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A Trivariate Weibull Model For Effects of Drospirenone and Estrogen in Postmenopausal Women with Hypertension

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Abstract

The usage of weibull distribution is wide in parametric analysis of failure time data. The simple form of the weibull survivor function is an attractive property for right-censored observation which occurs frequently in survival studies. The corresponding hazard rate which increases, constant or decrease according to the value of one parameter. This behavior is commonly accepted as appropriate in many situation. In the application part, Drospirenone (DRSP), a progestin with antialdosterone activity, had been developed for hormone therapy in combination with 17-β-estradiol(E2) in postmenopausal women. The antihypertensive efficacy and safety of various doses of DRSP and E2 and estradiol alone in postmenopausal women with hypertension using ambulatory and clinic blood pressure (BP) monitoring is evaluated. In conclusion the mathematical model we constructed support the medical result that DRSP combined with E2 significantly reduces BP in postmenopausal women with hypertension and did not induce significant increases in serum potassium. These characteristics may lead to a new benefit for this novel hormone therapy in postmenopausal women with hypertension

INTRODUCTION

Weibull models are used to describe various types of observed failures of components and phenomena. They are widely used in reliability and survival analysis. In addition to the traditional two-parameter and three-parameter Weibull distributions in the reliability or statistics literature, many other Weibull-related distributions are available. The Weibull distribution is widely used for the parametric analysis of failure time data. For right - censored observations, which occur frequently in survival studies, the simple form of the Weibull survivor function is an attractive property. It also has a hazard rate, increasing, constant or decreasing according to the value of one parameter, and this behavior is commonly accepted as appropriate in many situations, though not all **[2].** In certain circumstances an argument can be made out for believing that the distribution of survival times really should be Weibull [**14,15**]. For multivariate failure time data the same considerations apply and it would be useful to have a multivariate Weibull distribution with simple, interpretable and flexible application. Several mültivariate exponential distributions have been proposed by Johnson & Kotz and we can obtain a corresponding multivariate Weibull distribution by power transformation of the individual variates [**6**]. However, each of these distributions has at least one disadvantage for practical application to failure time data. Gumbel proposed two bivariate exponentials which have rather restricted ranges of values [**5**]. Marshall & Olkin's multivariate exponential is a singular distribution with non - zero probability concentrated on a certain subspace **[11].** The other distributions described by Johnson & Kotz either do not have exponential marginals or have complicated forms for the density and survivor functions [**6**]. Clayton and Cusick's bivariate proportional hazards models are very general but do not allow negative association [**3**]. The form of multivariate distribution proposed here is with basic properties and behavior [**8**].

MATHEMATICAL MODEL

Trivarite Weibull Distribution:

Lu & Bhattacharyya [**10**] developed a joint survival function by letting $h_1(x)$ and $h_2(y)$ be two arbitrary failure rate functions on [0, ∞), and $H_1(x)$ and $H_2(y)$ be their corresponding cumulative failure rate. Given the stress $S = s > 0$, the joint survival function conditioned on *s,* as they defined, is

$$\bar{F}(x, y/s) = \exp\{-[H_1(x) + H_2(y)]^{\gamma} s\},$$

where γ measures the conditional association of X and Y. Further, based on the joint survival function, they proved a theorem that a bivariate survival function $\bar{F}$(x, y/s) can be derived with the marginals

$\bar{F}_x$ and $\bar{F}_y$ given the assumption that the Laplace transform of the stress S exists on [0, ∞) and is strictly decreasing.

From the theorem, they derived a bivariate Weibull Distribution

$$\bar{F}(x, y/s) = exp\left\{-\left[\left(\frac{x}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}}\right]\right\}$$

Where $0 < \alpha \leq 1, 0 < \lambda_1, \lambda_2 < \infty, 0 < \gamma_1, \gamma_2 < \infty$

Following the same steps, the theorem can be expanded to more than to random variables, and therefore, a multivariate survival function of Weibull distribution is constructed as

$$S(x_1, x_2, \ldots . x_n) = exp\left\{-\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \cdots + \left(\frac{x_n}{\lambda_n}\right)^{\frac{\gamma_n}{\alpha}}\right]^{\alpha}\right\}$$

Where α measures the association among the variables, $0 \leq \alpha < 1$, and $0< \lambda_1, \lambda_2, \ldots . \lambda_n < \infty$, and $0 < \gamma_1, \gamma_2, .. \gamma_n < \infty$

