Clinical and Hemodynamic Characterization Super Responders to IV Prostacyclin in Pulmonary Arterial Hypertension

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Research

Keywords: Pulmonary Hypertension, super responders, right heart failure, prostacyclin

Posted Date: February 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-70022/v2

Abstract

Background: Parenteral prostacyclins are the only therapy proven to extend survival in pulmonary arterial hypertension (PAH), yet at the bedside clinicians have no tools to predict which patients are most likely to benefit from this medication class.

Methods: We retrospectively analyzed all PAH patients treated with IV epoprostenol therapy at our center from 1/1/1996 to 12/31/2016. We analyzed survival in patients and defined the 90 th percentile of survival. Patients were divided into those who survived past this point (super responders) and those who had had an event prior to this time point after initiation of iv epoprostenol (usual responders).

Results: The median survival after IV epoprostenol initiation was 4.32 years, and the 90 th percentile of event-free survival was 11.09 years. Fourteen patients met criteria for super responder and 45 had a survival <90 th percentile, comprising the usual responder group. Super responders tended to be younger, have longer six-minute walk distances and higher mean pulmonary arterial pressure ($p<0.05$ for all). In follow up, super responders continued to have a higher six-minute walk distance and were more likely to have achieved normal or only mildly impaired right ventricular function, though no differences in hemodynamics were observed.

Conclusions: There may be a super responder phenotype that can be defined in patients with PAH by >90 th percentile of survival. Super responders were more likely that usual responders to be younger and were more likely to have achieved favorable right ventricular function at follow up, however, differences in hemodynamics were not observed.

Introduction

Pulmonary arterial hypertension (PAH) is a disease characterized by increasing pulmonary vascular resistance due to pulmonary vascular remodeling. Untreated, the disease is progressive and ultimately leads to right heart failure and death (Rubin et al., 2002; Sastry, Narasimhan, Reddy, & Raju, 2004; Zhao et al., 2001). Although the incidence of the disease is low(Jacobs et al., 2010; McLaughlin, 2006), the median survival without treatment is 2.8 years(Pulido et al., 2013). Though no curative treatment options are available, four classes of drugs, each targeting different mechanisms, are FDA approved for treatment of PAH. Phosphodiesterase type 5 inhibitors(Sastry et al., 2004; Zhao et al., 2001), endothelin-receptor antagonists[3-5,7], guanylate cyclase agonists(Ghofrani et al., 2013), and prostaglandin analogues(Badesch et al., 2000; Barst, Rubin, Long, McGoon, Rich, Badesch, Groves, Tapson, Bourge, Brundage, Koerner, Langleben, Keller, Murali, Uretsky, Clayton, Jobsis, Blackburn, Shortino, Crow, et al., 1996; Higenbottam, Butt, McMahon, Westerbeck, & Sharples, 1998; McLaughlin, Shillington, & Rich, 2002; Rubin et al., 1990; Shapiro et al., 1997) have been shown to improve exercise capacity, hemodynamic parameters, and are recommended therapy by evidence based guidelines(Benza et al., 2015; Rich et al., 2010; Robbins et al., 2009; Sastry et al., 2004). Prostacyclin therapy, in particular, has been known to improve PAH survival for over two decades(Barst, Rubin, Long, McGoon, Rich, Badesch, Groves, Tapson,

Bourge, Brundage, Koerner, Langleben, Keller, Murali, Uretsky, Clayton, Jobsis, Blackburn, Shortino, & Crow, 1996; McLaughlin et al., 2002; Rubin et al., 1990; Sitbon et al., 2002), yet at the bedside, clinicians cannot predict which patients are most likely to benefit from this medication class.

