Potential Cardioprotective Effects of HM15275, a Novel Long-Acting GLP-1/GIP/GCG Triple Agonist, in Animal Models of Hypertension

798-P

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ABSTRACT

Introduction & Objective: Obesity is a major risk for development of cardiovascular disease (CVD). Both cardiac output and total blood volume are elevated in obesity, which eventually leads to cardiac hypertrophy and fibrosis. To date, therapeutic benefits of several incretin drugs were observed in cardiovascular outcomes trials. Based on these findings, the present study evaluates the cardioprotective effects of HM15275, a novel long-acting GLP-1/GIP/GCG triple agonist, in animal models of hypertension.

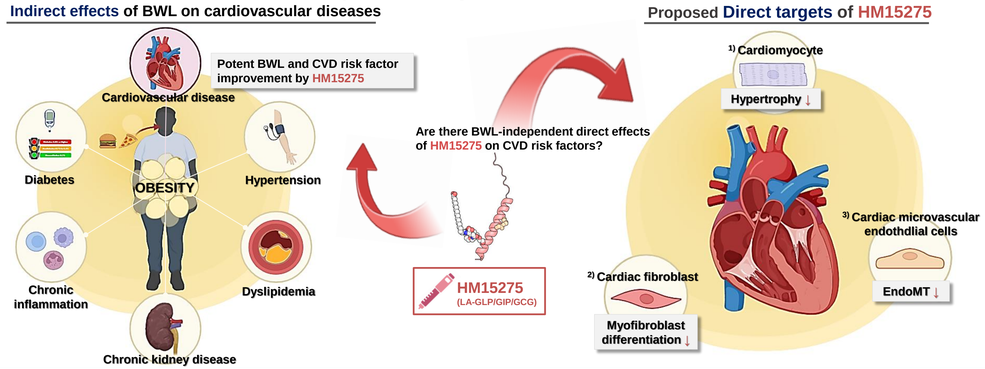
Methods: Spontaneously hypertensive rat (SHR) was administered with HM15275 for 16 weeks. In angiotensin II (Ang II)-infused mice and AMLN mice, HM15275 was administered for 2 ~ 6 weeks, followed by the determination of cardiomyocytes size, and cardiac fibrosis (MT staining, collagen levels). To highlight CV benefits of HM15275, tirzepatide (TZP) was included as comparative control.

Results: In SHR, cardiomyocytes cell size determined by WGA staining was significantly reduced by HM15275 treatment compared to TZP (-52.3% *vs.* TZP; p<0.001). In line with these results, both interstitial and perivascular fibrosis (% of extracellular collagen area using MT staining) were significantly improved by HM15275 treatment (-52.8% *vs.* TZP; p<0.001). In Ang II mice, the levels of pro-collagen-1α1 were significantly decreased by HM15275 in the heart (-40.5% *vs.* TZP; p<0.001). Moreover, cardiomyocyte enlargement caused by Ang II was significantly reduced by HM15275 treatment for 2 weeks. Similar benefits were also confirmed in AMLN mice.

Conclusion: Collectively, the results showed that HM15275 could have more potent cardioprotective effects than TZP in hypertension mediated cardiac damage. Further mechanistic studies are needed to elucidate the MoA for the beneficial effects of HM15275.

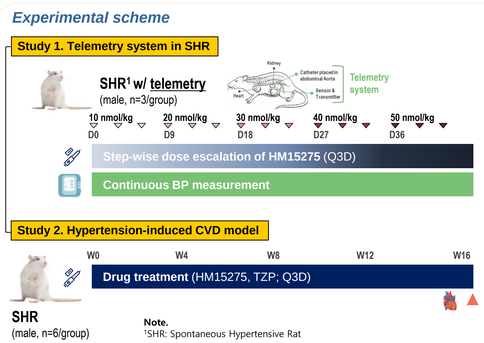
BACKGROUND

HM15275 could be an optimized treatment option for CVD management as it has the potential to act directly on heart tissue as well as to improve obesity-related metabolic risk factors with a potent BWL



METHODS

Experimental scheme

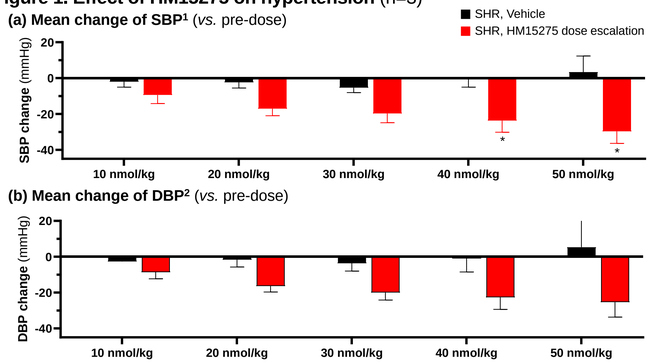


- Spontaneously hypertensive rat (SHR) is a genetic model of experimental hypertension.
- To evaluate BP lowering effect of HM15275, dose level of HM15275 was escalated step-wise manner (10, 20, 30, 40, 50 nmol/kg/Q3D) after implantation of a telemetry monitoring system into the abdominal aorta in SHR [Study 1].
- To evaluate therapeutic effect of HM15275 on hypertension-induced cardiac hypertrophy and fibrosis, HM15275 (or TZP) was administered for 16 weeks, followed by tissue analysis [Study 2].

