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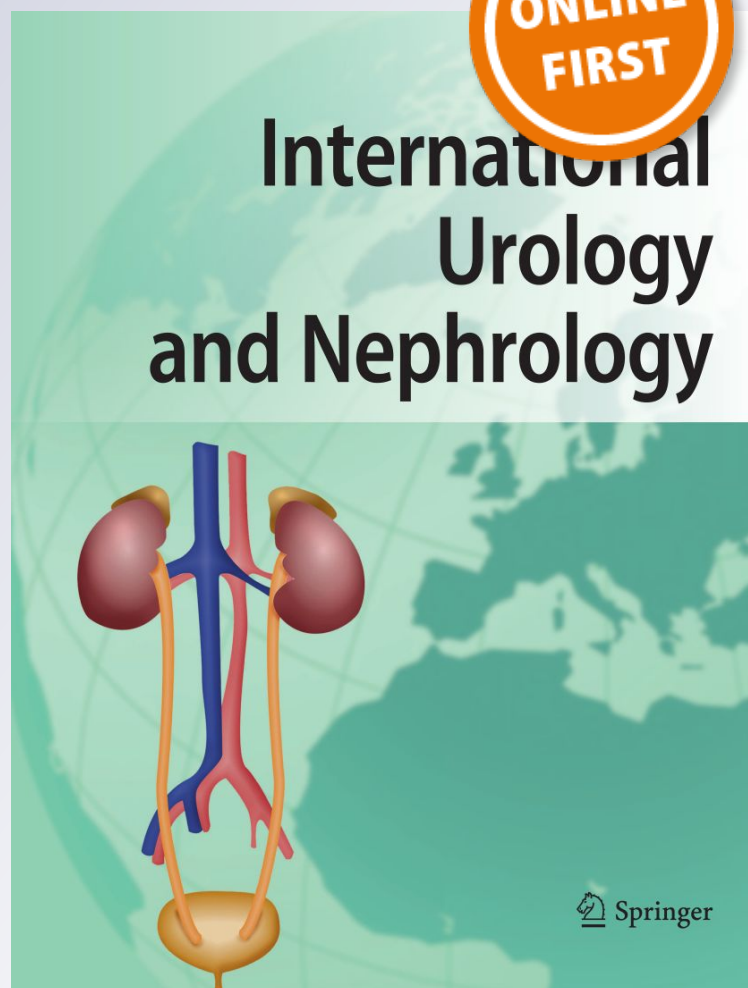
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Perioperative major acute cardiovascular events after 180-W GreenLight laser photoselective vaporization of the prostate

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Abstract

Background Major acute cardiovascular events (MACE) prevalence after 180-W GreenLight (180-W GL) laser photoselective vaporization (PVP) have never been explored. Aim of our study is to evaluate perioperative MACE that occurred concomitantly with 180-W GL PVP.

Materials and methods We relied on a multi-institutional database that included 14 centers. Data from 923 patients who underwent 180-W GL PVP were reviewed. We abstracted pre- and perioperative data of patients who experienced perioperative MACE, such as angina pectoris, acute myocardial infarction, other chronic ischemic heart disease, transient ischemic attack, or cerebrovascular accident as well as deep venous thrombosis with or without pulmonary embolism. We relied on a case-series format to report the main findings of our analyses.

Results 18 (1.9%) patients reported MACE in 7 centers. Median age was 69.5 (IQR 66.0–79.2) years. Of all, 7 patients underwent standard PVP and 11 anatomical PVP. Eleven patients (61.1%) were not under anticoagulant/antiplatelet treatment, 6 (33.3%) were under low dose aspirin, and 1 (5.6%) was under clopidogrel. Four patients (22.2%) had an instrumental and laboratory diagnosis of myocardial infarction, 7 (38.9%) had an episode of angina pectoris with or without rhythm alteration, 3 (16.7%) reported symptomatic deep venous thrombosis, and 4 (22.2%) had other MACE-like events.

Conclusions Physician should take in consideration the possibility of MACE or MACE-like events. The real MACE rate may be different as only half of included centers reported MACE. Since the main target of laser surgery are high-risk bleeding patients, prospective observational trials focused on detection of these possible complications are warranted.

