feasibility and safety of the procedure. Conversion to surgery was required in 1 case following superior vena cava valve migration after deployment. A second patient underwent surgery within 30 days after atrial migration of the inferior vena cava valve.

In all patients, CAVI resulted in full reduction of reverse caval flow as confirmed by a significant reduction of the inferior vena cava v-wave from 30.8 ± 6.7 mm Hg to 20.8 ± 4.7 mm Hg ($p < 0.0001$) and color Doppler investigation. Despite the excessive risk profile of the patient population, the procedure was associated with no intraprocedural mortality. However, in-hospital mortality occurred in 5 of 22 patients (22.7%). Seventeen of 22 (77.3%) patients were discharged alive. In this subgroup, transthoracic echocardiography obtained during follow-up confirmed appropriate function of all implanted devices. The longest follow-up of 51 months is available for a bi-CAVI patient with documented intact valve function. In patients discharged from hospital, symptoms improved in 88.2% (n = 15) by ≥1 New York Heart Association functional class. However, 12-month mortality was 63.6% (14/22), respectively, with the majority of patients dying from non-cardiovascular causes.

In summary, these early results suggest that treatment of severe TR and caval backflow with the CAVI technique is feasible and there are reproducible results in a reduction of caval backflow. This hemodynamic improvement may potentially translate into clinical improvement, as suggested by the present study. However, due to its exclusive compassionate use, the present clinical experience is currently limited to the most severely ill subgroup with a high proportion of patients also experiencing non-cardiovascular comorbidities. Therefore, it remains unclear whether the presented treatment modality results in a sustained clinical improvement or improved patient prognosis. Further studies including randomized trials are required to determine which patients benefit most from interventional treatment, adjusting clinical criteria for patient selection and evaluating long-term safety and efficacy.

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https://doi.org/10.1016/j.jacc.2017.12.056

Please note: Dr. Lauten is a consultant to P&F TricValve; and has received research support from Edwards Lifesciences. Dr. Grube is on the scientific advisory board for Mitralign, Millipede, MDT, and Boston Scientific; and holds equity in Mitraltech, Twelve, and Valtech. Dr. Sinning has received research grants and honoraria from Medtronic, Boston Scientific, and Edwards Lifesciences. Dr. Stangl has received proctoring fees and research support from Edwards Lifesciences. Dr. Figulla has received consulting fees from P&F TricValve. Dr. Laule has received a research grant and consulting fees from Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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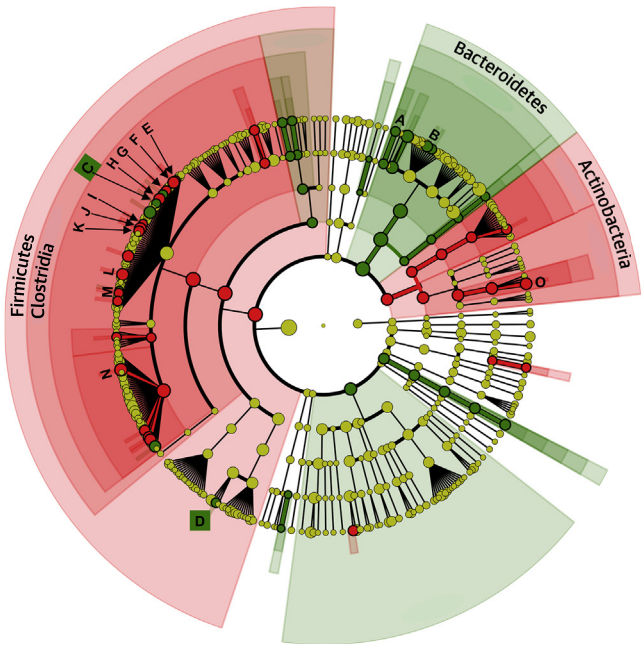
Gut Microbiota Signature in Heart Failure Defined From Profiling of 2 Independent Cohorts

Metabolic and inflammatory disturbances may play a role in the development and progression of chronic heart failure (HF), but the mechanisms are not completely understood. The potential role of the gut microbiota in HF remains elusive, and only small studies with diverse methods and results have been reported so far (1–3).

