Circulating adrenomedullin and B-type natriuretic peptide do not predict blood pressure fluctuations during pheochromocytoma resection: a cross-sectional study

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Circulating adrenomedullin and B-type natriuretic peptide do not predict blood pressure fluctuations during pheochromocytoma resection: a cross-sectional study

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Abstract

Background: Despite adequate presurgical management, blood pressure fluctuations are common during resection of pheochromocytoma or sympathetic paraganglioma (PPGL). To a large extent, the variability in blood pressure control during PPGL resection remains unexplained. Adrenomedullin and B-type natriuretic peptide, measured as MR-proADM and NT-proBNP, respectively, are circulating biomarkers of cardiovascular dysfunction. We investigated whether plasma levels of MR-proADM and NT-proBNP are associated with blood pressure fluctuations during PPGL resection.

Methods: Study subjects participated in PRESCRIPT, a randomized controlled trial in patients undergoing PPGL resection. MR-proADM and NT-proBNP were determined in a single plasma sample drawn before surgery. Multivariable linear and logistic regression analyses were used to explore associations between these biomarkers and blood pressure fluctuations, use of vasoconstrictive agents during surgery as well as the occurrence of perioperative cardiovascular events.

Results: A total of 126 PPGL patients were included. Median plasma concentrations of MR-proADM and NT-proBNP were 0.51 (0.41–0.63) nmol/L and 68.7 (27.9–150.4) ng/L, respectively. Neither MR-proADM nor NT-proBNP were associated with blood pressure fluctuations. There was a positive correlation between MR-proADM concentration and the cumulative dose of vasoconstrictive agents (03B2 0.44, P = 0.001). Both MR-proADM and NT-proBNP were significantly associated with perioperative cardiovascular events (OR: 5.46, P = 0.013 and OR: 1.54, P = 0.017, respectively).

Conclusions: plasma MR-proADM or NT-proBNP should not be considered as biomarkers for the presurgical risk assessment of blood pressure fluctuations during PPGL resection. Future studies are needed to explore the potential influence of these biomarkers on the intraoperative requirement of vasoconstrictive agents and the perioperative cardiovascular risk.

European Journal of Endocrinology
(2021) **185**, 507–514

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-20-1452

Published by Bioscientifica Ltd.

Introduction

Pheochromocytomas and sympathetic paragangliomas (PPGLs) are rare tumors localized in the adrenal medulla and extra-adrenal sympathetic paraganglia, respectively, sharing the capacity to synthesize and produce catecholamines (1). The clinical spectrum of PPGL is highly variable, ranging from asymptomatic to life-threatening cardiovascular complications, such as severe arrhythmias, hypertensive emergency, stroke or myocardial infarction. Surgical resection of a PPGL is the only option for cure but is known to be a high-risk procedure due to the uncontrolled release of catecholamines that might occur during surgery in response to a variety of mechanical and pharmacological stimuli (2). In order to prevent intraoperative hemodynamic instability and subsequent cardiovascular complications, it is recommended that blood pressure and heart rate are well controlled before surgery by treatment with antihypertensive medications, preferably with α-adrenergic receptor blockers. Despite adequate preoperative preparation, many patients still demonstrate significant intraoperative hemodynamic instability (3).

