BIO.DETECT HF IV - SELENE HF: selection of potential predictors of worsening heart failure - a prospective, multicentre, exploratory study

Alessio Gargaro

Potential conflicts of interest

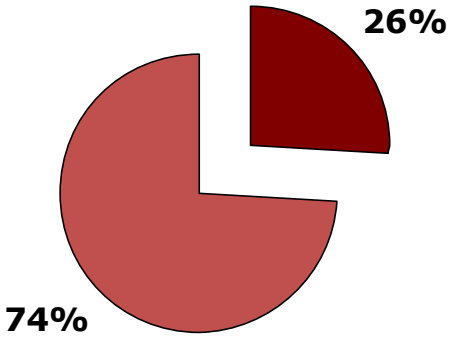
Speaker's name: Alessio Gargaro

☑ **I have the following potential conflicts of interest to report:**

Employment in industry: BIOTRONIK

Accuracy of Heart Failure prediction is poor

- Despite optimal therapy and Cardiac Resynchronization (CRT) 7% to 26% of HF patients are hospitalized for worsening Heart Failure (wHF) every year[1,2]
- This is mainly due to
  - Limited predictive value of single pieces of diagnostic information
  - Periodic, non-continuous monitoring of wHF indicators



Proportion of patients hospitalized every year

1, Bristow MR, et al. Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure. N Engl J Med 2004; 350: 2140-2150.
2. Cleland JGF, et al. The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure. N Engl J Med 2005; 352: 1539-49

Telemonitoring

- Advances in telecommunication technologies have created new opportunities to provide telemedical care as an adjunct to medical management of patients with heart failure.
- The mainstay of telemedicine is early detection of disease deterioration and prompt medical intervention.
- The key to success of this approach is the predictive value of the monitored variables.

Patient with a Home Monitoring device

Transmission unit Cardio Messenger II

GSM network for mobile phones transmission (GPRS protocol)