Probability Density Function of the Multivariate Weibull Distribution

The bivariate probability density function of a multivariate distribution function can be obtained by differentiating the multivariate survival function with respect to each variable. Li [**9**], and Yi and Weng [**24**] had shown that

$$f(x_1, x_2, \ldots . , x_n) = (-1)^n \frac{\partial^n S(x_1, x_2, \ldots . , x_n)}{\partial x_1 \partial x_2 \ldots . \partial x_n}$$

Using Li's derivation and one of the special cases of the multivariate Faa di Bruno formula by Constantine and Savits [**4**], the probability density function is

$$f(x_1, x_2, \ldots . , x_n) = \left(\frac{-1}{\alpha}\right) exp\left\{-\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \cdots + \left(\frac{x_n}{\lambda_n}\right)^{\frac{\gamma_n}{\alpha}}\right]\right\}$$

$$\left[\left(\frac{\gamma_1}{\lambda_1}\right)\left(\frac{\gamma_2}{\lambda_2}\right) \ldots . \left(\frac{\gamma_n}{\lambda_n}\right)\right]\left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}-1} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}-1} + \cdots + \left(\frac{x_n}{\lambda_n}\right)^{\frac{\gamma_n}{\alpha}-1}\right]$$

$$\sum_{i=1}^{p(n)} \left\{(-1)^{k_i} P_S(n,i) \left(\prod_{i=1}^{n} \alpha \underline{n_j} \left[\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \cdots + \left(\frac{x_n}{\lambda_n}\right)^{\frac{\gamma_n}{\alpha}}\right]^{k_i \alpha - n}\right)\right\}$$

Where k_i is the number of summands of the i th partition of n such that $n_1 + n_2 + \cdots + n_{ki} = n, n_1 \geq n_2 \geq \cdots n_{ki} > 0, 1 \leq k_i \leq n$: $\alpha \underline{n_j}$ is equal to $(\propto -1)$ $\ldots . \left(\alpha - n_j + 1\right)$, the falling factorial of α; $P(n)$ is the total number of set partitions of the set $S_n = \{1, \ldots n\}$ corresponding to the i th partition of n.

PDF of trivariate Weibull is

$$f(x_1, x_2, x_3) = (-1)^3 \frac{\partial^3 S(x_1, x_2, x_3)}{\partial x_1 \partial x_2 \partial x_3}$$

$$= \frac{\gamma_1 \gamma_2 \gamma_3}{\alpha^2 x_1, x_2, x_3} exp\left(-\left(\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right)^{\alpha}\right)$$

$$\text{x} \left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}} \left(\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right)^{-3+\alpha}$$

$$\text{x}\left\{2 + 3\alpha\left(-1 + \left(\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right)^{\alpha} + \alpha^2\left(1 - 3\left(\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right)^{\alpha} + \left(\left(\frac{x_1}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_2}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_3}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right)^{2\alpha}\right)\right\}$$

Let n denote the number of observations, then, the log – likelihood function becomes

$$\sum_{i=1}^{n} \log\left(f(x_1, x_2, x_3)\right)$$

$$\sum_{i=1}^{n} log\left(\frac{\gamma_1 \gamma_2 \gamma_3}{\alpha^2 x_1, x_2, x_3}\right) - \sum_{i=1}^{n} -\left(\left(\frac{x_{1i}}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_{2i}}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_{3i}}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right)^{\alpha}$$

$$+ \sum_{i=1}^{n} log\left(\left(\frac{x_{1i}}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_{2i}}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_{3i}}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}} \left(\left(\frac{x_{1i}}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_{2i}}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_{3i}}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right)^{-3+\alpha}\right)$$

$$+ \sum_{i=1}^{n} log\left(2 + 3\alpha\left(-1 + \left(\frac{x_{1i}}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_{2i}}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_{3i}}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right)^{\alpha}\right)$$

$$+ \alpha^2\left(1 - 3\left(\left(\frac{x_{1i}}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_{2i}}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_{3i}}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right)^{\alpha} + \left(\left(\frac{x_{1i}}{\lambda_1}\right)^{\frac{\gamma_1}{\alpha}} + \left(\frac{x_{2i}}{\lambda_2}\right)^{\frac{\gamma_2}{\alpha}} + \left(\frac{x_{3i}}{\lambda_3}\right)^{\frac{\gamma_3}{\alpha}}\right)^{2\alpha}\right)$$

