anecdotal experience in lamin A/C CMP, never reported elsewhere, confirms the extremely malignant arrhythmic phenotype of the disease showing recurrences despite ablation and BCSD. Finally, the robotic approach, which has never been reported for these indications, is proving to be feasible and safe.

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Safety of catheter-free VT ablation: Dose-dependent LVEF changes after proton beam therapy of the LV in a porcine model

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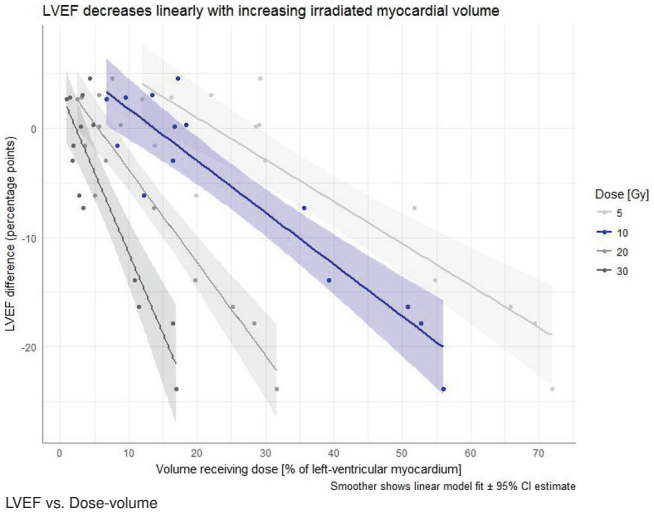
Background: Cardiac radiosurgery using methods established in radiation oncology has emerged as a promising tool for catheter-free arrhythmia ablation. Compared to x-rays, particle beams offer unique physical properties allowing to deliver less dose to organs at risk. Data on cardiac effects of radiation is derived mainly from collateral exposure in cancer treatment where single myocardial fractions are low. Here we report the dose effects on cardiac function of a single fraction ablative proton beam therapy of the left ventricle (LV) in a porcine model with up to 40 weeks follow-up.
Methods: 20 domestic pigs were treated with pencil-beam scanned proton therapy. Treatment planning was guided by end-expiration cardiac-gated 4D CT. Structures of interest were contoured on the 70% phase (diastolic) contrast-enhanced CT. Treatment planning and dose calculations reported were performed on the averaged 4D CT using the clinical treatment planning software. Between 1 and 3 transmural targets of various volumes were defined at arbitrary locations in the LV myocardium. Proton delivery was gated to expiration. Follow-up duration varied to allow for tissue analysis at different times. Cardiac MRIs were obtained at intervals of 4 weeks. LV ejection fraction (LVEF) was calculated from a stack of short axis 4D balanced steady-state gradient echo sequence MR images (slice thickness 8 mm).
Results: Of 20 animals treated (3 targets at 40 Gy, n=8; 2 targets at 30 Gy, n=4; 1 target at 40 Gy, n=8), 6 died suddenly during follow-up (all in the 3-target group). Myocardial volumes receiving at least 10 Gy (mean±SD) were 48±9 cm^3 in the 3-target group, 24±5 cm^3 in the 2-target group and 12±4 cm^3 in the 1-target group. 105 cardiac MRIs were analyzed. LVEF over time was largely stable in the 1- and 2-target groups but declined at approximately 90 days in the 3-target group. To compensate for daily variations in LVEF caused by loading conditions and autonomic tone, all LVEF measurements in a single animal obtained before 90 days were averaged and compared to the average of all measurements obtained after 90 days. The decline in LVEF in individual animals was strongly correlated with the myocardial volume irradiated (Pearson's r = -0.93, $p<0.001$, for the volume receiving more than 10 Gy). A decline in LVEF of more than 10 percentage points was observed if more than 35% of left ventricular myocardium had been exposed to at least 10 Gy.