In the recently published PRESCRIPT study, a randomized controlled trial comparing the efficacy of phenoxybenzamine and doxazosin on intraoperative hemodynamic instability during PPGL resection, only a small proportion of the variance in hemodynamic instability was explained by the choice of α-adrenergic receptor blocker, tumor size and presurgical plasma levels of catecholamines (3). In addition to catecholamines, PPGL produces a large variety of biologically active peptides (4). Among these, adrenomedullin (ADM) (5, 6, 7) and B-type natriuretic peptide (BNP) (7) might be relevant determinants of intraoperative hemodynamic instability. Adrenomedullin, originally isolated from human pheochromocytoma cells, is a potent vasodilator peptide (8, 9). It is synthesized by many tissues, including myocardial and vascular cells. The mid regional portion of proADM (MR-proADM) is a stable fragment of adrenomedullin, which is secreted stoichiometrically and can be used as a surrogate marker of adrenomedullin (10, 11). BNP is a hormone normally synthesized by cardiomyocytes in response to multiple physiological and neuroendocrine stimuli and induces several effects, including natriuresis, diuresis and vasodilation (12). It is generated by proteolysis of proBNP into equimolar amounts of the active BNP and the inactive N-terminal pro-B-type natriuretic peptide (NT-proBNP). MR-proADM and NT-proBNP can be regarded as circulating biomarkers of cardiovascular dysfunction, and previous studies have shown that preoperative levels of BNP and adrenomedullin are useful markers for the prediction and classification of perioperative cardiovascular risk in various types of surgical procedures (13, 14, 15, 16, 17, 18, 19, 20, 21, 22). In addition, elevated adrenomedullin was shown to be strongly correlated with the requirement of postsurgical organ support and 1-year mortality in critical care patients after discharge from the intensive care unit (23, 24).

In view of these observations, we hypothesized that the measurement of these hormones could improve presurgical risk stratification in patients with PPGL. If so, this might enable a more individualized approach to perioperative management. We, therefore, investigated whether presurgical plasma levels of MR-proADM and NT-proBNP could serve as biomarkers in order to assess the risk of blood pressure fluctuations during PPGL surgery. In addition, we sought to determine whether the plasma levels of these hormones were associated with the intraoperative use of vasoconstrictive agents (i.e. counteracting their vasodilating effects) or the perioperative cardiovascular risk.

Subjects and methods

Study population and design

Study subjects participated in the PRESCRIPT study, a randomized controlled trial comparing presurgical treatment with two different α-adrenergic receptor blockers in patients with PPGL (ClinicalTrials.gov number NCT01379898). This study has been described in detail elsewhere (3). In brief, the study population consisted of adult patients aged 18 years or older with non-metastatic PPGL, demonstrating elevated plasma or urinary (nor) metanephrine concentrations and a minimum tumor diameter of 1 cm. All patients received pretreatment with either phenoxybenzamine or doxazosin, which was started 2–3 weeks before surgery using blood pressure guided dose titration. Target values were blood pressure < 130/80 mmHg in the supine position and systolic blood pressure between 90 and 110 mmHg in the upright position. A calcium channel blocker was added when these targets were not reached despite the maximum dosage of the α-adrenergic receptor blocker. A β-adrenergic receptor blocker was added in case of a heart rate > 80 bpm or > 100 bpm in the supine and upright position, respectively. In addition, a high-salt diet was advised and an infusion of 0.9% saline was administered 24 h prior to surgery. Resection was postponed if the supine blood pressure was > 160/100 mmHg on the day before surgery. The majority of patients were operated by minimal invasive surgical techniques. Hemodynamic management during and after surgery was performed using a standardized operating procedure across all participating centers. Blood pressure and heart rate during surgery were monitored by continuous intra-arterial measurement. Intraoperative hemodynamic targets were: systolic blood pressure < 160 mmHg, mean arterial pressure (MAP) > 60 mmHg, and heart rate < 100 bpm. Administration of vasoconstrictive medication was only allowed when hemodynamic variables were outside these predefined targets. After surgery, patients were monitored at the post-anesthesia or intensive care unit.

Data recording and analysis

All data on blood pressure, heart rate, i.v. volume therapy, and vasoconstrictive medication were extracted from the electronic patient data monitoring system starting at induction of anesthesia and ending at discharge from the post-anesthesia care unit or intensive care unit. Both duration and amplitude of hemodynamic variables outside the target range were assessed and cumulative dosage of vasoconstrictive medication was calculated. The degree of intraoperative hemodynamic instability was also assessed by using the hemodynamic instability score (25). The following perioperative cardiovascular events were recorded: cardiac arrhythmias (atrial fibrillation/flutter $n=2$, asystole $n=1$), acute heart failure ($n=3$), pulmonary embolism ($n=1$), postoperative bleeding ($n=2$) and intestinal necrosis ($n=1$). The study was approved by the institutional review board of the University Medical Center Groningen, the University of Groningen, The Netherlands, in compliance with the Dutch Medical Research Involving Human Subjects Act and the Declaration of Helsinki. Written informed consent was provided by all participants.

