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Advances in coronary physiology

Instantaneous wave-free ratio: an adenosine-independent index to guide coronary revascularisation

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Summary

The use of coronary physiology to guide myocardial revascularisation was shown to improve clinical outcomes and reduce costs in patients with coronary artery disease. Fractional flow reserve (FFR) is the most commonly used pressure-derived physiological index for coronary lesion assessment, being supported by a body of compelling randomised evidence, but its uptake into clinical practice remains unacceptably low.

The instantaneous wave-free ratio (iFR) is a novel adenosine-free pressure-derived index of coronary stenosis severity that was recently introduced to circumvent the limitations of existing hyperaemic pressure-derived indices with the aim of increasing the widespread adoption of coronary physiology assessment. Following the recent publication of two large-scale, randomised, patient outcome clinical trials, iFR has emerged as a simpler, safe and effective alternative to FFR to guide coronary revascularisation. This has led to renewed interest in the field of coronary physiology and challenges current paradigms supporting the need for pharmacologically-induced maximal hyperaemia as an essential requirement for coronary stenosis assessment. This review aims at addressing the physiological concepts and patient outcome evidence supporting the use of iFR and discuss the recent development of novel iFR-based applications allowing full integration of invasive coronary physiology in percutaneous coronary intervention planning strategy.

Key words: instantaneous wave-free ratio; coronary physiology; coronary revascularization

Introduction

Inducible myocardial ischaemia is considered to be a prerequisite for the clinical benefit of coronary revascularisation [1]. In this regard, the introduction of invasive pressure-derived physiological indices to guide myocardial revascularisation represented a major breakthrough in the treatment of patients with coronary artery disease (CAD), by moving the focus of coronary revascularisation from anatomy to physiology [2] (table 1). The main premise of coronary physiology assessment is to determine the functional significance of individual stenoses at the time of clinical decision-making, providing an objective marker to identify ischaemic lesions, and therefore patients, most likely to benefit from coronary revascularisation [1]. Fractional flow reserve (FFR) is the most widely used pressure-derived invasive physiological index for coronary lesion assessment in contemporary clinical practice. FFR is the ratio of the mean distal coronary pressure (Pd) to the mean proximal coronary pressure (Pa) across a stenosis during maximal hyperaemia, a condition that is commonly achieved by the intracoronary or intravenous administration of a potent vasodilator agent, such as adenosine [3–5]. Based on the results of landmark clinical trials [6–11] (table 2), most recent guidelines recommend the use of FFR to identify haemodynamically significant coronary lesions in patients with stable CAD [1, 12]. Despite this, the worldwide adoption of FFR into current clinical practice remains limited [13], accounting for less than 10% of coronary procedures in Switzerland [14]. Potential reasons for the low uptake of coronary physiology assessment include technical challenges related to FFR measurements, time consumption, inadequate or lack of reimbursement, physician preferences, patient-related discomfort, and contraindications to or costs associated with adenosine. Furthermore, adenosine is either not licensed nor unavailable in some healthcare systems. The instantaneous wave-free ratio (iFR) is a novel pressure-based physiological index of coronary stenosis severity that is measured under resting conditions by making use of the unique properties of baseline coronary physiology and does not require the administration of vasodilator drugs, such as adeno-
Table 1: Invasive physiological indices to assess the functional significance of coronary artery stenosis.

<table>
<thead>
<tr>
<th>Index</th>
<th>Conditions of measurement</th>
<th>Interrogation level</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR</td>
<td>Hyperaemia</td>
<td>Epicardial level</td>
<td>• Established cut-off</td>
<td>• Need for hyperaemic agents&lt;br&gt;• High inter-patient variability in microvascular resistance during vasodilatation induced by adenosine&lt;br&gt;• Affected by haemodynamic variables</td>
</tr>
<tr>
<td>iFR</td>
<td>Baseline</td>
<td>Epicardial level</td>
<td>• No need for hyperaemic agents&lt;br&gt;• Established cut-off&lt;br&gt;• Assessment of tandem and/or diffuse coronary lesions</td>
<td>• Requires proprietary software&lt;br&gt;• Longer-term outcome results warranted&lt;br&gt;• Outcome data in higher-risk patient subgroups needed</td>
</tr>
<tr>
<td>Resting Pd/Pa</td>
<td>Baseline</td>
<td>Epicardial level</td>
<td>• No need for hyperaemic agents</td>
<td>• Not validated in randomised controlled trials&lt;br&gt;• Longer-term outcome results warranted&lt;br&gt;• Outcome data in higher-risk patient subgroups needed</td>
</tr>
<tr>
<td>Contrast FFR</td>
<td>Hyperaemia</td>
<td>Epicardial level</td>
<td>• Resting index correlating best with FFR</td>
<td>• No contrast dose established in randomised controlled trials&lt;br&gt;• Contrast induces short-lived hyperaemia</td>
</tr>
<tr>
<td>CFR</td>
<td>Hyperaemia</td>
<td>Epicardial level and microcirculation</td>
<td>• Prognostic marker</td>
<td>• Inability to differentiate the effects of microvascular dysfunction from effects of the epicardial lesion&lt;br&gt;• Need for hyperaemic agents&lt;br&gt;• Affected by haemodynamic variables</td>
</tr>
<tr>
<td>HSR</td>
<td>Hyperaemia</td>
<td>Epicardial level</td>
<td>• Combination of flow and pressure measurement&lt;br&gt;• Established cut-off</td>
<td>• Need for hyperaemic agents&lt;br&gt;• Largely confined to research setting owing to difficulty of measurement technique</td>
</tr>
<tr>
<td>BSR</td>
<td>Baseline</td>
<td>Epicardial level</td>
<td>• Combination of flow and pressure measurement&lt;br&gt;• No need for hyperaemic agents</td>
<td>• No established cut-off&lt;br&gt;• Less accurate than HSR&lt;br&gt;• Largely confined to research setting owing to difficulty of measurement technique</td>
</tr>
</tbody>
</table>

BSR: basal stenosis resistance; CFR: coronary flow reserve; FFR: fractional flow reserve; HSR: hyperaemic stenosis resistance; iFR: instantaneous wave-free ratio; Pd/Pa: ratio of the mean distal coronary pressure to the mean proximal coronary pressure.