Keywords Major acute cardiovascular events · Photoselective vaporization of the prostate · BPH · Cardiovascular safety · Transurethral surgery of the prostate · Green light laser

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Introduction

Lower urinary tracts symptoms (LUTS) are frequently associated with benign prostatic hyperplasia (BPH; LUTS/BPH) [1]. One of the main characteristics of LUTS/BPH is its progressive nature [1]. Indeed, after diagnosis, 9.04 per 1000 patients/year require a BPH-related hospitalization and 12.6 per 1000 patients/year require a BPH surgery [2]. Moreover, a growing body of evidence reported an association between LUTS and major adverse cardiac events (MACE), such as angina pectoris, acute myocardial infarction, other chronic ischemic heart disease, transient ischemic attack, or cerebrovascular accident [1].

For the vast majority of patients, transurethral resection of the prostate (TURP) is considered the standard of care. However, in high-bleeding risk patients, photoselective vaporization of the prostate (PVP) with GreenLight laser could be considered the first treatment choice [3]. Even though, most recent National Institute for Health and Care Excellence (NICE) guidelines caution physicians about the low-quality evidence of these recommendations (level of evidence 3, grade of recommendation B) [3, 4].

Nowadays, a low-grade evidence supports the use of GreenLight laser in patients who cannot suspend anticoagulant/antiplatelet drugs [4]. Moreover, there is a proven association of some non-cardiac surgery with MACE [5, 6]. In addition, patients with moderate or severe LUTS are at higher risk of MACE [1]. However, in spite of this lack of evidences, only few studies focused on, or at least reported, MACE or MACE-like events after PVP with 180-W GreenLight laser (180-W-GL PVP) [7, 8].

The aim of the current study is to explore in a large database the prevalence of MACE after or during 180-W-GL PVP. Moreover, we aim to summarize common features that may exist in those patients who experience MACE events.

Materials and methods

All cases of perioperative MACE or MACE-like events were abstracted from a large Italian multi-institutional database of patients treated with 180-W GL PVP from 2011 to 2016. Moreover, all the surgeon members of Green Laser Italian Group [7] were also asked for events that occurred and not reported in the database. MACE events were defined as angina pectoris, acute myocardial infarction, other chronic ischemic heart disease, transient ischemic attack, or cerebrovascular accident [1]. In addition, we also included those patients who experienced symptomatic deep vein thrombosis and/or pulmonary

embolism. Similarly, patients who experienced events that required the suspension of the procedure or supplementary medications were included.

Data about patients' age, pre-operative anticoagulant/antiplatelet and BPH-related treatment, American Society of Anesthesiologists (ASA) score, prostate volume (ml), PSA (ng/ml), maximum flow rate (Q_{max}), International Prostate Symptoms Score (IPSS), and serum hemoglobin (HGB) were collected. Moreover, energy used (kJ), laser, and operative time (min) as well as hospital stay were taken into account. All patients underwent loco-regional anesthesia. Low-dose aspirin was not suspended pre-operatively while anticoagulant and other antiplatelet were suspended and substituted with low-weight heparin in the majority of the cases. The main aspects about the post-operative and post-event management were noted.

The low events number prevented us from a formal statistical analysis. Instead, we preferred to report all cases in a case-series fashion including main patient's characteristics. Finally, lollipop plot graphically depicted pre-operative and intra-operative characteristics of patients with respect to the median value, grouped by the different MACE or MACE-like event category. Analyses and plots were performed using the R software environment for statistical computing and graphics (version 3.5.1; <http://www.r-project.org/>).