Laboratory methods

Preparation of blood samples

Blood samples were drawn before the start of pretreatment with an α-adrenergic receptor blocker after 30 min of supine rest. All samples were transported to the laboratory, centrifuged, aliquoted and stored at −80°C until assay within 2 h after blood collection.

Measurement of plasma free (nor)metanephrine, 3-MT, MR-proADM and NT-proBNP

Plasma free metanephrine, normetanephrine and 3-MT concentrations were measured using liquid chromatography with tandem mass spectrometry (LC-MS/MS) with online solid-phase extraction in a central reference laboratory (26). Analyses were performed for routine patient care. Interassay coefficients of variation for metanephrine ranged from 6.7 to 3.8% at levels of 0.23–4.48 nmol/L, for normetanephrine from 8.9 to 4.0% at levels of 0.051–10.1 nmol/L and for 3-methoxytyramine (3-MT) from 7.3 to 3.4% at levels of 0.04–2.2 nmol/L, respectively. Intra-assay coefficients of variation for metanephrine ranged from 7.1 to 3.6% at levels of 0.22–4.80 nmol/L, for normetanephrine from 3.7 to 1.9% at levels of 0.50–12.35 nmol/L and for 3-MT from 3.5 to 1.3% at levels of 0.11–3.10 nmol/L, respectively. Analyses of plasma NT-proBNP and MR-proADM were performed in a single batch. NT-proBNP was analyzed using an electrochemiluminescence immunoassay (Roche) on the Cobas 6000 immunoassay analyzer (Roche Diagnostics Ltd.). Intra-assay coefficients of variation were 1.8 and 1.5% at levels of 132 and 4289 ng/L, respectively. The upper reference limit for NT-proBNP concentrations for this assay was previously established at 125 ng/L (27). MR-proADM was measured by time-resolved amplified cryptate emission-based immunoassay on the Kryptor Compact immunoanalyzer from Thermo Fisher Scientific Inc.. Intra-assay coefficients of variation were 3.6 and 2.2% at levels of 0.73 and 4.5 nmol/L, respectively. Reference values for plasma MR-proADM concentrations for this assay have recently been published, showing a central 95% reference interval of 0.21–0.57 nmol/L (28).

Statistical analysis

Results were expressed as mean ± S.D. or median (interquartile range) for normally and non-normally distributed data, respectively. Nominal data were presented as an absolute number with a percentage.

In this *post hoc* analysis, we used univariate, multivariable linear and logistic regression analyses to investigate whether presurgical MR-proADM and NT-proBNP concentrations were associated with the primary endpoint, that is, the presence of blood pressure fluctuations during surgery. This was defined as the cumulative time of blood pressure outside the target range. In addition, we defined the cumulative doses of vasoconstrictive agents administered during surgery and the occurrence of perioperative cardiovascular events as secondary endpoints. Since MR-proADM and NT-proBNP values were non-normally distributed, logarithmic transformation (base 2) was applied to fulfill the criteria for linear regression analyses. Therefore, the standardized regression coefficients and odds ratios (OR) derived from linear and logistic regression were expressed as an increase per doubling of presurgical plasma MR-proADM and NT-proBNP concentrations. Models were built to adjust for possible confounders. We considered as possible confounders those variables that were previously suggested in the literature (3, 28) as well as the baseline characteristics that differed significantly between subjects in relation to their plasma concentration of MR-proADM and NT-proBNP. First, the univariable associations of $\log_2$ MR-proADM and $\log_2$ NT-proBNP with the primary and secondary endpoints were investigated. Multivariate linear regression was used for the continuous endpoints cumulative time outside blood pressure target range and cumulative doses of vasoconstrictive agents, with model 1 adjusted for randomization and preoperative total plasma catecholamines; model 2 also adjusted for age, sex, BMI and presurgical systolic blood pressure; model 3 also adjusted for serum creatinine levels and model 4 also adjusted for history of cardiovascular disease and diabetes mellitus. Multivariate logistic regression was used for the analysis of perioperative cardiovascular events. Given the relatively limited number of cardiovascular events, we decided to adjust one by one for each of the above-mentioned confounders. All statistical analyses were performed using SPSS version 23 (IBM Corporation). A two-sided P-value < 0.05 was considered to indicate statistical significance.

