated by hip fractures [48–55], rather than elective arthroplasty. Data from this select population may not be generalizable to patients undergoing elective TJA. Reasons not only include differences in clinical and patient characteristics, but also because levels of cTns drawn from patients undergoing emergency TJA may be higher than those having elective TJA, as muscle injury associated with fractures may further raise levels of cTns [55]. Specifically, cTns rise following elective TJA in only 0.0–8.9% of patients, but do so after hip fractures in 22–52% of patients [55]. Several of these studies also found that increased perioperative (either pre- and/or post-) cTn levels predicted postoperative cardiac complications that may not correlate to electrocardiographic changes [52], however did correlate with in-hospital cardiac events [50,55] and 1-year mortality [49,50]. Nevertheless, one study found that in older adults (age 85 ± 9.6 [mean $\pm$ SD] years) with multiple comorbidities, cTnI levels did not predict 6-month mortality or cardiac complications [53].

Very few studies evaluated cTns following elective TJA. These results are summarized in **Table 2**. In a mixed group of elective (approximately 51% of all surgeries performed in this study) and emergent hip

surgery, increased cTnI was associated with in-hospital myocardial ischemia, acute coronary syndrome and other cardiac events [56]. Importantly, increased cTns were evident in patients who did not exhibit clinical symptoms of underlying cardiac perturbations, but who had a history of co-morbid cardiovascular risk factors that were likely to increase risk of cardiac events [56]. Further, increased cTnI levels were associated with mortality at 1-year and a tenfold risk of cardiac events at 1 year; however, this was primarily observed in nonelective TJA patients [56]. Thus, these biomarkers could represent an additional mechanism for identifying at-risk patients, beyond standard medical history and clinical symptoms.

Troponins as a marker of cardiovascular risk in OSA

Studies observing the association between cTns and OSA have been conflicting. Increased levels of cTns have been found to be independently associated with severity of OSA and in patients with OSA having a history of coronary artery disease (see **Table 3**) [60,66–67, 72,129–130]. However, several studies have also found no association between levels of cTns and OSA [65,131–134]. One of the largest nationally conducted cross-sectional studies of middle aged to older adults (involving 1645 patients with a mean age of 60 years), the Atherosclerosis Risk in Communities (ARIC) and the Sleep Heart Health Study (SHHS) studies, found increased levels of hs-cTnT were independently associated with both OSA severity and risk of death or occurrence of heart failure in all OSA classified groups [66]. The association of increased levels of hs-cTnT and OSA in this study remained significant after adjusting for 17 major confounders including age, BMI, smoking status, alcohol intake, hypertension, diabetes, chronic lung disease, pulmonary function tests, estimated glomerular filtration rate, systolic blood pressure and blood levels of total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides and insulin [66].

Studies have suggested that the association between cTns and OSA is higher specifically in patients with OSA who have a known history of existing heart disease or a constellation of known cardiovascular risk factors [60,61,66,72,129–130]. In a 2014 cross-sectional study using only OSA patients from the Akershus Sleep Apnea Project (ASAP) cohort (AHI >5), Einvik and colleagues found that after adjustment for age, gender, CAD and a host of factors associated with cardiovascular risk, increased OSA severity and nocturnal desaturations were independently associated with increased levels of hs-cTnI [60]. The authors concluded that over time repeated episodes of hypoxemia could have contributed to changes in myocardial structure that con-

Table 3. Troponins as a marker of cardiovascular risk in obstructive sleep apnea.

Study (year)	Study design; biomarker; OSA diagnosis	n; OSA criteria	Use of PAP	Age ^a (years)	cTn measurement	Significant findings	Ref.
Valo et al. (2015)	Prospective; Hs-cTnT; In-hospital PSG. *The majority of patients were male	41; Group 1: AHI $\geq 15/h$ with OSA/CAD; Group 2: AHI $\geq 15/h$ with OSA/without CAD	No	Group 1: 61 ± 11 ; Group 2: 54 ± 12	Hs-cTnT and NT-proBNP before 9 pm, before sleep, and after 7 am the following day, after sleep	Neither group revealed a significant difference between hs-cTnT levels prior to sleep and those measured after sleep [131]	
Valo et al. (2015)	Prospective; Hs-cTnT; In-hospital PSG	AHI $\geq 15/h$ (mean 53 ± 21) with OSA/CAD	Yes, CPAP	61 ± 11	Hs-cTnT and NT-proBNP before 9 pm, before sleep, and after 7 am the following day, after sleep	Levels of hs-cTnT were not affected by CPAP. Although CPAP attenuated ST-segment depression during sleep, it was not significant [135]	
Maeder et al. (2015)	Prospective cross-sectional; Hs-cTnI; In-hospital PSG	98; Group 1: Moderate/severe OSA, AHI $39 \pm 20/h$; Group 2: Mild/No OSA, AHI $8 \pm 4/h$	No, on night 1; Yes, CPAP in a subgroup on night 2	Group 1: 54 ± 12 ; Group 2: 50 ± 17	Hs-cTnI, BNP, NT-proBNP, IL-6, VEGF, matrix metalloproteinase-9, and insulin drawn before (8–10 pm) and after sleep (6–7 am)	No difference in hs-cTnI, between groups 1 and 2. Biomarker concentrations were unaffected by CPAP use during sleep. Elevated insulin levels were seen in group 1 prior to sleep, and IL-6 was elevated in group 1 following sleep [136]	
Barbe et al. (2014)	Prospective; Ancillary study of the ISAACC trial; cTn unspecified; Cardio-respiratory polygraphy. * $>80\%$ of patients were male	431; Group 1: OSA, AHI $30 \pm 14/h$; Group 2: Control, AHI $6 \pm 4/h$	Yes, CPAP (but effects were not analyzed in this study)	Group 1: 61 ± 10 ; Group 2: 57 ± 12	cTn (unspecified) drawn following admission with acute coronary syndrome	Peak cTn levels were significantly elevated in group 1 after adjusting for smoking, age, BMI and hypertension. The diseased vessel count rose with increasing OSA severity. Mean LOS in coronary care unit was longer for group 1 [129]	
Hall et al. (2014)	Prospective; Hs-cTnT and cTnI; In-hospital PSG or in-home polygraphy. *71.2% of patients were male	222; Group 1: OSA, AHI ≥ 5 ; Group 2: AHI <5	No	Group 1: 50 ± 13 ; Group 2: 43 ± 11	Hs-cTnT and cTnI drawn the morning after sleep	The distributions of cTnI and hs-cTnT in group 1 were different than the distributions seen in group 2. A simple model in which hs-cTnT was assessed as a continuous response variable did show an association with AHI. When adjusted for predictors, neither hs-cTnT nor cTnI demonstrated significant independent associations with AHI [132]	

^aAge is given as mean and standard deviation unless otherwise specified.

AHI: Apnea-hypopnea index; ARIC: Atherosclerosis Risk in Communities; AST: Aspartate aminotransferase; BMI: Body mass index; BNP: Brain natriuretic peptide; CAD: Coronary Artery Disease; CK: Creatinine kinase isoenzyme; CK-MB: Creatinine kinase isoenzyme MB; CPAP: Continuous positive airway pressure; CRP: C-reactive protein; cTn: Cardiac troponin I; cTnI: Cardiac troponin T; h-fabp: Heart type fatty acid binding protein; hs-CRP: High-sensitivity C-reactive Protein; Hs-cTnT: High-sensitivity cardiac Troponin T; ISAACC: Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome. Effect of Intervention with Continuous Positive Airway Pressure; m: Median; MI: Myocardial infarction; MRI: Magnetic resonance imaging; NT-proBNP: NT-prohormone brain natriuretic peptide; OSA: Obstructive sleep apnea; OSAS: Obstructive sleep apnea syndrome; PAP: Positive airway pressure; proBNP: Prohormone brain natriuretic peptide; PSG: Polysomnography; RDI: Respiratory Disturbance Index; SHHS: Sleep Heart Health Study; TTE: Transthoracic echocardiogram.

Table 3. Troponins as a marker of cardiovascular risk in obstructive sleep apnea (cont.).

Study (year)	Study design; biomarker; OSA diagnosis	n; OSA criteria	Use of PAP	Age [†] (years)	cTn measurement	Significant findings	Ref.
Barcelo et al. (2014)	Prospective; Hs-cTnT (fifth generation); Full PSG. *All patients were male. Patients with severe cardiovascular diseases or chronic diseases were excluded	200; Group 1: OSA, AHI ≥10; Group 2: Control, AHI <10	Yes, for 12 months (minimum use of 4 h/night)	Group 1: 51 ± 9; Group 2: 48 ± 11	Hs-cTnT drawn between 8 and 10 am	Greater proportion of OSA patients had detectable hs-cTnT than in the control group. CPAP treatment resulted in a significant increase in hs-cTnT	[130]
Einvik et al. (2014)	Cross-sectional; Hs-cTnI; In-hospital PSG	514; Group 1: OSA, AHI ≥5; Group 2: No OSA, AHI <5	No	Group 1: 48 ± 11; Group 2: 52 ± 10; Group 3: 44 ± 11	Hs-cTnI drawn the morning following PSG	Elevated hs-cTnI was independently associated with increased AHI and lower mean SpO ₂ . After adjusting for CAD, demographics and cardiovascular confounders, elevated hs-cTnI was also associated with a larger proportion of total sleep time with SpO ₂ < 90%	[60]
Querejeta-Roca et al.; ARIC-SHHS study (2013)	Prospective; Hs-cTnT; Overnight home PSG	1645; Group 1: No OSA, RDI ≤5; Group 2: Mild OSA, 5 < RDI ≤15; Group 3: Moderate OSA, 15 < RDI ≤30; Group 4: Severe OSA, RDI >30	No	62.5 ± 5.5	Hs-cTnT drawn approximately 10 years following initial enrollment at follow-up visit (ARIC visit 4)	Hs-TnT was associated with OSA after adjusting for 17 potential confounders (including cardiovascular elements). Hs-cTnT was associated with risk of death or heart failure in all OSA groups over a median follow-up period of 12.4 years	[66]

[†]Age is given as mean and standard deviation unless otherwise specified.