Table 2: Summary of FFR pivotal patient outcome trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study question</th>
<th>Study population</th>
<th>Patients in the coronary physiology-guided group (n)</th>
<th>Study primary endpoint</th>
<th>FFR cut-off for treatment</th>
<th>Mean FFR values</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFER</td>
<td>Safety of deferral of PCI in patients with FFR &gt;0.75</td>
<td>Stable CAD</td>
<td>325</td>
<td>MACE1 at 4 months</td>
<td>≤0.75</td>
<td>• Defer group: 0.87 ± 0.07 (n = 91)&lt;br&gt;• Performance group: 0.87 ± 0.06 (n = 90)&lt;br&gt;• Reference group: 0.56 ± 0.16 (n = 144)</td>
<td>Deferral of PCI in lesions with FFR &gt;0.75 is safe</td>
</tr>
<tr>
<td>FAME 8</td>
<td>Efficacy of FFR-guided PCI vs angiography alone-guided PCI</td>
<td>Multivessel stable CAD / ACS with non-culprit stenosis</td>
<td>1005</td>
<td>MACE2 at 12 months</td>
<td>≤0.80</td>
<td>• Overall cohort: 0.71 ± 0.18&lt;br&gt;• Ischaemic lesions: 0.60 ± 0.14&lt;br&gt;• Non-ischaemic lesions: 0.88 ± 0.05</td>
<td>FFR-guided PCI is superior to angiography alone-guided PCI</td>
</tr>
<tr>
<td>FAME 2</td>
<td>FFR-guided PCI + OMT vs OMT alone in patients with FFR ≤0.80</td>
<td>Multivessel stable CAD</td>
<td>1220</td>
<td>MACE2 at 24 months (trial prematurely stopped at 7-month follow-up)</td>
<td>≤0.80</td>
<td>• FFR guided PCI + OMT: 0.68 ± 0.10&lt;br&gt;• OMT alone: 0.68 ± 0.15</td>
<td>FFR guided PCI + OMT reduces ischaemic outcomes compared with OMT alone</td>
</tr>
</tbody>
</table>

Total 2550 2054

ACS: acute coronary syndrome; CAD: coronary artery disease; FFR: fractional flow reserve; MACE: major adverse cardiac events; OMT: optimal medical treatment; PCI: percutaneous coronary intervention.

1 Composite of all-cause mortality, myocardial infarction, CABG, coronary angioplasty, and any procedure-related complication necessitating major intervention or prolonged hospital stay.

2 Composite of death, myocardial infarction, and any repeat revascularisation.

3 Composite of death from any cause, non-fatal myocardial infarction, or unplanned hospitalisation leading to urgent revascularisation.
sine [15]. iFR has recently emerged as a simpler, safe and effective alternative to FFR to guide coronary revascularisation, contributing to a renewed interest in the field of coronary physiology and challenging current paradigms supporting the need of pharmacologically induced maximal hyperaemia as an essential requirement for coronary stenosis assessment. The purpose of the present review is to address the rationale, fundamentals and available patient outcome data supporting the use of iFR for physiological lesion assessment and discuss present and future applications of the iFR technology.

**Fractional flow reserve**

FFR is currently considered the gold standard for assessment of the functional significance of coronary stenosis, being supported by a large body of randomised evidence demonstrating its value in clinical decision making [6–11]. FFR is defined as the ratio of maximum achievable coronary blood flow (CBF) in the presence of an epicardial coronary stenosis and the theoretical maximum CBF in the hypothetical absence of the coronary stenosis during maximal pharmacological vasodilation [3].

**Patient outcome trials**

The use of FFR to guide coronary revascularisation is supported by several randomised patient outcome trials (table 2). DEFER (Deferral versus performance of percutaneous transluminal coronary angioplasty (PTCA) in patients without documented ischaemia) was a prospective, randomised trial including 325 patients with stable CAD referred for elective percutaneous coronary intervention (PCI) who underwent FFR assessment of de novo intermediate coronary lesions [6]. Patients with FFR ≥0.75 were randomly assigned to deferral or PCI, whereas patients with FFR <0.75 underwent PCI as planned (reference group). The primary endpoint was the absence of major adverse cardiac events (MACE) during 24 months of follow-up. Event-free survival was similar between deferred and treated patients (89 vs 83% at 24 months), but was significantly lower in the reference group (78% at 24 months) [6]. Moreover, the proportion of patients free from angina was similar in deferral and PCI groups (70 vs 51%) but was significantly higher in the reference group (80%) [6]. Subsequently, 5-year follow-up of the DEFER cohort confirmed that long-term outcomes of patients after deferral of PCI in intermediate coronary stenosis with FFR ≥0.75 were excellent [7].

FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) was a prospective, multicentre trial that randomly assigned 1005 patients with multivessel CAD to FFR-guided or to angiography-alone-guided coronary revascularisation with drug-eluting stents [8]. The incidence of the primary endpoint of MACE, a composite of death, nonfatal myocardial infarction (MI) or repeat revascularisation at 1 year, was significantly lower in the FFR group compared with the angiography-alone group (13.2 vs 18.3%, respectively; relative risk 0.72, 95% confidence interval [CI] 0.54–0.96; p = 0.02) [8]. Furthermore, physiology-guided revascularisation using a FFR threshold >0.80 was associated with fewer stents, less contrast volume, and reduced costs compared with coronary revascularisation guided by visual assessment only.

In the prospective, multicentre, randomised FAME 2 trial, patients with angiographically documented stable CAD and candidates for PCI underwent FFR assessment to determine the haemodynamic severity of each indicated coronary stenosis [9]. Patients with an FFR ≤0.80 in at least one stenosis were randomly assigned to an FFR-guided PCI strategy plus optimal medical therapy (OMT) or OMT alone, whereas patients with an FFR >0.80 in all vessels with indicated coronary stenoses were enrolled in a registry and received OMT. The primary endpoint was a composite of death, MI, or unplanned hospitalisation leading to urgent revascularisation during the first 2 years. Recruitment was halted prematurely after enrolment of 1220 patients (median follow-up 7 months) owing to a large reduction in the primary composite endpoint in the FFR-guided PCI+OMT group compared with the OMT alone group (4.3 vs 12.7%, respectively; hazard ratio [HR] 0.32, 95% CI 0.19–0.53; p <0.001), driven by significantly lower rates of urgent revascularisation (1.6 vs 11.1%; HR 0.13, 95% CI 0.06–0.26; p <0.001) in the FFR-guided PCI arm. Notably, rates of death from any cause, cardiac death and MI were not statistically different between the two groups [9]. The longer-term follow-up of the FAME 2 trial demonstrated persistent lower rates of the primary composite endpoint in the FFR-guided PCI group compared with the angiography-alone group (13.2 vs 18.3%, respectively; relative risk 0.72, 95% confidence interval [CI] 0.54–0.96; p = 0.02) [8]. Furthermore, physiology-guided revascularisation using a FFR threshold >0.80 was associated with fewer stents, less contrast volume, and reduced costs compared with coronary revascularisation guided by visual assessment only.
use of FFR to guide coronary revascularisation in contemporary practice remains low.

Limitations of the hyperaemic pressure-derived physiological indices
The concept of FFR and hyperaemic pressure-derived indices of coronary stenosis severity depends on the fundamental physiological principle that coronary pressure is directly proportional to CBF when microvascular resistance is stable, a condition that is commonly achieved during the administration of hyperaemic agents, such as adenosine [3, 16]. Under these conditions, the decrease in pressure across a coronary stenosis reflects the decrease in CBF to the amount of subtended myocardium. This assumption was translated into the paradigm that coronary pressure can only be considered as a surrogate to CBF during maximal hyperaemia. Nonetheless, the cornerstone of FFR is based on a simplified theoretical model of the coronary circulation, thereby potentially limiting the diagnostic accuracy of FFR in clinical practice.

