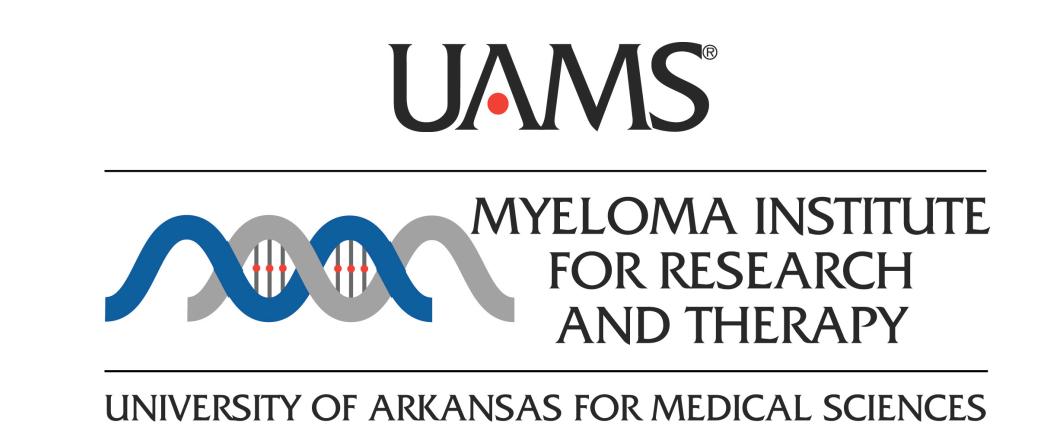


Retrospective Analysis of Cardiovascular (CV) Events Following Compassionate Use of Carfilzomib (CFZ) in Patients (Pts) With Relapsed and Refractory Multiple Myeloma (RRMM)



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Background:

Herein, we report CV events observed in late-stage, heavily pretreated pts who received salvage CFZ under a compassionate use protocol. UARK Phase II CFZ compassionate use trial (registered with ClinicalTrials.gov as NCT00999414).

Methods:

•Pts received single-agent CFZ (20-45 mg/m²) intravenously over 2-30 min on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle (C) with dexamethasone (4-40 mg) during C1, and 30 mL/kg/day (~6-8 cups liquid per day) starting 48 hours prior to first dose of CFZ, and pre-hydration with Normal Saline 250 ml, along with other agents (eg, lenalidomide, thalidomide, cyclophosphamide, doxorubicin, cisplatin, vorinostat) during C2 and beyond (Figure 1).
•CV events were grouped according to preferred terms. Serious CV events were defined as those that required hospitalization. B-type natriuretic peptide (BNP) values were measured at baseline; peak values were recorded during C1.

Results:

- •143 pts (median age, 61 years old; 70% were male) received treatment..
- •Prior to enrollment, pts received a median of 7 prior lines of therapy (range, 2-15), including doxorubicin (range, 0-360 mg/m²).
- •Most pts (92%) had prior autologous stem cell transplants (ASCT), with 74% receiving ≥2 ASCT (range, 0-5).
- •Pts received CFZ for a median of 2C (range, 1-36).
- •Overall, 27 pts (18.9%) experienced a serious CV event, 21 (77.7%) of which had preexisting CV conditions (like hypertension, coronary artery disease, or atrial fibrillation).
- •Of these 27 pts, 11 pts (7.7%) developed CHF (Grades III/IV)or worsening of existing CHF (confirmed by echocardiogram [ECHO] ≤1 month from diagnosis), and 13 (9.1%) required hospitalization for hypotension (n=6), arrhythmia (n=2), hypertension (n=2), pulmonary edema (n=1), pulmonary embolism (n=1), or pulmonary hypertension (n=1).
- •Additionally, 3 pts (2.1%) experienced cardiopulmonary arrest (see Figure 2).
- •Of the 11 CHF pts, 10 had a baseline ECHO (recorded ≤6 months before study); left ventricular ejection fraction decreased from a median of 55% (pretreatment) to 33% (post-treatment).
- •Of pts with available BNP values at baseline and during C1 (n=69; 48.3%), the median peak BNP increase from baseline was 407 pg/ml (P<0.001) (Figure 3).
- •Simple chi-square test to correlate hospital admissions with elevated BNP is shown in table 1 (P=0.056).

Conclusions:

- •Late-line, heavily pretreated pts with RRMM occasionally experienced CV events following the administration of CFZ with or without other antimyeloma agents.
- •Caution is warranted in patients with a history of serious cardiac disease; additional medical management of underlying cardiac comorbid conditions may be necessary.
- •Given the number of confounding factors and the uncontrolled nature of these data, causality for these CV events could not be definitively determined.
- •Cardiac and pulmonary AEs are being further characterized in ongoing randomized clinical trials.
- •Complications from our population was higher than earlier clinical trials (*) mostly do to the fact that our patients received more lines of chemotherapy.