AHI: Apnea-hypopnea index; ARIC: Atherosclerosis Risk in Communities; AST: Aspartate aminotransferase; BMI: Body mass index; BNP: Brain natriuretic peptide; CAD: Coronary Artery Disease; CK: Creatinine kinase isoenzyme; CK-MB: Creatinine kinase isoenzyme MB; CPAP: Continuous positive airway pressure; CRP: C-reactive protein; cTn: Cardiac troponin I; cTnI: Cardiac troponin I; h-fabp: Heart type fatty acid binding protein; hs-CRP: High-sensitivity C-reactive Protein; Hs-cTnT: High-sensitivity cardiac Troponin T; ISAACC: Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome. Effect of Intervention with Continuous Positive Airway Pressure; m: Median; MI: Myocardial infarction; MRI: Magnetic resonance imaging; NT-proBNP: NT-prohormone brain natriuretic peptide; OSA: Obstructive sleep apnea; OSAS: Obstructive sleep apnea syndrome; PAP: Positive airway pressure; proBNP: Prohormone brain natriuretic peptide; PSG: Polysomnography; RDI: Respiratory Disturbance Index; SHHS: Sleep Heart Health Study; TTE: Transthoracic echocardiogram.

Table 3. Troponins as a marker of cardiovascular risk in obstructive sleep apnea (cont.).

Study (year)	Study design; biomarker; OSA diagnosis	n; OSA criteria	Use of PAP	Age† (years)	cTn measurement	Significant findings	Ref.
Shah et al. (2013)	Prospective; Hs-cTnT (third generation); Portable sleep testing. *All patients in this study were diagnosed with acute MI	78; Group 1: OSA, AHI ≥ 5 ; Group 2: Non-OSA, AHI < 5	No	58 $\pm$ 18; Group 1: 62 $\pm$ 16; Group 2: 52 $\pm$ 14	Patients who had a positive cTnT value within 24 h of admission; CPK	Elevated AHI, in partially adjusted (age, gender, race) and fully adjusted models (smoking, hypertension, hyperlipidemia, BMI, history of prior cardiovascular or cerebrovascular disease, diabetes and baseline admission creatinine), was associated with lower peak hs-cTnT levels. The odds ratio for AHI suggests that OSA has a cardioprotective effect. Patients with OSA had significantly lower levels of CPK when compared with non-OSA patients	[137]
Won et al. (2013)	Retrospective; cTn unspecified; Overnight PSG. *Patients with documented MI or ischemic heart disease. 98% of patients were male	281; Group 1: Severe OSA, AHI ≥ 30 ; Group 2: Mild-to-moderate OSA, 5 $<$ AHI < 30	Yes	Group 1: 65.6 $\pm$ 11; Group 2: 64.6 $\pm$ 11	Documented increased cTn (unspecified) levels were used to determine if patients had an MI	The number of deaths reported for group 1 (41%) during follow-up (mean = 4.1 years) was significantly greater than that reported for group 2 (29%). Mortality for patients with severe OSA had an adjusted hazard ratio of 1.72	[72]
Randby et al. (2012)	Prospective cross-sectional; Hs-cTnT; In-hospital PSG	505; Group 1: No OSA, AHI < 5 ; Group 2: Mild-to-moderate OSA, 5 $\leq$ AHI < 30 ; Group 3: Severe OSA, AHI ≥ 30	No	Range: 30–65; Group 1: 44.0 $\pm$ 11.1; Group 2: 51.0 $\pm$ 10.5; Group 3: 54.5 $\pm$ 8.0	Hs-cTnT drawn the morning following PSG	Proportion of patients with detectable hs-cTnT increased with severity of OSA. AHI and hs-cTnT levels were not significantly associated after adjusting for univariate predictors of hs-cTnT	[67]
Inami et al. (2012)	Prospective cross-sectional; Hs-cTnT; Overnight ambulatory PSG. *Patients with stable CAD. 87% were male	69; Group 1: OSA, AHI < 15 ; Group 2: OSA, AHI ≥ 15	No	66 $\pm$ 11	Hs-cTnT, NT-proBNP, Hs-CRP drawn before coronary intervention; Calculation of Gensini coronary stenosis score	Gensini scores and NT-proBNP levels were significantly higher in patients with AHI ≥ 15 . Gensini scores and NT-proBNP levels were shown to correlate significantly with AHI. AHI and history of smoking were independently correlated with Gensini score among clinical and SDB-related parameters	[138]

†Age is given as mean and standard deviation unless otherwise specified.

AHI: Apnea-hypopnea index; ARIC: Atherosclerosis Risk in Communities; AST: Aspartate aminotransferase; BMI: Body mass index; BNP: Brain natriuretic peptide; CAD: Coronary Artery Disease; CK: Creatinine kinase isoenzyme; CK-MB: Creatinine kinase isoenzyme MB; CPAP: Continuous positive airway pressure; CRP: C-reactive protein; cTn: Cardiac troponin; cTnI: Cardiac troponin I; cTnT: Cardiac troponin T; h-fabp: Heart type fatty acid binding protein; hs-CRP: High-sensitivity C-reactive Protein; Hs-cTnT: High-sensitivity cardiac Troponin T; ISAACC: Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome. Effect of Intervention with Continuous Positive Airway Pressure; m: Median; MI: Myocardial infarction; MRI: Magnetic resonance imaging; NT-proBNP: NT-prohormone brain natriuretic peptide; OSA: Obstructive sleep apnea; OSAS: Obstructive sleep apnea syndrome; PAP: Positive airway pressure; proBNP: Prohormone brain natriuretic peptide; PSG: Polysomnography; RDI: Respiratory Disturbance Index; SHHS: Sleep Heart Health Study; TTE: Transthoracic echocardiogram.

Table 3. Troponins as a marker of cardiovascular risk in obstructive sleep apnea (cont.).

Study (year)	Study design; biomarker; OSA diagnosis	n; OSA criteria	Use of PAP	Age [†] (years)	cTn measurement	Significant findings	Ref.
Colish <i>et al.</i> (2012)	Prospective; cTnT (third generation); Overnight PSG. *All patients were CPAP naive and without cardiovascular diseases. 68% were male	47; Severe OSA, AHI 63 ± 30	Yes, CPAP for 12 months minimum >4.5 h use/night	51 ± 10	cTnT, CRP, NT-proBNP, TTE, completed: before CPAP was initiated, at 3, 6 and 12 months after the initiation of CPAP. Cardiac MRI was completed at baseline, 6 and 12 months	cTnT, CRP, NT-proBNP did not change from baseline after 12 months of CPAP therapy. Improvements in right ventricular end-diastolic diameter, left atrial volume index, right atrial volume index and degree of pulmonary hypertension were seen as early as 3 months and continued over 1-year follow-up. Decreased left ventricular mass size was seen as early as 6 months and continued to improve over the 1-year follow-up	[133]
Cifci <i>et al.</i> (2010)	Prospective; cTnI; Full-night PSG. *66.7% of patients were male	30; Group 1: No OSA, AHI <5; Group 2: Mild OSA, 5 ≤ AHI <15; Group 3: Moderate OSA, 15 ≤ AHI <30; Group 4: Severe OSA, AHI ≥30	Yes, CPAP. Adherence based on subjective reporting of 5 h/70% of night	49.97 ± 10.3	Pro-BNP, cTnI, CK, CK-MB, AST drawn between 9.30 and 11 am before and 6 months after CPAP initiation	At 6 months, neither cTnI nor the other biomarkers demonstrated a significant change from baseline	[134]
Oktay <i>et al.</i> (2008)	Prospective; cTnI; Standard PSG. *Patients with cardiac disease were excluded	69; Group 1: No OSA, AHI <5; Group 2: Mild OSA, 5 ≤ AHI <15; Group 3: Moderate OSA, 15 ≤ AHI <30; Group 4: Severe OSA, AHI ≥30	No	48.02 ± 9.5; Group 1: 43.2 ± 6.2; Groups 2–4: 49.7 ± 10.1	cTnI, h-fabp, CK, CK-MB, AST drawn at 9 pm and the following morning at 9 am	None of the groups demonstrated a change in CK, CK-MB, AST, cTnI or h-fabp levels following sleep. Between groups, only h-fabp was significantly different following sleep	[65]

[†]Age is given as mean and standard deviation unless otherwise specified.

AHI: Apnea-hypopnea index; ARIC: Atherosclerosis Risk in Communities; AST: Aspartate aminotransferase; BMI: Body mass index; BNP: Brain natriuretic peptide; CAD: Coronary Artery Disease; CK: Creatinine kinase isoenzyme; CK-MB: Creatinine kinase isoenzyme MB; CPAP: Continuous positive airway pressure; CRP: C-reactive protein; cTn: Cardiac troponin I; cTnT: Cardiac troponin T; h-fabp: Heart type fatty acid binding protein; hs-CRP: High-sensitivity C-reactive Protein; Hs-cTnT: High-sensitivity cardiac Troponin T; ISAACC: Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome. Effect of Intervention with Continuous Positive Airway Pressure; m: Median; MI: Myocardial infarction; MRI: Magnetic resonance imaging; NT-proBNP: NT-prohormone brain natriuretic peptide; OSA: Obstructive sleep apnea; OSAS: Obstructive sleep apnea syndrome; PAP: Positive airway pressure; proBNP: Prohormone brain natriuretic peptide; PSG: Polysomnography; RD: Respiratory Disturbance Index; SHHS: Sleep Heart Health Study; TTE: Transthoracic echocardiogram.

