RHU iVASC: CONSTANCE 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  

**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

Conventional Risk Factors
(Hypertension/cholesterol/smoking/diabetes/etc...)

Sleep Disordered Breathing

Atherothrombosis

MI

Stroke

Periodontitis
Atherothrombosis: How can we make progress?

1. We need new hypotheses

2. We need new tools
   - Validated surrogate markers (biomarkers, molecular imaging of atherothrombosis)
   - Simpler, cheaper and more externally valid trials...

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

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

iVASC – Academic and industry resources
**Tools**
- Registry
- Cohorts
- Biobanks
- Molecular Imaging

**Discovery**
- Sleep Disordered Breathing
- Oral Health

**Outputs**
- Improved prevention
- New therapies
- New biomarkers
- Tailored therapies
- Valorization/IP management
  Economical/Societal Impact

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**Training/communication/knowledge diffusion and exchange**

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**Regulatory**

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**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 8-item 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
MI survivors with severe periodontitis
Able to undergo periodontal surgical and non surgical Rx
Standardized post MI medical Rx

PET-FDG imaging
Gingival microbiome – systemic biomarkers

Usual care in the community

Intensive periodontal Rx in specialized center
Randomized Open-label

24 months PET FDG follow-up
Gingival microbiome – systemic biomarkers
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.

   - 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

Hazard ratio (95% CI) 1.10 (0.91 - 1.32)

McEvoy et al. NEJM 2016

**Primary outcome** - composite of MI, stroke, hospitalisation for UA, TIA or heart failure, and CV death
The SAVE trial of CPAP in pts with CAD or CVD and OSA

**ITT analysis**

**Matched Per protocol analysis**

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td><strong>Composite primary outcome, no. (%)</strong></td>
<td>0.80 (0.60 to 1.07)</td>
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<tr>
<td><strong>Components of primary endpoint</strong></td>
<td></td>
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<tr>
<td>CV Death</td>
<td>0.90 (0.41 to 2.01)</td>
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<tr>
<td>Myocardial infarction</td>
<td>1.19 (0.59 to 2.39)</td>
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<tr>
<td><strong>Stroke</strong></td>
<td>0.56 (0.32 to 1.00)</td>
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<tr>
<td>Hospitalisation for TIA</td>
<td>0.22 (0.03 to 2.01)</td>
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<tr>
<td><strong>Other vascular endpoints</strong></td>
<td></td>
</tr>
<tr>
<td>Composite of ischaemic CV events</td>
<td>0.81 (0.59 to 1.10)</td>
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<tr>
<td>Composite of major CV events</td>
<td>0.69 (0.46 to 1.04)</td>
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<tr>
<td><strong>Composite for cerebral events</strong></td>
<td>0.52 (0.30 to 0.90)</td>
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CPAP good compliers (i.e. >4 hrs/night; n=561) matched 1:1 with usual care patients by propensity scores

Improve science

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

- Oral Health
- Sleep disordered breathing
- Clinical applications of molecular imaging
- Treatments tested via registry-based RCTs
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**Create value**
- Annexin imaging
- DOTATATE CV applications
- CD-31 as biomarker
- SDB monitoring and treatment devices
- Registry data
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Disseminate knowledge
- iVASC workshops and conferences
- MOOC on atherothrombosis
- Public health awareness campaigns on oral health, SDB and CV disease

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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