Results

Main characteristics

The multi-institutional database includes data of patients from 14 centers. Among them, 7 centers reported at least one MACE. Out of 923 patients recorded in the database, 18 (1.9%) reported a MACE or MACE-like event. Median age was 69.5 (IQR 66.0–79.2) years. Of all, 7 underwent standard PVP and 11 anatomical PVP. The median prostate volume was 67.5 (IQR 41.0–107.5). Eleven patients (61.1%) were not under anticoagulant/antiplatelet treatment, 6 (33.3%) were under low-dose aspirin and 1 (5.6%) was under clopidogrel (Table 1). Four patients (22.2%) had an instrumental and laboratory diagnosis of myocardial infarction, 7 (38.9%) had an episode of angina pectoris with or without rhythm alteration, 3 (16.7%) reported symptomatic deep venous thrombosis, and 4 (22.2%) had other MACE-like events (Tables 1 and 2). None of them underwent transfusion. The median energy used during the procedure was 229.5 (IQR 174.0–328.5) kJ. The median laser and operative time were, respectively, 24.0 (IQR 17.9–31.8) and 60.0 (IQR 42.5–75.3) min. The median in-hospital stay after procedure was 3.0 (IQR 2.0–3.8) days (Table 2). Pre-operative and post-operative features stratified according to the different MACE or MACE-like event category were graphically

Table 1 Pre-operative characteristics of patients who experienced major acute cardiovascular events (MACE) or MACE-like events during or immediately after GreenLight laser photoselective vaporization

Case	Age	Anticoagulant/antiplatelet	BPH therapy	ASA score	Pre-operative prostate volume	Pre-operative hemoglobin	Pre-operative PSA	Pre-operative Q_{max}	Pre-operative IPSS
Myocardial infarction									
#1	60	None	Alpha-blocker	2	130	14.7	16.72	8	25
#2	74	Clopidogrel	Combination	3	74	13.8	2.25	9	22
#3	68	Low-dose aspirin	5-ARI	2	40	14.7	0.54	10	9
#4	83	Low-dose aspirin	Alpha-blocker	3	65	14.5	2.9	NA	25
Angina pectoris with or without rhythm alteration									
#5	70	Low-dose aspirin	Combination	3	32	14.8	1.08	7.5	27
#6	80	None	Alpha-blocker	2	160	12.4	4.3	5	35
#7	80	None	Alpha-blocker	2	31	12.8	0.25	8	35
#8	66	None	Alpha-blocker	2	62	15.9	3.16	8	27
#9	77	None	Alpha-blocker	2	26	NA	NA	NA	NA
#10	56	None	Alpha-blocker	1	44	15.9	2.45	NA	NA
#11	80	Low-dose aspirin	Alpha-blocker	2	70	NA	NA	NA	NA
Deep venous thrombosis with or without pulmonary embolism									
#12	71	None	5-ARI	2	100	15	0.9	9	19
#13	63	None	None	1	150	15	NA	9	22
#14	52	Low-dose aspirin	Alpha-blocker	1	79	16	2.5	4.3	25
Miscellanea									
#15	84	Low-dose aspirin	Alpha-blocker	3	40	9.3	2.9	6	11
#16	69	None	None	2	110	16.1	4.72	NA	28
#17	66	None	Alpha-blocker	2	45	14.8	2.23	5.6	21
#18	68	None	Alpha-blocker	2	140	15.8	8.72	7	25

NA not assessed, 5-ARI 5-alpha reductase inhibitors, IPSS International Prostatic Symptom Score, Q_{max} maximum flow rate

depicted compared to the median values for each patient in Fig. 1.

Cases description according to clinical presentation

Myocardial infarction

Of all, 4 patients were diagnosed with myocardial infarction during or after 180-W GL PVP. Of these, one patient had no history of anticoagulant/antiplatelet intake, one patient was under clopidogrel and two patients were under low dose aspirin. One patient was under treatment with 5-alpha reductase inhibitor, two were under treatment with alpha-blocker and one was under a combination treatment. The ASA score was 3 in two cases and 2 in the other two cases. Pre-operative Q_{max} was available for 3 of 4 patients. Median pre-operative Q_{max} was 9.0 (IQR 8.5–9.5) ml/s. Median pre-operative IPSS was 23.5 (18.7–25.0).

The median pre-operative serum hemoglobin was 14.6 (IQR 14.3–14.7) mg/dl. The median laser time was 27.0 (IQR 20.8–33.5) min. The median laser energy delivered was 267.0 (IQR 187.2–364.0) kJ. The median operative time was 68.5 (IQR 58.8–81.5) min.

Angina pectoris

Of all, 7 patients had an episode of angina pectoris during or after the 180-W GL PVP. Of those, two patients had a known history of coronaropathy and were under treatment with low-dose aspirin. Interestingly, several cases reported negative ECG and negative serum markers after the main event.