Table 4. Brain natriuretic peptides as a marker of cardiovascular risk in noncardiac surgery.

Study (year)	Study design; biomarker	Surgical procedure	n	Age* (years)	BNP measurement	Significant findings	Ref.
Borges <i>et al.</i> (2013)	Prospective observational; NT-proBNP	Elective (with 1 RCRI risk): abdominal, thoracic, vascular, prostate, hip	145	65.7 ± 9.8	NT-proBNP was drawn preoperation and on postoperative day 2	Elevated pre and postoperative NT-proBNP was associated with major adverse cardiac events. Elevated preoperative NT-proBNP was independently associated with adverse cardiac complications	[36]
Biccard <i>et al.</i> (2012)	Prospective observational; NT-proBNP	Elective vascular	788 *n varied per biomarker	58.2 ± 14.2	BNP, C-reactive protein and cTnI drawn 24 h before surgery; ST depression was monitored in 318 patients who wore a Holter monitor day before surgery to time for surgery	Elevated preoperative BNP and cTnI were independently associated with cardiac events. BNP was independently associated with adverse cardiac complications and improved risk stratification for all patients. cTnI stratification worsened the correct risk classification of patients who had major adverse cardiac events	[35]
Mercantini <i>et al.</i> (2012)	Prospective observational; BNP	Elective major abdominal surgery	205	64 ± 15	BNP drawn preoperation and following surgery	Elevated preoperative BNP was associated with adverse cardiac events. Elevated preoperative BNP was the only predictor of adverse postoperative cardiac events	[38]
Yang <i>et al.</i> (2012)	Prospective; NT-proBNP	Vascular surgery: AAA, suprainguinal, carotid artery, infrainguinal, extra-anatomic bypass	365	67.1 ± 8.5	Preoperative assessment within 2 weeks preceding surgery; daily measurements taken on postoperative days 1–5, and in accordance with clinical decision of surgeon or consulting physician	After adjusting for confounders, NT-proBNP and an indication of high risk by the modified RCRI were independent predictors of acute MI, CHF including PE and primary cardiac death (all occurring within 5 days of surgery). No statistical difference were observed in the predictive abilities of NT-proBNP and the modified RCRI	[44]
Biccard <i>et al.</i> (2012)	Prospective observational; BNP	Elective vascular	267	61; range: 20–86	Preoperative BNP and cTnI draws, and cTnI draws on postoperative days 1–3 (the primary end point was to evaluate for increased cTnI within the first 3 postoperative days)	Elevated preoperative BNP and the RCRI were independent predictors of increased postoperative cTnI. Risk stratification reclassification using three AHA risk categories and based on BNP tertiles was helpful for only intermediate risk patients. Reclassification based on optimal discriminatory point for BNP significantly improved risk stratification for the entire cohort	[35]

*Age is given as mean and standard deviation unless otherwise specified.

AAA: Abdominal aortic aneurysm; AHA: American Heart Association; BNP: Brain natriuretic peptide; cTnI: Cardiac troponin I; ECG: Electrocardiogram; h: Hour; hs-CRP: High-sensitivity C-reactive protein; MI: Myocardial infarction; NT-proBNP: NT-prohormone brain natriuretic peptide; RCRI: Revised Cardiac Risk Index

Table 4. Brain natriuretic peptides as a marker of cardiovascular risk in noncardiac surgery (cont.).

Study (year)	Study design; biomarker	Surgical procedure	n	Age ^a (years)	BNP measurement	Significant findings	Ref.
Payne <i>et al.</i> (2011)	Prospective observational; BNP	Elective vascular, laparotomy	345	68.4; range: 28–93	BNP drawn the evening before surgery	Elevated preoperative BNP was an independent predictor of long-term postoperative survival. Elevated BNP showed a mean survival of 731.9 days, whereas patients below the cut-off survived an average of 1284.6 days beyond surgery	[46]
Rajagopalan <i>et al.</i> (2011)	Prospective observational; NT-proBNP	Elective vascular	136	69; median: 62–75	NT-proBNP drawn preoperation; cTnI drawn before surgery and immediately after surgery, and postoperative days 1, 2, 3 and 5 and subsequent follow-up	Elevated preoperative NT-pro-BNP independently predicted and was associated with postoperative myocardial injury (evidenced by increase in cTnI), odds ratio of 3.4. Following adjustment for cardiac risk, site of surgery and type of procedure, increased preoperative NT-proBNP and hs-CRP were independent predictors for postoperative cardiac complications	[47]
Goei <i>et al.</i> (2009)	Prospective; NT-proBNP	Elective vascular	592	70; 62–76	NT-proBNP and hs-CRP drawn preoperation	Following adjustment for cardiac risk, site of surgery and type of procedure, increased preoperative NT-proBNP and hs-CRP were independent predictors for postoperative cardiac complications within 30 days following surgery	[37]
Schutt <i>et al.</i> (2009)	Prospective; NT-proBNP	Intermediate or high-risk noncardiac surgery (with more than one risk factor for CAD)	83	69.5 ± 11	Preoperative measurement; postoperative measurements on days 1 and 3	Preoperative NT-proBNP was associated with postoperative cardiac events	[43]

^aAge is given as mean and standard deviation unless otherwise specified.

AAA: Abdominal aortic aneurysm; AHA: American Heart Association; BNP: Brain natriuretic peptide; cTnI: Cardiac troponin I; ECG: Electrocardiogram; h: Hour; hs-CRP: High-sensitivity C-reactive protein; MI: Myocardial infarction; NT-proBNP: NT-prohormone brain natriuretic peptide; RCRI: Revised Cardiac Risk Index

Table 4. Brain natriuretic peptides as a marker of cardiovascular risk in noncardiac surgery (cont.).

Study (year)	Study design; biomarker	Surgical procedure	n	Age ^a (years)	BNP measurement	Significant findings	Ref.
Yun <i>et al.</i> (2008)	Prospective; NT-proBNP	Elective surgeries	279	68 ± 8	NT-proBNP collected within 5 days prior to surgery; primary endpoint was adverse cardiovascular event as measure by 12 lead ECG, and CK-MB and cTnT concentrations immediately following surgery and on postoperative day 1	NT-proBNP and the modified RCRI were independent predictors of perioperative cardiac complications	[42]
Rajagopalan <i>et al.</i> (2008)	Prospective; observational; NT-proBNP	Elective vascular	136	76; median: 75–81	NT-proBNP drawn preoperation and first postoperative day	Over a 2-year follow-up, preoperative NT-pro-BNP independently predicted all-cause mortality. Postoperative NT-pro-BNP predicted mortality, but not major adverse cardiac events	[143]
Cuthbertson <i>et al.</i> (2007)	Prospective; BNP	Elective vascular, gastrointestinal, pelvic	204	66; range: 57–74	Preoperative BNP and cTnI; cTnI also drawn at postoperative h 24 and 72	During a median of 654 days: Increased preoperative BNP resulted in a 3.5-fold increase in the hazard of death and 6.9-fold increase in hazard of cardiovascular mortality	[24]
Gibson <i>et al.</i> (2007)	Prospective; observational; BNP	Elective vascular	190	68 ± 10	Preoperative BNP; cardiac events included increased levels of cTnI on days 2, 5 and 42; serial ECG	Increased preoperative BNP predicted postoperative cardiac events, independent of risk factors and after adjusting for: sex, ischemic heart disease, heart failure, cerebrovascular disease, renal impairment, type of surgery, use of beta-blockers and statins	[40]
Dernellis <i>et al.</i> (2006)	Prospective; BNP	Orthopedic, abdominal, obstetric, gynecological, head and neck	1590	70 ± 7	Preoperative BNP (within 3 days before surgery)	BNP independently predicted postoperative cardiac events (cardiac deaths, nonfatal MI, pulmonary edema, ventricular tachycardia). BNP was superior to categorizations by clinical variables in identifying risk for postoperative events	[41]

^aAge is given as mean and standard deviation unless otherwise specified.
 AAA: Abdominal aortic aneurysm; AHA: American Heart Association; BNP: Brain natriuretic peptide; cTn: Cardiac troponin; cTnI: Cardiac troponin I; ECG: Electrocardiogram; h: Hour; hs-CRP: High-sensitivity C-reactive protein; MI: Myocardial infarction; NT-proBNP: NT-prohormone brain natriuretic peptide; RCRI: Revised Cardiac Risk Index

sequently contributed to the release of cTns [60]. Additionally, the authors state, the use of a high-sensitive assay could have been more useful in detecting the smaller sized cTnI molecule [60]. However, after controlling for potential confounding variables (such as age, sex, hypertension, diabetes and other cardiovascular risk factors) other studies have not corroborated this finding [131,132]. Using data from the ASAP cohort, Randby and colleagues examined three groups of OSA patients and observed that the prevalence of elevated *hs-cTnT* increased in proportion with severity of OSA [67]; however, this association was no longer significant after adjusting for covariates such as age, sex, hypertension and diabetes [67]. Interestingly, in a 2014 cross-sectional study using only OSA patients from the ASAP cohort (AHI >5), Maeder and colleagues did not find any differences in levels of *hs-cTnI* in a group with severe OSA compared with a group with mild OSA [136]. Hall *et al.* also did not observe any significant differences in levels of *hs-cTnT* or a single molecule cTnI when comparing patients with varying severity of OSA to controls without OSA [132].