Recent registry data supports improving survival in PAH, which is likely due to the advent of targeted therapies(Jacobs et al., 2010; Sitbon et al., 2002). The US REVEAL registry demonstrated a mean survival for incident PAH cases of 6.5 years(Benza et al., 2012). A major contributor to this improved mortality is thought to be the use of parenteral prostaglandin analogues, including intravenous epoprostenol and treprostinil, and subcutaneous treprostinil. Additionally, combination therapies of PDE5i and ERA antagonists have also demonstrated improved mortality in this patient population(Galiè et al., 2015). Current guidelines recommend stratifying patients initially at the time of right heart catheterization via acute vasodilatory response. Patients with an acute response are initially treated with calcium channel blockers and have been shown to have longer survival as compared to non-acute responders. (Halliday & Hemnes, 2017; McLaughlin et al., 2002; Rich et al., 2010; Sitbon et al., 2005; Sitbon et al., 2002) Unfortunately, acute responders only represent <10% of IPAH patients in most published registries(Sitbon et al., 2005).

For the remaining patients, clinical practice guidelines recommend risk stratification of individual patients based on clinical and hemodynamic characteristics, with treatment recommendations based on risk category(Galie et al., 2019). Generally, parenteral prostacyclins are recommended for long-term treatment of PAH in patients with World Health Organization (WHO) functional class III and IV symptoms, right heart failure, and in patients who fail to respond to oral or inhaled treatments(Benza et al., 2015; Galie et al., 2019; Rich et al., 2010; Robbins et al., 2009; Sastry et al., 2004) Though we know from randomized trials and observational data that overall survival is better with parenteral prostacyclins(Galie et al., 2019; Hemnes et al., 2015; Kuhn et al., 2003; Sitbon et al., 2002), it is still largely unknown if there are phenotypes of PAH or specific demographic characteristics that predict who will respond better or worse to parenteral prostaglandin therapies outside of acute responders to vasodilators. There is no consensus definition of good, or even “super response” to IV prostaglandin therapy as yet(Halliday & Hemnes, 2017), however, the definition of acute responders in other classes of PAH therapies(Sitbon et al., 2005) has yielded peripheral blood signatures that may be useful in predicting drug responses and understanding underlying pathology(Benza et al., 2015; Hemnes et al., 2015; Hemnes et al., 2016). Thus, there is a potential significant benefit to understanding super responders to all classes of PAH therapies. In our center’s clinical experience, we have seen a dramatic effect on outcomes with IV epoprostenol and have a long anecdotal experience with patient’s whose response to parental prostaglandins appears to be more robust than their counterparts.

In this study, we sought to describe variability in survival among patients receiving parenteral prostaglandin, and determine if there is a population of “super responders”. We further compared demographic and clinical variables in patients with super response and usual response to understand if demographic or clinical features associate with better responses in PAH patients treated with IV

prostacyclin. We hypothesized that PAH patients with super response to IV prostacyclin would be demographically and clinically different from usual responders.

Methods

Patient Selection

We retrospectively analyzed all patients treated with IV epoprostenol therapy for PAH at the Vanderbilt Center for Pulmonary Vascular Disease from 1/1/1996 to 12/31/2016 (Vanderbilt University Medical Center IRB # 160765). Patients with pulmonary hypertension other than WHO Group 1 PAH were excluded. PAH was diagnosed according to standard criteria(Sastry et al., 2004) and medical therapy was at the discretion of the treating physician in accordance with accepted guidelines(Rich et al., 2010; Sastry et al., 2004) Date of death or lung transplant were collected from the medical record. Date of initial diagnosis was recorded as the earliest documentation of PAH in the medical record; the closest WHO functional class, six-minute walk distance, right heart catheterization, echocardiogram results, and other clinical data were collected at 6 months and 1 year after drug initiation. Demographic data, selected prior to study initiation, included: age at diagnosis, sex, BMI, WHO group of PAH, diabetes diagnosis, hypertension diagnosis, and hyperlipidemia. Event-free survival (from death or lung transplant) was defined as time from initiation of IV epoprostenol. We included only patients on IV epoprostenol in this study, as our institution has very few patients on IV or subcutaneous treprostinil and including these patients could potentially introduce bias because of treatment patterns.