The relationship between pressure and flow is indeed not linear but curvilinear. The pressure-flow correlation is straight in the physiological range of perfusion pressures (incremental-linear relationship) and curves towards the pressure axis at lower perfusion pressures (non-zero pressure intercept), owing to several conditions such as central venous pressure (deducted from both proximal and distal coronary pressure in the experimental validation of FFR, because considered as negligible), collateral flow, epicardial capacitance and intramyocardial compliance [17]. Furthermore, microcirculatory resistance, which is influenced by many factors including capacitive, inertial and resistive forces, or the complex effects of systolic contraction, fluctuates in a phasic pattern throughout the cardiac cycle even after administration of potent pharmacological agents [15]. These fluctuations reflect the close interaction between myocardium and microcirculation during systole (high intracoronary resistance, microvasculature compression) and diastole (lower intracoronary resistance, microvasculature decompression) [18]. To minimise these effects, the FFR is calculated during hyperaemia and time-averaged over several cardiac cycles to ensure constant intracoronary resistance. Importantly, the actual coronary microvascular resistance values are not routinely measured in clinical practice as they cannot be derived from pressure measurements alone; thus, coronary resistance is assumed to be constant (and minimal). This represents a potential source of error in the assessment of FFR, as any unaccounted variability in minimal microvascular resistance will influence FFR values. The impact of this variability is more relevant in lesions within the intermediate range of coronary stenosis severity than for minimally obstructed coronary arteries [17].

The achievement of maximal hyperaemia in clinical practice is less attainable than currently acknowledged. Adenosine is the most widely used vasodilatory pharmacological agent and represents the current gold standard to induce maximal hyperaemia during FFR measurements [19]. Nevertheless, the vasodilatory response to adenosine may be incomplete in some patients as a result of the complex physiological mediation of vascular tone, therefore precluding achievement of a true and predictable maximal hyperaemic state in all patients [17]. Accordingly, hyperaemic microvascular resistance during vasodilatation induced by adenosine is highly variable between patients, and between adjacent perfusion territories within the same patient, thus compromising the validity of the FFR concept [17]. Finally, adenosine is associated with significant adverse effects and patient discomfort such as dyspnoea, chest pain and headache, and is contraindicated in patients with documented allergy to adenosine or severe asthma.

Hyperaemia-free pressure-derived indices of coronary stenosis severity
Adenosine-free pressure-derived physiological indices were recently introduced to further simplify physiological coronary assessment. By negating the need for administration of pharmacological agents such as adenosine, saving time, and reducing costs and side effects, hyperaemia-free pressure-derived physiological indices were developed to increase adoption of physiological coronary revascularisation into routine clinical practice. Pioneering studies performed more than 40 years ago demonstrated that, whereas hyperaemic CBF was affected only when the coronary lumen was reduced by at least 50%, resting CBF remained unaltered until the coronary lumen diameter was reduced by at least 85%, owing to the counteractive effects of coronary autoregulation [20]. With progressive narrowing of the coronary lumen, coronary autoregulation maintains a constant CBF through compensatory vasodilatation of the distal coronary resistance vessels. The stable baseline CBF conditions therefore provide an ideal environment for the development of resting pressure-based indices of coronary stenosis severity.

Instantaneous wave-free ratio
Fundamentals
iFR is a novel non-hyperaemic pressure-derived index of coronary stenosis severity, which is measured at rest
by using the unique properties of baseline coronary physiology, and does not require administration of potent pharmacological vasodilator agents, such as adenosine. iFR is measured during a specific period of diastole, called the wave-free period (WFP), when CBF is intrinsically at its highest compared with the whole cardiac cycle [15]. By means of measurement during a higher flow velocity, the capacity to discriminate between stenosis severities at rest is amplified and greater than during any other phase of the cardiac cycle.

The WFP was originally isolated by application of wave-intensity analysis (WIA). Pioneering work using WIA demonstrated that the forces propagating from the proximal vessel (aorta and other systemic arteries) conflict with those travelling from the distal end (microcirculation) [18]. During the WFP, a specific diastolic period, no new waves are generated and competing waves affecting CBF are quiescent [15] (fig. 1). During this time window, coronary flow velocity is approximately 30% higher than whole-cycle resting flow velocity, intracoronary pressure and flow decline linearly and microcirculatory resistance is significantly more stable and lower than over the rest of cardiac cycle [15]. Importantly, this period of the cardiac cycle was found to have the lowest and most stable resistance attainable under resting conditions without the need for maximal pharmacological vasodilation [15]. Accordingly, the iFR is calculated as the ratio of distal coronary pressure to proximal aortic pressure during the WFP [15]. Notably, iFR can be calculated on a beat-by-beat basis without requiring several beats to be averaged, including during irregular heart rhythms, such as atrial fibrillation [15]. The IDEAL (Iberian-Dutch-English) study provided the physiological framework for iFR by analysing pressure-flow relationship in a wide range of stenosis severities under both resting and hyperaemic conditions [22]. The study demonstrates that pressure gradients across coronary stenosis at rest are predominantly determined by compensatory vasodilator changes in microvascular resistance due to coronary autoregulation [22]. These findings supported the translation of early coronary physiological concepts derived from animal models to CAD patients by

Figure 1: Basic concepts of iFR. (A) Wave-intensity analysis demonstrates the proximal and distal (microcirculatory) originating waves generated during the cardiac cycle. A wave-free period is identified in diastole when no new waves are generated (green) corresponding to a time period in which there is minimal microcirculatory-originating pressure, minimal and constant resistance and a nearly constant rate of change in coronary flow velocity. (B) Coronary flow velocity, proximal and distal pressure traces and instantaneous resistance demonstrate the beat-to-beat stability of the wave-free period. Flow velocity over the wave-free period is higher than that over the whole cardiac cycle, allowing greater discrimination between stenosis severities than over the whole cycle at rest. Reprinted with permission from Nijjer SS, Sen S, Petraco R, Davies JE. Advances in coronary physiology. Circ J. 2015;79(6):1172–84.
suggested that resting pressure-derived indices could be used to determine haemodynamic significance of coronary artery stenoses in clinical practice.

**Early validation studies**

The ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) [15] and ADVISE registry [23] studies assessed the diagnostic accuracy of iFR compared with FFR. In the ADVISE validation study, iFR was found to correlate closely with FFR with excellent diagnostic accuracy (receiver-operating characteristic [ROC] area under the curve 93%, at FFR cut-off threshold of 0.80), specificity (91%), sensitivity (85%), negative (85%) and positive (91%) predictive values [15]. In a large-scale core laboratory-based analysis, the overall linear correlation between iFR and FFR was moderate with an overall diagnostic accuracy of >80% using the optimal ROC-determined iFR cut-off of 0.90 to predict a FFR ≤0.80, which can be improved to ≥90% in a subset of lesions [24]. In the international ADVISE registry including 312 patients with angiographically intermediate stenoses, a close classification agreement was found between iFR and FFR (area under ROC curve 86%). To match an FFR value of 0.80, the ROC curve identified an optimal iFR cut-off value of 0.89. Further validation studies showed that iFR with a cut-point of 0.89 had diagnostic accuracy that was at least as good as, and in some cases superior to, FFR when compared with hyperaemic stenosis resistance [25, 26], myocardial perfusion studies [27] and positron emission tomography [28].