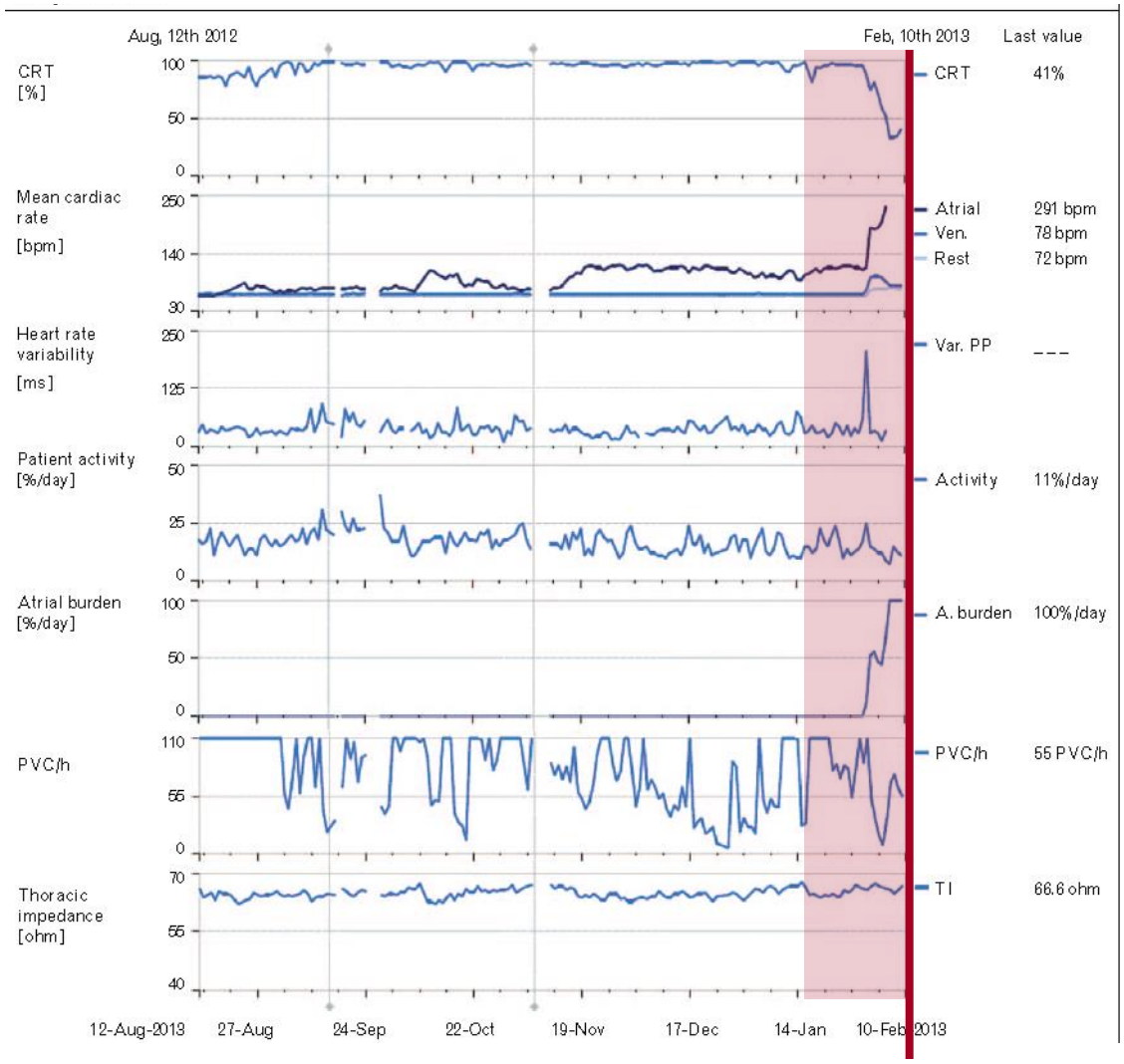
Service Center

Physician review Internet, email, SMS

Longitudinal Indexes

▪ Mean Heart Rate	⇨	▪ 1.8% increased risk of wHF per 1 bpm increase of mean heart rate
▪ Atrial Arrhythmias	⇨	▪ Well assessed predictor of wHF
▪ PVC frequency	⇨	▪ Associated with 5.5-fold increased risk of cardiovascular death
▪ Exercise and daily activity	⇨	▪ Inability to maximal exercise for at least 4 minutes predicts death and wHF
▪ Heart Rate variability	⇨	▪ HRV reduction is associated with wHF
▪ Thoracic Impedance	⇨	▪ 60% Positive Predictive Value

Example of longitaduinal indexes collected before a wHF hospitalization



hospitalization

Bio.Detect HF IV-SELENE HF Study. Objective

- We currently do not know how to interpret HF-related parameters and what is their predictive value in early detection of a worsening HF episode.
- The main objective of the SELENE HF study is to systematically analyze HM trends before wHF hospitalizations, to derive a possible recursive or typical dynamics likely predictive of an impeding acute episode.

Bio.Detect HF IV-SELENE HF Study. Endpoints

- Primary endpoint
  - *First* HF-related hospitalization
- Secondary endpoint
  - A composite of
    - death for worsening HF,
    - hospitalizations for worsening HF,
    - acute interventions for worsening HF.

- Blinding
  - Investigators are blinded to HF-related Home Monitoring indexes.
- Adjudication
  - wHF hospitalizations are being adjudicated by a 3-member independent CEC who review pseudomyzed hospital source documents.

