38. Investigation of Multitarget Therapy in Cancer Therapy-Related Cardiac Dysfunction by Using Murine Model

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Body

Background: Although the advances in the early diagnosis and therapies improved cancer treatment and patient outcomes over the years, cardiovascular disease risk has been increased in the cancer survivors, which might be due to the exposure to cardiotoxic-chemotherapeutic agents such as an anthracycline and immune/radiotherapy.

Recently, sodium-glucose cotransporter 2 inhibitor (SGLT2i) has proven cardiovascular protection in type 2 diabetes patients, while angiotensin receptor-neprilysin inhibitor (ARNI) has shown the efficacy for chronic heart failure (HF) patients. We hypothesized that concomitant therapy with SGLT2i and ARNI will attenuate the anthracycline-induced cardiac dysfunction.

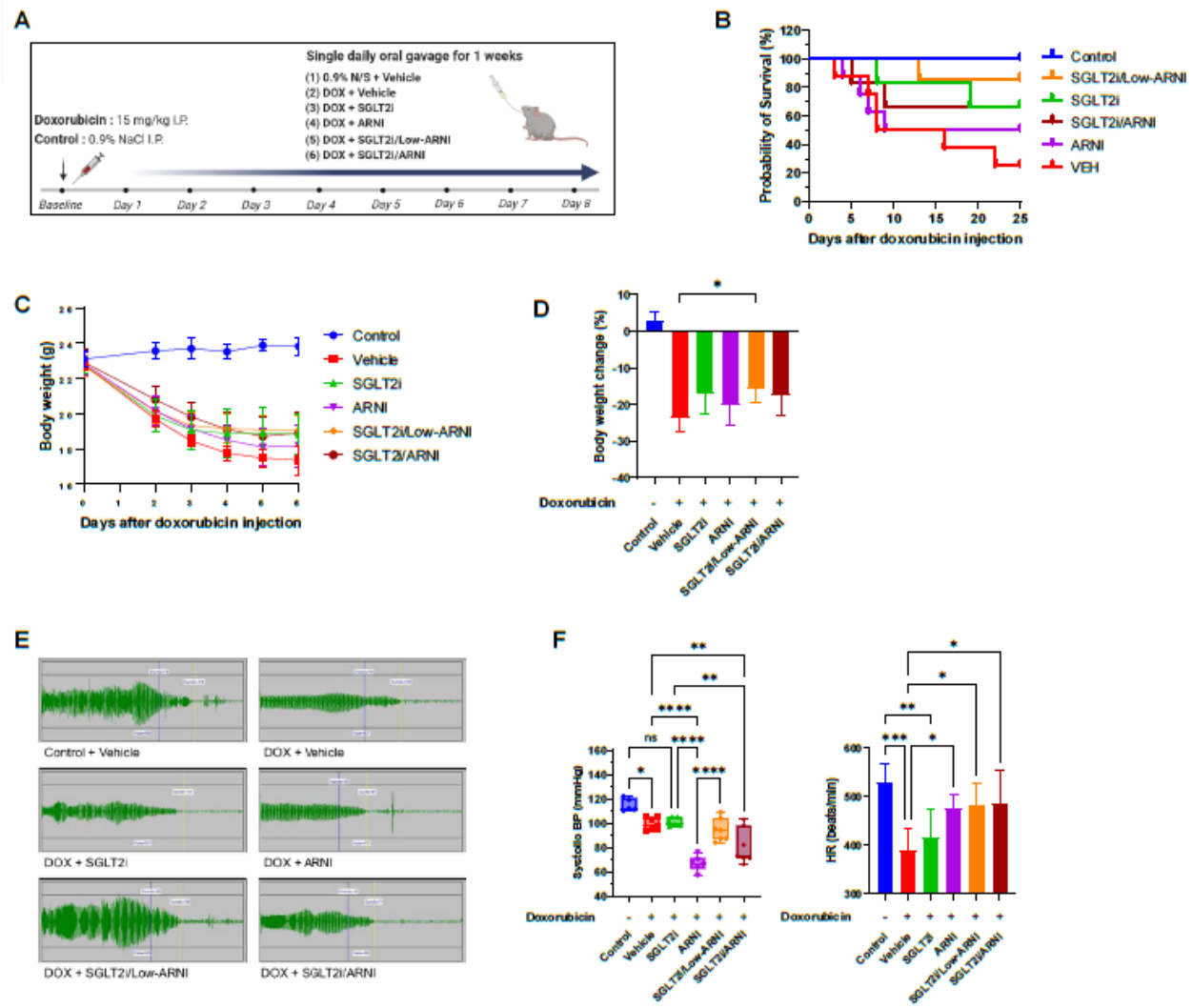
Methods: The acute and chronic doxorubicin (DOX) heart failure models were used to evaluate the potential efficacy of SGLT2i and ARNI combo-therapy on chemotherapy-induced cardiomyopathy.