To define a more robust gut microbiota signature in HF, we investigated 2 independent cross-sectional cohorts of patients with stable systolic HF (discovery, n = 40; and validation, n = 44; all >6 months in New York Heart Association functional class II-IV) and population-based control subjects (n = 266, randomly allocated to the 2 cohorts for comparison).

FIGURE 1 Taxonomic Changes in Patients With Heart Failure



↑ in Heart Failure

↓ in Heart Failure

	Order	Family	Genus
A	Bacteroidales	Uncultured	Uncultured bacterium
B	Bacteroidales	Prevotellaceae	Prevotella (7)
C	Clostridiales	Lachnospiraceae	Hungatella
D	Selenomonadales	Acidaminococcaceae	Succiniclasticum
E	Clostridiales	Lachnospiraceae	Anaerostipes
F	Clostridiales	Lachnospiraceae	Blautia
G	Clostridiales	Lachnospiraceae	Coprococcus (3)
H	Clostridiales	Lachnospiraceae	Fusicatenibacter
I	Clostridiales	Lachnospiraceae	Lachnospiraceae FCS020
J	Clostridiales	Lachnospiraceae	Lachnospiraceae NC2004
K	Clostridiales	Lachnospiraceae	Lachnospiraceae ND3007
L	Clostridiales	Lachnospiraceae	Pseudobutyrivibrio
M	Clostridiales	Lachnospiraceae	Eubacterium hallii group
N	Clostridiales	Ruminococcaceae	Faecalibacterium
O	Bifidobacteriales	Bifidobacteriaceae	Bifidobacterium

Phylogenetic tree showing differentiating taxa at the genus level between heart failure (HF) (n = 84) and control subjects (n = 266). The majority of depleted taxa in HF microbiomes **(red)** have butyrate-producing potential. **Green** indicates taxa enriched in HF. Only validated taxa are reported (Mann Whitney U: $p < 0.05$, $Q_{FDR} < 0.2$ in both cohorts and the linear discriminant analysis effect size tool: $Q_{FDR} < 0.01$ in the combined cohort).

Only significant differences between HF and control subjects ($p < 0.05$ and $Q_{FDR} < 0.2$) in both cohorts are reported. Sample collection, DNA extraction, sequencing (16S rRNA, V3-V4), and post-sequencing processing was performed as previously described (4), but with operational taxonomic unit mapping to the Silva database (Max Planck Institute for Marine Microbiology and Jacobs University, Bremen, Germany).

In both cohorts, patients with HF had decreased microbial richness even after adjustment for age, sex, body mass index (BMI), hypertension, and diabetes (Chao 1 index, median [range]: 936 [423 to 1,361] vs. 1,025 [328 to 1,418]; $p = 0.001$, in the merged cohort). We further identified changes in 15 taxa in both cohorts (Figure 1), including a depletion of taxa in the *Lachnospiraceae* family, several of which are known producers of butyrate, a short-chain fatty acid. Prediction of microbial genes (using Tax4Fun, Institute of Microbiology and Genetics, Georg-August-University Göttingen, Göttingen, Germany) in the merged cohort confirmed low genetic potential for butyrate production in HF microbiomes compared with control subjects (relative abundance of genes encoding for butyrate-acetoacetate coenzyme A-transferase, 2.1×10^{-5} [4.4×10^{-6} to 4.9×10^{-5}] vs. 2.3×10^{-5} [7.2×10^{-6} to 6.2×10^{-5}], respectively), also after adjustment for age, sex, BMI, hypertension, and diabetes ($p = 0.004$).

