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RHU iVASC: CONSTANCES et la recherche cardiovasculaire

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iVASC: Innovations in atherothrombosis science

Atherothrombosis: a major public health issue

Worldwide causes of death - 2010

- **1** Coronary Artery Disease
- 2 Stroke
- 3 COPD
- 4 Respiratory infections
- 5 Lung cancer

Lozano et al. Lancet 2012;380: 2095.

Multiple recent RCT failures in atherothrombosis

- •CETP inhibitors (Dal Outcomes, Illuminate, Accelerate)
- •Niacin (HPS2/Aim-High)
- Darapladib/varespladib (Solid/Stability/Vista16)
- Ivabradine (Beautiful/Signify)
- Losmapimod (Latitude)



Atherothrombosis: How can we make progress?

1. We need new hypotheses

Neglected cofactors in atherothrombosis initiation, progression and complication



iVAS

Atherothrombosis: How can we make progress?

- **1. We need new hypotheses**
- 2. We need new tools
 - Validated surrogate markers (biomarkers, molecular imaging of atherothrombosis)



Coronary plaques in TEP-DOTATATE

• Simpler, cheaper and more externally valid trials...

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

Lauer MS et al. *N Engl J Med* 2103; 369:1579.





Présentation du projet iVASC : présentation scientifique

iVASC – Academic and industry resources





Training/communication/knowledge diffusion and exchange

Regulatory

Governance



the iVASC cohort of MI survivors

- Create a multicenter prospective cohort of MI patients (approximately 7400 pts/year)
- Leveraging the FACT academic research network of 20+ clinical sites in France
- Collect detailed phenotypic information at baseline (hospital phase) including on periodontitis and sleep-disordered-breathing
- Use the expertise of CONSTANCES to link the registry to administrative/reimbursement databases (PMSI, SNIIRAM), to accrue comprehensive and continuous follow-up regarding survival, hospital admissions and procedures, morbid outcomes, health care consumption





Oral Health and atherothrombosis

- 1. Prevalence of periodontitis and association with incident CAD in the french general population
 - Development and validation of a questionnaire (based on the CDC/AAP 8item self-reported questionnaire
 - Evaluation in CONSTANCES to
 - Evaluate the prevalence of periodontitis in 100 000 cohort participants
 - Investigate the association of SDB with subsequent incidence of CV events (accounting for large number of potential confounders)





Oral Health and atherothrombosis

- **1.** Prevalence of periodontitis and association with incident CAD in the french general population
- 2. Prevalence of periodontitis and association with subsequent CV events in MI survivors
 - Cross sectional application of questionnaire in 7400 iVASC Cohort participants.
 - Longitudinal observation: prospective follow-up to study the association of good vs poor oral health with recurrent CV events. A medico economic study will be embedded to compare healthcare resource utilisation





Oral Health and atherothrombosis

- 1. Prevalence of periodontitis and association with incident CAD in the french general population
- 2. Prevalence of periodontitis and association with subsequent CV events in MI survivors
- 3. Intervention trial: treatment of severe periodontitis on PET-FDG uptake in atherosclerotic plaques in MI survivors





Rudd et al JACC 2017





SDB and atherothrombosis

- 1. Co-Sleep: SDB prevalence and association with incident CAD in the french general population
 - E-questionnaire (based on Berlin/STOP-Bang and Epworth) application in CONSTANCES to
 - Evaluate the prevalence of SDB in a sample of > 120 000 cohort participants
 - Investigate the association of SDB with the subsequent incidence of CV events (accounting for large number of potential confounders)





SDB and atherothrombosis

- 1. Co-Sleep: SDB prevalence and association with incident CAD in the french general population
- 2. AMI-Sleep: Prevalence of SDB and association with subsequent CV events in MI survivors
 - Systematic screening for SDB in 4000 iVASC Cohort participants using simplified polygraphy device (ApneaLink), with core lab telescoring using cloud-based data management, and telecounselling.





VAS

 Longitudinal observation: prospective follow-up to study the association of SDB (AHI and oxygen desaturation parameters) with recurrent CV events. A medico economic study will be embedded to compare healthcare resource utilisation





SDB and atherothrombosis

- 1. Co-Sleep: SDB prevalence and association with incident CAD in the french general population
- 2. AMI-Sleep: Prevalence of SDB and association with subsequent CV events in MI survivors
- 3. Intervention trial: treatment of SDB in MI or Stroke survivors





The SAVE trial of CPAP in pts with CAD or CVD and OSA

ITT analysis



Primary outcome - composite of MI, stroke, hospitalisation for UA, TIA or heart failure, and CV death

McEvoy et al. NEJM 2016

The SAVE trial of CPAP in pts with CAD or CVD and OSA

ITT analysis



Primary outcome - composite of MI, stroke, hospitalisation for UA, TIA or heart failure, and CV death Matched Per protocol analysis

	Hazard Ratio	
	(95% CI)	Р
Composite primary outcome, no. (%)	0.80 (0.60 to 1.07)	0.13
Components of primary endpoint		
CV Death	0.90 (0.41 to 2.01)	0.81
Myocardial infarction	1.19 (0.59 to 2.39)	0.63
Stroke	0.56 (0.32 to 1.00)	0.05
Hospitalisation for TIA	0.22 (0.03 to 2.01)	0.18
Other vascular endpoints		
Composite of ischaemic CV events	0.81 (0.59 to 1.10)	0.17
Composite of major CV events	0.69 (0.46 to 1.04)	0.08
Composite for cerebral events	0.52 (0.30 to 0.90)	0.02

CPAP good compliers (i.e. >4 hrs/night; n=561) matched 1:1 with usual care patients by propensity scores

McEvoy et al. **NEJM** 2016

Improve science

- Epidemiology
- •Registry based RCTs
- Molecular imaging
- Biomarkers
- •Oral microbiome





Improve Health

- Oral Health
- Sleep disordered breathing
- Clinical applications of molecular imaging
- Treatments tested via registrybased RCTs

- Improve science
- •Epidemiology
- Registry based RCTs
- •Molecular imaging
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Improve science

- Registry based RCTs
- Molecular imaging
- Biomarkers
- Oral microbiome
- Epidemiology

TANCES

Improve Health

- Oral Health
- Sleep disordered breathing
- Clinical applications of molecular imaging
- Treatments tested via registry-based RCTs

Create value

- Annexin imaging
- DOTATATE CV applications
- CD-31 as biomarker
- SDB monitoring and treatment devices
- Registry data



Create value Improve

- Annexin imaging
- DOTATATE CV applications
- CD-31 as biomarker
- SDB monitoring and treatment devices
- Registry data

Disseminate knowledge

- iVASC workshops and conferences
- MOOC on atherothrombosis
- Public health awareness campaigns on oral health, SDB and CV disease

Improve science

- Registry based RCTs
- Molecular imaging
- Biomarkers
- Oral microbiome



Oral Health

Health

- Sleep disordered breathing
- Clinical applications of molecular imaging
- Treatments tested via registry-based RCTs

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CONSTANCES is a critical component of the iVASC consortium

CONSTANCES provides a cohort in which cross sectional and longitudinal studies can be conducted

The CONSTANCES infrastructure provides know-how for linking the iVASC cohort to large databases (SNIIRAM) for comprehensive follow-up

For more information: www.ivasc.eu