APPLICATION

Introduction

Drospirenone (DRSP) is a novel progestin with antialdosterone effects that, in combination with 17-β-estradiol (E2), has been developed for use in postmenopausal women as a hormone therapy[**7,12,13**] The combination DRSP/E2 was approved for estrogen deficiency symptoms in postmenopausal women. During its development for relief of menopausal symptoms, DRSP/E2 was shown to have significant antihypertensive effects in studies of postmenopausal, hypertensive women alone or in combination with enalapril[**16,17,21**]. Furthermore, DRSP/E2 was found to have a significant antihypertensive effect in patients with and without type 2 diabetes mellitus and concomitant use of angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists[**17**]. When compared with other hormone therapies and oral contraceptives, DRSP results in a significantly greater increase in plasma aldosterone[**7,12,13]** in response to the antialdosterone effect of the compound. The primary objective of this study was to determine whether this new hormone therapy has clinically significant effects on 24-hour ambulatory and clinic blood pressure (BP) in a large population of hypertensive postmenopausal women using varying doses of 1 mg DSRP with E2 compared with placebo.The reductions in clinic BP were significantly greater on 2- and 3-mg DRSP/E2 compared with placebo at the end of the study, whereas changes from baseline for 1-mg DRSP/E2 and E2 alone were similar to placebo. Reductions in BP occurred at 4 weeks of DRSP/E2 therapy and stabilized by 6 weeks of therapy (**Figure 1**). At the end of the study, the mean reductions in clinic BP in the 3- and 2-mg DSRP/E2 groups averaged −13.8/−8.5 mm Hg and −12.1/−9.2 mm Hg respectively, whereas the reductions for placebo were −8.7/−5.0 mm. The changes from baseline in heart rate were similar for DRSP/E2 and placebo.

