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Scientific Update™

Combining Different Risk Interventions into a Single Formulation Contribute to Improved Cardiovascular Disease Risk Reduction: Preliminary Results of the JEWEL Program

Originally presented by: FDR Hobbs, MD; G. Gensini, MD; GBJ Mancini, MD; AJ Manolis, MD; B. Bauer, PhD; S Böhler, MD; J. Genest, MD; R. Feldman, MD; P. Harvey, MD; TG Jenssen, MD; M. Metcalfe, MD; and P. Marques da Silva, MD

A Discussion and Analysis of a moderated Poster Presentation at the American Society of Hypertension 21st Annual Scientific Meeting and Exposition

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By GORDON MOE, MD

A great number of the patients encountered in clinical practice have more than one condition contributing to their global risk of cardiovascular disease (CVD). Up to 50% of those presenting with hypertension also have dyslipidemia. Despite the presence and widespread implementation of treatment guidelines, many patients still receive suboptimal therapy and are not treated to recommended therapeutic targets. Poor adherence to multiple therapeutic agents may account, in part, for the treatment gaps. Accordingly, a single-pill combination therapy, designed to treat hypertension and additional risk factors, may address this issue. The JEWEL program was designed to evaluate the efficacy of a single-pill combination in controlling hypertension and dyslipidemia in a clinical practice setting. In this issue of *Cardiology Scientific Update,* the preliminary results of the JEWEL program and their clinical implications are discussed.

Cardiovascular (CV) risk factors rarely occur in isolation and many patients present with a combination of conditions that contribute to their overall risk of CVD.[1] Hypertension and dyslipidemia are 2 of the most common concurrent CV risk factors. Indeed, >50% of patients with hypertension are also known to have dyslipidemia.[2] Prevention guidelines from Canada, the United States, and Europe all underscore the need for a global approach towards assessment of a patient's risk of morbidity and mortality from CVD.[3-5] However, despite the availability and implementation of these guidelines, many patients continue to receive suboptimal therapy and are not treated to locally recommended therapeutic targets.[6,7] One important mechanism underlying suboptimal therapy is poor adherence related to the frequent need for multiple classes of pharmacologic agents.[8] Accordingly, a single-pill combination therapeutic strategy, aimed at treating hypertension and additional risk factors such as dyslipidemia, may be an effective way to address the needs of patients with multiple risk factors. A single pill combining the calcium channel blocker (CCB), amlodipine besylate, and the HMG CoA-reductase inhibitor, atorvastatin calcium, has been developed[9] and approved for clinical use in Canada and other countries. The efficacy and safety of this single-pill combination has recently been demonstrated in the United States.[9] The JEWEL Program was, therefore, designed to evaluate the single-pill combination in Canada, the United Kingdom (UK), and Europe.[10]

The JEWEL program

The rationale and the detailed methodology of the JEWEL program was published recently.[10] In brief, the primary objective of the program was to assess the effectiveness of single-pill amlodipine/atorvastatin therapy by assessing the percent of patients who reached blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) levels as defined by local governing guidelines (Table 1). Additional objectives included an assessment of the percent of patients reaching BP and LDL-C goals separately, effects on BP and lipids, safety, and the patients' view on the single-pill, dual therapy approach using a newly developed questionnaire. Patients were recruited if they were:

- treated or untreated individuals diagnosed with concurrent hypertension (uncontrolled) and dyslipidemia (controlled or uncontrolled), qualifying for drug treatment according to governing guidelines

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

Table 1: Recommended BP and LDL-C goals according to: A. European guidelines;[4] B. Canadian guidelines;[11] C. UK Guidelines[12]

A. European treatment targets

Patient's level of CV risk	BP goal	LDL-C goal*
Patients without diabetes	<140/90 mm Hg	
Patients with diabetes	<130/80 mm Hg	
High risk Established CV disease or diabetes		<2.5 mmol/L
Moderate risk (Asymptomatic patients with total risk remaining ≥5%† over 10 years despite lifestyle advice)		<2.5 mmol/L
Low risk In general		<3 mmol/L

B. Canadian treatment targets

Patient's level of CV risk	BP goal	LDL-C goal§‡
Patients without diabetes	<140/90 mm Hg	
Patients with diabetes	<130/80 mm Hg	
High risk (10-year risk** ≥20%, diabetes or any atherosclerotic disease)		<2.5 mmol/L (TC/HDL-C <4.0 mmol/L)
Moderate risk (10-year risk** 11%-19%)		<3.5 mmol/L (TC/HDL-C <5.0 mmol/L)
Low risk (10-year risk** ≤10 %)		<4.5 mmol/L (TC/HDL-C <6.0 mmol/L)

C. UK treatment targets††

Patient's level of CV risk		BP goal	LDL-C goal
Patients without diabetes	Target	<140/85 mm Hg	<2.0 mmol/L
	Audit standard	<150/90 mm Hg	<3.0 mmol/L
Patients with diabetes	Target	<130/80 mm Hg	<2.0 mmol/L
	Audit standard	<140/80 mm Hg	<3.0 mmol/L

TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; CHD = coronary heart disease.