Six patients were under treatment with alpha-blocker and only one was under combination treatment. The ASA score was 2 in five cases, 1 in one case, and 3 in another one. Pre-operative Q_{max} was available for 4 of 7 patients. Median pre-operative Q_{max} was 7.8 (IQR 6.9–8.0) ml/s. Pre-operative IPSS was also available for 4 of 7 patients. Median pre-operative IPSS was 31 (IQR 27–35).

Pre-operative serum hemoglobin was available for 5 of 7 patients. The median pre-operative serum hemoglobin was 14.8 (IQR 12.8–15.9) mg/dl. The median laser time was 20.5 (IQR 16.0–22.5) min. The median laser energy delivered was 195.0 (141.0–217.0) kJ. The median operative time was 50 (IQR 40.0–70.0) min.

Table 2 Intra- and post-operative characteristics of patients who experienced major acute cardiovascular events (MACE) or MACE-like events during or immediately after GreenLight laser photoselective vaporization

Case	Energy (Kj)	Laser time (min)	Operative time (min)	Acute urinary retention	Main presentation and diagnostic aspects
Myocardial infarction					
#1	460	44.0	77.0	No	
#2	332	30.0	95.0	No	
#3	143	11.0	60.0	No	
#4	202	24.0	55.0	No	Acute myocardial infarction the night of procedure
Angina pectoris with or without rhythm alteration					
#5	150	17.0	85.0	Yes	History of coronaropathy, cardiac markers, and ECG negative Change cardiologic therapy
#6	224	24.0	30.0	No	Procedure interrupted for angina pectoris with ventricular extra-systole
#7	210	20.5	40.0	No	Procedure interrupted for angina pectoris with arrhythmia, hypotension, and dyspnea
#8	132	15.0	70.0	No	Procedure interrupted for angina pectoris
#9	129	15.0	50.0	Yes	Procedure interrupted for angina pectoris irradiate to left harm, cardiac markers, and ECG negative
#10	318	31.0	70.0	No	Intensive coronary unit recovery for angina pectoris
#11	195	21.0	40.0	No	Angina pectoris with ECG alteration. Cardiac necrosis markers and coronary angiography negative for myocardial infarction
Deep venous thrombosis with or without pulmonary embolism					
#12	307	32.0	50.0	No	The event occurred after that patient was discharged
#13	413	43.0	70.0	No	The event occurred after that patient was discharged
#14	395	41.0	90.0	No	
Miscellanea					
#15	167	16.0	30.0	No	St-tract depression, coronary angiography negative
#16	291	30.4	145.0	No	Supraventricular tachycardia with ventricular overload
#17	235	24.0	35.0	Yes	Procedure interrupted for general malaise
#18	577	35.0	60.0	No	Atrial fibrillation during the surgery treated with amiodarone

Deep venous thrombosis and/or pulmonary embolism

Of all, 3 patients had an episode of deep venous thrombosis and/or pulmonary embolism after the 180-W GL PVP and 2 of them were already discharged from the hospital at the moment of the episode. Of those, only one patient was under treatment with low-dose aspirin. Moreover, one patient was not pharmacologically treated for BPH/LUTS, one was under treatment with alpha-blocker and one with 5-alpha reductase inhibitor. The ASA score was 1 in two patients and 2 in the other one.

The median pre-operative Q_{max} was 9.0 (IQR 6.7–9.0) ml/s. Median pre-operative IPSS was 22.0 (IQR 20.5–23.5). The median pre-operative serum hemoglobin was 15.0 (IQR 15.0–15.5) mg/dl. The median laser time was 41.0 (IQR 36.5–42.0) min. The median laser energy delivered was 395.0 (351.0–404.0) kJ. The median operative time was 70.0 (IQR 60.0–80.0) min.

Miscellanea

Four patients also experienced MACE-like events that could not be classified in the categories expressed above. Specifically, one patient had an ECG anomaly with no sign of infarction at coronary angiography. One patient reported a supraventricular tachycardia with ventricular overload, in another case the procedure was interrupted for general malaise with hypotension and vagal reflexes and one had an episode of atrial fibrillation. Of all, only one of these patients was under treatment with low-dose aspirin.