Further illustrating the discrepancies in the literature examining cTns in OSA, a recent study by Shah and colleagues has focused on the phenomena of ischemic preconditioning developing over time from repeated cycles of hypoxia and re-oxygenation. This confers an element of cardio-protection and results in decreased cardiac injury and *hs-cTnT* (third generation) levels in patients with OSA [137]. However, further studies are necessary to confirm this hypothesis.

The role of PAP therapy & troponins

Data evaluating the impact of PAP therapy, the mainstay treatment of OSA, on cardiac cTns are limited and mixed. Current evidence (see Table 3) primarily suggests that PAP adherence does not affect cTns [133–135] in the overall OSA population. However, one study showed a change in the levels of cTn, an increase in *hs-cTnT* levels with CPAP use [130].

In a small study of 21 patients with severe OSA and presence of CAD, Valo and colleagues found that levels of *hs-cTnT* drawn before and after sleep were not affected by one night of CPAP use [135]. Further, in this study, electrocardiogram monitoring of ST segments were conducted throughout the night of sleep to document any evidence of myocardial ischemia [135]. Although use of CPAP reduced ST segment depression during the lowest point of oxygen desaturation with sleep, this finding was not significant. The authors concluded that attenuation of ST segment depression could have been more evident at alternate time-points of sleep such as during post-apnea tachycardia or with an alternate measurement interval. Similarly,

Maeder *et al.* and Cifci *et al.* did not find an association between *hs-cTnI* or cTnI levels and use of CPAP over one night or 6 months, respectively [134,136]. In a CAD naive population, Colish and colleagues found no change in levels of a third-generation cTnT from baseline following 1 year of CPAP therapy in patients with severe OSA. However, in this study both echocardiography and cardiac magnetic resonance imaging revealed that CPAP use contributed to improvements in cardiac remodeling properties and reversal of systolic and diastolic changes as seen with pulmonary hypertension in as early as 3 months, with continued improvements at 1 year [133].

In an interesting finding, Barcelo and colleagues found an unanticipated increase in *hs-cTnT* levels after treatment with PAP for 12 months, compared with controls without OSA [130]. Subjective assessment of PAP adherence was not explicitly described in this study, and as such this may impact interpretation of the results. The study was conducted in a male population with OSA and hypertension (including elevated glucose and triglycerides in the OSA group), but excluded patients with prior myocardial infarction, unstable angina, stroke and most of other cardiovascular-related co-morbidities. Potential mechanisms by which PAP therapy may in fact raise *hs-cTnT* levels have been suggested and include cardiac adaptation, turnover of cardiomyocytes and a reversible change in the membrane permeability of cardiomyocytes, along with variations in intrathoracic pressures leading to increased *hs-cTnT* levels. The rise in this biomarker may therefore signal a repair process or evidence of cardiac stress that could occur with PAP therapy within this particular subgroup [130].

Brain natriuretic peptides: a marker of cardiovascular risk

Brain natriuretic peptide (BNP) belongs to a group of vasodilator and anti-proliferative neurohormonal natriuretic polypeptides that are produced primarily by the cardiac ventricles (and in lesser amounts by the brain and adrenal glands) in response to stretching of cardiac myocytes or increased cardiac wall stress [139]. ProBNP, a biologically inactive prohormone, is secreted by the ventricles in response to ventricular dysfunction and cleaved into the physiologically active BNP and the biologically inactive N-terminal fragment (NT-proBNP) [139]. BNP has a half-life of approximately 20 min, and is cleared actively and passively through the renal system. NT-proBNP has a plasma half-life of approximately 2 h, and is cleared primarily through the renal system (as well as through muscles and the liver) [139]. BNP and NT-proBNP increase with age, and are found in higher levels in women and in lower

Table 5. Brain natriuretic peptides as a marker of cardiovascular risk in elective total joint arthroplasty.

Study (year)	Study design; biomarker(s)	Surgical procedure	n	Age [†] (years)	BNP measurement	Significant findings	Ref.
Park <i>et al.</i> (2012)	Prospective observational; BNP. *All patients in study must have hypertension. *67% (group 1) and 79% (group 2) were women	Total knee or hip replacement. Group 1: hospitalized ≥30 days; Group 2: Hospitalized <30 days	97	73.12 ± 10.05	Preoperation (within 7 days of surgery) and postoperation (drawn within 24 h of surgery)	Elevated postoperative BNP was associated with increased hospital length of stay. Elevated postoperative BNP may predict hospital stay of ≥30 days	[45]
Villacorta Jr <i>et al.</i> (2010)	Prospective; BNP. *71.6% were women	Elective THA or TKA, femur fracture	208	72.6 ± 8.8	BNP drawn up to 48 h before surgery and 24 h postoperation	BNP was significantly higher in the 8% of patients who experienced cardiac events. Preoperative BNP was an independent predictor of postoperative cardiac events (MI, angina, PE, heart failure, atrial fibrillation, ventricular tachycardia, cardiac death)	[58]
Breidhardt <i>et al.</i> (2010)	Prospective; BNP	Elective orthopedic surgery (hip, knee, spine, lower leg, ankle, foot, other)	270	64; range: 16–93	Telephone follow up, and database search at 12 months to determine cardiac events, re-hospitalizations and mortality	Elevated preoperative BNP levels correlated with ASA score and with in-hospital postoperative cardiac events (angina, ST segment elevation, non ST segment elevation MI, acute heart failure, atrial fibrillation). Elevated preoperative BNP levels correlated with postoperative cardiac events (atrial fibrillation, non-ST segment elevation MI, ST segment elevation, heart failure) at 1-year follow-up. Re-hospitalizations were cardiac related and due to infection	[57]
Montagnana <i>et al.</i> (2008)	Prospective longitudinal; NT-proBNP	THA and TKA, spine stabilization	37	59 ± 21.4	NT-proBNP, cTnT, CK-MB, myoglobin drawn 3 h prior to surgery and at 4 and 72 h postoperation	NT-proBNP levels were elevated at postoperative hour 72, relative to preoperative and other postoperative (hour 4) levels	[148]

[†]Age is given as mean and standard deviation unless otherwise specified.

ASA: American Society of Anesthesiologists; BNP: Brain natriuretic peptide; CK-MB: Creatinine kinase isoenzyme MB; cTn: Cardiac troponin; cTnT: Cardiac troponin T; MI: Myocardial infarction; NT-proBNP: NT-prohormone brain natriuretic peptide; PE: Pulmonary embolus; THA: Total hip arthroplasty; TKA: Total knee arthroplasty.

levels in patients who are obese [139]. BNP levels are established hallmark biomarkers in the detection of acute or chronic congestive heart failure. Their levels are independently associated with major cardiovascular events such as myocardial infarction, stroke and unstable angina in patients aged 50–89 years [140], and 1-year mortality in patients with congestive heart failure or acute coronary syndrome [141]. Elevated BNP levels can also be seen with valvular heart disease, atrial fibrillation, pulmonary embolism, severe pulmonary hypertension, inflammatory cardiac disease, acute or chronic renal failure, liver cirrhosis, sepsis, trauma, endocrine disorders, severe neurological disorders such as stroke and subarachnoid hemorrhage [139].

Brain natriuretic peptides as a marker of cardiovascular risk in noncardiac surgery

Studies measuring BNP levels in patients undergoing noncardiac surgery have investigated the role in the perioperative period for risk prediction or associations with adverse postoperative myocardial events [35–44], prolonged hospital stay [45] and mortality [24,46–47] (see Table 4). Most of the studies evaluating BNP levels had levels drawn within 2 weeks prior to the day of surgery, typically at one time-point, however recent studies have incorporated perioperative BNP levels (levels drawn preoperatively and up to 5 days following surgery) [36,38,43,45–46]. Preoperative BNP levels have been found to be an independent predictor or associated with increased postoperative cardiac events [35–44,47,142] or mortality [24,41,46–47] in noncardiac surgery, including cardiac morbidity at 30 days following discharge from hospitalization [38]. Additionally, postoperative BNP levels [36,45] were associated with cardiac events, but not always [47], and predictive for mortality over a 2-year follow-up [47]. These findings were typically representative of patients who were aged 60 years and older with cardiovascular co-morbidities.

Compared with cTns, studies evaluating BNP levels in noncardiac surgeries have fewer number of patients enrolled. A study by Dernellis and colleagues, with the most number of patients (1590) noted increased preoperative BNP levels independently predicted cardiac death as well as a host of adverse cardiac events [41]. The majority of patients (40%) underwent elective orthopedic-related surgeries [41]. Further, in Dernellis' study, increased preoperative BNP levels were superior to clinical categorization for ascertaining risk for adverse postoperative events including cardiac death [41]. The authors of this study utilized findings regarding BNP levels to alter the clinical management and treatment of patients thus confounding the study results [41]. In a study of older patients (median age of 70 years) with a host of cardiac diseases, Goei *et al.*, observed that after

adjusting for cardiac risk factor, procedure type and location of surgery, increased levels of preoperative NT-proBNP increased the odds (by fourfold) of predicting postoperative cardiovascular events including cardiac death within 30 days following surgery [37]. Increased presence of cardiac risk factors was associated with increased risk of cardiac events [37]. The authors noted that the longer half-life of NT-proBNP compared with BNP may make NT-proBNP superior to BNP in select cohorts in the screening for cardiac risk [37].