Bio.Detect HF, SELENE HF Study Inclusion/Exclusion Criteria

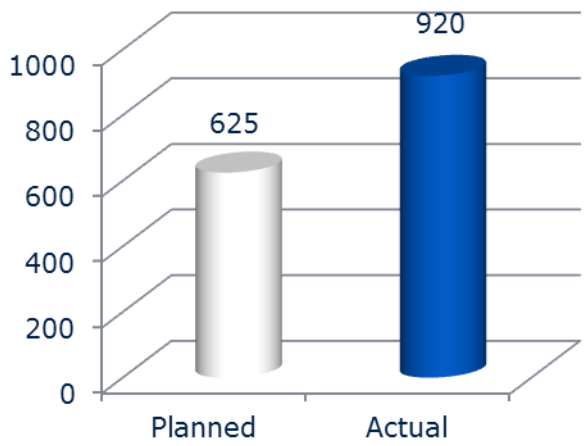
- Inclusion
  - subjects who have already received and ICD and/or CRT-D therapy within 12 months before study participation.
  - LVEF ≤ 35%;
  - NYHA Class II or III Heart Failure;
  - Men and women 18 years of age or older;
  - Understand the nature of the procedure;
  - Give written informed consent

- Main Exclusion Criteria
  - No indication or contraindication for ICD or CRT-D therapy;
  - Permanent AF;
  - NYHA Class IV Heart Failure;
  - Subjects with irreversible brain damage from preexisting cerebral disease;
  - Subjects with acutely decompensated heart failure;
  - Expected heart transplantation within next six months or planned cardiac surgery within next 3 months, or life expectancy less than six months.
  - Unstable geographical residence and/or GSM-free residence.

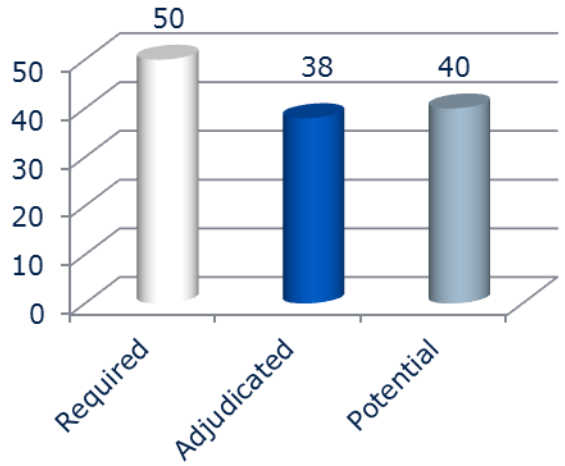
Current status

Primary endpoint:	first adjudicated hospitalization for worsening HF (wHF)
Study design	Event-driven
Required number of primary endpoints:	50
Initial estimate of required patients:	625
Actual	920
Current number of wHF hospitalizations	78
Adjudicated wHF	38
Adjudicated primary endpoints	25
Further Potential primary endpoints to be adjudicated	40
Follow-up closure estimate	Q3 2016

Enrolments



Primary endpoints



Population characteristics

Characteristics	All 921	ICD sub-group 517	CRT-D subgroup 404	p
Age	69 (61-76)	67 (59-74)	71 (64-78)	<0.001
Gender (male)	747 (81%)	441 (85%)	306 (76%)	<0.001
BMI (Kg/m2)	26.7 (24.2-29.4)	26.6 (24.2-29.4)	26.9 (24.3-29.8)	0.55
NYHA Class III	445 (48%)	230 (45%)	215 (53%)	0.009
Primary aetiology				
CAD with previous MI	402 (44%)	267 (52%)	135 (33%)	<0.001
CAD without MI	91 (10%)	51 (10%)	40 (10%)	0.54
DCM	369 (40%)	167 (32%)	202	<0.001
Valvular disease	18 (2%)	7 (1%)	11 (3%)	0.10
Other	32 (4%)	18 (4%)	4 (1%)	
AF history	128 (14%)	62 (12%)	66 (16%)	0.07
Echo				
LVEF (%)	30 (25-34)	30 (25-34)	30 (25-34)	0.45
LVESV (ml)	120 (94-159)	114 (90-150)	130 (97-172)	0.01
LVEDV (ml)	175 (140-223)	165 (133-209)	186 (147-238)	0.002
SHFM score	0.17 (-0.40/0.75)	0.13 (-0.44/0.68)	0.23 (-0.35/0.87)	0.04