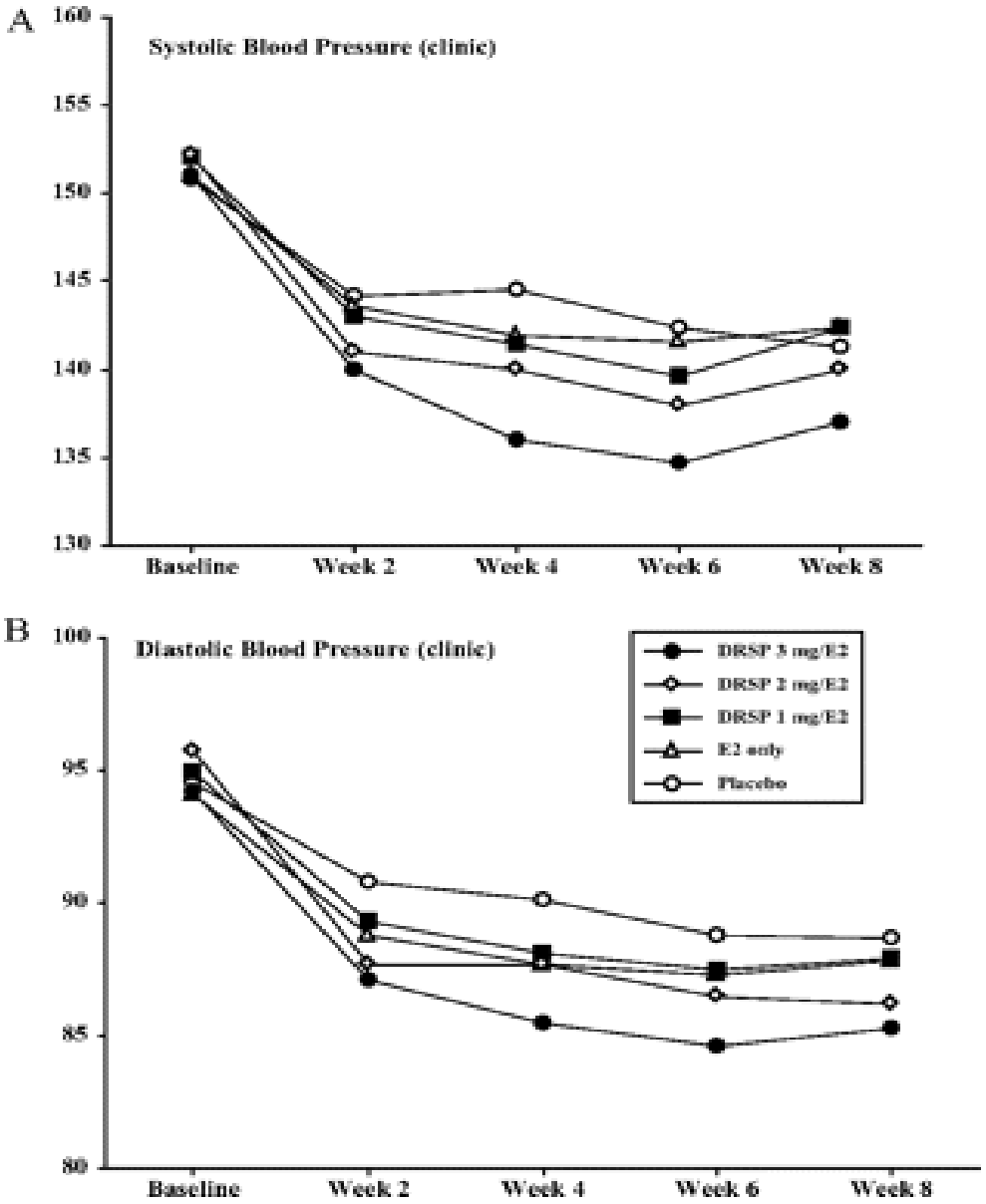


Figure 1. Effects of DRSP/E2 vs placebo on clinic BP after 8 weeks of double-blind therapy. A is changes in systolic BP and B is changes in the diastolic BP. Changes from baseline were significant for the 3- and 2-mg DRSP/E2 groups only (systolic BP, P=0.0004 and 0.0195 for 3- and 2-mg DRSP/E2 groups, respectively; diastolic BP, P<0.001 for both 3- and 2-mg groups).

The mean changes from baseline in the 24-hour ambulatory BPs are shown in **Figure 2**. Significant reductions from baseline in the coprimary end point of mean 24-hour systolic BP were observed in the 2- and 3-mg DRSP/E2 treatment group compared with placebo. In contrast, there were no differences in ambulatory BP for 1-mg DRSP/E2 and E2 alone versus placebo. As shown in the 24-hour curves of the systolic BP in **Figure 2**, the reductions in systolic BP were greater as the dose of DRSP increased and persisted for all 24 hours of the dosing period. Less pronounced dose-related reductions in 24-hour diastolic BP were observed on DRSP/E2 compared with E2 alone or with placebo.