Results

A total of 126 evaluable patients with either a pheochromocytoma (93.7%) or a sympathetic paraganglioma (6.3%) were included in this study. Baseline characteristics are shown in Table 1. The mean age of the study population was 54.3 ± 15.3 years, 47.6% of patients were male. Median plasma MR-proADM and NT-proBNP concentrations were 0.51 (0.41–0.63) nmol/L and 68.7 (27.9–150.4) ng/L, respectively.

Both univariate and multivariate analyses demonstrated that plasma MR-proADM and NT-proBNP were not significantly associated with the cumulative time outside the blood pressure target range during surgery (β: −0.03, P = 0.78 and β: −0.02, P = 0.83, respectively, Table 2, model 1–4).

There was a significant positive correlation between the plasma level of MR-proADM and the cumulative dose of vasoconstrictive agents administered during surgery (β: 0.30, P = 0.001). This association remained significant after further adjustment for potential confounders (Table 3, models 1–4). Univariate analysis did not demonstrate a significant association between plasma levels of NT-proBNP and the cumulative dose of vasoconstrictive agents administered during surgery (β: 0.17, P = 0.066).

Table 1 Baseline characteristics of the study population (n = 126). Data are presented as n (%), mean ± s.d. or as median (interquartile range).

Characteristics	Values
Demographics	
Male gender	60 (47.6)
Age (years)	54.3 ± 15.3
BMI (kg/m^2)	26.1 ± 4.8
Smoking	35 (27.8)
Diabetes mellitus	28 (22.2)
History of CVD	22 (17.5)
History of heart failure	8 (6.3)
Serum creatinine (μmol/L)	75.7 ± 21.2
HD features preoperative	
Supine SBP (mmHg)*	127.4 ± 18.5
Upright SBP (mmHg)*	118.4 ± 19.1
Baseline heart rate (bpm)	74 ± 12.3
Medication	
Doxazosin	63 (50.0)
Phenoxybenzamine	63 (50.0)
CCB	53 (42.1)
β-blocker	97 (77.0)
Tumor characteristics	
sPGL	8 (6.3)
Tumor size (mm)	59.5 (19.6–166.0)
Mutation	28 (22.2)
Biochemical profile¶	
Plasma epinephrine (0.04–0.80 nmol/L)	0.44 (0.20–1.55)
Plasma free MN (0.07–0.29 nmol/L)	1.09 (0.27–3.89)
Plasma norepinephrine (0.8–4.3 nmol/L)	4.55 (3.01–14.87)
Plasma free NMN (0.17–0.77 nmol/L)	3.77 (1.64–9.75)
Plasma dopamine (0.03–0.18 nmol/L)	0.15 (0.09–0.26)
Plasma 3-MT (<0.04 nmol/L)	0.06 (0.04–0.11)
Surgical approach	
Laparoscopy	89 (70.6)
Laparotomy	20 (15.9)
Posterior retroperitoneoscopic	17 (13.5)

*With α-adrenergic receptor blockade. ¶reference range is provided within parentheses in the rows below; Metoprolol was prescribed in 88% of patients receiving a β-adrenergic receptor blocker. Nifedipine was prescribed in 89% of patients receiving a calcium channel blocker. 3-MT, 3-methoxytyramine; CCB, calcium channel blocker; CVD, cardiovascular disease; DBP, diastolic blood pressure; MN, metanephrine; NMN, normetanephrine; SBP, systolic blood pressure; sPGL, sympathetic paraganglioma.