Definition of Super Responder and Usual Responder

We defined super responders as patients in the top 10% of survival among PAH patients after initiation of IV epoprostenol. For our primary analysis, we also included censored patients (still alive at the time of data collection) with event-free survival greater than the 90^{th} percentile as super responders (Figure 1). Those patients who had an event before the 90^{th} percentile of survival were included and defined as “usual responders”, while those patients who were alive, but had not yet achieved the 90^{th} percentile were not included in the analysis as they cannot yet be defined as super responders or usual responders. As we focused on usual and not exceptionally poor response, patients with death or transplant within six months of starting therapy were excluded (n=4). All events described in the study represent death since only 2 patient’s underwent transplantation and were excluded from the study as described above.

Statistical Analysis

Data are presented as number and percentage or median (interquartile range). Continuous and ordinal variables are compared using the Mann-Whitney U test. For all analyses, a p value of <0.05 was considered significant. For survival analyses, subjects became ‘at risk’ on the date of epoprostenol initiation, and were censored as of March 26, 2017, and missing data were excluded. Statistical analyses were performed using Stata version 15.1 for Mac and GraphPad Prism (GraphPad Prism version 7 for Mac, GraphPad Software, La Jolla California USA, www.graphpad.com).

Results

Overall Patient Population Characteristics

We identified 144 patients treated with IV epoprostenol for PAH at the Vanderbilt Center for Pulmonary Vascular Disease (**Figure 1**). Of these 144, 18 were excluded as shown in **Figure 1,** most commonly because of lack of baseline data. Demographic data from the remaining 126 patients treated with IV epoprostenol are presented in **Table 1**. The median age was 45, 77% were female and had a BMI similar to our prior publications(Robbins et al., 2009). The majority (70/126) had heritable or idiopathic PAH. As expected, the patients had advanced PAH with 93% functional class III or IV and 77% had moderate or severe right ventricular (RV) dysfunction noted on echocardiography. Median time from diagnosis to initiation of IV epoprostenol was 68 days. Survival in the non-censored patients is shown in **Figure 2.** The median survival after IV epoprostenol initiation was 4.32 years, and we found that the 90^{th} percentile of event-free survival was 11.09 years.

Table 1. Demographics and Clinical Characteristics for Complete Cohort (n=126)	
Age (years)	45 (35 – 55)
Sex (Female)	97 (77%)
BMI (kg/m^2)	29 (25.7 – 34.7)
Diagnosis	
Idiopathic PAH	50 (40%)
Heritable PAH	20 (26%)
Connective Tissue Disease PAH	32 (35%)
Congenital Heart Disease PAH	5 (4%)
Other	19 (15%)
Comorbidities	
Diabetes Mellitus	19 (15%)
Hypertension	54 (43%)
Hyperlipidemia	28 (22%)
Six-Minute Walk Distance (m)	303 (187 – 380)
WHO Functional Class	
II	8 (7%)
II	87 (72%)
IV	26 (21%)
Echocardiogram findings	
Right Ventricular Function	
Normal	9 (8%)
Mild Dysfunction	19 (16%)
Moderate Dysfunction	43 (36%)
Severe Dysfunction	49 (41%)
Right Ventricular Dilatation	
Normal	2 (3%)
Mild	20 (17%)
Moderate	33 (28%)
Severe	64 (53%)
Right Heart Catheterization Results	
Right Atrial Pressure (mmHg)	16 (10 – 20)
Mean Pulmonary Arterial Pressure (mmHg)	58 (52 – 65)
Cardiac Output (L/min)	3.4 (2.9 – 4.3)
Cardiac Index (L/min/m^2)	1.8 (1.6 – 2.3)
Pulmonary Vascular Resistance (Woods Units)	1146.9 (369 – 2458)

Comparison of Usual vs. Super Responders

Of the 126 included patients, 50 patients had an event during follow up. Of these 50 patients, those with survival ≤ the 90th percentile (n = 45) constituted the “usual responder” group. Seventy-six patients remained event-free at the time of analysis, and among these, 9 had survival ≥ the 90th percentile. These 9 patients, in addition to the 5 patients with events that occurred after the cutoff for the 90th percentile constituted the 14 super responders (**Figure 1**). Kaplan Meier survival curves for usual and super responders are shown in **Figure 3**. By definition, there were no events in the super responder group prior to the 90th percentile of survival in the group as a whole.