LVEF vs. Dose-volume

Conclusion: Possible adverse effects on LV function from a single fraction particle irradiation can be expected to be seen around 90 days after treatment. Changes in LVEF are strongly correlated to the overall LV volume exposed. Therefore, precise definition of the target and highly focused delivery of radiation energy are paramount when considering catheter-free ablation using radiosurgery. The lack of exit dose and the sharp lateral dose fall-off in particle beam therapy make proton beams an attractive choice for this application.
Funding Acknowledgements: Mayo Clinic Clinician Investigator Programm (DLP). Deutsche Forschungsgemeinschaft (SH).

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Six-month treatment with novel oral anticoagulants ameliorates cerebral blood flow, as evaluated with brain perfusion SPECT

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Background: Dementia is a serious clinical problem. Cerebral blood flow is decreased even in patients with mild cognitive impairment, and the dysregulation of cerebral blood flow contributes to the pathogenesis of Alzheimer disease. Decreases in regional cerebral blood flow have been reported, as detected by brain perfusion positron-emission single-photon emission tomography (SPECT). Novel oral anticoagulants (NOACs) are used to treat patients with non-rheumatic atrial fibrillation (AF). However, the effects of NOACs on cerebral blood flow remain unknown.
Purpose: The purpose of this study was to determine whether six-month treatment with NOACs in patients with cardiovascular diseases such as hypertension, dyslipidemia, and angina pectoris ameliorates cerebral blood flow using brain perfusion SPECT.
Methods: We performed technetium-99m ethyl cysteinate dimer SPECT on 50 consecutive Japanese patients (30 men and 20 women, aged 74.9±9.9 years) with hypertension (31), dyslipidemia (8), angina pectoris (8), diabetes mellitus (6), or AF (5), but without thoracic surgery or catheter ablation, before and after six-month treatment with NOACs.
Results: The results of brain perfusion SPECT before and after six months of treatment with NOACs were respectively 1.26±0.36 and 1.17±0.43 for severity ($p<0.01$), 13.3±11.9% and 12.0±12.9% for extent ($p<0.05$), and 1.44±1.06 and 1.24±1.05 for the ratio (p=0.097). Significant differences ($p<0.05$) were obtained in the patients before and after six-month treatment with NOACs, as assessed based on severity and extent according to the eZIS system.
Improvement of cerebral blood flow, which was assessed based on severity, was found in 36 (72%) patients (22 men and 14 women, aged 75.4±9.5 years). Among the patients with improved cerebral blood flow, 18 (50%) patients were treated with edoxaban; 8 (22%), with apixaban; 6 (16%), with rivaroxaban; and 4 (11%), with dabigatran.
Among 22 patients treated with edoxaban, cerebral blood flow was increased in 18 (82%) patients, and among 11 patients treated with rivaroxaban, cerebral blood flow was increased in 6 (55%) patients. There was no statistically significant difference between edoxaban and rivaroxaban. Among 5 AF patients, 4 (80%) patients had improved cerebral blood flow. Additionally, the results of brain perfusion SPECT before and after six-months of treatment with edoxaban were 1.18±0.26 and 1.02±0.34 for severity ($p<0.01$), 10.1±6.2% and 6.7±6.6% for extent ($p<0.01$), and 3.72±6.96 and 0.88±0.74 for ratio (p=0.052), respectively.
NOACs can possibly prevent dementia by increasing cerebral blood flow.
Conclusion: Six-month treatment with NOACs improved cerebral blood flow in patients with cardiovascular diseases such as hypertension, dyslipidemia, angina pectoris, diabetes mellitus, and AF, as evaluated with brain perfusion SPECT.