Population characteristics

Characteristics	All 921	ICD sub-group 517	CRT-D subgroup 404	p
Comorbidities/previous procedures				
Stroke/TIA	64 (7%)	32 (6%)	32 (8%)	0.36
PCI	334 (36%)	228 (44%)	106 (26%)	<0.001
CABG	166 (18%)	102 (20%)	64 (16%)	0.14
Valvular surgery	70 (8%)	29 (6%)	41 (10%)	0.01
Chronic Kidney Disease	184 (20%)	94 (18%)	90 (22%)	0.12
Therapy at enrolment				
Antiplatelets/Anticoagulants/OAT	758 (82%)	443 (87%)	315 (78%)	0.002
Betablockers	773 (84%)	431 (83%)	342 (85%)	0.60
Calcium channel blockers	68 (7%)	37 (7%)	31 (8%)	0.77
Aldosterone blockers	228 (25%)	128 (25%)	100 (25%)	0.99
Digitals	44 (5%)	19 (4%)	25 (6%)	0.08
Nitrates	116 (13%)	57 (11%)	59 (15%)	0.10
Antiaarhythmics/Amiodarone	168 (18%)	89 (17%)	79 (19%)	0.36
ACE inhibitors	513 (56%)	289 (56%)	224 (55%)	0.89
Angiotensin II receptor antagonist	176 (19%)	85 (16%)	91 (22%)	0.02
Ivabradine	128 (14%)	84 (16%)	44 (11%)	0.02
Diuretics	775 (84%)	419 (81%)	356 (88%)	0.004

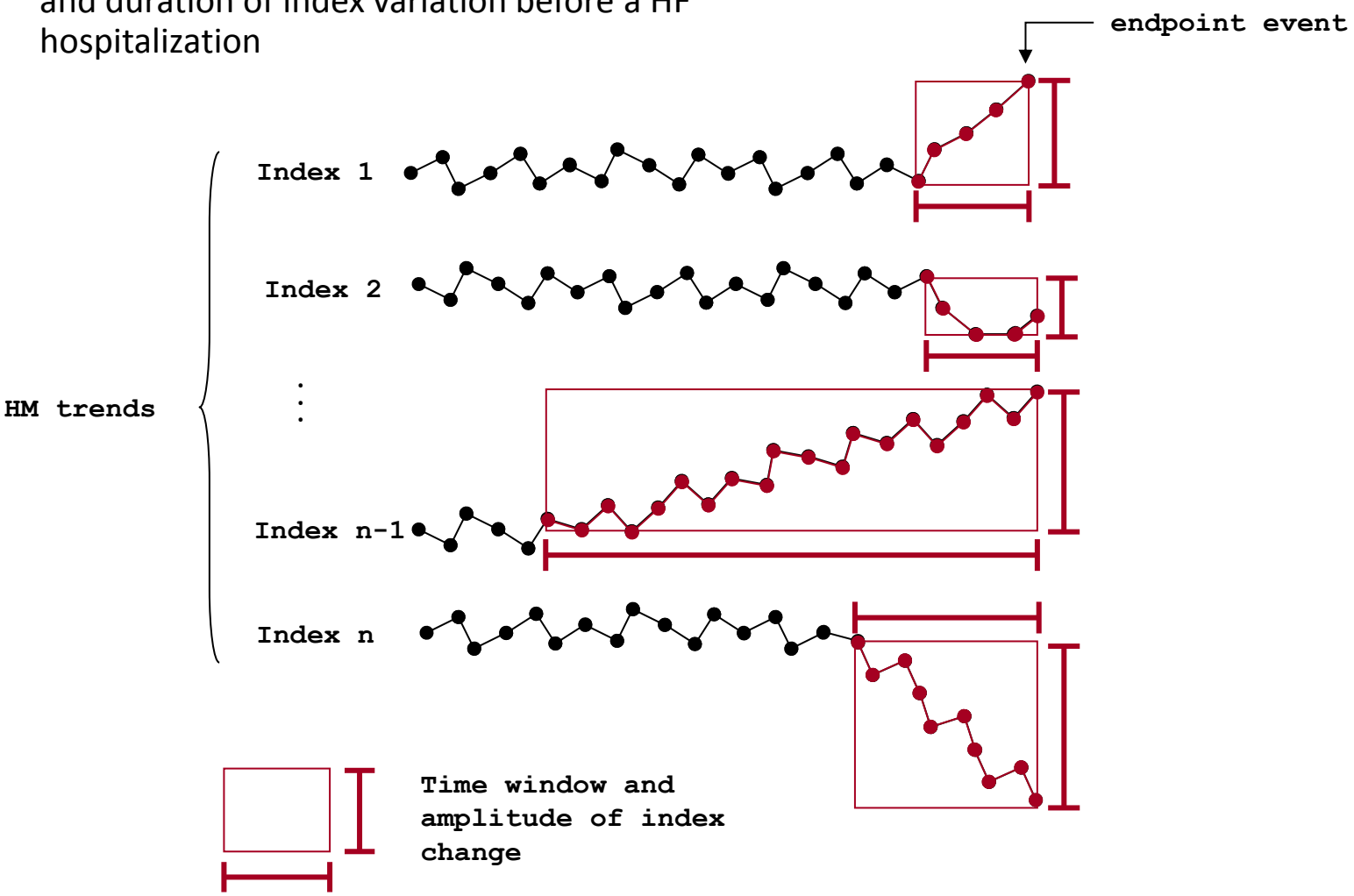
BIO.DETECT HF IV Study. Two analysis approaches