Demographic data on the usual responders vs. the super responders are presented in **Table 2**. At baseline, the super responders were younger, with median age of 43 vs. 52 years (p=0.02), and had a more preserved six-minute walk distance 365 (279-462) vs. 267 (139-339m). There were no differences, however, in type of PAH, severity of RV impairment on echocardiogram or WHO functional class. In comparing the most recent right heart catheterization prior to starting IV epoprostenol, the super responders had higher mean pulmonary arterial pressure and tended to have lower cardiac output (2.9 (2.7 – 4.7) vs. 3.8 (3.1 – 4.8) L/min, p=0.09).

Table 2. Demographics and Baseline Clinical Characteristics of Super Responders Versus Patients with Usual Response

	Super Responders (n=14)	Usual Responders (n=45)	p-value
Age	43 (36 – 47)	52 (41 – 61)	0.02
Sex (Female)	11	36	0.91
BMI (kg/m^2)	28 (25 – 33)	29 (25 – 33)	0.73
Diagnosis			0.15
Idiopathic PAH	5	17	
Heritable PAH	4	3	
Connective Tissue Disease	3	14	
PAH	1	1	
Congenital Heart Disease PAH	1	10	
Other			
Comorbidities			
Diabetes Mellitus	2	9	0.63
Hypertension	5	18	0.77
Hyperlipidemia	4	14	0.86
Percentage of patients on combination therapy with other treatment modalities (endothelian receptor antagonists or phosphodiesterase inhibitors)	70%	69%	
Six-Minute Walk Distance (m)	365 (279 – 462)	267 (139 – 339)	0.02
WHO Functional Class			0.42
II	0	2	
III	9	28	
IV	5	11	
Echocardiogram findings			
Right Ventricular Function			0.54
Normal	1	1	
Mild Dysfunction	3	6	
Moderate Dysfunction	4	18	
Severe Dysfunction	5	17	
Right Ventricular Dilatation			0.36
Normal	0	1	
Mild	4	7	
Moderate	4	13	
Severe	5	22	
Right Heart Catheterization Results			
Right Atrial Pressure (mmHg)	15 (10 – 20)	15 (12 – 20)	0.58
Mean Pulmonary Arterial Pressure (mmHg)	64 (61 – 71)	55 (49 – 62)	0.002
Cardiac Output (L/min)	2.9 (2.7 – 4.7)	3.8 (3.1 – 4.8)	0.09
Cardiac Index (L/min/m^2)	1.7 (1.4 – 2.1)	2.0 (1.6 – 2.6)	0.10
Pulmonary Vascular Resistance (Woods Units)	16.7 (14.8 – 25.2)	12.3 (8.6 – 14.9)	0.009

We also compared clinical characteristics of usual and super responders at follow up to detect any possible differences (Table 3). We found that median six-minute walk distance remained higher in the super responders, (436m (399 – 497m) vs. 337 (258 – 369m), p=0.0001). There was a trend towards more functional class I and II symptoms in the super responders (p=0.07) and on echocardiography, super responders were more likely to have achieved normal or only mildly dilated RV size (p=0.04), although there were no differences in RV function. There were no significant differences in invasively measured hemodynamics.