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TAFI level dynamics during long-term warfarin therapy as a predictor of recurrent bleedings in a target INR

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Background: Our previous pilot study showed that low thrombin activatable fibrinolysis inhibitor (TAFI)level may increase the risk of bleedings in a target international normalized ratio (INR) during long-term warfarin (W) therapy, but it was limited by the only one measurement of TAFI level. TAFI level dynamics during W therapy has not yet been studied.
Purpose: To study the TAFI level dynamics during the long-term W therapy and its influence on the risk of bleedings.
Methods: We observed 78 pts (40 men) aged 28–85 (mean 64±12) years who started W therapy for the first time. Atrial fibrillation (AF) was observed in 81% of pts, venous thromboembolism (VTE) – in 10% of pts, AF + VTE – in 9% of pts. TAFI level was measured before the start and 3 months after W therapy (time therapeutic range 71,5±19,9%) by using a chromogenic assay. The follow-up period was 6–18 months. Endpoints were bleedings. Results presented as a median (interquartile range).
Results: In all pts, TAFI level was 106 (97; 124)% at baseline and 101 (84; 128)% after 3 months (p=0,04). During 3 months, TAFI level decreased in 51 (65%) pts and increased in 27 (35%) pts. We calculated Δ% of TAFI level for each patient. Median of TAFI Δ% was -8,0 (-19,8; 11,1)%. During the follow-up period (median 12 months), minor bleedings occurred in 47 (60%) pts, 21 pts had single bleeding, 26 – recurrent bleedings in a target INR (2,0–3,0). Pts with bleedings had lower TAFI Δ% than pts without bleedings: -14,4 (-23,8; 15,5) vs -5,4 (-12,6; -8,0); p=0,039. As we assumed that low TAFI level is associated with bleedings in a target INR, further analysis was performed among pts with bleedings only. Before the start and 3 months after W therapy, pts with single bleeding (n=21) and recurrent bleedings in a target INR (n=26)had a similar TAFI level, however TAFI Δ% was lower in pts with recurrent bleedings in a target INR: -18,3 (-26,4; -1,9)%

vs 4,6 (-19,4; 20,8)% respectively (p=0,047). ROC-analysis showed an area under the ROC-curve for TAFI Δ% as a marker of recurrent bleedings in a target INR of 0,670 (95% CI 0,509 to 0,832); p=0,047; criterion <-15%; sensitivity 65%; specificity 76%. We also investigated about 60 clinical, laboratory, and genetic parameters to define factors which are associated with recurrent bleedingsin a target INR. Multivariate regression analysis with age and sex adjustment showed that TAFI Δ% ≤-15% (OR 4,0; 95% CI 1,1 to 14,9; p=0,041) and HEMORR2HAGES score ≥3 (OR 4,9; 95% CI 1,2–20,0; p=0,026) are independent predictors of recurrent bleedings in a target INR during long-term W therapy.
Conclusion: During 3 months of W therapy, TAFI level decreased on average by 8%. Decrease of TAFI level may be a novel mechanism of W anticoagulant action, and the degree of TAFI decrease determines the risk of bleedings. Thus, the decrease of TAFI level over 15% during W therapy and HEMORR2HAGES score ≥3may indicate pts with high risk of recurrent bleedings in a target INR.

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Pharmacokinetics and pharmacodynamics of alirocumab in patients with autosomal dominant hypercholesterolemia associated with PCSK9 gain-of-function or ApoB loss-of-function mutations