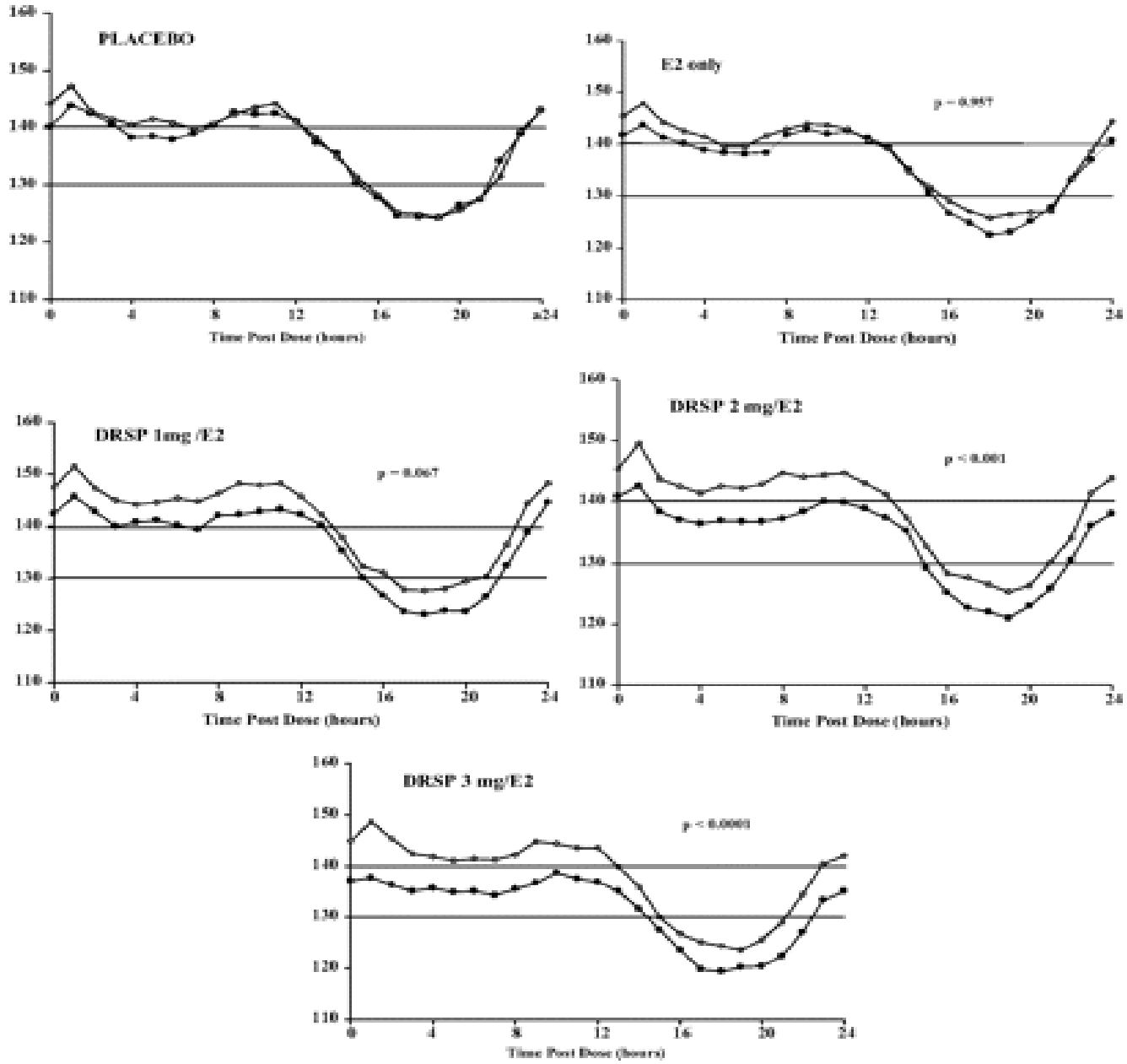


Figure 2. Effects of DRSP/E2 vs placebo on the co-primary end point of ambulatory systolic BP over 24 h ours at baseline and after 8 weeks of double-blind therapy that included placebo, E2 alone, 1-mg DRSP/E2, 2-mg DRSP/E2, and 3-mg DRSP/E2. Baseline period is the ○, —, and treatment period is the •, —.

Five patients in each of the 3 DRSP/E2 groups and 5 patients in the placebo group developed a serum potassium of ≥5.5 meq/L. The mean maximal change from baseline in the DRSP group was not significantly different for the 5 treatment groups and ranged between 0.29 meq/L and 0.37 meq/L (*P*=0.48). In addition to no differences in the proportion of patients developing predefined hyperkalemia (> 5.5 meq/L), there were also no differences for ≥1 increase of serum potassium between >0.5 meq and <1.0 meq as noted here: 3 mg DRSP/E2: n=44 (29.1%); 2 mg DRSP/E2: n=45 (30.2%); 1 mg DRSP/E2: n=25 (16.6%); 1 mg E2: n=41 (27.3%); and placebo: n=43 (29.3%).

Reductions in total and low-density lipoprotein cholesterol were significantly greater with all of these active treatment groups compared with placebo, with the largest reduction on 3-mg DRSP/E2. There were no changes in serum triglycerides in any of the treatment groups. There were mixed findings for the high-density lipoprotein cholesterol. Dose-related increases in the serum aldosterone concentrations were observed on 2- and 3-mg DRSP/E2.

First of all, all subgroups showed significantly differential conditioning in men or in women, as compared to their respective control groups. The survival functions for corresponding values of E2, DRSP1, DRSP2, DRSP3 combined with E2 functions for placebo and cortisol have been found.

Clinic and Ambulatory BP

As shown in **Figure 1**, DRSP/E2 lowered both the clinic and 24-hour ambulatory BPs significantly compared with placebo, whereas E2 alone had no effect on BP levels. There was evidence of a dose-related reduction in both types of BP measurements, although the most distinct relationship was for the 24-hour systolic BP. The antihypertensive effect of DRSP/E2 becomes significant with 2-mg DRSP but the higher dose (3-mg DRSP) yielded more consistent and larger decreases in both clinic and 24-hour BP (**Figure 2**).