Several studies utilizing perioperative BNP levels have focused on vascular surgery patients. In a study of 788 patients undergoing vascular surgery, Biccari *et al.* observed increased preoperative BNP levels were superior to alternate biomarkers such as C-reactive protein and cTnI in predicting overall risk for adverse postoperative cardiac events independent of the clinical oriented Revised Cardiac Risk Index (RCRI) [142]. Utilizing a Holter heart monitor in the perioperative period to detect presence of myocardial ischemia in 318 of their patients, the authors found no significant findings between BNP and Holter monitor analysis [142]. In a smaller study, also of vascular patients, increased preoperative BNP levels along with the RCRI were independent predictors of postoperative cardiac events as evidenced by elevated levels of cTnI [35]. Further, in this study, increased levels of preoperative BNP improved the overall risk classification for postoperative cardiac complications [35]. A study by Yang and colleagues in high-risk vascular patients observed that the use of preoperative levels of NT-proBNP was not significantly different compared with the use of RCRI in screening for cardiac risk; however, NT-proBNP levels predicted postoperative cardiac events such as heart failure, MI and cardiovascular death [44]. Further, to improve the power of detecting asymptomatic cardiac events, the authors validated the use of NT-proBNP levels in conjunction with the use of myocardial stress thallium test [44].

Other studies evaluating preoperative BNP levels have also observed that increased levels were associated or predicted the following: adverse postoperative cardiac complications within 30 days following abdominal surgery [38], and up to 6 weeks post vascular surgery [40]; a 3.4-fold odds of having myocardial injury post-vascular surgery [39]; and, increased risk of postoperative cardiac events in patients aged 68 ± 8 years undergoing nonvascular surgeries [42]. In addition to increased postoperative morbidity, preoperative BNP has been associated with predicting postoperative mortality and long-term survival in vascular and laparotomy patients [46]; whereas, preoperative NT-proBNP has been associated or predicted postoperative all-cause mortality over a 2-year follow-up in a vascular surgery

Table 6. Brain natriuretic peptides as a marker of cardiovascular risk in obstructive sleep apnea.

Study (year)	Study design; biomarker; OSA diagnosis	n	Use of PAP	Age ^a (years)	BNP measurement	Significant findings	Ref.
Valo et al. (2015)	Prospective; NT-proBNP; in-hospital PSG. *The majority of patients were male	41; Group 1: OSA with CAD, AHI $\geq 15/h$; Group 2: OSA without CAD, AHI $\geq 15/h$	No	Group 1: 61 ± 11 ; Group 2: 54 ± 12 (control)	NT-proBNP before 9 pm, before sleep, and after sleep, after 7 am; ECG analysis conducted to detect ST segment depression during sleep	No significant difference were observed in NT-proBNP levels before and after sleep. In patients with OSA and CAD, NT-proBNP levels were significantly higher than for patients with OSA alone. No significant ST depression was detected in either groups	[131]
Valo et al. (2015)	Prospective; NT-proBNP; In-hospital PSG	21; OSA with CAD, AHI $\geq 15/h$ (mean 53 ± 21)	Yes, CPAP on one night	61 ± 11	NT-proBNP before 9 pm, before sleep, and after sleep, after 7 am	CPAP reduced NT-proBNP levels during sleep and decreased ST segment depression (by <1 mm)	[135]
Maeder et al. (2015)	Prospective cross-sectional; BNP and NT-proBNP	98; Group 1: AHI $39 \pm 20/h$; Group 2: AHI $8 \pm 4/h$	No, on night 1; Yes, CPAP in a subgroup on night 2	Group 1: 54 ± 1 ; Group 2: 50 ± 17	BNP, NT-proBNP, hs-cTnI, IL-6, VEGF, matrix metalloproteinase-9 and insulin drawn before (8–10 pm) and after sleep (6–7 am)	Reduction of BNP during sleep was relatively greater in the moderate-to-severe OSA group when compared with the mild or no OSA group. Biomarker concentrations were unaffected by short-term CPAP	[136]
Querejeta-Roca et al.; ARIC-SHS study (2013)	Prospective; NT-proBNP; Overnight home PSG	1645; Group 1: No OSA, RDI ≤ 5 ; Group 2: Mild OSA, $5 < \text{RDI} \leq 15$; Group 3: Moderate OSA, $15 < \text{RDI} \leq 30$; Group 4: Severe OSA, RDI > 30	No	62.5 ± 5.5	Approximately 10 years following initial enrollment at follow-up visit (ARIC visit 4)	NT-proBNP was not associated with OSA after adjusting for 17 potential confounders (including cardiovascular elements)	[66]

^aAge is given as mean and standard deviation unless otherwise specified.

AHI: Apnea-Hypopnea index; ARIC: Atherosclerosis Risk in Communities; AST: Aspartate aminotransferase; BIPAP: Bi-level positive airway pressure; BMI: Body mass index; BNP: Brain natriuretic peptide; CAD: Coronary artery disease; CK: Creatinine kinase isoenzyme; CK-MB: Creatinine kinase isoenzyme MB; CPAP: Continuous positive airway pressure; C-reactive protein; cTn: Cardiac troponin; cTnI: Cardiac troponin I; cTnT: Cardiac troponin T; ET-1: Endothelin-1; GLVD: Global left ventricular dysfunction; hs-CRP: High-sensitivity C-reactive protein; hs-cTnI: High-sensitivity cardiac troponin I; hs-cTnT: High-sensitivity cardiac troponin T; HRR: Heart rate recovery; LVH: Left ventricular hypertrophy; LVMI: Left ventricular mass index; mm: Millimeter; MRI: Magnetic resonance imaging; nCPAP: Nasal continuous positive airway pressure; NT-ANP: NT-atrial natriuretic peptide; NT-proBNP: NT-prohormone brain natriuretic peptide; OSA: Obstructive sleep apnea; OSAS: Obstructive sleep apnea syndrome; PAP: Positive airway pressure; proBNP: Prohormone-brain natriuretic peptide; PSG: Polysomnography; RDI: Respiratory Distress Index; SDB: Sleep-disordered breathing; SHHS: Sleep Heart Health Study; TTE: Transthoracic echocardiogram; VO_2 : Maximal oxygen consumption.

Table 6. Brain natriuretic peptides as a marker of cardiovascular risk in obstructive sleep apnea (cont.).

Study (year)	Study design; biomarker; OSA diagnosis	n	Use of PAP	Age [†] (years)	BNP measurement	Significant findings	Ref.
Zhao <i>et al.</i> (2011)	Prospective; NT-proBNP; Overnight PSG. *Patients with CAD. The majority were male	151; Group 1: severe OSA, AHI ≥ 30 ; Group 2: moderate OSA, $15 \leq \text{AHI} < 30$; Group 3: Mild OSA, $5 \leq \text{AHI} < 15$; Group 4: no OSA, AHI < 5	Yes, CPAP for 27 patients with severe OSA (minimum 4.9 + 1.2 h/day)	Group 1: 63.2 ± 12.3 ; Group 2: 57.6 ± 10.5 ; Group 3: 57.7 ± 11.1 ; Group 4: 56.1 ± 9.3	NT-proBNP, hs-CRP, ET-1, and fibrinogen were drawn between 6 and 6.30 am, and repeated in patients with severe OSA following 3 months of CPAP	NT-proBNP was not associated with OSA. Hs-CRP levels correlated with AHI and decreased after 3 months of CPAP	[73]
Colish <i>et al.</i> (2012)	Prospective; cTnT; Overnight PSG. *All patients were CPAP naive and without cardiovascular diseases. 68% were male	47; Mean AHI 63 ± 30	Yes, CPAP for 12 months; minimum use/night > 4.5 h	51 $\pm$ 10	NT-proBNP, cTnT, CRP, TTE, completed: before CPAP was initiated, at 3, 6 and 12 months after the initiation of CPAP. Cardiac MRI was completed at baseline, 6 and 12 months	There was no change in levels of NT-proBNP. There was decreased/improvement in right ventricular end-diastolic diameter, left atrial volume index, right atrial volume index and degree of pulmonary hypertension at 3 months and continued to 1 year following CPAP. Left ventricular mass size was also decreased/improved	[133]
Inami <i>et al.</i> (2012)	Prospective cross-sectional; BNP; Overnight ambulatory PSG. *Patients with stable CAD. 87% were male	69; Group 1: OSA, AHI < 15 ; Group 2: OSA, AHI ≥ 15	No	66 $\pm$ 11	NT-proBNP, Hs-cTnT, Hs-CRP drawn before coronary intervention; Calculation of Gensini coronary stenosis score	Gensini scores and NT-proBNP levels were significantly higher in patients with AHI ≥ 15 . Gensini scores and NT-proBNP levels were shown to correlate significantly with AHI. AHI and history of smoking were independently correlated with Gensini score among clinical and SDB-related parameters	[138]

[†]Age is given as mean and standard deviation unless otherwise specified.

AHI: Apnea-Hypopnea index; ARIC: Atherosclerosis Risk in Communities; AST: Aspartate aminotransferase; BIPAP: Bi-level positive airway pressure; BMI: Body mass index; BNP: Brain natriuretic peptide; CAD: Coronary artery disease; CK: Creatinine kinase isoenzyme; CK-MB: Creatinine kinase isoenzyme MB; CPAP: Continuous positive airway pressure; CRP: C-reactive protein; cTn: Cardiac troponin; cTnI: Cardiac troponin I; cTnT: Cardiac troponin T; ET-1: Endothelin-1; GLVD: Global left ventricular dysfunction; hs-CRP: High-sensitivity C-reactive protein; hs-cTnI: High-sensitivity cardiac troponin I; hs-cTnT: High-sensitivity cardiac troponin T; HRR: Heart rate recovery; LVH: Left ventricular hypertrophy; LVMI: Left ventricular mass index; mm: Millimeter; MRI: Magnetic resonance imaging; nCPAP: Nasal continuous positive airway pressure; NT-ANP: NT-atrial natriuretic peptide; NT-proBNP: NT-prohormone brain natriuretic peptide; OSA: Obstructive sleep apnea; OSAS: Obstructive sleep apnea syndrome; PAP: Positive airway pressure; proBNP: Prohormone-brain natriuretic peptide; PSG: Polysomnography; RDI: Respiratory Distress Index; SDB: Sleep-disordered breathing; SHHS: Sleep Heart Health Study; TTE: Transthoracic echocardiogram; VO_2 : Maximal oxygen consumption.