* 10-year risk of absolute fatal CV disease for patients without diabetes should be determined using the SCORE chart as published from the SCORE project group].[13] The 'low risk chart' was used for the following countries: Belgium, France, Greece, Italy, Luxembourg, Spain, Switzerland and Portugal; the 'high risk' chart should be used in all other countries of Europe. Patients were then stratified into their respective treatment group based on the SCORE chart and history of diabetes or atherosclerotic disease and treated to the targets as specified.

† High fatal CV disease risk ≥15% over 10 years corresponds to the formerly used 20% absolute risk of a composite of CHD events.

§ For the purposes of this trial, the primary endpoint in Canada was the attainment of the LDL-C goal. TC/HDL-C ratio was a secondary endpoint.

‡ Subjects requiring a statin based on the CHEP 'ASCOT' criteria (i.e. those with elevated BP and risk factors that did not include LDL-C above threshold as delineated above)[11] were not included.

** 10-year risk of CHD for patients without diabetes was determined using the Framingham Study equations as published in the NCEP ATP III report.[14] Patients were then stratified into high, moderate or low risk based on Framingham risk score and history of diabetes or atherosclerotic disease and treated to the specified targets.

†† For the purposes of the trial, the primary endpoint in the UK was the Audit Standard BP/LDL-C level. However, titration of the amlodipine and atorvastatin component was based on target BP/LDL-C levels.

- receiving lipid-lowering and/or antihypertensive therapy at screening and receiving stable doses of medication for at least 6 weeks prior to baseline assessments.

Patients were excluded if they:

- had adequately controlled BP at baseline
- were receiving treatment with:
  - amlodipine and atorvastatin.
  - atorvastatin 80 mg and had LDL-C ≥ 2.6 mmol/L
- were treated with amlodipine 10 mg or another CCB at maximum dose.

The program consisted of two 16-week open-label, titration-to-goal studies in patients with hypertension and dyslipidemia. The two studies were similar in design, but differed with respect to country of enrolment; JEWEL 1 was in Canada and the UK, while JEWEL 2 was in Europe (in 11 countries). The 2 programs also had country-specific BP and LDL-C treatment targets (Table 1). The study design of the 2-week screening period and 16-week open-label phase and up-titration of the JEWEL 1 and JEWEL 2 studies are shown in Figure 1.

Eight different dosage strengths of single-pill amlodipine/atorvastatin therapy (5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80, 10/80 mg) were employed. The initial dosage was based on each patient's current level of BP and LDL-C control, and their BP and LDL-C lowering therapy at the time of screening (Table 2). Titration of doses was left to the discretion of the physicians, based on the individual country's guidelines (Table 1 and Figure 1). For the purposes of dosing, patients were categorized according to their treatment prior to study entry as follows:

Table 2: Amlodipine/atorvastatin single-pill dispensing guidelines at baseline

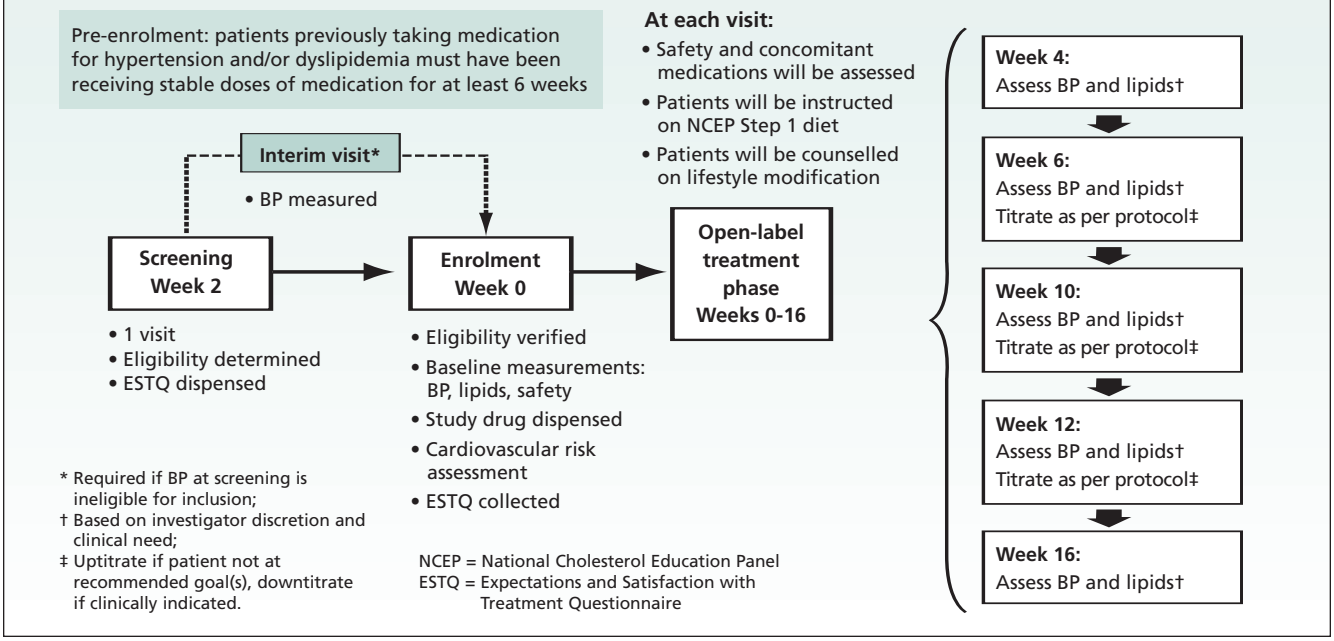
	Prior therapy	At goal	Not at goal
Blood pressure	Drug-naïve	Excluded from study	Initiate amlodipine 5 mg
	CCB users (not amlodipine)	Excluded from study	Switch to amlodipine 5 mg
	Amlodipine 5 mg	Excluded from study	Substitution with increased dose (amlodipine 10 mg)
	Amlodipine 10 mg or maximum dose of other CCB	Excluded from study	Excluded from study
	Non-CCB antihypertensive	Excluded from study	Add-on amlodipine 5 mg
Lipids	Drug-naïve	Excluded from study	Initiate atorvastatin 10-80 mg†
	Atorvastatin§	Substitution, same dose of atorvastatin	Substitution, increase atorvastatin dose to next dose level
	Other statins	Switch to atorvastatin (10-80 mg) at equivalent dose	Switch to atorvastatin at equivalent dose

CCB = calcium channel blocker; LDL-C = low-density lipoprotein cholesterol

† Atorvastatin dosage determined depending on the reduction in LDL-C required to reach target level.

§ Patients receiving atorvastatin 80 mg with LDL-C levels ≤2.5 mmol/L were excluded from the study.

Figure 1: Design of JEWEL 1 and JEWEL 2



- Substitution therapy– if they previously received amlodipine or atorvastatin.
- Switch therapy – If they were previously treated with another CCB and/or lipid-lowering therapy.
- Add-on therapy – If they were already taking non-CCB antihypertensive therapy.
- Drug-naïve: If they had no prior experience with antihypertensive and/or lipid-lowering medications.

Results of the JEWEL program

The preliminary results of the primary and selected secondary efficacy assessments have recently been presented. It should be noted, however, that these results have not yet been published and may be subject to modification. A total of 2245 patients (JEWEL 1, n = 1138 and JEWEL 2, n = 1107) were treated across the 2 studies. Over 90% were white and 58% were male. The initial and final doses of the amlodipine/atorvastatin single-pill are shown in Figure 2.

Results of the primary efficacy assessment on the intent-to-treat population are shown in Figure 3. Over 50% of the patients achieved country-specific or common goals. Based on the percentage of patients achieving both BP and lipid targets, a greater proportion of Canadian patients achieved target levels (55.6%) compared with UK patients (30.6%). It should be noted, however, that in the UK, although achieving "target" BP and lipid levels was the prespecified endpoint, practitioners may have been "operationally" geared towards achieving less rigorous "audit" levels. In Canada, there was no such differentiation between levels. Furthermore, the UK sites enrolled only high-risk patients; whereas, in Canada, all risk groups were included and patients were stratified and treated accordingly. Thus, on average, target cholesterol levels were lower in the UK and may have been more difficult to achieve.