The level of ambulatory BP reductions observed in this study is comparable to many other antihypertensive agents, including the selective aldosterone blocker eplerenone[**20**]. For example, the placebo-subtracted mean reduction from baseline in 24-hour BP on eplerenone was &7/4 mm Hg for the 50-mg dose, a value similar to what was observed with the 3-mg dose of DRSP both in the present study (**Figure 2**) and in our preliminary study with DRSP/E2 [**21**]. In addition, Preston et al[**16**] reported that 3-mg DRSP/E2 lowered 24-hour ambulatory BP by 9/5 mm Hg when the drug was added to enalapril after just 2 weeks of therapy. As in our present study, these reductions in BP **are** associated with increases in aldosterone by &3 ng/dL (40% above baseline), attesting to the pharmacological effect of DRSP in blocking the mineral corticoid receptor. Reductions from baseline in the clinic BP versus reductions in the 24-hour ambulatory BP for DRSP/E2 are variable. Differential effects for clinic and ambulatory BP measurements are commonly observed in antihypertensive therapy trials, but typically the mean reduction in ambulatory pressures in clinical trials is &40% less than the average reduction in the clinic BP[**21**]. In the present trial, there is a fairly large BP reduction in the placebo group for both the clinic systolic and diastolic pressure (−8.6/−5.0 mm Hg), which are attributable in part to both observer bias and in part to regression to the mean [**22**].

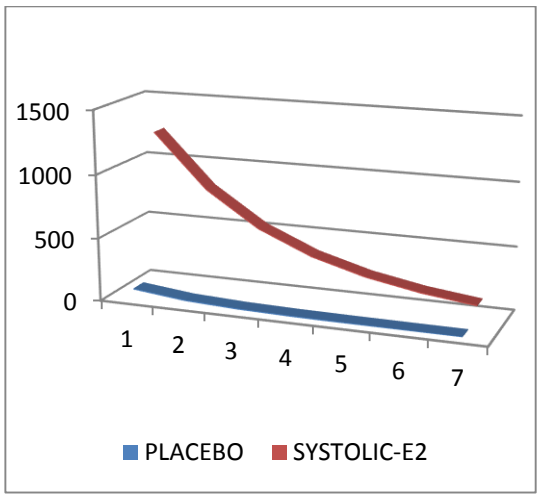
Because each treatment group had between 119 and 129 patients who underwent ambulatory BP recordings, the findings for those data are exceedingly robust and, unlike the clinic BP measurements, show that 2 of 3 doses of DRSP/E2 have antihypertensive activity (**Figure 2**) and that a dose-related response occurs among the 3 doses tested in our study. Finally, it appears that the antihypertensive effect of DRSP/E2 is attributable primarily to the effects of DRSP, because E2 alone did not induce any reduction in either clinic or ambulatory BP. Alternatively, there may be synergism between DRSP and E2.

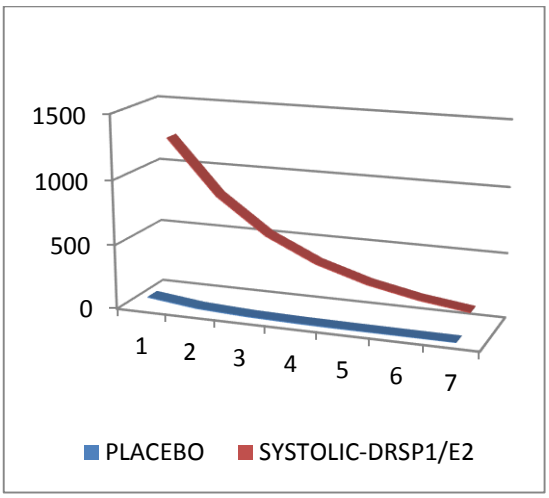
Conclusions provided in biological system

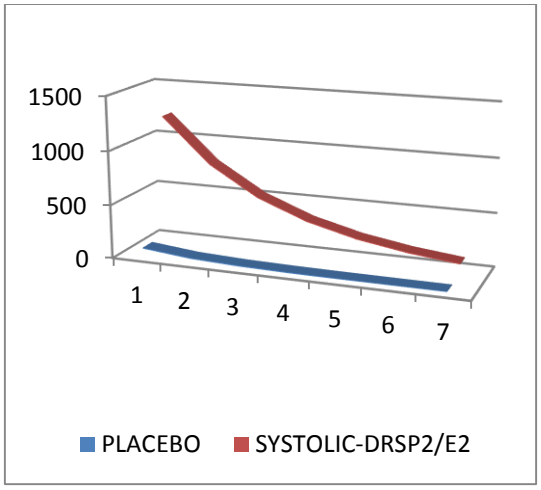
The study demonstrated that DRSP/E2, a new hormone therapy with aldosterone blocking activity, was effective in reducing ambulatory systolic and diastolic BP with dose-related reductions between 1 and 3 mg of DRSP. The 2-mg DRSP is the lowest effective dose that provided significant and adequate BP reduction in postmenopausal hypertensive women. The hormone therapy was well tolerated for the 2-month period with modest subjective or objective adverse events. Because reduction of systolic BP of the magnitude observed in our study has significant implications in postmenopausal women with hypertension,[**18,19,23**] especially for reducing stroke and heart failure, DRSP/E2 may have an advantage for the treatment of menopausal symptoms over conventional progestins. Future studies designed to evaluate the longer-term (ie,≥ 2 years) cardiovascular effects associated with these significant antihypertensive effects of DRSP/E2 might be warranted at this time.