- Analysis is really challenging
- We will use two approaches:
  - standard modelling
  - an unconventional approach based on system complexity.

Analysis. Standard approach

Standard model

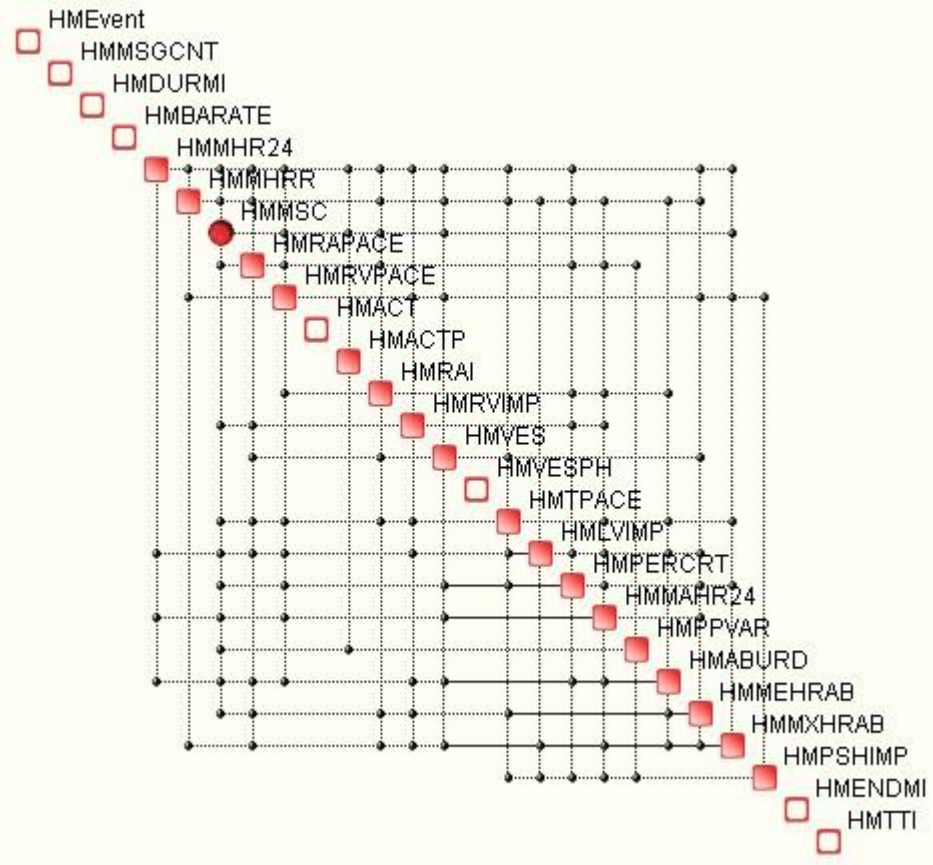
a multivariate model based on the amplitude and duration of index variation before a HF hospitalization



