$= 1.7 \times 10^{-34}$). Men in MVP with the 5% highest PRS and over 50 years of age had a disease prevalence of 7.8% (142/1680), higher than that observed in AAA screening trials informing current guidelines.

Conclusions: Here, we identify novel AAA genetic associations with therapeutic implications and identify a subset of the population at significantly increased risk of AAA. Our data suggest that extending current screening guidelines to include testing for those with high polygenic AAA risk would significantly increase the yield of current screening.

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ABSTRACT SESSION III: AORTOPATHIES AND NOVEL VASCULAR DEVICES

The Perfuse Dual Chamber Stent Improves Donor Organ Recovery in a Porcine Model

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Background: Amid a critical shortage of organs for transplantation, ischemic injury from malperfusion during the agonal period remains a prohibitive barrier. We hypothesized that a dual chamber stent graft could isolate visceral perfusion from the agonal systemic circulation, while respecting the ethics of organ donation.

Methods: A retrievable dual chamber stent graft was welded from nitinol and covered with polymer. A central lumen maintained aortic flow, with an outer visceral chamber perfused by an oxygenator. Anesthetized pigs were assigned to either control (n = 7) or the dual chamber stent (n = 6). A 1-hour agonal phase of hypoxia (saturations <60%-70%) and hypotension (mean arterial pressure, <25 mm Hg) was simulated both medically and with partial balloon occlusion. The Perfuse stent visceral flow totaled 500 mL/min during the agonal phase followed by stent recapture and resuscitation to an end point of 2 days.

Results: Study groups had comparable agonal O_2 saturations, heart rate, and mean arterial pressure. Cardiac output and right ventricular end diastolic volume did not change during stent graft deployment. Compared with the low pO_2 of controls (48 mm Hg) and systemic stent animals (49 mm Hg), the visceral pO_2 averaged 413 mm Hg and visceral flow was significantly higher in stent animals. Five of seven controls were humanely killed from acute renal failure and volume overload; all stented animals survived without renal impairment. Transaminases were between 1.8- and 3-fold increase in control as compared with stented animals.

Conclusions: During a simulation of the agonal period, a dual chamber stent provided endovascular separation and marked improvement in perfusion and organ outcome. This goal was accomplished without significant impact on cardiac function, respecting current ethical considerations of the donation after cardiac death donor. The ability to separate the perfusion of the abdominal organs from the agonal systemic circulation without the need for open surgery might significantly improve the availability of donor organs for transplant.

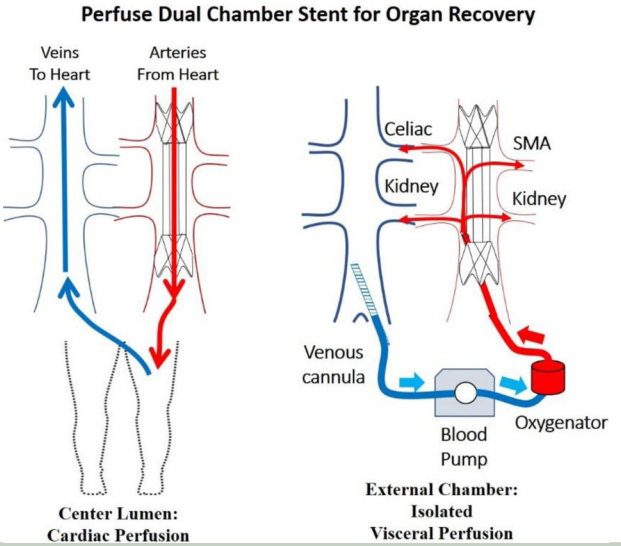

Fig.

Author Disclosures: B. W. Tillman: Nothing to disclose; **C. Go:** Nothing to disclose; **B. Frenz:** Nothing to disclose; **M. Elsisy:** Nothing to disclose; **Y. Chun:** Nothing to disclose.

Maresin 1 Attenuates Murine Abdominal Aortic Aneurysms Via Vascular Smooth Muscle Cell-Dependent Transforming Growth Factor-β Signaling

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Introduction: The endogenous pro-resolving lipid mediator Maresin 1 (MaR1) is derived from the ω-3 polyunsaturated fatty acid docosahexaenoic acid and is involved in the resolution phase of inflammation. Specifically, MaR1 has been shown to attenuate inflammatory signaling in smooth muscle cells. It was hypothesized that exogenous administration of MaR1 would attenuate abdominal aortic aneurysm (AAA) growth via smooth muscle cell-dependent transforming growth factor (TGF)-β signaling.