Table 3. Clinical Characteristics of Super Responders versus Patients with Usual Response at 1 year Follow-up

	Super Responders	Usual Responders	p-value
Six-Minute Walk Distance*	436 (399 – 497)	337 (258 – 369)	0.0001
WHO Functional Class			0.074
I	2	1	
II	6	13	
III	4	19	
IV	0	1	
Echocardiogram findings#			0.14
Right Ventricular Function			
Normal	2	3	
Mild Dysfunction	2	4	
Moderate Dysfunction	1	22	
Severe Dysfunction	8	6	
Right Ventricular Dilatation			0.044
Normal	3	1	
Mild	1	4	
Moderate	7	15	
Severe	2	15	
Right Heart Catheterization Results#			
Right Atrial Pressure (mmHg)	7 (5 – 13)	11 (6 – 16)	0.15
Mean Pulmonary Arterial Pressure (mmHg)	53 (49 – 60)	50 (44 – 57)	0.30
Cardiac Output (L/min)	4.4 (4.1 – 4.7)	4.5 (3.7 – 5.2)	0.66
Cardiac Index (L/min/m^2)	2.4 (2.0 – 2.8)	2.4 (2.0 – 2.9)	0.81
Pulmonary Vascular Resistance (Woods Units)	9.7 (6.6 – 13.2)	8.2 (5.9 – 10.8)	0.48

*Best six-minute walk distance within the first year after drug initiation
#For echocardiogram and right heart catheterization reports, the values closest to one-year follow-up were used

Discussion

We sought to determine if there are demographic, echocardiographic or hemodynamic differences between PAH patients treated with IV epoprostenol with super response compared to usual response. As there is no agreed-upon definition of super response to IV epoprostenol, we chose a survival >90th percentile, which was 11.09 years in our cohort. Using this definition, we compared demographic and clinical data in the super responders and usual responders. In general, the super responders were younger,

and had potentially more severe hemodynamics as evidenced by higher mean pulmonary artery pressure and a trend to lower cardiac index. Nevertheless, these patients had longer six-minute walk distances at baseline and, in follow up, were more likely to have normal or only mildly abnormal right ventricular size despite similar degrees of RV dysfunction at initiation. Overall, these data suggest that, aside from age, there are few features available to clinicians at the bedside to predict patients likely to be super responders and there may be value in research into other factors, such as biomarkers that may better identify these patients. However, it should be noted that we did not collect all comorbities on these patients that would be required to calculate traditional life expectancy including coronary artery disease, peripheral vascular disease, chronic obstructive pulmonary disease, dementia, or malignancy. Though this could introduce some confounders to our study, given the diagnostic process for idiopathic PAH and clinical decision-making to treat with parental prostacyclins which generally requires no known life-limiting disease other than PAH in our practice, it is likely that the prevalence these confounders are likely low.

We and others have attempted to define predictors of prostacyclin response previously, however, none have attempted to define the super responder phenotype, which we have done here. This has been done successfully in the past in PAH with definition of so-called vasodilator responders to calcium channel blockers(Sitbon et al., 2005), however it has been less clear how to define a super responder to other PAH-directed therapies. Part of the success in studying vasodilator responsive PAH has been the ability to predict patients by provocative testing with nitric oxide or other vasodilators at the time of right heart catheterization(Galie et al., 2019), however, no such test is clinically available to determine which patients are likely to respond to IV prostacyclins. We chose survival as a concrete endpoint that is clearly highly desirable to practitioners and patients but recognize that we may lose some patients from our analysis who are presently alive but without adequate exposure to prostacyclin to be defined as a super responder. Presently there is no accepted “super-responder” phenotype to any PAH therapy, with the exception of calcium channel blockers, thus we chose the upper 10% as a reflection of a clinically meaningful outlier survival endpoint. We also recognize that there are other important outcomes that we did not include such as quality of life, six-minute walk distance, and freedom from adverse events of PAH-directed therapy that may alternatively define a super responder(Halliday & Hemnes, 2017). It is also important to recognize that using the definition we have, it is not known why the super responders had such prolonged survival, as it may be a particularly robust RV response to therapy, and not regression of pulmonary vascular disease, as suggested by a case report by Rich et al(Rich et al., 2010). The lack of significant change in super responders’ hemodynamics and significantly improved RV function on echo may support this hypothesis.