Table 2 Multivariable regression models with the primary endpoint, that is, the cumulative time outside the blood pressure target range during surgery as dependent variable*.

	Log$_2$ MR-pro ADM			Log$_2$ NT-pro BNP		
	β	*P*-value	R^2	β	*P*-value	R^2
Model 1	0.01	0.91	0.06	−0.10	0.91	0.06
Model 2	0.14	0.27	0.10	0.06	0.56	0.09
Model 3	0.18	0.19	0.10	0.08	0.47	0.09
Model 4	0.16	0.25	0.11	0.06	0.62	0.10

*The dependent variable cumulative time outside the blood pressure target range during surgery was square root transformed. Model 1: adjusted for randomization and total plasma catecholamines; model 2: model 1 + adjusted for age, sex, BMI and presurgical systolic blood pressure; model 3: model 2 + serum creatinine; model 4: model 3 + history of diabetes mellitus and cardiovascular disease.
β, standardized regression coefficient.

After adjustment for potential confounders there was a positive trend toward significance (Table 3: β: 0.20, $P=0.053$ and $P=0.062$ in model 3 and 4, respectively).

Both plasma concentration of MR-proADM and NT-proBNP were significantly associated with perioperative occurrence of cardiovascular events (Table 4: OR: 5.46, $P = 0.013$ and OR: 1.54, $P = 0.017$, respectively). These associations remained significant after combining these markers in a multivariate model with potential confounders one by one. The association of MR-proADM with cardiovascular events, however, lost significance after adjustment for age and history of diabetes mellitus (Table 4).

Discussion

We here describe the relationship between the presurgical plasma concentration of MR-proADM and NT-proBNP and the blood pressure fluctuations in a large and well-defined group of patients undergoing resection of a PPGL. We demonstrated that the cumulative time of blood pressure values outside the target range during PPGL surgery was not related to the presurgical plasma concentration of MR-proADM or NT-proBNP. We did find, however, that an elevated plasma MR-proADM concentration before surgery was associated with a higher intraoperative requirement of vasoconstrictive agents. In addition, we found a positive relationship between the plasma concentration of MR-proADM and NT-proBNP and the occurrence of perioperative cardiovascular events.

Our observation of elevated plasma concentrations of MR-proADM and NT-proBNP in PPGL patients is in agreement with previous studies (5, 6, 7). There has been much interest in the pathophysiological role of plasma MR-proADM and NT-proBNP, but the possible relationship between these cardiovascular biomarkers and the blood pressure profile during PPGL resection has been mainly speculative thus far. The PRESCRIPT randomized controlled trial offers the very first opportunity to explore this relationship, representing the largest database available with detailed information on pre-, intra- and postoperative hemodynamics under strict management study protocol.

Our main finding might in part be explained by the fact that the composition of the PPGL secretome is highly heterogeneous and dynamic (4), and it is, therefore, conceivable that presurgical plasma levels of biomarkers do not sufficiently reflect plasma concentrations during surgery. In addition, the response to a particular hormone is not only dependent on its concentration but also on many other factors, such as co-factors, receptor density and affinity as well as various postreceptor mechanisms.