The mean changes from baseline in BP and LDL-C levels are shown in Figure 4. Systolic and diastolic BP were reduced by averages of >20 and 10 mm Hg, respectively. LDL-C was

Figure 2: Initial and final dosages

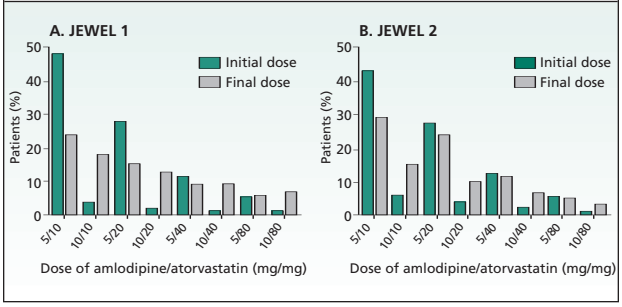


Figure 3: Primary efficacy assessment – Percentage of patients achieving both BP and LDL-C goals when A) country-specific, or B) common goals were employed

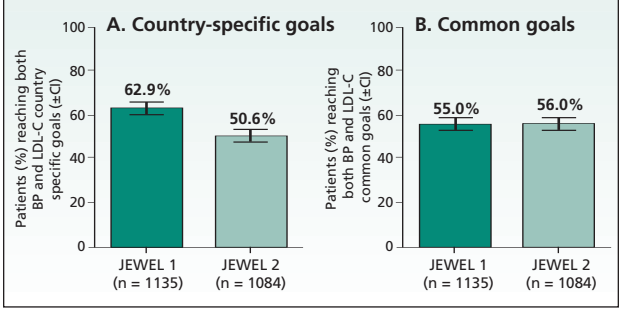
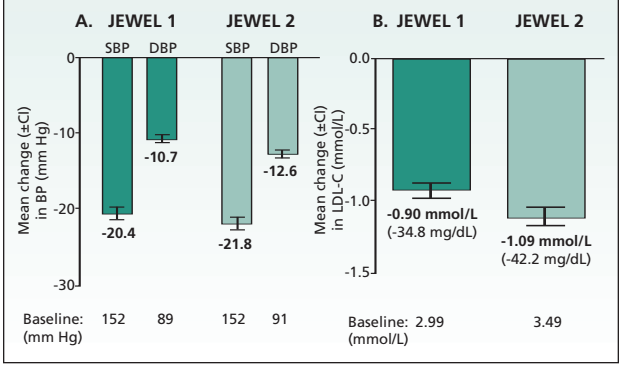


Figure 4: Mean changes from baseline in A) systolic and diastolic BP and B) LDL-C levels



reduced by >0.9 mmol/L. The percentages of patients that achieved BP targets were similar when stratified according to prior antihypertensive therapy.

Data on safety and tolerability are shown in Table 3. In the entire program, only 166 patients (7.4%) discontinued due to adverse events. A total of 704 patients (61.9%) had at least 1 treatment-emergent adverse event in JEWEL 1. The incidence in JEWEL 2 was much lower, with only 362 (32.7%) patients experiencing at least one adverse event. The most common adverse events (all causalities) were peripheral edema (11.0%), headache (2.9%), and joint swelling (2.9%).

Clinical implications

By using a novel, single-pill, dual treatment approach, a total of 62.9% and 50.6% of the patients in JEWEL 1 and JEWEL 2 programs, respectively, achieved both BP and LDL-C therapeutic goals as recommended by local treatment guidelines applicable to particular geographic regions. The results of the JEWEL program are, therefore, of important clinical relevance to practitioners in multiple countries.

The findings reported in the JEWEL program are consistent with those from an earlier study with a similar design that was conducted in the US.[9] In the US-based GEMINI study, a total of 1220 patients with uncontrolled hypertension at baseline received various doses of single-pill medications. At study end, 57.7% of patients had achieved both their BP and LDL-C goals. Both JEWEL and GEMINI demonstrated that co-administration of amlodipine and atorvastatin is well-tolerated. The JEWEL program is of sufficient sample size, that future subgroup analyses on patients (eg, those with diabetes and metabolic syndrome) will provide useful information regarding efficacy and safety in a particular subgroup. Finally, validation of the newly developed *Expectations and Satisfaction with Treatment Questionnaire* (ESTQ) that will likely be reported later will potentially provide valuable information on patients' attitudes and behaviours that may help to improve adherence.

Table 3: Treatment-emergent adverse events

Patients, n (%)	JEWEL 1	JEWEL 2
Patients evaluated for adverse events	1138	1107
Number of adverse events	1463	601
Patients with adverse events	704 (61.9)	362 (32.7)
Patients with serious adverse events	21 (1.8)	23 (2.1)
Patients discontinued due to adverse events	97 (8.5)	69 (6.2)

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