(*) previous clinical tirals:

- 1.Jagannath S, Vij R, Stewart AK, Trudel S, Jakubowiak AJ, Reiman T, Somlo G, Bahlis N, Lonial S, Kunkel LA, Wong A, Orlowski RZ, Siegel DS. An open-label single-arm pilot phase II study (PX-171-003-A0) of low-dose, single-agent carfilzomib in patients with relapsed and refractory multiple myeloma. Clin Lymphoma Myeloma Leuk. 2012;12(5):310-8.
- 2.Siegel DS, Martin T, Wang M, Vij R, Jakubowiak AJ, Lonial S, Trudel S, Kukreti V, Bahlis N, Alsina M, Chanan-Khan A, Buadi F, Reu FJ, Somlo G, Zonder J, Song K, Stewart AK, Stadtmauer E, Kunkel L, Wear S, Wong AF, Orlowski RZ, Jagannath S. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood. 2012;120(14):2817-25.
- 3.Vij R, Wang M, Kaufman JL, Lonial S, Jakubowiak AJ, Stewart AK, Kukreti V, Jagannath S, McDonagh KT, Alsina M, Bahlis NJ, Reu FJ, Gabrail NY, Belch A, Matous JV, Lee P, Rosen P, Sebag M, Vesole DH, Kunkel LA, Wear SM, Wong AF, Orlowski RZ, Siegel DS. An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. Blood. 2012;119(24):5661-70.
- 4. Vij R, Siegel DS, Jagannath S, Jakubowiak AJ, Stewart AK, McDonagh K, Bahlis N, Belch A, Kunkel LA, Wear S, Wong AF, Wang M. An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib. Br J Haematol. 2012;158(6):739-48.
- 5. Badros AZ, Vij R, Martin T, Zonder JA, Kunkel L, Wang Z, Lee S, Wong AF, Niesvizky R. Carfilzomib in multiple myeloma patients with renal impairment: pharmacokinetics and safety. Leukemia. 2013;Epub ahead of print.