Out of 4 patients, 3 were under BPH/LUTS treatment with alpha-blocker. The ASA score was 2 in three patients and 3 in the other one. Pre-operative Q_{max} was available for 3 of 4 patients. The median pre-operative Q_{max} was 6.0 (IQR 5.8–6.5) ml/min. The median pre-operative IPSS was 23.0 (IQR 18.5–25.8). The median pre-operative serum hemoglobin was 15.3 (IQR 13.4–15.9) mg/dl. The median

laser time was 27.2 (IQR 22.0–31.6) min. The median laser energy delivered was 263.0 (218.0–362.5) kJ. The median operative time was 47.5 (IQR 33.8–81.3) min.

Discussion

Literature lacks of reports specifically based on MACE or MACE-like events during or immediately after 180-W-GL PVP. Our aim was to explore the MACE prevalence after or during 180-W-GL PVP in a large multi-institutional database. Moreover, we aimed to summarize common features among those patients who experience MACE.

Our multi-institutional database includes 923 patients, of these 18 (1.9%) experienced a MACE or MACE-like event. However, only 4 (0.4%) were confirmed myocardial infarction. The vast majority of cardiac events (11/15, after exclusion of venous thrombosis events) were transient arrhythmia and/or angina pectoris with no evidence of myocardial infarction.

These results in terms of prevalence are quite similar to those of previous studies. In particular, Bhojani et al. relied on a large cohort of patients from the American College of Surgeon National Surgical Quality Improvement Program database to explore differences in terms of outcomes after different surgical techniques such as TURP, laser vaporization, or prostate enucleation. Authors reported cardiovascular complications in the 0.3% of patients with no statistically significant differences between the different techniques used. In addition, authors reported thromboembolic complications in 0.4% of patients ($p > 0.05$). Moreover, perioperative mortality rates were also overall 0.4% with no statistically significant differences according to the surgical technique used [9]. Those rates are similar to ours and validate our findings and the database used for our analyses. However, unlike the current analyses where only the 180-W-GL PVP was considered, Bhojani et al. could not stratify according the different energy sources; thus, the generalizability of their results could be questioned.

Similarly, Smilowitz et al. reported MACE frequency after genitourinary surgery ranging between 1 and 2%; however, authors did not stratify according to specific genitourinary surgical procedure and included all surgeries [6]. Nonetheless, other authors reported the rates of cardiovascular events after transurethral surgery of the prostate to relief BPH/LUTS symptoms. Specifically, Raj et al. retrospectively reviewed a series of 305 patients who underwent TURP in a tertiary hospital. They reported that an overall incidence of cardiovascular and cerebrovascular events were, respectively, 0.98 and 0.65% with no significant differences between patients who routinely received anticoagulant and those who did not [10]. Similarly, Taylor et al. retrospectively reviewed data of 163 consecutive patients undergoing