Other groups have described clinical response to prostacyclin and found baseline and improvement in functional class after therapy to be highly predictive of survival(Kuhn et al., 2003; Sitbon et al., 2002; Weatherald et al., 2018). Other studies have not had as extensive follow up duration and did not find age to be a predictor of positive response, however our own cohort with over a decade of follow up has consistently demonstrated that younger age is strongly associated with improved survival(Halliday et al., 2018), again found here.

A significant finding of this study was that despite increased mean pulmonary arterial pressure, increased pulmonary vascular resistance, and a trend to reduced cardiac index, super responders were able to achieve excellent survival, suggesting that baseline hemodynamics are useful for appropriate treatment recommendations, but not necessarily long-term prognostication regarding drug response. Further, the super responder group could not be identified by change in hemodynamics within a year. Notably, prior studies have shown that higher mPAP at baseline and improvement at 3 months following treatment had previously been shown to improve long-term survival; however, these studies included patient's with acute vasodilatory response at catheterization (Sitbon et al., 2002). Our data suggest that there is a unique super responder clinical phenotype different from prior described acute vasodilatory responders. And these patients may not be easily discerned at the bedside. It is possible there are genetic or molecular predictors of prostacyclin response that could be used to a) select the patients most likely to receive a benefit from these therapies, b) select patients who are unlikely to benefit and may be better served with evaluation of possible lung transplantation, c) identify patients who may benefit from earlier initiation of prostacyclin therapy. Further research will be required to identify these predictors.

A limitation to this study relates to the single-center design which introduces treatment and referral bias and decreases the number of patient's included in the analysis, especially at the later time points. Due to the smaller patient numbers, the study may be under-powered to detect some differences between the groups. However, in terms of the overall population, the baseline demographic data appeared to align well with previous registry data, especially the calculated survival rate when compared with the US-REVEAL study (6.3 years vs 6.5 years) (Benza et al., 2012). In addition, we chose not to include patients with a death or transplant within six months of initiation as these patients are relatively easy to identify early in the course of their treatment and their response is not "usual" rather unusually poor (n=4). It may be surprising that our transplant number is low over the course of this study (n=2). However, this is reflective of our center's current practice pattern with a long exposure to prostacyclin, often in decades, and comorbidities that preclude transplant. Additionally, as our center uses relatively little treprostinil, we excluded patients receiving this therapy in an attempt to reduce treatment bias. We are unable to account for referral bias over the timeframe of this analysis but to the author's knowledge no large PAH centers were opened in our catchment area.

Given the retrospective nature of this study, the analysis was performed starting with date of diagnosis not initiation of drug in order to reduce lead-time bias. While many cases were prevalent, the median number of days between date of diagnosis and initiation of IV epoprostenol was 68 days. The present study does not account for inherit immortal time bias caused by the changes in management of PAH that occurred over the study period.

In conclusion, using >90th percentile of survival after IV epoprostenol initiation, a cohort of super responders can be identified. These patients are younger, have evidence of more severe hemodynamics at baseline, yet higher six-minute walk compared to the usual responder; given the younger age of this group it is not a surprise as six-minute walk distance is related to age (Enright & Sherrill, 1998). In one year of follow up, super responders are more likely to have achieved normal or near normal RV function with no

significant change in mean pulmonary artery pressure, suggesting possibly improved RV responses to IV epoprostenol. Further study is warranted to determine if molecular features may better predict clinical responses to IV epoprostenol.

Abbreviations

PAH - pulmonary arterial hypertension

IV - intravenous

mPAP – mean pulmonary arterial pressure

PVR – pulmonary vascular resistance

RV – Right ventricle

Declarations

Ethics Approval and Consent to Participate: The study was approved though the Vanderbilt University Institutional Review Board (Number 160765). No consent was required for the purposes of this study.