For the acute DOX model, mice were administered a single dose of DOX (15mg/kg, i.p.), and for the chronic, six serial DOX (2.5mg/kg/dose, total 15mg/kg). Mice were then treated with oral gavage of the following drugs (vehicle, SGLT2i, ARNI, SGLT2i/Low-ARNI, SGLT2i/ARNI), then cardiac function was evaluated and histology, immunoblots, and blood parameters were examined.

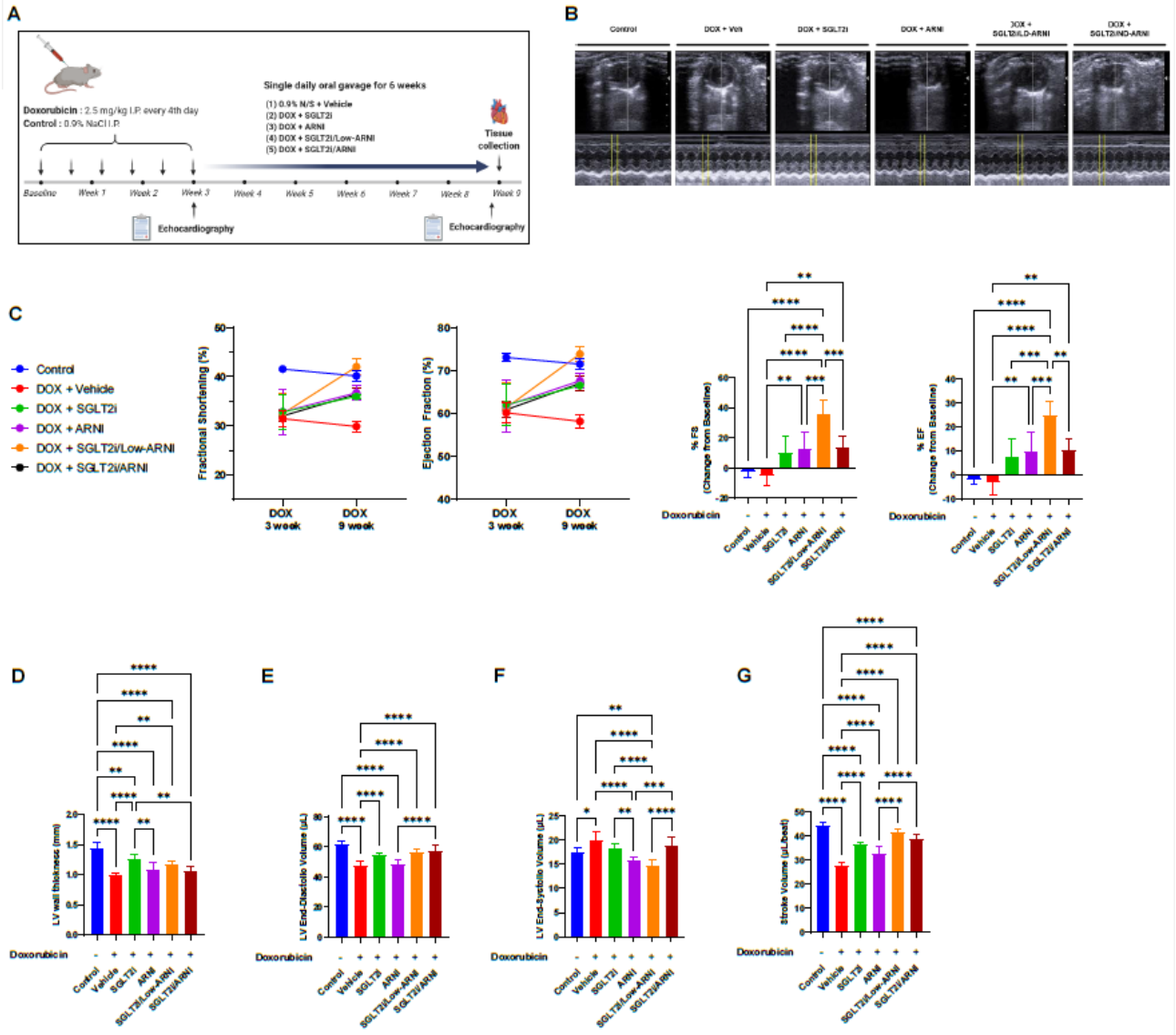
Results: In general, survival rates in drug-treated groups were extended compared to the vehicle-treated group. The lowest mortality was seen in SGLT2i/Low-ARNI group, displaying significantly alleviated body weight loss. Furthermore, in the chronic model, SGLT2i/Low-ARNI combo-treatment markedly improved cardiac structural remodeling and cardiac systolic function.