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Introduction: We examined pharmacokinetics and pharmacodynamics of the PCSK9 inhibitor alirocumab in patients with apolipoprotein B loss-of-function mutations (ApoB_LoFm) versus patients with PCSK9 gain-of-function mutations (PCSK9_GoFm).
Methods: Patients (LDL-C ≥70 mg/dL despite maximally tolerated lipid-lowering therapies) received alirocumab 150 mg at Week (W) 0, 2, 4, and 6, placebo at W8, alirocumab at W10, then placebo to W22. Alirocumab levels, free (unbound) and total (bound+unbound) PCSK9 concentrations and LDL-C were analyzed. LDL-C was calculated using the Friedewald formula. Concentrations of alirocumab and total/free PCSK9 were determined by ELISA.
Results: Patients included 6 ApoB_LoFm carriers (Arg3500Gln) and 17 PCSK9_GoFm carriers (6 Asp374Tyr, 4 Ser127Arg, 2 Leu108Arg, 1 Arg218Ser, and 4 Asp374Tyr). Mean±SE plasma LDL-C and PCSK9 concentrations for ApoB_LoFm and PCSK9_GoFm groups at baseline, respectively, were: LDL-C: 3.41±0.33 and 3.58±0.43 mmol/L; free PCSK9: 0.32±0.06 and 0.40±0.06 mg/L; and total PCSK9: 0.77±0.11 and 0.50±0.06 mg/L. Alirocumab reduced free PCSK9 (with a corresponding increase in total PCSK9) during W0–8, when 4 consecutive alirocumab doses were administered, resulting in sustained LDL-C reduction (Figure) during that period. Administration of placebo at W8 resulted in fluctuations in alirocumab, PCSK9 and LDL-C concentrations. Compared with PCSK9_GoFm, at W8, ApoB_LoFm carriers had higher levels of mean (±SE) total PCSK9 (6.56±0.73 versus 4.21±0.35 mg/L, ApoB_LoFm versus PCSK9_GoFm), lower mean alirocumab concentrations (12.12±1.81 versus 16.74±2.53 mg/L), and a lower level of free PCSK9 (0.025±0.016 versus 0.11±0.035 mg/L). Despite this greater suppression of free PCSK9 levels, LDL-C reduction at W8 was 55.3±1.0% (ApoB_LoFm) versus 73.1±0.9% (PCSK9_GoFm). Higher total PCSK9 levels in ApoB_LoFm (versus PCSK9_GoFm) during treatment may be related to higher baseline levels.

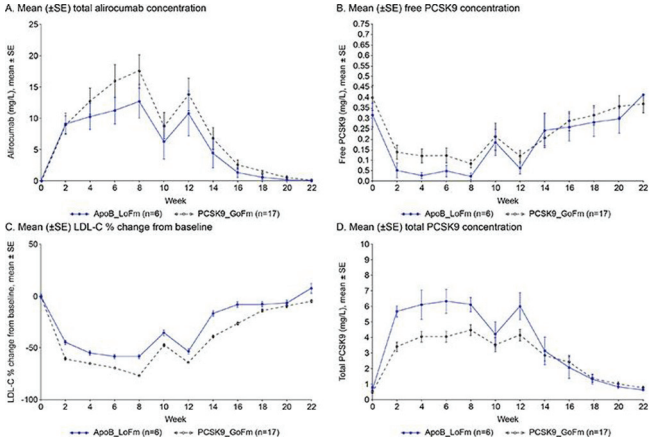

Figure 1

Conclusions: The differences in free/total PCSK9 concentrations and lower alirocumab concentrations observed in ApoB_LoFm versus PCSK9_GoFm carriers are consistent with greater drug-complex formation and target-mediated clearance of alirocumab. The apparent paradoxical relationship in this study between free PCSK9 lowering and LDL C response observed between ApoB_LoFm and PCSK9_GoFm carriers may be partially explained by reduced affinity of ApoB_LoFm for the LDL-receptor.

Funding Acknowledgements: Sanofi and Regeneron Pharmaceuticals Inc.

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Evaluation of the pharmacokinetics and pharmacodynamics of subcutaneously administered dutogliptin for daily injection with granulocyte colony stimulating factor (G-CSF) for AMI