Consent for Publication:No consent was required for the purposes of this study.

Availability of data and material: Please contact the authors if any scientist is wishing to use or view the database associated with this study.

Funding: No source of funding was used in the design, collection, analysis, or interpretation of this data.

Competing Interests:The authors declare that they have no financial or non-financial competing interests.

Author's Contributions:AC participated in the design of the study, the chart review process for patient characteristics and outcomes, aided with statistical analysis, and drafted the manuscript. SH performed the majority of the statistical analysis and aided with manuscript editing and review. MP performed manuscript editing and review. IR performed manuscript editing and review. AH conceived of the study, and participated in its design, coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgements: Not applicable

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Figures

Figure 1

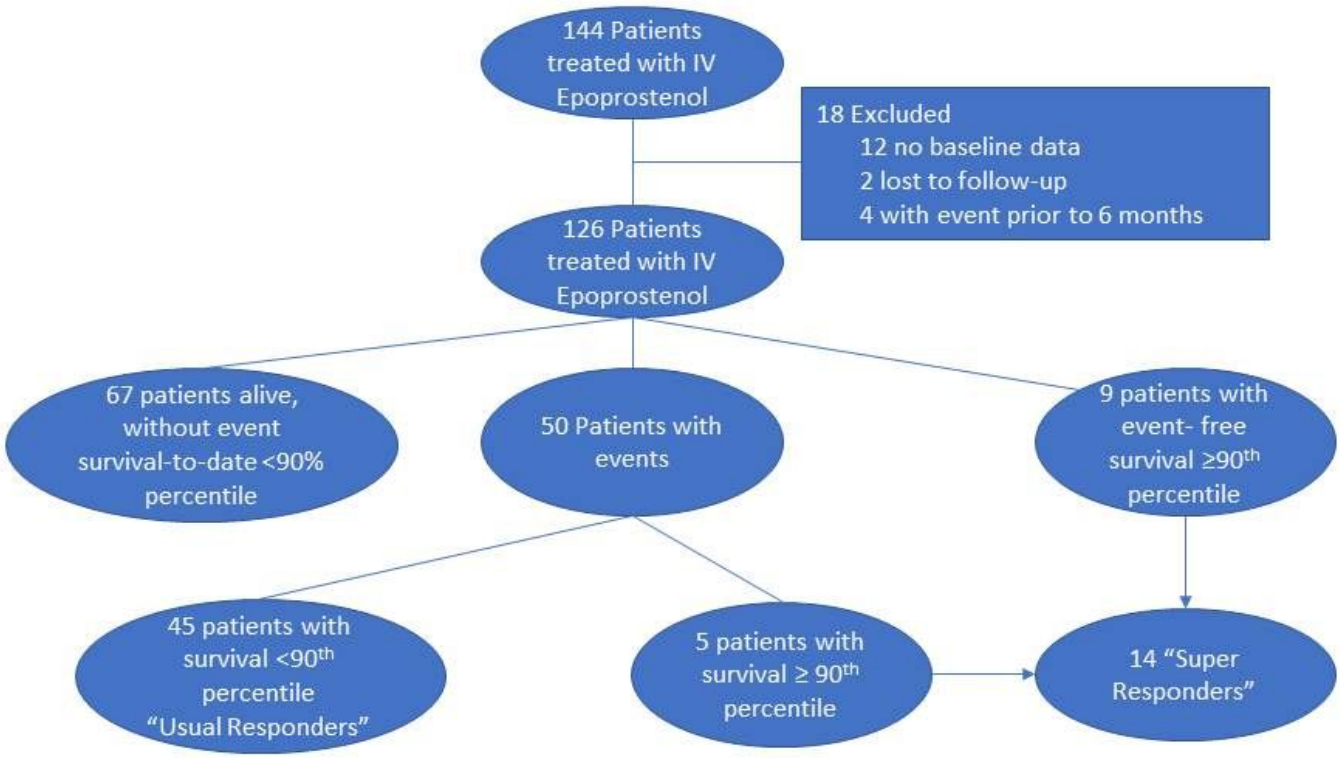

Figure 1

Patient disposition

Figure 2

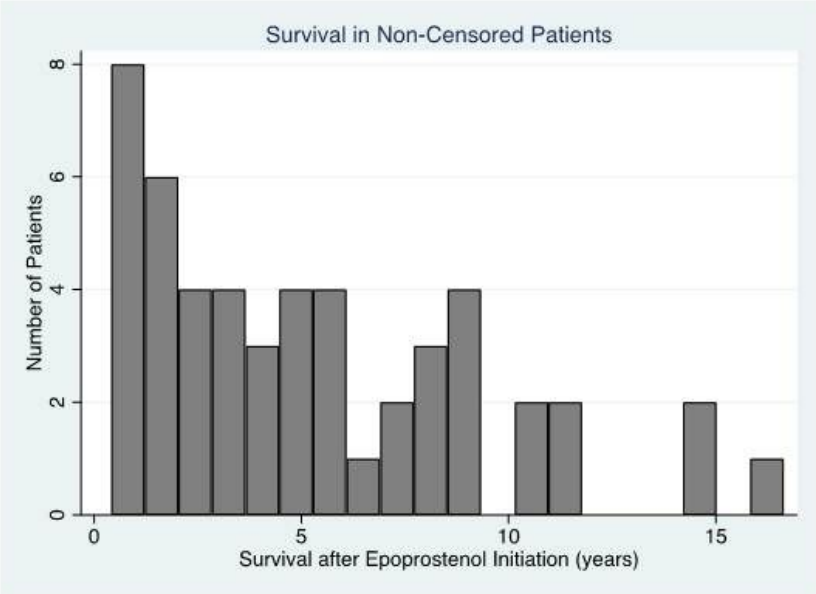

Figure 2

Survival distribution Histogram of survival in 50 patients with events in follow up showing distribution of survival.

Figure 3

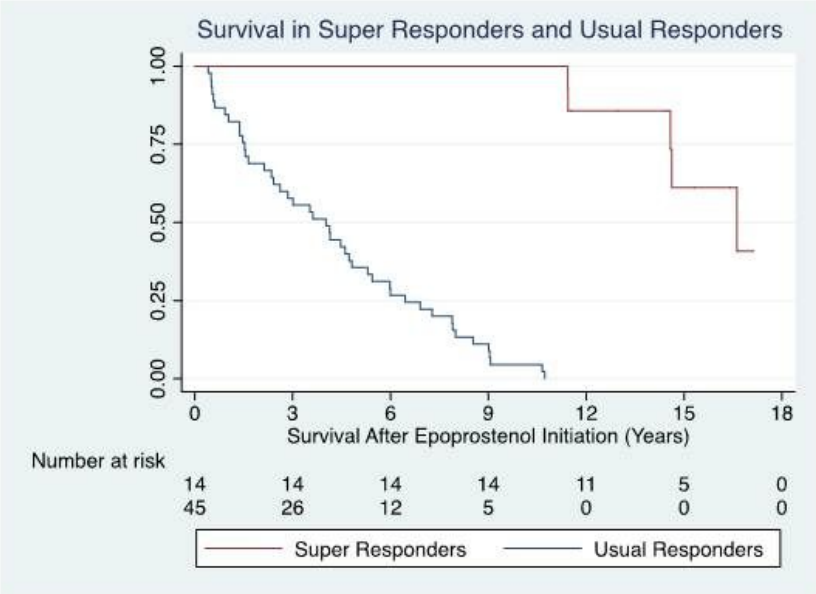

Figure 3

Survival in Super Responders and Usual Responders. The difference in survival demonstrated in super responders vs. usual responders, $p<0.5$.