In addition, we examined the changes in renal function. A marker for renal epithelial injury, neutrophil gelatinase-associated lipocalin (NGAL) was significantly decreased in SGLT2i/Low-ARNI group. Also, glomerular tuft area and volume shrinkage were alleviated in SGLT2i/Low-ARNI group.

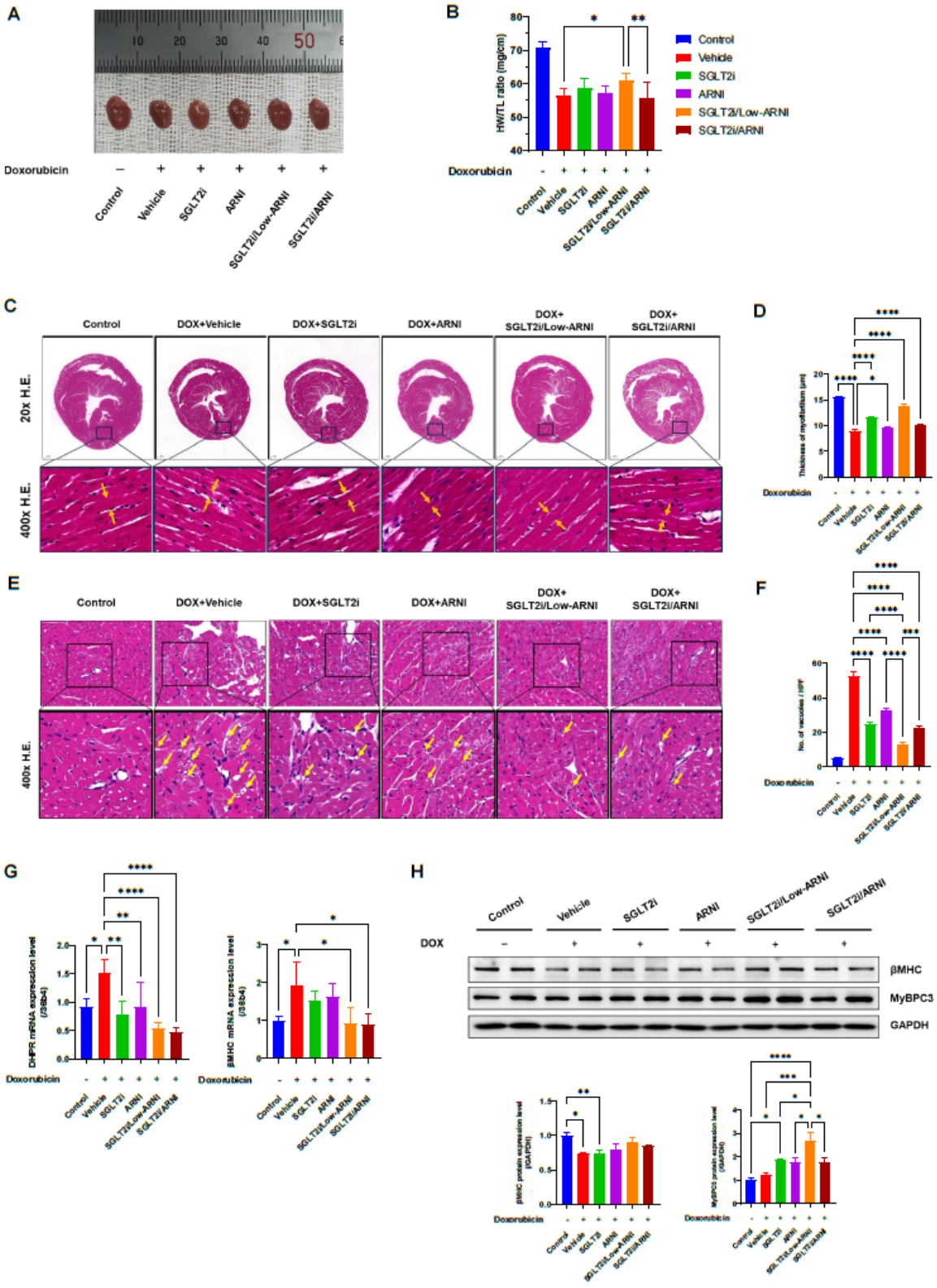
Conclusion: Concomitant therapy with SGLT2 inhibitor and ARNI showed a cardioprotective effect in an anthracycline-induced HF murine model. Our finding suggests that combination therapy as a new strategy might offer therapeutic benefits for patients with HF.