Figure 1: Protocol Design

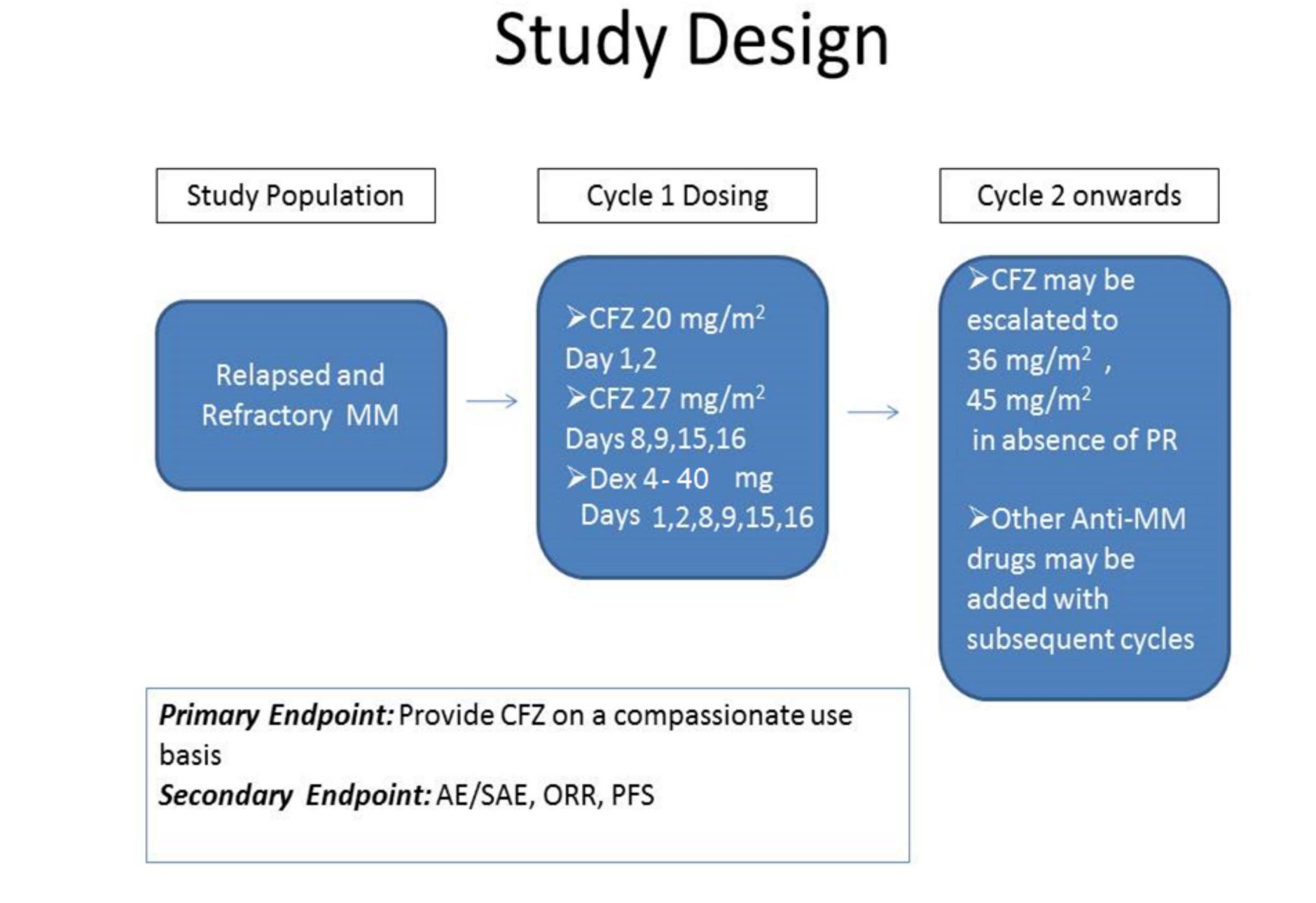


Figure 2: Breakdown of Cardiovascular(CV) Complications

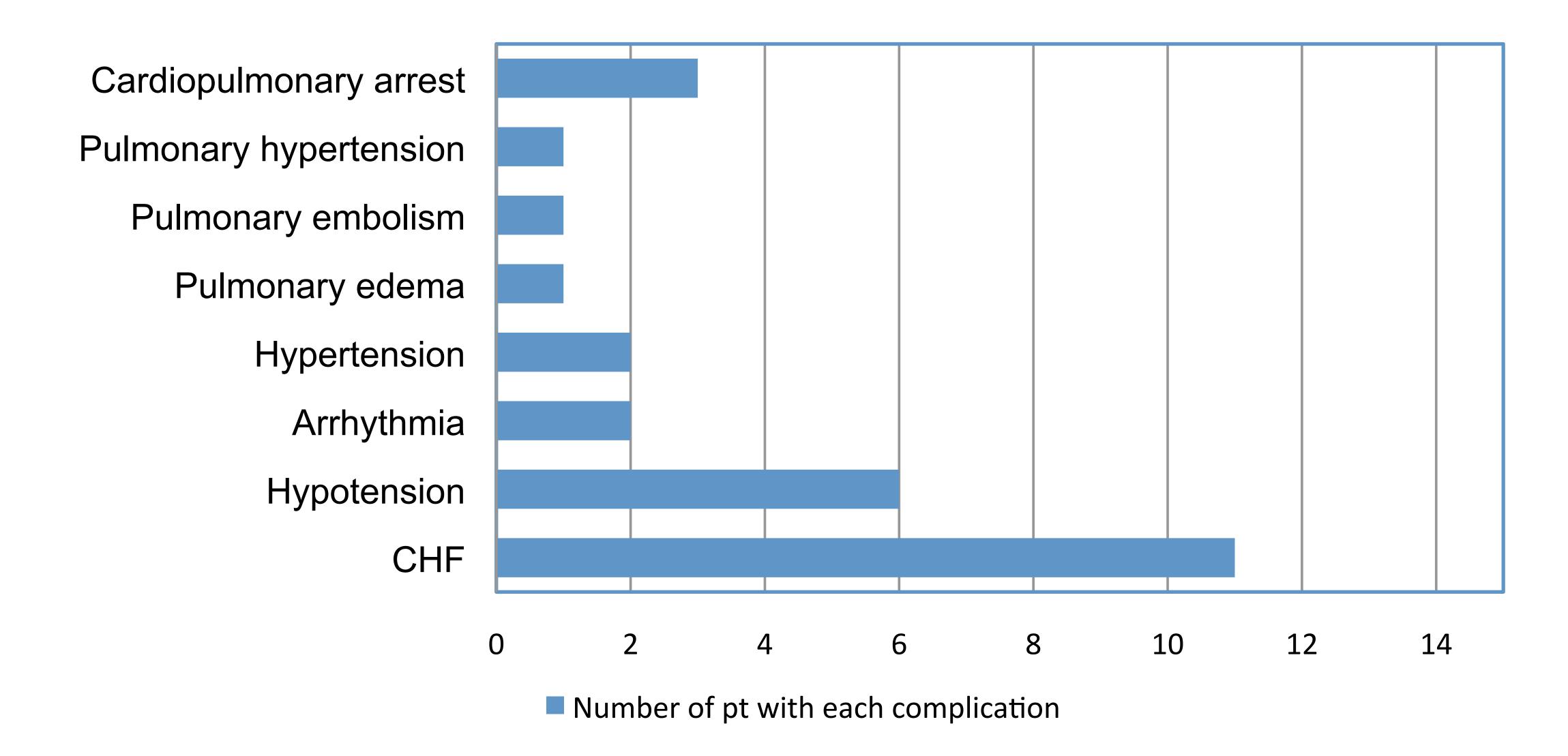


Figure 3: Effect of CFZ on BNP levels before and during treatment

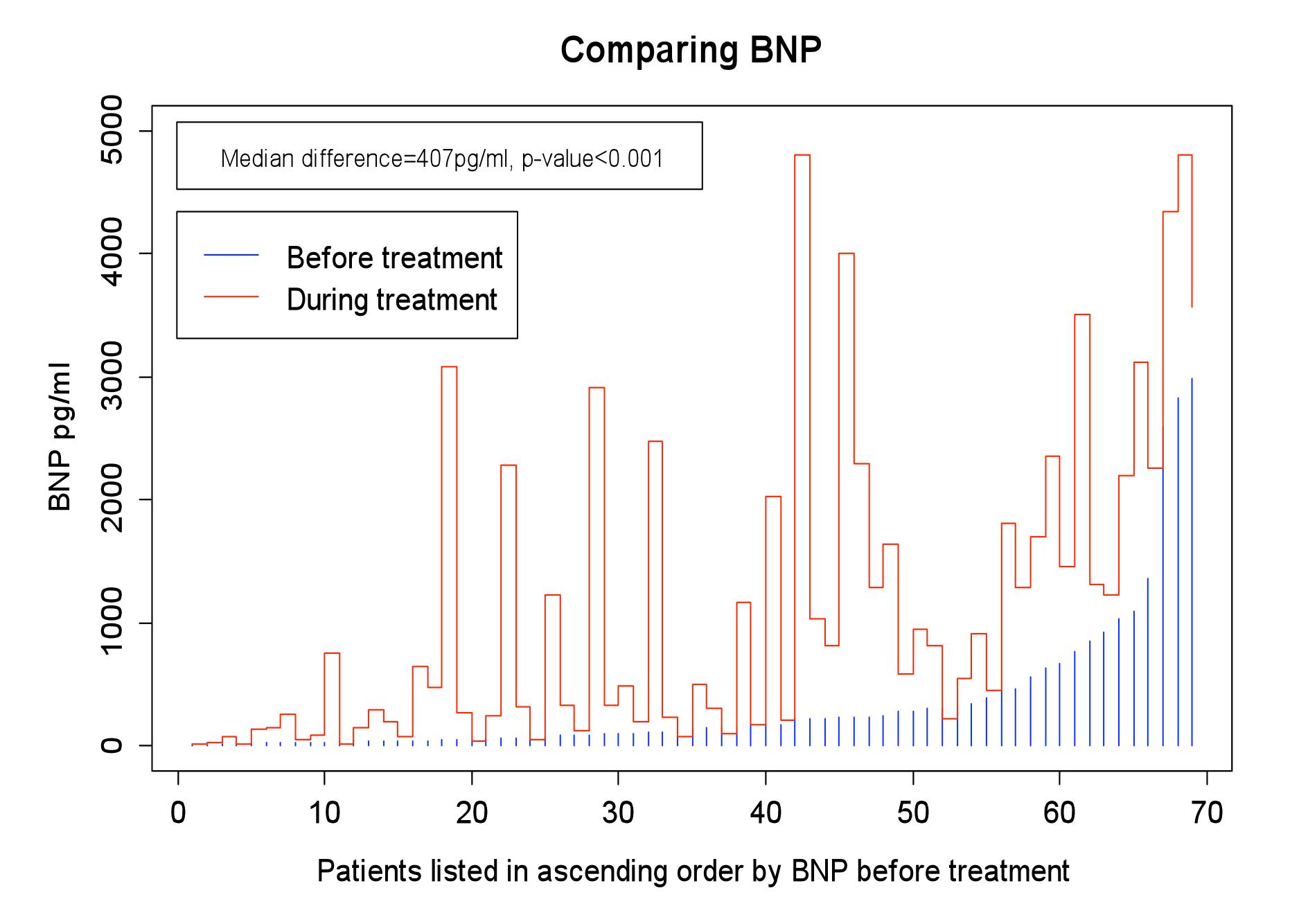


Table 1. Correlation between hospital admissions for cardiovascular (CV) complications and change in BNP >400 pg/ml (baseline BNP – during treatment BNP).

BNP is done with Unicel DXI 800 Beckman Coulter, INC. triage CALIBERATORS Cat. NO. 33345:S0-S5

	Admitted for severe CV complications	Not admitted for severe CV complications
Change BNP>400	11	22
Change BNP≤400	5	31

There is a correlation between BNP elevation of more than 400 pg/ml and hospital admissions for CV complications. Simple chi-square test p = 0.056