Methods: AAAs were induced in C57BL/6 wild-type mice (n = 9 elastase + MaR1 [4 ng/g] or n = 10 elastase + vehicle) using an established topical elastase AAA model. Mice were treated with MaR1 or vehicle via intraperitoneal injection on days 7, 9, 11, and 13 after AAA induction. Abdominal aortas were harvested on day 14 for phenotypic evaluation of aortic diameter. Histologic analysis of smooth muscle actin (n = 3-4/group) and Western blot of TGF-β1 expression (n = 6-7/group) were performed. Additionally, AAAs were induced in smooth muscle cell specific TGF-β2 receptor knockout mice and treated with MaR1 (n = 7) versus vehicle (n = 10) and harvested on day 14 for phenotypic evaluation of aortic diameter. Groups were analyzed using one-way analysis of variance with the post hoc Tukey test and data presented as mean ± standard error of the mean.

Results: MaR1 treatment significantly attenuated AAA growth compared with vehicle (121.4 ± 9.4% vs 165.3 ± 9.4%; $P < .01$). A significant increase in aortic wall smooth muscle cell actin was identified in MaR1-treated mice compared with vehicle (27.1 ± 3.4% vs 14.2 ± 2.4%; $P = .03$). TGF-β1 expression was also significantly higher in MaR1 treated mice compared with vehicle ($2.95 \times 10^6 \pm 11.1 \times 10^5$ vs $1.63 \times 10^6 \pm 2.6 \times 10^5$ densitometry units; $P = .02$). Finally, smooth muscle cell-specific TGF-β2 receptor knockout mice showed no difference in AAA diameter in MaR1-treated mice compared with vehicle (133.9 ± 8.0% vs 123.8 ± 7.9%; $P = .4$).

Conclusions: These results demonstrate that MaR1, important in the resolution of inflammation, attenuates murine AAA growth, preserves aortic wall smooth muscle cell actin, and increases TGF-β1 expression. This attenuation in AAA growth is lost in smooth muscle cell-specific TGF-β2 receptor knockout mice further suggesting that MaR1 modulates TGF-β signaling in aortic smooth muscle cells.

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A Theranostic Role for Ccr2 in Rodent Abdominal Aortic Aneurysm Development and Rupture

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Introduction: Abdominal aortic aneurysm (AAA) is common in the aging population, and its rupture carries a high mortality risk. AAA is characterized by mononuclear phagocyte destructive aortic extra cellular matrix remodeling. Monocyte chemoattractant protein/C-C chemokine receptor type 2 (CCR2) axis plays an important role in AAA development. We sought to evaluate if increased murine AAA ^{64}Cu-DOTA-ECL1i uptake, a radiolabeled CCR2 binding peptide, by positron emission tomography (PET), is predictive of rupture, as well as if CCR2 inhibition prevents rupture.

Methods: Sprague-Dawley rats and C57BL/6 (wild-type [WT]) mice underwent intraluminal aortic exposure to porcine pancreatic elastase (PPE). Four groups were considered: (1) active PPE (AAA), (2) heat-inactivated PPE (sham), (3) APPE + β-aminopropionitrile (a lysyl oxidase inhibitor to stimulate rupture) (ruptured AAA [RAAA]), and (4) APPE + β-aminopropionitrile + RS-504393 (CCR2 inhibitor, CCR2i). WT and CCR2$^{-/-}$ mice were also exposed to angiotensin II. ^{64}Cu-DOTA-ECL1i PET imaging was performed at 7 and 14 days post AAA induction.

Results: In rates, AAA demonstrated significantly greater ^{64}Cu-DOTA-ECL1i uptake by PET and autoradiaography compared with sham ($P <$ .05). RAAA that subsequently ruptured demonstrated significantly greater uptake compared with those animals that did not rupture ($P <$ .001). RAAA and CCR2i rupture rates were 56% and 0%, with mean aortic diameter percent increases of 353 ± 43% and 171 ± 26%, respectively ($P <$ .0001). CCR2i PET uptake decreased by 60%. In mice, WT, CCR2i, and CCR2$^{-/-}$ rupture rates were 53%, 33%, and 6%, with mean aortic diameter percent increases of 330 ± 62%, 191 ± 67%, and 101 ± 16%, respectively ($P <$ .01). Quantification of tracer uptake by PET was significantly greater in AAA compared with sham and CCR2$^{-/-}$ ($P <$ .0001).