Table 6. Brain natriuretic peptides as a marker of cardiovascular risk in obstructive sleep apnea (cont.).

Study (year)	Study design; biomarker; OSA diagnosis	n	Use of PAP	Age* (years)	BNP measurement	Significant findings	Ref.
Ljunggren <i>et al.</i> (2012)	Prospective; BNP; Overnight PSG. *All patients were women from the community	349; Group 1: control; Group 2: mild OSA; Group 3: moderate OSA; Group 4: severe OSA	No	49.8 ± 11.3	BNP, CRP drawn morning after PSG	Mean BNP level increased with severity of OSA. Odds for elevated BNP increased with OSA severity after adjusting for age, BMI, systolic blood pressure, anti-hypertensives and creatinine	[63]
Cifci <i>et al.</i> (2010)	Prospective; pro-BNP; Full-night PSG. *66.7% of patients were male	30; Group 1: control; Group 2: mild OSA; Group 3: moderate OSA; Group 4: severe OSA	Yes, CPAP. Adherence based on subjective reporting of 5 h/70% of night	49.9 ± 10.3	Pro-BNP, cTnI, CK, CK-MB, AST drawn between 9:30 and 11 am, prior to and 6 months following CPAP initiation	Pro-BNP levels were not associated with OSA severity. No differences were observed between baseline and 6-month pro-BNP or other biomarkers	[134]
Maeder <i>et al.</i> (2009)	Prospective; NT-proBNP	40; Group 1: Mild-to-moderate OSA, AHI <30/h; Group 2: severe OSA, AHI ≥30/h	Yes, nCPAP, minimum 3.5 h/night use	50 ± 9	NT-proBNP drawn at baseline and 7.9 ± 1.4 months of CPAP; peak VO ₂ and heart rate recovery at 1 (HRR-1) and 2 (HRR-2) min after exercise	There were no difference observed in NT-proBNP levels. nCPAP was associated with an improvement in peak VO ₂ and heart rate recovery in patients with OSA	[64]
Maeder <i>et al.</i> (2008)	Prospective; NT-proBNP; PSG. *Majority of patients were male	89; Group 1: mild OSA, AHI 5–15/h; Group 2: moderate OSA, AHI 15–30/h; Group 3: severe OSA, AHI >30/h	No	49.5 ± 9.7	NT-proBNP drawn at 7 am; creatinine, echocardiography and cardiopulmonary exercise testing-measuring peak VO ₂	NT-proBNP levels and peak VO ₂ were not associated with OSA severity. NT-proBNP levels were poorly associated with LVH. Increased NT-proBNP was weakly associated with lower peak VO ₂ (cardiorespiratory fitness)	[150]

*Age is given as mean and standard deviation unless otherwise specified.

AHI: Apnea-Hypopnea index; ARIC: Atherosclerosis Risk in Communities; AST: Aspartate aminotransferase; BIPAP: Bi-level positive airway pressure; BMI: Body mass index; BNP: Brain natriuretic peptide; CAD: Coronary artery disease; CK: Creatinine kinase isoenzyme; CK-MB: Creatinine kinase isoenzyme MB; CPAP: Continuous positive airway pressure; CRP: C-reactive protein; cTn: Cardiac troponin; cTnT: Cardiac troponin T; ET-1: Endothelin-1; GLVD: Global left ventricular dysfunction; hs-CRP: High-sensitivity C-reactive protein; hs-cTnI: High-sensitivity cardiac troponin I; hs-cTnT: High-sensitivity cardiac troponin T; HRR: Heart rate recovery; LVH: Left ventricular hypertrophy; LVMI: Left ventricular mass index; mm: Millimeter; MRI: Magnetic resonance imaging; nCPAP: Nasal continuous positive airway pressure; NT-ANP: NT-atrial natriuretic peptide; NT-proBNP: NT-prohormone brain natriuretic peptide; OSA: Obstructive sleep apnea; OSAS: Obstructive sleep apnea syndrome; PAP: Positive airway pressure; proBNP: Prohormone-brain natriuretic peptide; PSG: Polysomnography; RDI: Respiratory Distress Index; SDB: Sleep-disordered breathing; SHHS: Sleep Heart Health Study; TTE: Transthoracic echocardiogram; VO₂: Maximal oxygen consumption.

Table 6. Brain natriuretic peptides as a marker of cardiovascular risk in obstructive sleep apnea (cont.).

Study (year)	Study design; biomarker; OSA diagnosis	n	Use of PAP	Age [†] (years)	BNP measurement	Significant findings	Ref.
Koga <i>et al.</i> (2008)	Prospective; BNP; Overnight PSG. *All patients were men	49; Group 1: AHI mean 42.2 ± 21.5; Group 2: control (Epworth sleepiness scale <10)	Yes, nCPAP	Group 1: 56 ± 11; Group 2: 50 ± 12	BNP drawn before PAP, and after PAP was initiated at 1 and 3 months; Tei index to evaluate GLVD	BNP levels were increased in the OSA group but the difference was not significant. BNP levels decreased 3 months after nCPAP. Following 1 and 3 months of nCPAP, Tei index decreased in OSA group; and prevalence of GLVD decreased from 19 to 4%	[62]
Usui <i>et al.</i> (2008)	Prospective cross-sectional; BNP; Overnight PSG. *Most patients were male	235; Group 1: mild/moderate OSA, AHI 19.3 ± 7.1; Group 2: severe OSA, AHI 56.5 ± 22.0	No	52 ± 14	BNP was drawn the morning after PSG. Patients had a TTE prior to PSG	LVMI (prevalence of LVH and BMI) were increased in the severe OSA group. Increased BNP was an independent variable to determine LVH in the severe OSA group	[70]
Hubner <i>et al.</i> (2007)	Prospective; NT-proBNP; Overnight PSG	60; Group 1: AHI <22.4 events/h; Group 2: AHI >22.4 events/h	Yes, nCPAP or BIPAP	Median: 55.7 (43–62)	NT-proBNP drawn at 6–6:30 am following PSG; echocardiography; 28 out of 60 patients were re-evaluated 3 months following PAP treatment	NT-proBNP levels were not associated with AHI. Increased NT-proBNP levels correlated with left ventricular ejection fraction, creatinine clearance and arterial hypertension	[149]
Tasci <i>et al.</i> (2006)	Prospective; NT-proBNP; Overnight PSG	69; Group 1: Hypertensive OSA, mean AHI 36.7 ± 4.2; Group 2: Normotensive OSA, mean AHI 40.6 ± 5.0; Group 3: Control-Normotensive without OSA, mean AHI 2.7 ± 0.5	Yes, nCPAP	Group 1: 56.3 ± 1.5; Group 2: 48.5 ± 2.3; Group 3: 49.8 ± 2.7	NT-proBNP drawn between 9 and 10 am on admission and day 3 following CPAP intervention/or second PSG	No difference in baseline NT-proBNP levels between OSA groups and control. nCPAP was associated with decreased NT-proBNP levels in both OSA groups; however, CPAP was most effective in decreasing NT-proBNP in the hypertensive OSA group	[69]

[†]Age is given as mean and standard deviation unless otherwise specified.

AHI: Apnea-Hypopnea index; ARIC: Atherosclerosis Risk in Communities; AST: Aspartate aminotransferase; BIPAP: Bi-level positive airway pressure; BMI: Body mass index; BNP: Brain natriuretic peptide; CAD: Coronary artery disease; CK: Creatinine kinase isoenzyme; CK-MB: Creatinine kinase isoenzyme MB; CPAP: Continuous positive airway pressure; CRP: C-reactive protein; cTn: Cardiac troponin; cTnI: Cardiac troponin I; cTnT: Cardiac troponin T; ET-1: Endothelin-1; GLVD: Global left ventricular dysfunction; hs-CRP: High-sensitivity C-reactive protein; hs-cTnI: High-sensitivity cardiac troponin I; hs-cTnT: High-sensitivity cardiac troponin T; HRR: Heart rate recovery; LVH: Left ventricular hypertrophy; LVMI: Left ventricular mass index; mm: Millimeter; MRI: Magnetic resonance imaging; nCPAP: Nasal continuous positive airway pressure; NT-ANP: NT-atrial natriuretic peptide; NT-proBNP: NT-prohormone brain natriuretic peptide; OSA: Obstructive sleep apnea; OSA_S: Obstructive sleep apnea syndrome; PAP: Positive airway pressure; proBNP: Prohormone-brain natriuretic peptide; PSG: Polysomnography; RDI: Respiratory Distress Index; SDB: Sleep-disordered breathing; SHHS: Sleep Heart Health Study; TTE: Transthoracic echocardiogram; VO₂: Maximal oxygen consumption.

Table 6. Brain natriuretic peptides as a marker of cardiovascular risk in obstructive sleep apnea (cont.).

Study (year)	Study design; biomarker; OSA diagnosis	n	Use of PAP	Age† (years)	BNP measurement	Significant findings	Ref.
Vartany <i>et al.</i> (2006)	Prospective; NT-proBNP; Overnight PSG	30; Mean AHI 38.4 ± 26.1	No	Median: 47 ± 13	NT-proBNP drawn at night before sleep and the morning after sleep	NT-proBNP values decreased overnight and increased in the morning but was not significant	[71]
Patwardhan <i>et al.</i> (2006)	Retrospective; BNP; NT-ANP; Overnight PSG	623; Group 1: AHI <5; Group 2: 5 ≤AHI <15; Group 3: 15 ≤AHI <30; Group 4: AHI ≥30	No	Group 1: 56 ± 8; Group 2: 59 ± 9; Group 3: 60 ± 8; Group 4: 61 ± 9	BNP and NT-ANP testing was done an average of 79 days prior to study. BNP and NT-ANP levels following sleep were collected from fasting samples between 8 and 9 am	No statistically significant relation between OSA and BNP was observed. No statistically significant relation between NT-ANP and AHI was observed. These findings suggest that undiagnosed OSA may not be a associated with major alterations in left ventricular function	[151]

†Age is given as mean and standard deviation unless otherwise specified.