**The iFR-FFR hybrid strategy**

The high classification agreement between FFR and iFR outside of the intermediate zone provided the rationale for the use of a staged, hybrid iFR-FFR decision-making strategy, in which only patients within a certain range of intermediate iFR values (0.86–0.93) would require adenosine for FFR classification of lesions [29]. With an FFR cut-off value of 0.80, an iFR ≤0.86 was associated with a high positive predictive value (92%) to confirm treatment, whereas an iFR >0.93 was associated with a high negative predictive value (91%) to defer treatment. Limiting the use of adenosine to cases with iFR values between 0.86 to 0.93 obviated the need for a vasodilator drug in 57% of patients (76% in the FFR 0.75–0.80 range), while maintaining 95% agreement with an FFR-only strategy [29]. However, with the recent publication of randomised patient outcome trials comparing iFR using a single cut-off value with FFR to guide coronary revascularisation, the routine use of an iFR-FFR hybrid strategy is currently not recommended.

**Patient outcome trials**

Recently, two large-scale, randomised, controlled, patient outcome trials, DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) [30] and iFR-SWEDEHEART (Evaluation of iFR versus FFR in Stable Angina or Acute Coronary Syndrome) [31], addressed the question as to whether iFR was a safe and effective alternative to the established gold standard FFR to guide to coronary revascularisation in patients with CAD. The DEFINE-FLAIR and iFR-SWEDEHEART studies were designed similarly, with prespecified single thresholds for treatment (iFR ≤0.89, FFR ≤0.80) and deferral (iFR >0.89, FFR >0.80), and the primary endpoint was standardised as the 1-year risk of MACE, defined as a composite of all-cause death, nonfatal MI or unplanned revascularisation. The DEFINE-FLAIR and iFR-SWEDEHEART trials were designed to investigate the noninferiority of iFR to FFR with respect to noninferiority margins of 3.4 and 3.2% for the difference in risk. Importantly, these noninferiority margins were more conservative than margins commonly used in studies evaluating medical devices or drugs [31, 32]. Overall, the main results of DEFINE-FLAIR and iFR-SWEDEHEART trials were remarkably concordant in demonstrating that coronary revascularisation guided by iFR was noninferior to an FFR-guided strategy with respect to 1-year clinical outcomes. The DEFINE-FLAIR and iFR-SWEDEHEART studies represent a major step forward in the field of invasive coronary physiology assessment by expanding significantly the available randomised patient outcome data for physiology-guided coronary revascularisation (table 3).

Moreover, DEFINE-FLAIR and iFR-SWEDEHEART trials provide the first randomised evidence for iFR-guided decision making for coronary revascularisation and validated the use of a single iFR 0.89 cut-off value in clinical practice, thereby eliminating the need of a diagnostic grey zone or a hybrid approach. DEFINE-FLAIR is the largest randomised trial to date assessing use of coronary physiology to guide myocardial revascularisation. DEFINE-FLAIR was a prospective, multicentre, international, double-blinded, randomised, noninferiority trial that randomly assigned 2492 patients with at least one intermediate coronary artery stenosis of questionable physiological severity in a 1:1 ratio to undergo either iFR-guided or FFR-guided coronary revascularisation [30]. Patients with stable CAD or with acute coronary syndrome (ACS) with bystander intermediate CAD in non-culprit vessels were included. Unlike the study populations included in the landmark DEFER and FAME trials (mean FFR values 0.71 and 0.75, respectively), the mean FFR value of patients...
Table 3: Summary of pivotal iFR patient outcome trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study population (n)</th>
<th>Patients in the coronary physiology-guided group (n)</th>
<th>Mean FFR value</th>
<th>Mean IFR value</th>
<th>Patients deferred by FFR (n, % total assessed)</th>
<th>Patients deferred by IFR (n, % total assessed)</th>
<th>MACE rate in the FFR arm (%)</th>
<th>MACE rate in the IFR arm (%)</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>p-value for superiority</th>
<th>p-value for noninferiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFINE-FLAIR [23]</td>
<td>2492</td>
<td>[29]</td>
<td>[29]</td>
<td>[29]</td>
<td>0.83 ± 0.09 (n = 1250)</td>
<td>0.91 ± 0.09 (n = 1242)</td>
<td>583 (46.6)</td>
<td>652 (52.5)</td>
<td>7.0</td>
<td>6.8</td>
<td>0.95 (0.68–1.33)</td>
</tr>
<tr>
<td>IFR-SWEDEHEART [30]</td>
<td>2037</td>
<td>0.82 ± 0.10 (n = 1019)</td>
<td>0.91 ± 0.10 (n = 1018)</td>
<td>438 (43.5)</td>
<td>476 (46.7)</td>
<td>6.1</td>
<td>6.7</td>
<td>1.12</td>
<td>(0.79–1.58)</td>
<td>0.53</td>
<td>0.007</td>
</tr>
<tr>
<td>Total</td>
<td>4529</td>
<td>4529</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>

FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; MACE: major adverse cardiac events, defined as a composite of death from any cause, non-fatal myocardial infarction, or unplanned revascularisation, at 12 months.

included in DEFINE-FLAIR was 0.83 ± 0.09 (table 3), emphasising that the majority of patients presented with lesions that truly fell in the intermediate severity range, and therefore that conclusions from the study are relevant for the patients whom iFR and FFR were originally designed to investigate. The primary endpoint was the 1-year risk of MACE, a composite of death from any cause, nonfatal MI, or unplanned revascularisation. At 1-year follow-up, coronary revascularisation guided by iFR was noninferior to revascularisation guided by FFR with respect to the risk of MACE (6.8 vs 7.0%; difference in risk 0.2 percentage points; 95% CI 2.3–1.8; p <0.001 for noninferiority; HR 0.95; 95% CI 0.68–1.33; p = 0.78). The incidence of individual components of the composite endpoint did not differ significantly between the two groups. Importantly, the number of patients who had adverse procedural symptoms and clinical signs was significantly lower (3.1 vs 30.8%, p <0.001) and the median procedural time was significantly shorter (40.5 vs. 45.0 minutes, p = 0.001) in the iFR group than in the FFR group.

iFR-SWEDEHEART was a multicentre, open-label, registry-based, randomised, controlled clinical trial that used the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) for enrolment [31]. iFR-SWEDEHEART randomly assigned 2037 participants with stable CAD or ACS with an intermediate stenosis in a non-culprit artery, and an indication for physiologically guided assessment of coronary artery stenosis in a 1:1 ratio to undergo revascularisation guided by either iFR or FFR. The primary endpoint was the rate of a composite of death from any cause, nonfatal MI infarction, or unplanned revascularisation at 12 months. At 1-year follow-up, the primary endpoint occurred similarly in the iFR and FFR groups (6.7 vs 6.1%, respectively; difference in risk 0.7%; 95% CI 1.5–2.8; p = 0.007 for noninferiority). There were no significant between-group differences in the risk of each component of the composite endpoint. The study results were consistent within major subgroups, and the rates of ischaemic endpoints, including MI, target-lesion revascularisation, in-stent restenosis and stent thrombosis, did not differ significantly between the two groups. Similarly to DEFINE-FLAIR, a significantly higher proportion of patients in the FFR group than in the iFR group reported chest discomfort during the procedure (68.3 vs 3.0%, respectively; p <0.001). Furthermore, the total number of lesions assessed was significantly greater in the iFR group than in the FFR group, which was possibly related to the fact that operators using FFR are unlikely to persist with additional lesion assessment in patients experiencing adenosine-related chest discomfort. These findings tend to support the central notion that iFR is a much more tolerable procedure and therefore permits an easier and a more complete assessment of coronary anatomy.