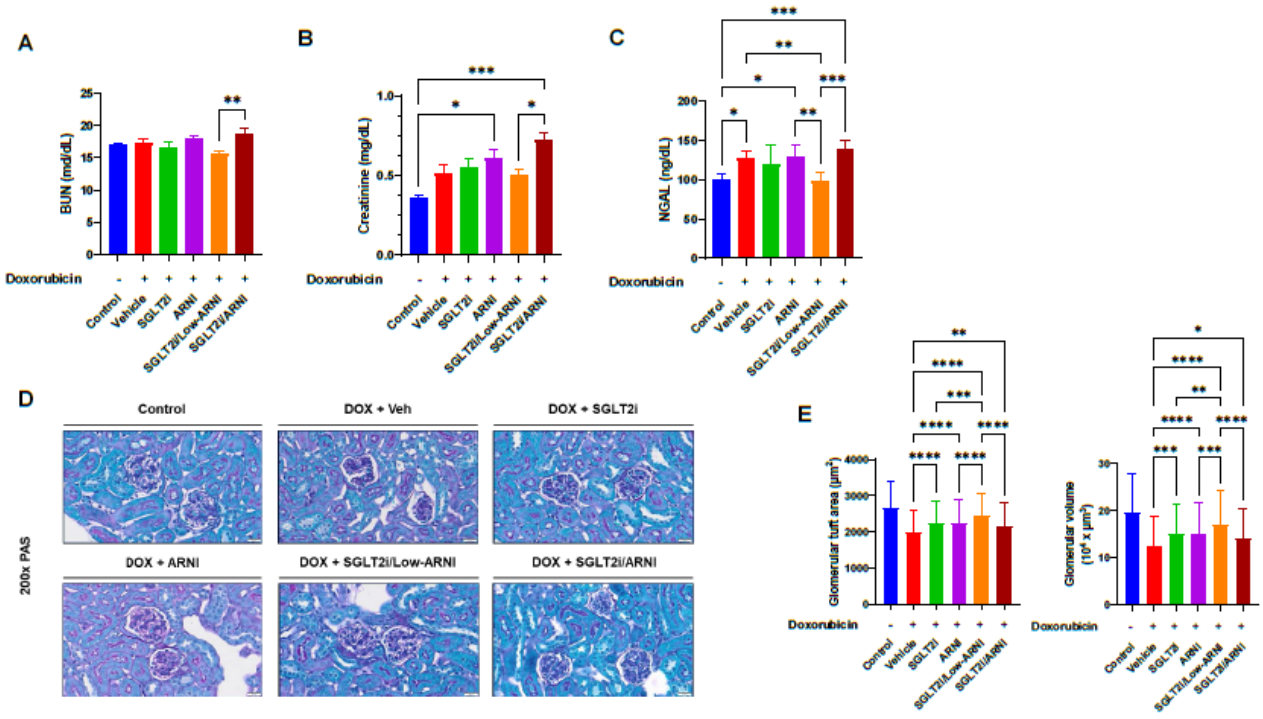
(A) Schematic design of the acute doxorubicin challenge experiment.
(B) Survival curves of mice after acute DOX treatment(15 mg/kg i.p) were created by Kaplan-Meier method.
(C) Body weight changes in acute doxorubicin challenged mice after treatment with the individual treatment.
(D) Percent change from the baseline body weigh on 6 day after the doxorubicin injection.
(E) Representative of photoplethysmography at 4days after the initiation of the acute DOX treatment(15 mg/kg i.p).
(F) Systolic blood pressure and heart rate were measured by a tail cuff method after the initiation of the acute doxorubicin treatment.