AHI: Apnea-Hypopnea index; ARIC: Atherosclerosis Risk in Communities; AST: Aspartate aminotransferase; BIPAP: Bi-level positive airway pressure; BMI: Body mass index; BNP: Brain natriuretic peptide; CAD: Coronary artery disease; CK: Creatinine kinase isoenzyme; CK-MB: Creatinine kinase isoenzyme MB; CPAP: Continuous positive airway pressure; CRP: C-reactive protein; cTnI: Cardiac troponin; cTnT: Cardiac troponin T; ET-1: Endothelin-1; GLVD: Global left ventricular dysfunction; hs-CRP: High-sensitivity C-reactive protein; hs-cTnI: High-sensitivity cardiac troponin I; hs-cTnT: High-sensitivity cardiac troponin T; HRR: Heart rate recovery; LVH: Left ventricular hypertrophy; LVMI: Left ventricular mass index; mm: Millimeter; MRI: Magnetic resonance imaging; nCPAP: Nasal continuous positive airway pressure; NT-ANP: NT-atrial natriuretic peptide; NT-proBNP: NT-prohormone brain natriuretic peptide; OSA: Obstructive sleep apnea; OSAS: Obstructive sleep apnea syndrome; PAP: Positive airway pressure; proBNP: Prohormone-brain natriuretic peptide; PSG: Polysomnography; RDI: Respiratory Distress Index; SDB: Sleep-disordered breathing; SHHS: Sleep Heart Health Study; TTE: Transthoracic echocardiogram; VO₂: Maximal oxygen consumption.

cohort [47], and a 3.5-fold odds of death [24], 6.9-fold odds of cardiovascular related mortality following vascular surgery [24].

Fewer studies have found utility in the use of postoperative BNP in the perioperative patient. Rajagopalan and colleagues observed, increased postoperative levels of NT-proBNP in vascular surgery patients predicted mortality over a follow-up of 2 years; however, NT-proBNP levels were not associated with postoperative cardiac events [47]. Borges and colleagues found, in intermediate and high-risk vascular patients, although both preoperative and postoperative levels of NT-proBNP were associated with postoperative cardiac events in the unadjusted model, preoperative but not postoperative levels was associated with a fourfold odds of adverse major postoperative cardiac events after adjusting for clinical factors [36]. The authors concluded although postoperative NT-proBNP levels were increased, there was lack of significance potentially attributed to the perioperative release of surgery-related catecholamine contributing to subtle postoperative myocardial ischemia and elevation of NT-proBNP levels in a higher cardiac risk cohort [36]. This finding was similar to a study by Schutt *et al.*, who observed increased preoperative NT-proBNP but not postoperative NT-proBNP levels were associated with postoperative cardiac events; however, increased postoperative levels of NT-proBNP were common in all patients [43]. There are several meta-analyses and systematic reviews of studies evaluating BNP in the surgical population; and they consistently demonstrate that BNP, in particular when drawn preoperation compared with postoperation, are independent predictors of both short- and long-term adverse cardiac events, including cardiac deaths and all-cause mortality [143,144]. In addition, BNP were found to be useful as a stratification tool to assess risk for postoperative cardiovascular complications [145]. A meta-analysis of vascular surgery patients found that increased preoperative BNP levels (including NT-proBNP) were associated with increased risk of 30-day postoperative cardiac events, cardiac-related mortality and all-cause deaths up to 180 days [144]. Using preoperative BNP significantly improved the preoperative predictive risk classification of the traditionally utilized RCRI [145]. Furthermore, higher postoperative BNP levels obtained from 1 h to 7 days postoperation following noncardiac surgery (primarily vascular surgery but also included emergent and elective orthopedic surgery), were independently associated with nonfatal myocardial infarction, cardiac failure, cardiac mortality, cardiac arrest and all-cause mortality [146]. Another meta-analysis evaluating the role of BNP following major noncardiac surgery found that increases in both preoperative BNP and

NT-proBNP identified patients at risk for myocardial injury, nonfatal myocardial infarction, all-cause mortality and cardiac death [143]. Further in this study, preoperative BNP was also associated with increased risk for major adverse cardiovascular events and all-cause mortality that occurred within 6 months following surgery [143]. Last, a recent systematic review and meta-analysis found that in the noncardiac surgery patient population, increased postoperative BNP levels were the strongest predictors of nonfatal MI and death at 30 days and ≥ 180 days following surgery, adding prognostic value in risk stratification for postoperative complications [147].

Brain natriuretic peptides as a marker of cardiovascular risk in TJA

Data regarding the role of BNP in predicting future cardiovascular risk in TJA, like the data regarding cTns, largely comes from patients having emergency procedures (e.g., those following acute fractures) with a cohort that includes non-TJA surgeries [57,58,148] rather than elective procedures [45]. As with cTns, four studies showed that a rise in NT-proBNP levels after emergency TJA predicts in-hospital cardiac events [129, 134] and increased 1- [128,129] and 2-year [130] mortality in patients aged 60–86 years, but did not predict 6-month mortality or cardiac complications in older adults aged 85 ± 9.6 years [132], who may have other competing co-morbidities.

Table 5 summarizes data from studies that evaluated BNP following elective TJA. These studies suggest that increased BNP predicted in-hospital myocardial ischemia, injury and fatal cardiovascular events.

BNPs added value in scenarios where patients did not report clinical symptoms of a cardiac condition, but who had a history of cardiovascular risk factors. Thus, BNP may be more valuable than standard clinical symptoms in predicting cardiovascular risk. In the singular study of older patients (aged 73.12 ± 10.05 years) with hypertension who underwent elective TJA, Park and colleagues observed increased *postoperative* but not *preoperative* levels of BNP predicted length of hospital stay that was ≥ 30 days; however, BNP levels were not associated with adverse postoperative cardiac events [45]. The majority of patients in Park and colleagues' study were women who did not have extreme cardiovascular risk factors (such as stroke and ischemic heart disease) [45].

Brain natriuretic peptides as a marker of cardiovascular risk in OSA

The majority of studies evaluating BNP in patients with OSA found no association between levels of BNP and OSA severity [62,64,66,69–71,73,133,134,149,150],

although some studies have found an association [63] (see Table 6). Association between BNP levels and OSA severity appears most useful in select sub-groups including a cohort of only women, or in patients with varying severity of coronary artery disease (CAD).

Notably, in the largest study conducted to date with 1645 patients, the ARIC-SHHS study did not find an association between NT-proBNP levels and the severity of OSA in their subjects, despite adjusting for 17 confounders [66]. The authors concluded that the association between OSA severity and NT-proBNP was confounded by BMI. Although, statistical adjustment for BMI reduced the negative association between OSA and NT-proBNP levels, this finding was not significant following further adjusted analysis [66]. Similarly, in a community cohort with stable cardiovascular risk from the Framingham Offspring Study, Patwardhan and colleagues also did not find an association between OSA severity and BNP nor NT-atrial NP (a marker belonging to the natriuretic peptide family that is sensitive to stimuli contributing to cardiac atrial stretch) [151]. The authors conclude that timing of the blood draws (between 8 and 9 in the morning), sample selection bias or the prolonged time between when BNP levels were drawn and PSG (median of 79 days) could have all affected the final findings [151]. In a cohort of patients with some cardiovascular co-morbidities, Vatany and colleagues observed, NT-proBNP levels decreased following a night's sleep compared with the morning-after levels but this finding was not significant [71].

Studies evaluating the utility of BNP levels and OSA severity in patients with background CAD have been informative. Valo and colleagues observed in patients with untreated OSA, NT-proBNP levels did not significantly change when compared before sleep to after sleep; however, levels in patients with OSA and background CAD were higher than in those with OSA without a history of CAD [131]. Maeder *et al.*, observed overnight BNP but not NT-proBNP levels had a larger relative (but not absolute) reduction following sleep in patients with moderate/severe OSA compared with those with mild/no OSA [136]. Patients with moderate/severe OSA were mostly male and on a beta-blocker medication [136]. The authors postulate that the lack of affect observed in NT-proBNP levels may be attributed to differences in half-life between the two BNPs (longer for NT-proBNP) and distinct individual biological variability that may be present [136]. In patients with stable CAD, NT-proBNP levels were not only increased but correlated with severity of coronary stenosis [136]. Other studies have found although there were no differences in levels of BNP between moderate compared with severe OSA groups, BNP levels

grouped by quintile were associated with improvement in cardiac architecture such as left ventricular hypertrophy [70]. In a interesting community-based study evaluating the effect of OSA severity and levels of morning BNP in a women only cohort, Ljunggren and colleagues observed that mean BNP levels (drawn in the morning following sleep) increased as the severity of OSA increased (further associated with oxygen desaturation index levels implying a dose–response relationship) [63]. The authors conclude BNP levels could have been affected by episodes of hypoxia during sleep [63].

The role of PAP therapy & brain natriuretic peptides

The effects of PAP therapy on BNP levels have been mixed, with a number of studies demonstrating PAP did not significantly alter levels of BNPs [64,73,133,134] versus other studies observing PAP decreased levels of BNPs [62,69,135,149] (see Table 6). However, some evidence seems to suggest that significant changes in BNP levels with PAP therapy occurs, particularly in patients with OSA and known left ventricular dysfunction or who have pre-existing cardiovascular risk factors.