Pooled patient-level meta-analysis of DEFINE-FLAIR and iFR-SWEDEHEART

The pooled patient-level meta-analysis of DEFINE-FLAIR and iFR-SWEDEHEART studies yields the largest dataset of CAD patients managed with coronary physiology assessment in contemporary clinical practice and provides outcome data for a total of 4529 patients with intermediate coronary artery lesions undergoing physiology-guided coronary revascularisation. Overall, all the patient-level meta-analysis confirmed the noninferiority of iFR versus FFR to guide coronary revascularisation (HR 1.03, 95% CI 0.81–1.31; p = 0.81) [33]. Physiology-guided deferral of coronary revascularisation occurred more frequently in the pooled iFR group than in the pooled FFR group (50.0 vs 45.0%, respec-
Deferral of physiologically insignificant lesions was found to be safe with similarly low rates of MACE at 12 months, irrespective of iFR- or FFR-based deferral (4.12 vs 4.05%, respectively; HR 1.05, 95% CI 0.69–1.60; p = 0.82). These results suggest similar patient outcomes with iFR- and FFR-guided deferral despite coronary revascularisation being performed less frequently in the iFR arm, and highlight the fundamental physiological differences between iFR and FFR concepts. Particularly, iFR has been shown to be more closely linked to CBF than FFR [34], and a previous study demonstrated higher revascularisation rates associated with physiological assessment guided by FFR than by coronary flow rate (CFR) [35]. Finally, the combined patient-level analysis of DEFINE-FLAIR and iFR-SWEDEHEART trials provides unique randomised evidence comparing iFR with FFR for the physiological assessment of non-culprit coronary stenoses in a subgroup of 440 patients with ACS. FFR-guided deferral of intervention in ACS patients was associated with a significantly increased risk of MACE compared with FFR-guided deferral in patients with stable CAD (HR 0.52, 95% CI 0.27–1.00; p <0.05), whereas iFR-guided deferral was associated with similar rates of MACE, irrespective of the clinical presentation (HR 0.74, 95% CI 0.38–1.43; p = 0.37) [33]. These data suggest that FFR may be an inferior prognostic marker for deferring treatment of non-culprit lesions in ACS patients compared with iFR, probably because of a blunted response to hyperaemic agents in the stunned myocardium following ACS [33].

Limitations of the iFR concept

Despite being supported by robust preclinical studies and validated by randomised patient outcome trials, iFR has experienced significant scrutiny and sparked intense debate in the literature over recent years. By making use of baseline coronary physiology properties, the iFR concept undoubtedly has limitations [34–36] (table I). Furthermore, longer-term outcome results of the DEFINE-FLAIR trial are warranted, particularly with respect to deferred-intervention patients, on the assumption that the use of iFR may reduce referrals for coronary revascularisation compared with FFR. Randomised outcome data are also needed in higher-risk patient subgroups with more complex coronary lesions (left main or proximal coronary artery disease) and higher baseline cardiovascular risk (bystander coronary lesions in patients with ACS, including ST-elevation MI), where coronary revascularisation may result in survival benefit. Finally, randomised clinical studies are warranted to determine clinical outcomes in patients with discordant iFR and FFR values, particularly for iFR negative and FFR positive patients.

Novel iFR-based physiological applications

iFR pullback

Tandem lesions and diffusely diseased vessels represent a challenge to hyperaemic indices such as FFR, owing to the haemodynamic interdependence (“cross-communication”) between serial stenoses under hyperaemic conditions [38]. Hyperaemic flow across one coronary stenosis is limited by presence of another stenosis in the same coronary vessel and vice versa, thereby precluding the simple and accurate determination of FFR for each individual coronary stenosis. As a result, removal of one coronary stenosis by means of PCI increases hyperaemic flow, thereby changing the pressure gradient across the residual stenosis. The unique properties of baseline physiology assessment may overcome the intrinsic limitations of hyperaemic pressure-derived indices and offer a potential solution for the assessment of tandem and/or diffuse lesions [38]. Unlike hyperaemic flow, resting coronary flow is preserved across nearly the entire range of coronary stenosis severities until stenoses become critical or subtotally occluded [20]. Resting pressure changes along the vessel length as measured by iFR are therefore more consistent and predictable than hyperaemic pressure gradients. Resting pressure tracings can be generated on a beat-to-beat basis using iFR pullback, thus permitting haemodynamic significance of each individual coronary stenosis to be accurately mapped and quantified. Importantly, resting coronary flow is not altered by removing a coronary stenosis by the means of PCI, and iFR pressure gradients across any residual coronary stenosis in the same vessel remain therefore unchanged [38]. In a first-in-man pilot study, automated iFR pullback recordings were made in 29 patients with tandem and/or diffuse CAD [39]. A post-hoc iFR physiological map integrating pullback speed and physiological data, co-registered with the patient coronary angiogram, was generated using a dedicated software to calculate physiological stenosis severity, length, and pressure-drop intensity (∆iFR/mm) across individual coronary stenoses to predict post-PCI iFR, which was ultimately compared with the observed post-PCI iFR (fig. 2). With use of computer-assisted simulations to model the haemodynamic impact of removing a coronary stenosis on the iFR pullback recording, virtual PCI was performed to estimate post-PCI iFR values (fig. 2). The iFR pullback was associated with a high degree of accuracy for predicting post-PCI iFR val-
ues, thereby offering a potential solution to facilitate PCI planning strategy in clinical practice [39]. Despite the promising results of this proof-of-concept study, the need for offline analysis and motorised pressure-wire pullback limited the subsequent clinical application of the technology.

**iFR co-registration**

Further developments of the iFR algorithm combined with real-time computer to track the pressure-wire movement progressively removed the remaining technical barriers to facilitate complete integration of the iFR pullback concept into clinical practice. The iFR co-registration technology uses a dedicated proprietary software to create a fully integrated real-time physiological map of the coronary vessel under manual pullback that is co-registered with the patient coronary angiogram (fig. 3). The iFR co-registration technology permits the instantaneous calculation of predicted post-PCI iFR values, thereby determining the potential physiological benefit of different treatment strategies. Revascularisation strategies that maximise the physiological benefit with a minimum of stents over more extensive PCI approaches may be planned to potentially improve patient outcomes. Contrariwise, the iFR co-registration may identify patients for whom greater numbers or longer stents are required in order to achieve haemodynamic improvement. Finally, the iFR

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**Figure 2:** iFR pullback. (A) iFR pullback recording throughout the coronary vessel. Post hoc co-registration of the iFR pullback trace with the coronary angiogram identifies pressure loss along the length of the vessel and distinguishes focal from diffuse disease. (B) Prediction of the post-PCI iFR result. Virtual PCI calculates the expected post-PCI iFR result for the area selected for PCI. LAD: left anterior descending artery; PCI: percutaneous coronary intervention. Reprinted with permission from Elsevier from Nijjer SS, Sen S, Petraco R, Escaned J, Echavarria-Pinto M, Broyd C, et al. Pre-angioplasty instantaneous wave-free ratio pullback provides virtual intervention and predicts hemodynamic outcome for serial lesions and diffuse coronary artery disease. JACC Cardiovasc Interv. 2014;7(12):1386–96.
co-registration technology enables accurate physiological documentation of angiographically diffuse CAD, thus contributing to the tailoring of treatment strategies at a patient level and the choice appropriate alternative approaches to PCI (medical therapy or surgical revascularisation) in selected patients.