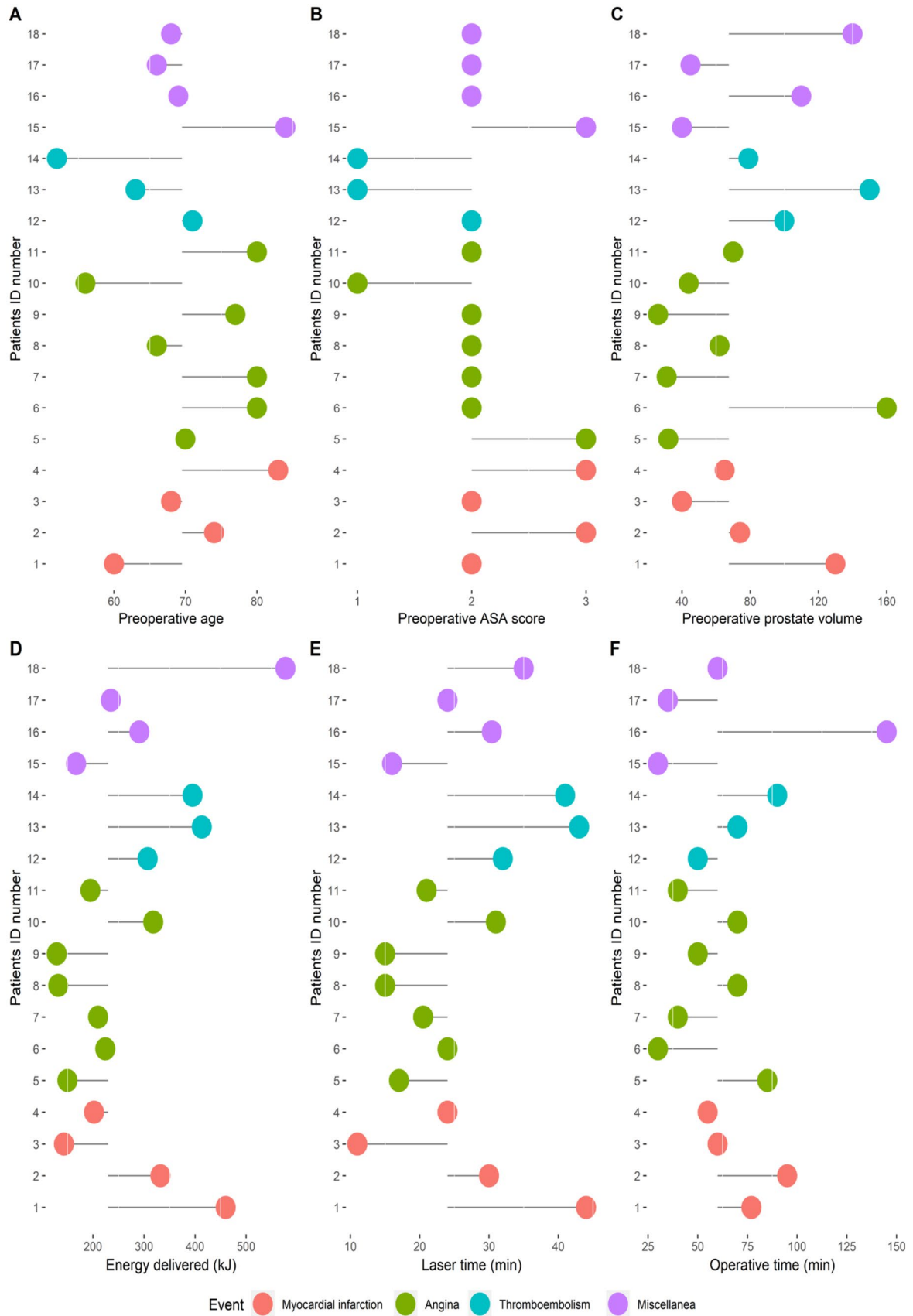
TURP. These investigators stratified patients according to antiplatelet or anticoagulant use in three groups: those with no prescription of antiplatelet/anticoagulants, those on antiplatelet/anticoagulants who had ceased perioperatively, and those who continued antiplatelet/anticoagulants treatment. They observed cardiovascular complications in 6 of 65 (9.2%) patients who perioperatively ceased antiplatelet/anticoagulants. Overall, the reported rate was 3.7% (6/163 patients) [11].

The pathological reasons that might lead to cardiovascular events were previously analyzed in patients undergoing TURP. Bell et al. ascertain the potential thrombotic risk associated with TURP evaluating the changes in several coagulation variables [12]. They prospectively analyzed data from 40 patients undergoing TURP showing a post-operative hypercoagulable state and a physiological fibrinolytic response after TURP [12]. This hypercoagulable prothrombotic state may occur as a physiological response to stress mediated by catecholaminergic system that may be enhanced by the blood loss [12]. Moreover, the haemodilution per se may be a trigger of coagulation system. Finally, the presence of circulating prostatic thromboplastins may also promote a low-grade disseminated intravascular coagulopathy state [12].

Absorption of irrigation fluid during GL-180 W XPS, as well as during other laser surgeries, was also reported [13, 14]. Indeed, Wettstein et al. prospectively investigated the volume of irrigation fluid absorption in 54 patients undergoing GL-180 W XPS [13]. They found positive breath ethanol tests in 22 patients. High-volume absorption was detected in almost 20% of procedures [13]. Even though the absorption of saline irrigation fluid does not result in a TUR syndrome, there could be a chloride overload that can lead to serious complications, in particular in cardiovascular high-risk patients [13]. Wettstein et al. results corroborate those of Hermanns et al. that investigated the absorption of irrigation fluid during 120 W photoselective vaporization of the prostate [15].