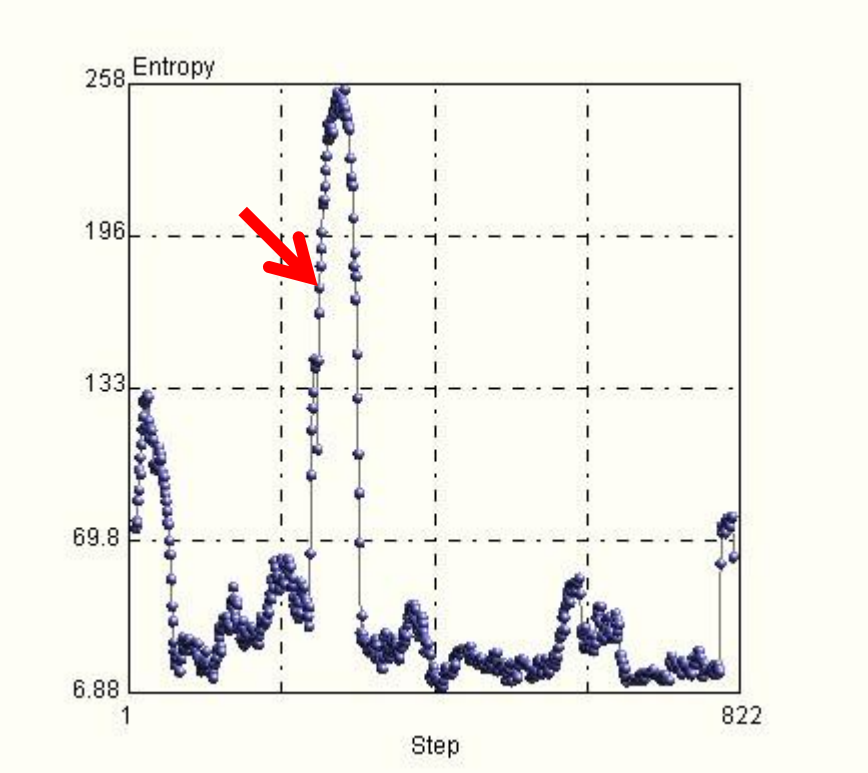
Model-free approach based on intrinsic amount of information (complexity)

Complexity analysis

- Complexity is a function of the internal entropy (total amount of information) which is an attribute characterizing every system, just like energy.
- It can be measured in every multiparameter system with supposed internal correlation.
- Correlation is not modelled, and no assumption is required
- Complexity has been used in economics, predicting many financial crisis



Patient ITA004-004
Complexity trend before wHF hospitalization



The arrow shows when the patient ITA004004 is hospitalized

Conclusions

- Nowadays Remote Monitoring (RM) has become part of routine HF patient follow-up management.
- The clinical benefit of RM is especially related to early detection and intervention in worsening HF.
- Several HF-related indexes are currently available remotely on daily basis.
- However
  - single pieces of information have a limited predictive value
  - a proper combination of more variables and their 24-hour sampling may allow developing a combined diagnostic algorithm to effectively predict HF worsening within given time windows.
- The BIO.DETECT HF IV study is collecting RM and HF hospitalization data which will be analyzed with a standard multivariate model and a model-free approach based on complexity.
- Results of final analysis are expected by the end of 2016.