Conclusions

iFR is a novel adenosine-independent pressure-derived physiological index that recently emerged as a safe and effective alternative to FFR for the invasive assessment of coronary stenosis severity with the potential to increase the widespread adoption of physiology-guided coronary revascularisation into routine clinical practice. By harnessing the unique properties of resting coronary physiology and addressing the drawbacks of pharmacologically-induced maximal hyperaemia, iFR challenges the paradigm of FFR as the reference standard for invasive assessment of coronary lesions. Emerging evidence suggests that iFR may be a superior prognostic marker compared with FFR for deferring intervention for non-culprit coronary lesions in patients with ACS. Finally, fully integrated virtual PCI planning using the promising real-time iFR co-registration technology is unveiling a new era in the field of coronary physiology by shifting the paradigm of coronary revascularisation from simply physiological justification towards precise guidance of coronary intervention at both vessel and lesion levels.

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**References**

The full list of references is included in the online version of the article at www.cardiovascmed.ch (DOI https://doi.org/10.4414/cvm.2018.00566).

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**Figure 3:** iFR co-registration. (A) Co-registration of iFR pullback traces with corresponding coronary angiograms demonstrates three distinct patterns of pressure loss along the length of coronary vessels: focal stenosis, diffuse coronary disease, focal stenosis and diffuse coronary disease. (B) iFR co-registration allows virtual percutaneous coronary interventional (PCI) planning with real-time calculation of expected post-PCI iFR results. Reprinted with permission from Elsevier from Göteborg M, Cook CM, Sen S, Nijjer S, Escaned J, Davies JE. The evolving future of instantaneous wave-free ratio and fractional flow reserve. J Am Coll Cardiol. 2017;70(11):1379–402.
For symptomatic patients with heart failure and preserved or moderately reduced ejection fraction

A shunt device to reduce left atrial pressure

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is a frequent disease with a prevalence of 1.1–5.5% in the general population in Europe \cite{1}. From a pathophysiological point of view, symptoms and a prognosis may depend on lack of stroke volume reserve and/or elevated pulmonary artery pressure \cite{2, 3}. In fact, it was shown that left atrial pressure as a major determinant of pulmonary venous and pulmonary artery pressure correlates with symptoms and prognosis \cite{4}. Accordingly, reduction of left atrial pressure may be a promising therapeutic strategy. Consequently, devices have been developed to reduce left atrial pressure through creation of a shunt between the left and right atria \cite{5, 6}. While the V-Wave device (V-Wave, Caesarea, Israel) has been studied in a small number of patients with HFrEF (heart failure with reduced ejection fraction), the Corvia-device (IASD, Corvia Medical Inc., Tewksbury, MA, USA) has been evaluated in a larger number of patients with HFpEF and HFmrEF (heart failure with mid-range ejection fraction).

Findings

In the REDUCE LAP-HF-Trial, the IASD was studied in 64 patients with HFpEF and HFmrEF in a multicentre, open-label, single-arm, phase I trial \cite{5}. Patients were included if they had evidence of functional class II, III or IV heart failure, an ejection fraction $\geq 40\%$ and a pulmonary capillary wedge pressure (PCWP) $\geq 15$ mm Hg at rest or $\geq 25$ mm Hg during supine bike exercise.

Reducing pulmonary artery pressure with the IASD may be a new therapeutic option to treat symptomatic heart failure patients with preserved or moderately reduced ejection fraction.

Figure 1: Interatrial shunt device (IASD). A: Device placement in the interatrial septum, arrow indicates right to left atrial blood flow. B: Echocardiographic image showing colour flow from the left to the right atrium. (Reproduced with permission from Hasenfuss et al. 2016 \cite{5}).
As a prerequisite for a left atrial to right atrial pressure gradient on the one hand, and to exclude right ventricular failure on the other, central venous pressure (CVP) had to be lower than 14 mm Hg, and tricuspid annular plain systolic excursion (TAPSE) had to be above 14 mm.

Patients had an average age of 69 years, 66% were female, 72% were in New York Heart Association class III, 81% suffered from hypertension and 33% from diabetes. Patients underwent right heart catheterisation at rest and during supine bicycle exercise, both at baseline and 6 months after device implantation. The latter was performed percutaneously via the femoral vein, and the device was positioned using a transseptal puncture of the interatrial septum. IASD placement was successful in 64/66 patients. In two patients, implantation of the device was abandoned without any further consequences for the patients.

No patient had a major adverse cardiac or cerebrovascular event or a need for cardiac surgical intervention for a device-related complication during 6 months of follow-up. Accordingly, no patient met the primary safety endpoint. The IASD resulted in a pulmonary to systemic flow ratio (Qp/Qs) of 1.27 at 6 months as compared to 1.06 at baseline (p = 0.0004). All patients with adequate echocardiographic image quality at 6 months (n = 50) had evidence of left to right flow through the device on colour flow Doppler echocardiography without any right to left flow (fig. 1). Exercise haemodynamic measurements before device implantation showed significant rises in PCWP from 17 ± 5 to 35 ± 8 mm Hg, and in RA from 9 ± 4 to 11 ± 5 mm Hg from rest to peak exercise. The shunt driving pressure (PCWP–CVP) increased from rest to exercise from 8 ± 4 to 17 ± 8 mm Hg. The mean exercise time before device implantation was 7.3 ± 3.1 min at a work load of 43 ± 18 W. Exercise time increased to 8.2 min ± 3.4 (p = 0.0275) and work load increased to 49 ± 20 W at 6 months after IASD implantation. These favourable changes were associated with a reduction of peak exercise PCWP from 34 ± 8 to 32 ± 8 mm Hg (p = 0.0025) (fig. 2). The reduction in PCWP should be interpreted relative to the increased exercise duration at a higher work load. Consequently, workload- and weight-normalised PCWP (PCWP/W/kg) may most appropriately assess the impact of IASD on exercise performance. Workload- and weight-normalised PCWP at peak exercise was reduced from 84 ± 45 to 69 ± 40 mm Hg/W/kg (p = 0.0001).

At 6 months, resting right atrial pressure had increased slightly compared with baseline, from 9 ± 4 to 11 ± 5 mm Hg (p = 0.0270). Pulmonary vascular resistance was unchanged. Right ventricular diastolic volume index increased from 22 ± 9 to 27 ± 11 ml/m² (p <0.0001) and right atrial volume index increased from 35 ± 17 to 40 ± 22 ml/m² (p <0.045). Left ventricular diastolic volume index decreased from 68 ± 13 to 62 ± 17 ml/m² (p = 0.0004), and left atrial volume index did not significantly change. TAPSE was not influenced by the IASD (20 ± 4 mm before and after implantation of the device).