The apparent absence of a relevant effect on the intraoperative blood pressure, however, could also be interpreted as part of a compensatory response, in the sense that without a rise in plasma adrenomedullin, blood pressure would probably have been higher and blood pressure fluctuations would have been worse. It has been suggested that adrenomedullin plays a key role in organ protection from hypertension, both by regulation of blood flow via increased NO-synthesis and by exerting antioxidant effects (9). Moreover, both hypertension and excess catecholamines are known to induce oxidative stress, which in itself enhances adrenomedullin production (9, 29, 30). The hypothesis of adrenomedullin as an endogenous organ protective agent counteracting oxidative stress in the cardiovascular system and thereby preventing circulatory failure is corroborated by previous studies showing aggravation of cardiovascular damage induced by oxidative stress in adrenomedullin knock-

Table 3 Multivariable regression models with the secondary endpoint, that is, cumulative doses of vasoconstrictive agents administered during surgery as dependent variable*.

	Log$_2$ MR-pro ADM			Log$_2$ NT-pro BNP		
	β	*P*-value	R^2	β	*P*-value	R^2
Model 1	0.31	0.001	0.11	0.17	0.066	0.04
Model 2	0.35	0.004	0.22	0.15	0.12	0.18
Model 3	0.44	0.001	0.25	0.20	0.053	0.19
Model 4	0.44	0.001	0.25	0.20	0.062	0.20

*The dependent variable; cumulative doses of vasoconstrictive agents (ɥa) administered during surgery, was square root transformed. Model 1: adjusted for randomization and total plasma catecholamines; model 2: model 1 + adjusted for age, sex, BMI and presurgical systolic blood pressure; model 3: model 2 + serum creatinine; model 4: model 3 + history of diabetes mellitus and cardiovascular disease.
β, standardized regression coefficient.

Table 4 Logistic regression models* with the secondary endpoint, that is, perioperative cardiovascular events as dependent variable.

	Log₂ MR-pro ADM			Log₂ NT-pro BNP		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Crude	5.46	1.43–20.89	0.013	1.54	1.08–2.20	0.017
Randomization	5.60	1.44–21.75	0.013	1.55	1.08–2.22	0.017
Catecholamines	6.70	1.66–27.10	0.008	1.55	1.09–2.22	0.016
Age	3.58	0.72–17.76	0.12	1.41	0.96–2.07	0.078
Sex	5.70	1.46–22.23	0.012	1.54	1.08–2.19	0.017
Preoperative BP	6.46	1.59–26.29	0.009	1.54	1.07–2.19	0.019
Serum creatinine	4.61	1.04–20.31	0.044	1.46	1.01–2.13	0.046
Diabetes Mellitus	4.00	0.97–16.49	0.055	1.52	1.06–2.18	0.024
History of CVD	4.64	1.13–19.09	0.033	1.48	1.00–2.20	0.049
BMI	16.30	2.88–92.33	0.002	1.63	1.12–2.37	0.011

*Logistic regression analyses: univariate and multivariate with one by one adjustment for the confounders randomization, total plasma catecholamines, age, sex, BMI, preoperative systolic blood pressure, serum creatinine and a history of diabetes mellitus or cardiovascular disease.
BP, blood pressure; CVD, cardiovascular disease.

out mice as well as the observation that adrenomedullin supplementation ameliorated the hemodynamics in patients with congestive heart failure or hypertension (9, 31, 32, 33, 34).

There was a positive association between the presurgical plasma concentration of MR-proADM and NT-proBNP and the perioperative cardiovascular risk, which remained significant after adjustment for potential confounders. This observation is in agreement with studies in patients without PPGL undergoing various types of surgery (13, 19, 20, 22, 24). Although limited by a few number of cardiovascular events in our study, it is suggested that presurgical determination of the plasma MR-proADM and NT-proBNP concentration could represent a useful biomarker to assess the perioperative cardiovascular risk in patients scheduled for PPGL resection. Additional studies in sufficiently large cohorts of patients with PPGL are needed to further explore this relationship.

Adrenomedullin has a longer plasma half-life than catecholamines (22 min vs 1–2 min, respectively) (35). Thus, it might be expected that after ligation of the adrenal vein, the vasodilating effects of adrenomedullin will last longer than the vasoconstrictive effects of catecholamines. We speculate that this pharmacokinetic difference could at least in part explain the finding that multivariate analyses demonstrated a positive association between presurgical plasma concentration of MR-proADM and the cumulative dosage of vasoconstrictive agents needed intraoperatively. It should be noted that this effect is short-lasting, as shown by the absence of postoperative hypotension (data not shown).