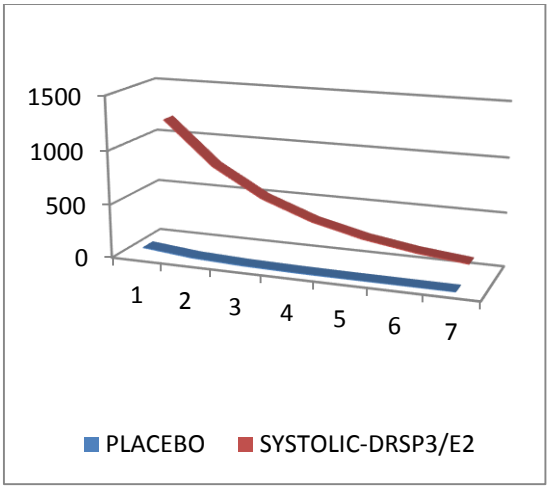
RESULTS

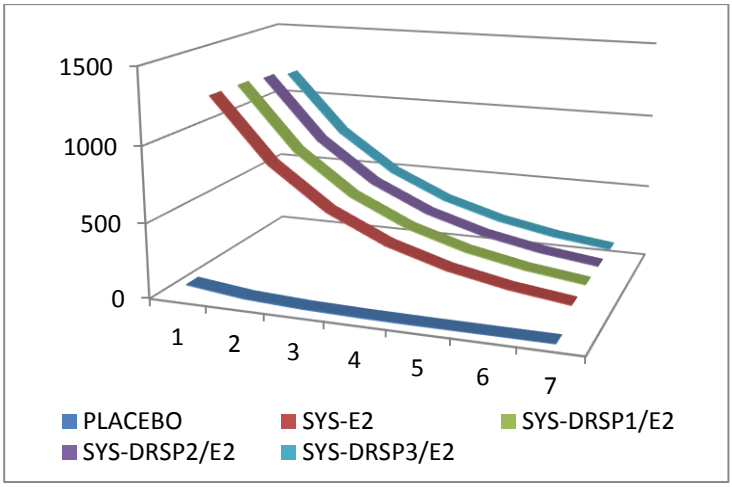
Estrogen's Effect on Diastolic Blood pressure combined with DRSP