RESULTS

Blood pressure lowering effect in SHR

Figure 1. Effect of HM15275 on hypertension (n=3)

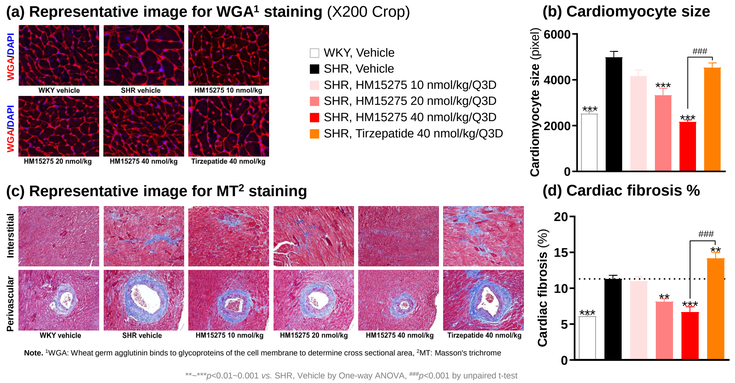


Note. [1]SBP: Systolic Blood Pressure, [2]DBP: Diastolic Blood Pressure *$p<0.05$ *vs.* SHR, Vehicle by One-way ANOVA

➢ In SHR, HM15175 treatment reduced both SBP and DBP in a dose-dependent manner

Cardiac protection effect (*vs.* tirzepatide) in SHR

Figure 2. Effect of HM15275 on cardiac hypertrophy and fibrosis (n=6)



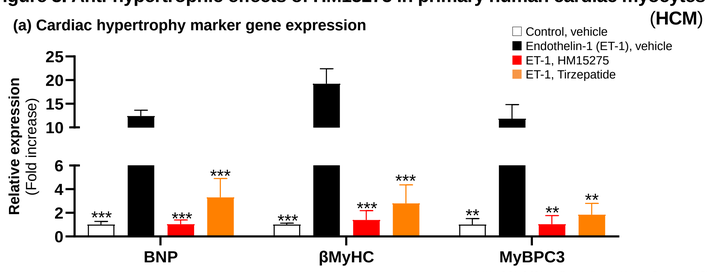
Note. [1]WGA: Wheat germ agglutinin binds to glycoproteins of the cell membrane to determine cross sectional area, [2]MT: Masson's trichrome

**$p<0.01–0.001$ *vs.* SHR, Vehicle by One-way ANOVA, ###$p<0.001$ by unpaired t-test

➢ In SHR, HM15275 effectively improved cardiac hypertrophy and perivascular and interstitial fibrosis, demonstrating therapeutic potential of HM15275 on CVD

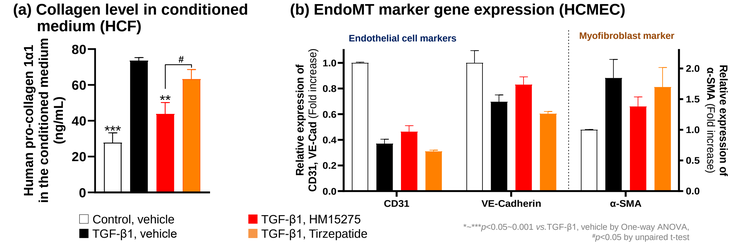
In vitro evidence for direct cardioprotective effects (*vs.* tirzepatide)

Figure 3. Anti-hypertrophic effects of HM15275 in primary human cardiac myocytes (HCM)



**$p<0.01–0.001$ *vs.* Endothelin-1, vehicle by One-way ANOVA

Figure 4. Anti-fibrotic effects of HM15275 in primary human cardiac fibroblast (HCF) and microvascular endothelial cell (HCMEC)



*~***$p<0.05–0.001$ *vs.* TGF-β1, vehicle by One-way ANOVA, *$p<0.05$ by unpaired t-test

➢ HM15275 not only prevented ET-1-induced human cardiomyocytes hypertrophy, but also TGF-β induced myofibroblast activation (FMT, EndoMT) in cardiac fibroblasts and endothelial cells, demonstrating the direct cardiac tissue improvement effect of HM15275

CONCLUSIONS

- **HM15275 has been confirmed to have excellent BWL efficacy in preclinical studies (please visit 776-P), which is expected to improve indirect cardiovascular disease**
- **HM15275 is efficacious for BP lowering and cardiac protection in SHR**
- **Notably, HM15275 treatment reduces human cardiomyocytes hypertrophy and myofibroblast activation, indicating direct cardioprotective effects of HM15275**
- **Similar benefits were also demonstrated in kidney tissue/function of SHR and animal models of heart failure (please visit 799-P and LB-1872)**
- **Both for *in vitro* and *in vivo* setting, more benefits of HM15275 were demonstrated compared to tirzepatide, demonstrating the essential role of glucagon engagement for direct tissue improvement effect**
- **Therefore, HM15275 might provide beneficial effects on CVD improvement in addition to obesity management, and the clinical relevance of these findings will be evaluated**

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