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Background: Stromal cell-derived factor-1 (SDF-1) represents the major chemokine for initiating stem cell migration and homing to cardiac sites of ischemia with consequent neovascularisation, activation of residual cardio-blasts, and anti-apoptotic pleiotropic effects. Thus, the local preservation of SDF-1 represents a promising approach to treat acute MI. An approach to increase SDF-1 in the injured heart is inhibition of CD26/dipeptidylpeptidase IV (DPP-IV), which is responsible for cleavage and inactivation of SDF-1. Dutogliptin, a novel DPP-IV inhibitor, when combined with stem cell mobilization by G-CSF, significantly improved survival and reduced infarct size in a murine model. (Nix and Schenk 2016).
Methods: A two part Phase 1 study in healthy human volunteers was conducted to assess the safety/tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single and repeated parenterally dosed dutogliptin, and establish the dose for a Global Phase 2 study in AMI.
Part A, a single ascending dose study (SAD) with five dosing cohorts (n=5/cohort). The doses administered were: 30 mg i.v., 30, 60, 90, and 120 mg s.c.
Part B, a multiple ascending dose (MAD) study (n=5/cohort) with three dose cohorts 60, 90, and 120 mg sc on Days 1–7. PK/PD was fully characterized (0–24 h post dose) on Days 1 and 7, with trough (pre-dose) and 8 hr post dose assessments made on Days 2–6.
Results: Parenterally administered dutogliptin was well tolerated at all doses evaluated. No serious, drug-related adverse events (AE) and no premature terminations due to AEs were reported. Following a single i.v. dose of 30 mg, the mean t1/2 was 3.68 h. The systemic bioavailability of dutogliptin was approximately 100% following a single s.c. injection of 30–120 mg when compared to the i.v. exposure. Following a single s.c. injection, exposure increased with increasing dose in an approximately dose-proportional manner.
Peak dutogliptin plasma concentrations were achieved within 1 h post dose for all MAD cohorts on Days 1 and 7. Following daily s.c. injection of dutogliptin, mean exposure values increased with increasing dose in an approximately dose-proportional manner. Accumulation of dutogliptin was not observed with daily dosing.
Plasma DPP-IV activity was quickly and completely inhibited by all doses of dutogliptin. The duration of the maximal inhibition was dose dependent, where increasing dose resulted in longer periods of maximal inhibition. Multiple daily doses of dutogliptin produced a sustained inhibition of plasma DPP-IV.
Conclusion: A novel s.c. formulation of dutogliptin was demonstrated to be well tolerated following single and multiple daily administration in healthy volunteers. Dutogliptin is readily bioavailable and sustained plasma DPP-IV inhibition was achieved with increasing s.c. doses. A global, multicenter Phase 2 study to demonstrate safety and efficacy of dutogliptin in combination with G-CSF in AMI will begin in early 2018.
Funding Acknowledgements: Supported by RECARDIO Inc

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Multiple ascending doses of recombinant human lecithin-cholesterol acyltransferase in patients with atherosclerosis: phase 2a primary results

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Background: Reverse cholesterol transport (RCT) has the potential to remove cholesterol and stabilize vulnerable plaques in patients with atherosclerosis. In addition, high-density lipoprotein (HDL) may be cardioprotective in the setting of acute MI. Lecithin-cholesterol acyltransferase (LCAT) plays a key role in reverse cholesterol transport (RCT) and increased expression of LCAT may increase RCT and raise HDL cholesterol.
Purpose: To test the pharmacokinetics (PK), pharmacodynamics (PD), and safety of multiple ascending doses of recombinant human LCAT (MEDI6012) in patients with atherosclerosis.
Methods: This Phase 2a study was a randomized, blinded, placebo-controlled, dose-escalation study of intravenous (IV) MEDI6012. Stable patients with atherosclerosis were randomized in 3 standard dosing cohorts (40, 120, 300 mg each with 3 weekly doses) as well as a 4th cohort exploring a loading dose IV push (300 mg loading, 150 mg at 48 hours and 100 mg 1 week later). All cohorts were planned for 8 patients with a randomization ratio of 6:2 to receive intravenous MEDI6012 or placebo. The primary efficacy endpoint was baseline-adjusted area under the concentration-time curve from time 0 to 96 hours post dose 3 (AUC0–96hr) for HDL-C, HDL cholesterol ester (HDL-CE), and total