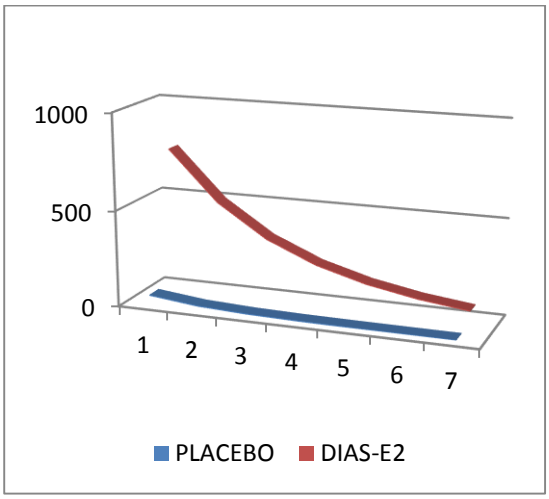


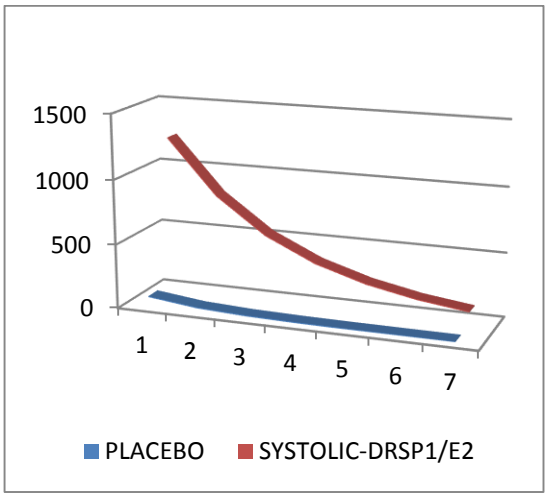


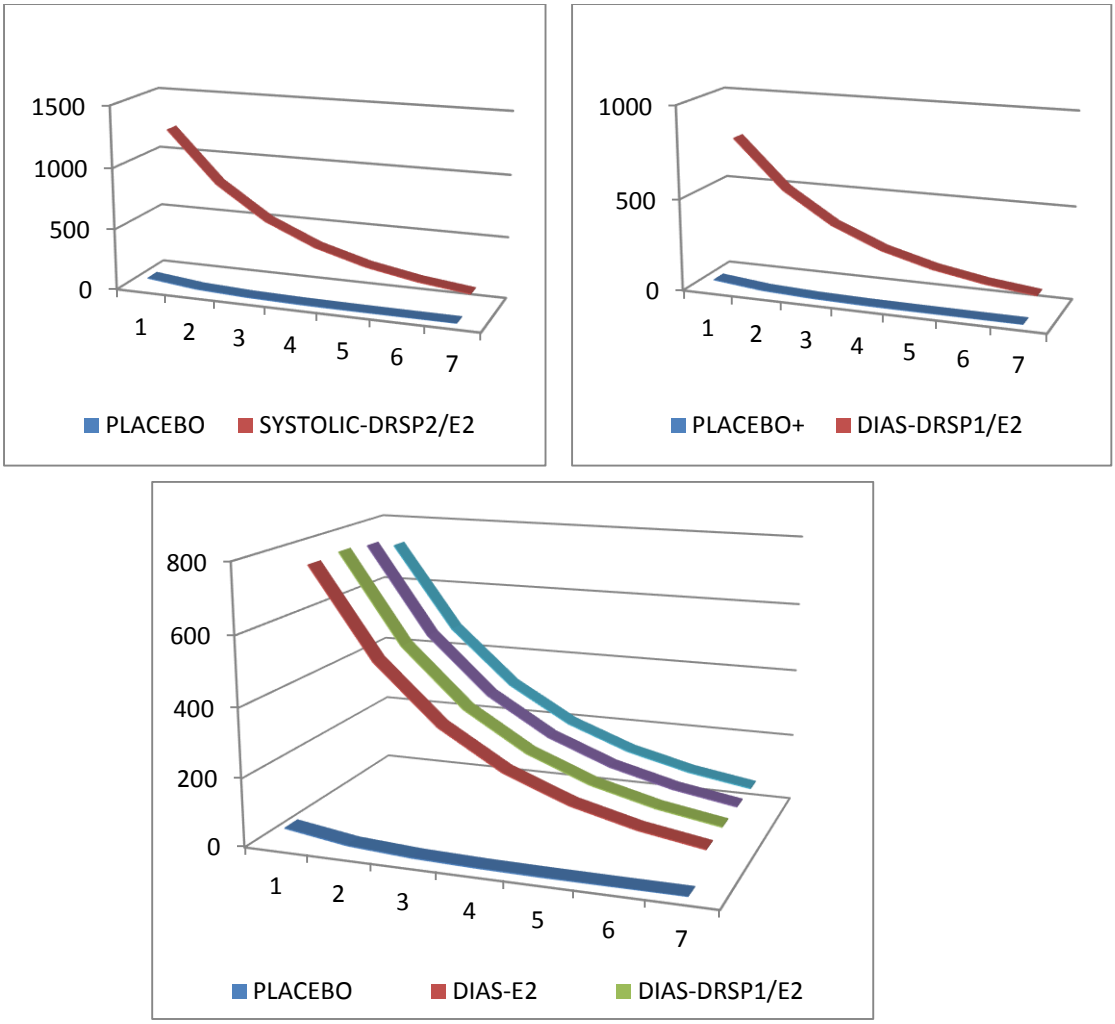




Estrogen's Effect on Diastolic Blood pressure combined with DRSP







CONCLUSION

In section 4, we have developed mathematical curves which show the declining effect of DRSP with E2 over the week time period. In particular, all the dosages of DRSP with E2 are compared with placebo which are significant in toto. It reaches the X-axis declined towards the time period which shows that blood pressure reduces until the 5^{th} week and stabilizes over the 6^{th} and 7^{th} week period. In conclusion the mathematical model we constructed supports the medical result that DRSP combined with E2 significantly reduces BP in postmenopausal women with hypertension and did not induce significant increases in serum potassium. These characteristics may lead to a new benefit for this novel hormone therapy in postmenopausal women with hypertension

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