In evaluating a number of biomarkers including BNP and NT-proBNP levels drawn pre-and post-one night of CPAP in a cohort with moderate-to-severe OSA, Maeder and colleagues did not observe significant findings [136]. Zhao and colleagues observed a reduction in high sensitivity C-reactive protein levels but not in NT-proBNP levels following 3 months of CPAP in a cohort of patients with CAD and severe OSA who were previously CPAP naive [73]. In an interesting discussion, the authors observe how medications used to treat CAD may blunt or reverse OSA-related cardiac strain, thus potentially contributing to the lack of association seen with NT-proBNP levels [73]. Cifci *et al.*, also did not observe an association between pro-BNP levels and OSA severity or the use of CPAP following 6 months of therapy. The authors acknowledge adherence to CPAP was evaluated subjectively [134] and may have a role in their findings.

Other studies have observed that although BNP levels were unaffected, initiation of CPAP [133] or nasal CPAP [64] improved cardiac structure and cardio-respiratory physiology including left ventricular mass size and pulmonary hypertension (improvements seen at 3 months and up to 1 year) [133] or peak maximal oxygen consumption and heart rate recovery (following approximately 8 months of PAP therapy) [64]. This phenomena was also observed by Hubner and colleagues, who did not find any association between NT-proBNP levels and OSA severity either before or after nasal or bi-level CPAP; however, NT-proBNP levels

were associated with impaired left ventricular ejection fraction and systemic arterial hypertension [149]. NT-proBNP levels were reduced following nasal CPAP in a handful of patients but this finding was not significant quite possibly due to the small number of patients in this subgroup [149].

Last, several studies have observed changes in BNP levels that were associated with PAP use. Valo and colleagues observed, not only did a night of CPAP therapy reduce NT-proBNP levels in patients with severe OSA with presence of CAD, it decreased ST-segment depression monitored at the time of peak oxygen desaturation during sleep [135]. Koga *et al.*, observed BNP levels decreased following 3 months of nasal CPAP [62]. Further, prevalence for global left ventricular dysfunction decreased significantly in the treated OSA group [62]. Finally, although Tasci and co-workers did not observe any changes in baseline NT-proBNP levels between hypertensive and normotensive OSA groups compared with controls without OSA, use of CPAP reduced NT-proBNP levels in both groups, especially in the hypertensive group [69].

Limitations & challenges

Overall, studies of cTn and BNP levels utilized as risk stratification tools or predictors of outcomes in patients with OSA undergoing TJA are lacking. Recommendations for the use of cTn and BNP levels in the diagnosis of acute coronary syndromes or other etiologies have been established by the National Academy of Clinical Biochemistry laboratory medicine practice guidelines [61], and the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for Universal Definition of Myocardial Infarction [77]. However, the routine use of cTns and BNPs to stratify risk for cardiovascular events following surgical procedures remains in its early stages and is currently being explored as delineated in this review.

There are many limitations in existing research that must be considered prior to the use of cTns or BNPs for outcomes in the patient with OSA presenting for TJA. These limitations and challenges derived from the studies presented can be categorized into the following: clinical use of biomarkers and study design.

Clinical use of biomarkers

Earlier studies utilized different generations of cTn or BNP assays that may have had a role in the preciseness of the assay results and thus offer conflicting results. Additionally, fundamental differences in the size of cTnI versus cTnT to facilitate the subtle detection of myocardial injury may be an issue. Pathophysiological differences in the release or clearance mechanisms

of both cTns and BNP could affect detection of circulating concentrations. Further, the interchangeable use of either plasma or serum samples, the timing of when the biomarker is drawn in consideration of sleep architecture, the inconsistent number of blood samples obtained during each study, variation in time points of blood sample collection, variation in elapsed time from collection to performance of the assay contributing to the stability or degradation of proteins, lack of synchronous collection of biomarkers during PSG recordings and consideration in half-life difference between BNP and NT-proBNP may have effected study results and comparison of studies.

Study design

Most of the studies consisted of small sample sizes, exhibited selection bias, lacked subject randomization, lacked objective measures to evaluate myocardial function such as echocardiography, varied in the severity and duration of OSA of the subject population, lacked control for adherence to PAP therapy, and varied in the presence of baseline cardiovascular disease or risk factors. Additionally, the nature of disease manifestation leading to surgery itself may have an effect on results.

Other limitations to be addressed include differentiating whether cTns or BNP could guide medical care and whether these markers are better utilized as a surrogate marker for cardiovascular risk stratification in the preoperative or postoperative setting. Most importantly, studies would have to explore the variability in preoperative or perioperative cTns or BNP and if these levels are predictive of worse postoperative cardiovascular outcomes in specific subgroups of surgical patients.

Future research directions

Given the evidence illustrating the association of cTns and BNP and cardiovascular events in patients undergoing noncardiac and TJA surgeries, and in select patients with OSA, future studies should explore the role of cTns and BNP as potential tools to stratify patients with OSA having TJA who are at increased risk for cardiovascular morbidity. Studies should focus on several key areas. First, they should assess whether cTns and BNP could be used as part of a preoperative risk stratification algorithm in order to predict postoperative cardiovascular complications. Second, studies should explore whether using novel clinical management pathways that incorporate perioperative cTns and BNP in TJA patients with OSA can reduce postoperative cardiovascular complications, as well as healthcare utilization, length of stay and medical costs. Such studies should explore the impact of perioperative cTns and BNP for the perioperative patient with OSA in TJA concomitant with use of the guidelines recommended

by the ASA, American College of Cardiology/American Heart Association (ACC/AHA) or the European Society of Cardiology/European Society of Anaesthesiology (ESC/ESA), AASM and American College of Physicians [84, 85]. Both the ACC/AHA and ESC/ESA have explored the role of sleep apnea and the use of biomarkers, separately, in evaluating risk of the development of postoperative cardiovascular complications.

Finally, future studies evaluating the potential independent association between perioperative cTns or BNP in OSA patients who undergo TJA and the risk for developing primary cardiovascular (e.g., acute myocardial infarction or nonmyocardial infarction cardiac complications), pulmonary (e.g., pulmonary embolism) and infectious complications (e.g., pneumonia, sepsis and periprosthetic joint or wound infection) would be helpful [1, 83].

Conclusion

Data from studies presented here examining levels of cTns and BNP suggest that these markers appear useful in identifying the subset of patients who are most likely to experience postoperative cardiovascular complications while undergoing noncardiac surgery, including TJA. In particular, results suggest these biomarkers may perform best in patients who are older (age > 60) and/or have underlying cardiovascular disease or risk factors. However, we have very limited and inconclusive evidence about the role of these biomarkers in predicting cardiovascular risk in the subgroup of patients who have OSA at the time of surgery. This gap in our knowledge exists in the face of rising numbers of patients with background OSA who have elective TJA. The limited evidence we do have, however, hints that patients who are older and have a higher risk or presence of cardiovascular disease (attributes that are common in TJA and OSA) are more likely to have increased postoperative cardiovascular morbidity or mortality. Some evidence, albeit conflicting, also suggests that this increased risk is associated with elevations in cTns and or BNP. Further data are needed to confirm whether these biomarkers, measured perioperatively in the patient with OSA undergoing TJA, may indeed differentiate patients at highest risk for adverse postoperative cardiovascular complications and death.

Present trends show that patients having TJA are older and more obese than in prior years, a group that is at particular risk for OSA and its potential downstream cardiovascular complications, which are higher still following surgery. Given that preliminary data support a role for biomarkers in predicting this cardiovascular risk, future studies should address a further exploration and refinement of the role of these biomarkers in patients having TJA.

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Executive summary

Obstructive sleep apnea (OSA) is a risk factor for postoperative cardiovascular complications, increased health care utilization and negative downstream economic costs in patients undergoing elective total hip and knee joint arthroplasty (TJA)

- Obstructive sleep apnea (OSA) is highly prevalent and a risk factor for major postoperative cardiovascular complications, including lethal arrhythmias, thromboembolism and death in adult patients undergoing total hip and knee joint arthroplasty (TJA).
- Failure to implement special considerations in the perioperative clinical management of the TJA patient with OSA may also lead to increased postoperative healthcare utilization (transfers to an intensive care unit), length of stay, costs and medical litigation.

Perioperative risk stratification for postoperative cardiovascular complications in patients undergoing TJA & having OSA remains inadequate

- Despite guidelines established by the American Society of Anesthesiologists, many patients at risk or having OSA and undergoing TJA are not stratified as at risk for increased postoperative complications.
- The number of patients presenting for TJA are rising while there are limited resources to efficiently stratify those at risk for developing post-TJA cardiovascular-specific complications.

Perioperative cardiac troponins (cTns) & brain natriuretic peptides (BNPs) may help stratify risk for postoperative cardiovascular complications in the TJA patient having OSA

- Cardiac biomarkers such as cTns and BNPs are associated with OSA and also predictive of postoperative cardiovascular complications and death in patients having noncardiac surgery including TJA.
- The utility of cardiac biomarkers, cTns and BNPs, in OSA patients undergoing TJA remains undefined and should be explored.

Future perspective

- In patients undergoing TJA and having OSA, future research should attempt to:
 - Develop efficient ways to identify those patients who are at highest risk for having postoperative cardiovascular complications, and evaluate whether perioperative measurement of biomarkers such as cTns and BNPs has a role in such risk assessment.
 - Develop and evaluate the utility of perioperative management protocols for OSA, which may include cTns and BNPs, in reducing postoperative cardiovascular complications, healthcare utilization and medical costs.

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