The major strength of the current study is the fact that all measurements are derived from a randomized controlled trial examining hemodynamic instability in patients undergoing surgical resection of a PPGL. Thus, our observations are based on unique and prospectively collected high-quality data. A potential limitation of our study is that plasma levels of MR-proADM and NT-proBNP were only assessed once at baseline. Plasma concentration of MR-proADM, however, was measured with a method demonstrating a low intra-assay coefficient of variation. In addition, we did not measure MR-proADM and NT-proBNP after the institution of the α-adrenergic receptor blockers, but previous studies have not revealed a significant influence of α-adrenergic receptor blockers on the plasma concentration of adrenomedullin and BNP (7, 36, 37, 38). Our study was not designed to establish the source of the elevated plasma MR-proADM. It seems likely, however, that at least part of the circulating adrenomedullin was secreted by the PPGL, which has been shown to synthesize this hormone. In support of this, plasma concentrations of adrenomedullin have previously been found to be significantly higher in patients with PPGL than in subjects with essential hypertension (5, 7). At variance with these observations, we were not able to demonstrate a relationship between plasma concentration of adrenomedullin and tumor size or plasma concentration of catecholamines. Taken together, it is possible that the elevated plasma concentration of adrenomedullin originates from increased secretion by the PPGL itself and by non- chromaffin tissues, as was also suggested previously (5, 39).

In conclusion, plasma MR-proADM or NT-proBNP should not be considered biomarkers for the presurgical risk assessment of blood pressure fluctuations during PPGL resection. Future studies are needed to explore the potential influence of these biomarkers on the intraoperative requirement of vasoconstrictive agents and the perioperative cardiovascular risk.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding
This study was supported by Thermo Fisher Scientific Inc. through free of charge supply of MR-proADM reagent kits. Thermo Fisher Scientific Inc. had no role in the design, execution, analyses, and interpretation of the data, nor in the decision to submit the results.

Acknowledgements
The authors thank all co-investigators of the PRESCRIPT study: N A M Alagla, and W J Sluiter, Department of Endocrinology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; N J G M Veeger, Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; M I van der Velde, Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; J de Vries, and P H J Hemmer, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; I P Kema, Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; S A A Willems, Department of Anesthesiology, Radboud University Medical Center, Nijmegen, The Netherlands; J F Langenhuijsen, Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands; D H Thone-Passchier, L A Schwarte, and W D Lubbers, Department of Anesthesiology, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; H J Bonjer, C Dickhoff, and H H Eker, Department of Surgery, Amsterdam; University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; P van der Valk, Department of Pathology, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; P de Graaf and P G H M Raijmakers, Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; P Thoral, Department of Intensive Care, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; E W C M van Dam, Department of internal Medicine, Endocrinology section, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; W W de Herder and J Hofland, Department of Internal Medicine, Section of Endocrinology, Erasmus Medical Center, Rotterdam, The Netherlands; C T Favoccia and C G O T Bouman, Department of Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands; G D Slooter, Department of Surgery, Maxima Medical Center, Eindhoven, The Netherlands; L P H M Le Mair, Department of Anesthesiology, Maxima Medical Center, Eindhoven, The Netherlands; P C M Wouters-van Poppel, Department of Internal Medicine, Maxima Medical Center, Eindhoven, The Netherlands; J Vuyk, Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands; M W Hollmann, Department of Anesthesiology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; E J M Nieveen van Dijkum, Department of Surgery, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; and R G Hoff, Department of Anesthesiology, University Medical Center Utrecht, Utrecht, The Netherlands.

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Received 23 December 2020
Revised version received 19 July 2021
Accepted 28 July 2021