The favourable haemodynamic effects of IASD observed in the open-label single-arm study were confirmed in a double blind randomised sham-controlled trial (REDUCE LAP-HF I Trial). The inclusion criteria were similar to those of the REDUCE LAP-HF-Trial. Twenty-two patients were randomised to IASD implantation and 22

![Figure 2: Haemodynamic effects of an interatrial shunt device (IASD) before and 6 months after implantation. Left: pulmonary capillary wedge pressure (PCWP) at peak exercise. Right: workload- and weight-normalised PCWP. (Reproduced with permission from Hasenfuss et al. 2016 [5].)](http://emh.ch/en/services/permissions.html)
to a control sham procedure. The latter included femoral venous access with intracardiac echocardiography, but no IASD placement. Haemodynamics during rest and exercise at baseline and at 1 month after randomisation were compared. There were no peri-procedural or 1-month major adverse cardiovascular, cerebrovascular and renal events in the IASD group. The primary performance endpoint, exercise PCWP at 1 month, decreased significantly in the IASD-treated group compared with the sham control group. The secondary endpoints – exercise duration, peak exercise workload, and workload- and weight-corrected PCWP – all improved in the IASD treatment group compared with the control group, although the differences did not achieve statistical significance as the trial was not powered to demonstrate effectiveness in these endpoints [7].

Favourable haemodynamic changes with the IASD explain the symptomatic and functional improvement of the patients after 6 and 12 months of follow-up [8]. Patients in the REDUCE LAP-HF-Trial showed significant improvements in NYHA functional class, Minnesota Living with Heart Failure Questionnaire and 6-minute walk distance. The latter was 313 ± 105 m at baseline, 345 ± 106 m at 6 months and 363 ± 93 m at 12 months (fig. 3).

Haemodynamic findings at 12 months in a subset of patients were comparable to those at 6 months with a persisting improvement in workload- and weight-normalised PCWP (fig. 3). Importantly, there was no haemodynamic or echocardiographic evidence of shunt-induced pulmonary hypertension or right ventricular failure.

**Discussion**

The studies show that the IASD is safe, reduces PCWP and functions properly through 12 months of follow-up. The persistent left to right shunt reduces exercise PCWP without any adverse effects on right heart function and pulmonary circulation. Beneficial haemodynamic effects are associated with symptomatic and functional improvement of patients with HfPEF and HfMrEF.

The data available from the IASD studies support the hypothesis that elevated left atrial pressure (as indicated by PCWP) inducing post-capillary pulmonary hypertension significantly contributes to the symptoms of patients with “diastolic heart failure” and that reducing left atrial pressure may represent a new therapeutic approach in these patients. This conclusion is consistent with previous work indicating that pulmonary artery pressure is of key pathophysiological relevance in patients with HfPEF [9]. Moreover, there is considerable evidence that pulmonary artery pressures are predictors of mortality in these patients [4, 10].

Pulmonary artery pressure can be reduced by vasodilators and diuretics, and it has been shown that medical therapy guided by pressure monitoring reduces heart failure hospitalisation, whereas no other therapeutic approach (with the exception of exercise training) has yet shown to be effective in this group of patients [9]. These data, together with the available data from the IASD creates much enthusiasm that reducing pulmonary artery pressure by a persistent shunt may be a new therapeutic option in patients with HfPEF and HfMrEF, and perhaps also in HfrEF.

The IASD approach critically depends on the left to right pressure gradient to drive the shunt and the size of the hole in the atrial septum. As an inclusion criterion in the IASD studies, PCWP had to be above 15 mm Hg, and CVP below 14 mm Hg. These inclusion criteria resulted in an average PCWP−CVP difference of 8 mm Hg at rest and 17 mm Hg at peak exercise. The ISAD device creates a septal defect of 8 mm cross-section, which in turn results in a Qp/Qs of 1.27. This communication appears to be large enough for continuous shunting and long-term patency without any evidence of paradoxical embolisation. Moreover, in these patients without right heart failure before device implantation (TAPSE >14 mm) the shunt did not result in

![Figure 3: Symptomatic and functional improvement after intra-atrial shunt device (IASD over 12 months). A: NYHA class = New York Heart Association Functional Class; B: MLWHF score = Minnesota Living With Heart Failure Questionnaire; C: 6MWD = 6-minute walking distance; D: Work-normalised PCWP at peak exercise = work- and weight-normalised pulmonary capillary wedge pressure at peak exercise. (Reproduced with permission from Kaye et al. 2016 [8].)
impaired right ventricular function or increased pulmonary vascular resistance. The latter is consistent with previous recommendations that an atrial septal defect needs no therapeutic closure below a Qp/Qs of 1.5.

Finally, the haemodynamic findings support previous recommendations that HFpEF (or HFmrEF) may require haemodynamic testing during exercise [2, 11]. In all IASD-studies, 30% of patients would not have met the inclusion criteria at rest, but showed clearly elevated pulmonary artery pressures during exercise. In conclusion, reducing pulmonary artery pressure with the IASD may be a new therapeutic option to treat symptomatic HFpEF and HFmrEF patients.

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References
What added value do these compounds bring?

New compounds for the treatment of pulmonary hypertension

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Summary
Survival with pulmonary arterial hypertension has significantly improved in the last two decades with the development and approval of different compounds. This review highlights the properties of molecules that more recently became available for specific treatment of pulmonary hypertension.

Key words: pulmonary arterial hypertension; endothelin receptor antagonist; soluble guanylate cyclase stimulator; prostacyclin receptor agonist

Introduction
Pulmonary hypertension (PH) was reported for the first time in 1891 when the autopsy of a patient with sudden death revealed right ventricular hypertrophy and pulmonary artery sclerosis without any apparent cause. PH is a progressive disease with elevated pulmonary vascular resistance (PVR) as the basic cause for increased right ventricular afterload and hypertrophy, which eventually proceeds to right ventricular dilatation and failure, and premature death [1]. The prevalence of PH is 97 cases per million, with a female to male ratio of 1.8:1 and an age-standardised annual mortality rate between 4.5 and 12.3 per 100,000 people in the population [1].

PH is clinically classified into five groups: pulmonary arterial hypertension (PAH) (group 1), PH related to left heart disease (group 2), PH due to lung disease and/or hypoxia (group 3), chronic thromboembolic PH and other pulmonary artery obstructions (group 4), and PH with unclear and/or multifactorial mechanisms (group 5).

The present review focuses on PAH, which is haemodynamically characterised by the presence of a mean pulmonary artery pressure (PAP) >25 mm Hg, a pulmonary artery wedge pressure (PWP) ≤15 mm Hg and a PVR of >3 Wood units.

The pathophysiology of PAH is characterised by an imbalance between molecules mediating vasoconstriction (e.g., endothelin or thromboxane) or vasodilation (e.g., prostacyclin). Furthermore, mitogenic effects of these molecules, with specific pathomorphological changes in the pulmonary circulation are involved in disease progression.

Currently available compounds approved for specific treatment of PAH are in three different groups: endothelin receptor antagonists, phosphodiesterase type 5 inhibitors (PDE-5is) and soluble guanylate cyclase stimulators, and molecules interfering with the prostacyclin pathway. Treatment with these compounds in combination with general measures has increased 3-year survival after first diagnosis of idiopathic PAH from 48% in the 1980s to 74% in the last two decades, as shown in the REVEAL registry [1].

Treatment of pulmonary arterial hypertension
Treatment of pulmonary hypertension is a three-step strategy starting with general measures, which is followed by supportive drug therapy and specific pharmacological treatment [2].

General measures are physical activity, birth control and post-menopausal hormonal therapy, infection prevention, psychosocial support, adherence to treatment, genetic counselling and counselling about travel. Only the specific pharmacological treatment of PAH is discussed here, because supportive drug treatment is extensively reviewed elsewhere [3–8].