The fluid absorption may be relied to fluid overload. Fluid overload could explain the angina events with and without evidence of myocardial infarction. In fact, angina could be as a consequence of increased work and oxygen request in myocardium [15]. Moreover, isotonic saline irrigation fluid might lead to hyperchloremic acidosis which could stimulate sympathetic nervous system and weaken the myocardial pumping capacity. In addition, they could be associated with reduced glomerular filtration rate, abdominal pain, and mental dizziness [16].

Furthermore, the products derived from the cytotoxic effect of laser energy could exert a direct toxic effect. However, the possible acute toxic effect of prostatic extracts was tested by Zhang et al. on isolated cardiomyocytes from rats [17]. Authors showed that electrolyte-free irrigating fluids



◀**Fig. 1** Lollipop plot graphically depicted pre-operative and intra-operative characteristics of each patient compared to the median value, grouped by the different MACE or MACE-like event category. Pre-operative characteristics of interest were **a** age at surgery, **b** ASA score, and **c** prostate volume. Intra-operative characteristics of interest were **d** energy delivered, **e** laser time, and **f** operative time

but not prostate extracts have mild cardiotoxic properties. This cardiotoxic effect may be related to the devitalizing effect of absorbed fluid during TURP on the heart [17].

Finally, patients with LUTS and those who underwent BPH/LUTS surgery are well known to be at higher cardiovascular risk [1]. Other pre-operative risk factors such as the age ≥ 75 year, that represent about the 33% of patients with MACE in our experience, male sex, chronic conditions, recent acute cardiovascular events, as well as perioperative factors such as hypotension, tachycardia, bleeding, hypoxemia, and pain, are associated with perioperative cardiac complications in patients undergoing major non-cardiac surgery [18]. Thus, the urologist and the anesthesiologist should evaluate each patient and the specific risk of cardiac complications.

In summary, our report would like to emphasize the risk of acute MACE or MACE-like events. The etiology of such events is likely to be multifactorial. Several confounders should be addressed to really explore the safety of 180 W GL XPS PVP, especially in high-risk patients. Thus, prospective observational studies with a rigorous design are warranted.

Several limitations affect the current report. First, the length of hospitalization is referred to the length of stay in the urologic unit and no further data are available on the discharge from those departments to coronary unit or similar. Furthermore, all patients were treated according to good clinical practice guidelines and all patients recovered. However, details about the specific treatments are available only for a proportion of them. This lack of information is the consequence of the treatment performance in emergency/cardiology departments by dedicated specialists, outside the urologic units of provenance. Finally, the multi-institutional nature of our dataset leads to a poor standardization in treatments and diagnosis. This is highlighted by the fact that only 7 over 14 centers reported MACE events. Indeed, the singular cardiovascular risk could be neither examined nor standardized throughout the different centers.

Taking together all the above considerations, the use of 180-W-GL PVP is still a valid option for the BPH/LUTS treatment. However, as discussed within the NICE guidelines [4], future studies should clarify who are those who could experience the largest benefit from this surgical technique. Indeed, our study showed that maybe there are some patients in whom the use of 180-W-GL PVP could not be the best choice. For these reasons, prospective studies, even observational, with a robust design, are warranted

to further clarify the safeness profile of this technique and better stratify patients according to their own surgical success probability.

Conclusion

Our report would like to emphasize the risk of acute MACE or MACE-like events. The etiology of such events is likely to be multifactorial. Several confounders should be addressed to really explore the safety of 180 W GL XPS PVP, especially in high-risk patients. Thus, prospective observational studies with a rigorous design are warranted.

Author contributions MM, LC, FG: Project development, Data analysis, Manuscript writing. All the authors: Data collection. LS, LC, GF: Supervision. All the authors: Project development, Manuscript editing.

Compliance with ethical standards

Conflict of interest LC, LR, PD, GF do surgical tutorship for AMS and received honoraria for their tutorship.

Ethical approval For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study. This study and all the related procedures have been performed in accordance with the Declaration of Helsinki.

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