There were no significant associations between alpha diversity, the 15 bacterial genera (Figure 1), or genes for butyrate-acetoacetate coenzyme A-transferase, and clinical or hemodynamic markers of HF (New York Heart Association functional class, N-terminal pro-B-type natriuretic peptide, and echocardiography) or medication (including proton pump inhibitors, statins, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers). We hypothesized that a low abundance of butyrate-producing microbes could contribute to inflammatory changes, and indeed, several taxa of the *Lachnospiraceae* family correlated inversely with the T-cell activation marker soluble CD25 (sCD25). Following correction for multiple testing, an inverse correlation between *Lachnospiraceae NC2004* and sCD25 was detected (Spearman's rho −0.35; $p = 0.001$; $Q_{FDR} < 0.1$).

Furthermore, we explored associations with clinical endpoints in the discovery cohort. Eighteen patients died or were listed for heart transplantation during a median of 14 months (range: 0 to 31 months) follow-up. Of the 15 bacterial genera that were altered in HF (Figure 1), patients with endpoint had lower abundance

of the *Eubacterium hallii* group (relative abundance 2.5×10^{-4} [0 to 8.2×10^{-4}] vs. 4.1×10^{-4} [8.2×10^{-5} to 3.2×10^{-3}]) adjusted for age, sex, BMI, hypertension, diabetes, and chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73m^2; p = 0.015), and they had higher plasma levels of sCD25 (507 pg/ml [147 to 3,827 pg/ml] vs. 318 pg/ml [204 to 1,041 pg/ml]; p = 0.007) compared with patients without end point. In addition, the inverse correlation between *Lachnospiraceae NC2004* and sCD25 was even more pronounced in patients who reached an end point (Spearman's rho −0.52; p = 0.027).

Our study shows that the gut microbiota signature in chronic HF is characterized by large compositional shifts with low bacterial richness and depletion of bacteria with butyrate-producing potential. Butyrate exerts local anti-inflammatory effects in the gut mucosa, and stimulates regulatory T-cells, also in the periphery (5). Notably, we identified an inverse correlation between *Lachnospiraceae* and sCD25, which was even more pronounced in patients with more severe disease.

In summary, our results suggest that an altered gut microbiota in HF is associated with persistent T-cell activation, which could be involved in the chronic immune activation of the disease. This hypothesis should be tested in experimental studies and clinical trials targeting the gut microbiota.

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https://doi.org/10.1016/j.jacc.2017.12.057

Please note: Dr. Kummen has received a grant from the Regional Health Authorities South-Eastern Norway (2016067). Dr. Mayerhofer has received a grant from the Norwegian Health Association (6782). Dr. Hov has received a grant from the Norwegian Research Council (240787/F20). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Kummen and Mayerhofer contributed equally to this work and are joint first authors. Drs. Hov and Trøseid contributed equally to this work and are joint senior authors.

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Lesion Complexity and Prolonged Antiplatelet Therapy

The Missing Variable to Complete the Puzzle

We have read the paper by Yeh et al. (1) about the complexity of the lesion and prolonged double antiplatelet therapy (PDAT). Although it is easy to presume a benefit in complex anatomies, the first alarm against this claim comes from the PEGASUS (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) trial, in which no interaction was found with the entire cohort in the prespecified group of multivessel disease.

An endless list of publications are focused on this matter because its indication in all the patients with a PEGASUS profile would carry an undesirable rate of bleeding events and an economic impact that would be hardly bearable by any financier, accounting for $94,917/quality-adjusted life year (QALY) gained in the entire cohort (2). Yeh et al. (1) have completed the complex puzzle that combines the patient's and lesion's characteristics with the published indices which, all combined, provide the necessary information. Thus, lesion complexity has influence in the first year but not afterward (3). In addition, the dual antiplatelet therapy (DAPT) score, PARIS (Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients) registry, and PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score quantify the risks of ischemia and bleeding. Finally, the analysis by subgroups in PEGASUS shows an absolute risk reduction for major