Conclusions: CCR2-targeted PET imaging demonstrated inflammation associated with rodent AAA development. Increased radiotracer uptake by AAA that subsequently ruptured may aid in assessing AAA rupture potential. CCR2 inhibition with our model prevents AAA rupture and inhibits AAA associated inflammation, suggesting a theranostic role for CCR2 in the management of AAA patients.

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Pharmacologic Inhibition of Bruton's Tyrosine Kinase Attenuates Experimental Abdominal Aortic Aneurysms

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Objective: Macrophages are critical for abdominal aortic aneurysm (AAA) pathogenesis. Bruton's tyrosine kinase (BTK) contributes to macrophage-driven diseases such as atherosclerosis and ischemic stroke by modulating proinflammatory macrophage activation. It is not known whether BTK plays a role in AAA disease. This study investigated the influence of the US Food and Drug Administration-approved BTK inhibitor ibrutinib on the formation and progression of experimental AAAs.

Methods: AAAs were generated via intra-aortic elastase infusion in male normolipidemic C57BL/6J mice or subcutaneous angiotensin II infusion in male hyperlipidemic C57BL/6J mice (inoculated with an adeno-associated virus expressing a gain-of-function mutation of PCSK9 and fed a high-fat diet). Ibrutinib administration (30 mg/kg) was initiated 1 day prior to or indicated days after, AAA creation. Influence on AAAs was evaluated via ultrasonography and histology. The effect of ibrutinib on macrophage mediator messenger RNAs (mRNAs) was assessed via quantitative reverse transcriptase polymerase chain reaction assay.

Results: By ultrasound examination, ibrutinib pretreatment remarkably attenuated elastase infusion-induced aortic enlargement, in association with delayed onset and reduced incidence of AAAs, as compared with vehicle treatment. In established AAA mice, ibrutinib treatment limited further aneurysmal enlargement. On histology, ibrutinib treatment preserved medial elastin and smooth muscle cell cellularity and reduced mural macrophage, lymphocyte, and neocapillary density. Ibrutinib administration also reduced the incidence and severity of angiotensin II-induced AAAs in hyperlipidemic mice. Additionally, BTK treatment attenuated CCL2 and tumor necrosis factor-alpha mRNA expression, but accentuated IL-10 mRNA, in classically or alternatively activated macrophages.

Conclusions: BTK mediates AAA progression in two complementary experimental AAA models. Pharmacologic inhibition of BTK may represent a novel translational strategy for AAA disease suppression.

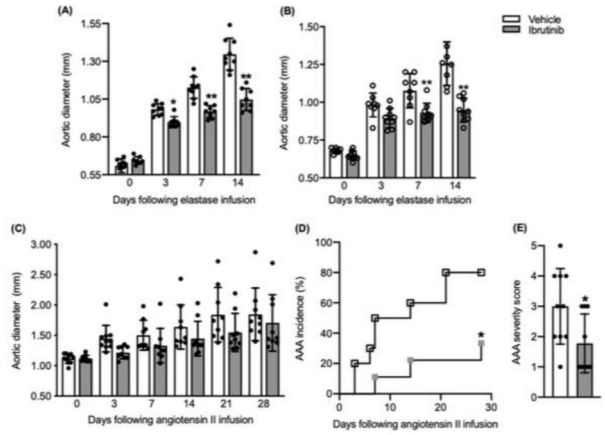

Fig. Influence of ibrutinib administion on experimental abdominal aneurysms. **A**, Infrarenal aortic diameter in porcine pancreatic elastase (PPE)-infused mice treated with ibrutinib (30 mg/kg) or vehicle. **B-D**, Suprarenal aortic diameter, aneurysm incidence, and severity in hyperlipdemic (adeno-associate virus [AAV]-PCSK9-injected, high-fat diet-fed) mice administered ibrutinib or vehicle following subcutaneous angiotensin II infusion. Abdominal aortic aneurysm (AAA): the presence of aortic dissection or a 50% or greated increase in aortic diameter over the baseline level. Two-way analysis of variance followed by a two-sample comparison **(A** and **B)**, Kaplan-Meier test **(C)** or Student *t*-test **(D)**. *$P <$ .05 and **$P <$ .01 compared with vehicle treatment; n = 8-10 mice per group.