(A) Schematic of the chronic doxorubicin challenge experiment.
(B) Representative M-mode echocardiography images in 9 weeks following the initiation of the doxorubicin treatment (15 mg/kg accumulation dose).
(C) 3 weeks and 9 weeks of fractional shortening (FS) and ejection fraction (EF) following the initiation of the doxorubicin treatment (15 mg/kg accumulation dose). FS and EF of individual drug-treated mice were expressed as change from baseline.
(D) LV wall thickness, **(E)** LV end-diastolic volume, **(F)** LV end-systolic volume, and **(G)** stroke volume at 9 weeks following the initiation of the doxorubicin treatment. (CTL, n=6; Vehicle, n=7; SGLT2i, n=7; ARNI, n=8; SGLT2i/Low-ARNI, n=6; SGLT2i/ARNI, n=7) *p<0.05, **p<0.01, ***p<0.001



(A) Whole-heart photograph of mice in the control, vehicle, SGLT2i, ARNI, SGLT2i/Low-ARNI, SGLT2i/ARNI groups after the doxorubicin treatment.
(B) Heart weight to tibia length ratio (HW/TL) was evaluated 9 weeks after following treatment .
(C) Representative H&E staining of heart cross-sections at 9 weeks after saline or DOX treatment.
(D) Quantitative results of thickness of myofibrillum were shown.
(E) Representative H&E staining of cytoplasmic vacuolization localized in the cardiac tissue at 9 weeks after saline or DOX treatment.
(F) Quantitative results of number of cytoplasmic vacuoles were shown.
(G) mRNA expression of cardiotoxicity-related genes in 9 weeks after the initiation of the doxorubicin treatment (15 mg/kg accumulation dose).
(H) Representative immunoblots of cardiac structural proteins after the following treatments and graphical quantification showing.
*p<0.05, **p<0.01, ***p<0.001. DHPR; dihydropyridine receptor, βMHC; beta-myosin heavy chain



(A) Plasma concentration of BUN, **(B)** Creatinine, **(C)** NGAL in 9 weeks following the initiation of the doxorubicin treatment (15 mg/kg accumulation dose).
(D) Representative Periodic Acid Schiff (PAS) staining of kidney cross-sections from the acute doxorubicin challenge experiment.
(E) Quantitative results of glomerular tuft area, and mean glomerular volume by Weibel-Gomez techniques were shown.
*p<0.05, **p<0.01, ***p<0.001

Clinical Implications: Our study will help enable cardiovascular clinicians to adjust this novel cardioprotective regimen in the management of LV dysfunction patients with cancer. Moreover, adjuvant therapy for the patients undergoing cancer treatment by potentially cardiotoxic components.