Endothelin receptor antagonists
The endothelin system is activated both in the plasma and the lung tissue of PAH patients. Two distinct endothelin receptor isoforms (type A, type B) are expressed in pulmonary vascular smooth muscle cells, where they mediate the vasoconstriction and mitogenic effects of the peptide hormone endothelin-1. Three endothelin-1 antagonists are available in Switzerland: bosentan since 2002, ambrisentan since 2008, and macitentan since 2014.

Bosentan, ambrisantan
Bosentan (Tracleer®) was the first oral active antagonist of both endothelin receptor types, A and B, and is licensed for the treatment of PH patients presenting...
with World Health Organization (WHO) functional class II to IV. Several randomised controlled trials evaluated bosentan in different forms of PH (IPAH [idiopathic PAH] and PH secondary to connective tissue disease or Eisenmenger syndrome). Bosentan treatment consistently improved exercise capacity, functional class, haemodynamics and echocardiographic variables, and prolonged time to clinical worsening [9–13]. However, an increase in hepatic aminotransferases is reported in approximately 10% of treated patients. This increase is most often reversible with dose reduction or drug discontinuation, but nevertheless mandates liver function monitoring on a monthly base.

Ambrisentan (Volibris®) attaches preferentially to the type A endothelin receptor. Ambrisentan is approved for treatment of patients with PH associated to connective tissue or IPAH in functional class WHO II or III [14]. In the US, there is no recommendation for monthly liver function testing [15] because of the low incidence of abnormal liver function tests even when patients had received bosentan beforehand (0.8–3%, respectively). This low incidence was confirmed by the Volibris Tracking (VOLT) study, which was an open-label, prospective observational, multicentre, post marketing study including 999 patients [16].

**Macitentan**

Macitentan (Opsumit®) is approved for treatment of PAH patients with WHO functional class II or III. This dual endothelin receptor antagonist was tested in the SERAPHIN trial [17], which showed in the group receiving 10 mg macitentan a 45% reduction of the incidence of the combined endpoint all-cause mortality, atrial septostomy, lung transplantation, initiation of therapy with intravenous or subcutaneous prostanoids or worsening PAH. In addition, macitentan 10 mg increased exercise capacity and decreased the risk of all-cause hospitalisation and PAH-related hospitalisation. In a prespecified haemodynamic substudy of the SERAPHIN trial, 6 months of macitentan treatment increased cardiac index and decreased mean PAP and PVR as well as levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP). These changes were irrespective of the baseline WHO functional class and PAH-specific therapy, which was sildenafil in the majority of patients participating in this substudy [18]. Of note, macitentan treatment was likewise beneficial in patients without previous treatment for PAH. Significant liver toxicity was not observed, but a haemoglobin level of ≤8 g/dl was noted in 4.3% (10/242) of patients in the macitentan 10 mg group, compared with 0.4% (1/249) in the placebo group [17].

**Phosphodiesterase type 5 inhibition and soluble guanylate cyclase stimulation**

PAH is associated with impaired synthesis of nitric oxide, resulting in insufficient stimulation of the nitric oxide / soluble guanylate cyclase (sGC) / cyclic guanosine monophosphate (cGMP) pathway. Inhibition of the catalytic activity of PDE-5 increases cGMP in the vascular smooth muscle cell. Cyclic GMP is involved in various regulatory processes such as maintenance of vascular tone, smooth muscle cell proliferation, fibrosis and inflammation, suggesting that a cGMP increase should have favourable effects on haemodynamics and vascular remodelling in PAH. Indeed, PDE-5 inhibition with sildenafil or tadalafil results in significant pulmonary vasodilation with a maximum effect observed after 40 to 90 minutes [19]. Furthermore, these two molecules and their metabolites have antiproliferative effects [20] (fig. 1). Sildenafil has been available on the Swiss market since 1998, tadalafil since 2004; the sGC activator riociguat (see below) became available on the Swiss market in 2013.

**Sildenafil, tadalafil**

The first orally active, potent and selective PDE-5i, sildenafil, is sold under the name of Viagra® or Revatio®. Randomised controlled trials in PAH patients treated with sildenafil 20 mg three times per day showed favourable effects on exercise capacity, clinical symptoms and/or haemodynamics [21]. Sildenafil in combination with epoprostenol improved 6-minute walking distance and prolonged time to clinical worsening, suggesting synergistic effects [22].

Tadalafil (Cialis®) is a once daily selective PDE-5i. A randomised controlled trial in 406 PAH patients (of whom...
53% were on background bosentan therapy) tested tadalafil at low, medium, and high doses. Only patients in the high-dose (40 mg per day) group showed favourable changes in exercise capacity, symptoms, haemodynamics and time to clinical worsening [23]. Similar results were reported more recently for vardenafil (Levitra®), from a randomised controlled trial including 66 treatment-naive PAH patients [24]. However, this drug is not approved for PAH treatment in Switzerland.

**Riociguat**
The sGC activator riociguat (Adempas®), the first molecule of its class, is approved for the treatment of patients with IPAH presenting in WHO functional class II or III, as well as patients with chronic thromboembolic PH (CTEPH). Riociguat directly activates GC; in addition, it sensitises sGC to endogenous nitric oxide. Riociguat treatment with up to 2.5 mg three times per day improved exercise capacity, haemodynamics and WHO functional class, and increased time to clinical worsening, as shown by a randomised controlled trial including 443 PH patients. The study patients were either without specific PAH therapy at baseline (50%), or on background therapy with an endothelin receptor antagonist (44%) or prostanoids (6%); altogether, the study indicates benefit from riociguat treatment independent of the presence or absence of complementary treatment [25]. However, riociguat did not decrease mortality of patients with IPAH or CTEPH in this study, and also no mortality benefit was demonstrated when data from 962 PH patients in five randomised trials were pooled [26].

The drug is well tolerated overall, and adverse events most commonly reported include headache, dyspepsia and gastritis, dizziness, nausea and diarrhoea. The most frequent serious adverse event reported was syncope, which occurred more often in the placebo group than in the 2.5-mg group (4 and 1%, respectively). Of note, the combination of riociguat and a PDE-5i is contraindicated because of the risk of hypotension and other relevant side effects detected in the open-label phase of a randomised controlled trial study [5]. Likewise, riociguat is contraindicated in patients with PH due to interstitial lung disease, since mortality was increased in the verum group of the RISE-IIP trial. Lastly, riociguat is contraindicated in pregnant women because of fetal harm.

**Prostacyclin analogues and prostacyclin receptor agonists**
Prostacyclin is produced by endothelial cells and acts as both a potent vasodilator and an endogenous inhibitor of platelet aggregation; in addition, cytoprotective and antiproliferative activities are reported. PAH is associated with dysregulation of the prostacyclin metabolic pathways and decreased expression of prostacyclin synthase. Synthetic prostacyclin analogues with similar pharmacodynamic effects but more favorable pharmacokinetic properties provided a dramatic therapeutic breakthrough in the last years in particular when PH is more severe. Epoprostenol was made available in Switzerland in 2000, teprostinil in 2004, and iloprost in 2005; the prostacyclin receptor antagonist selipag was approved in Switzerland in 2016.

**Epoprostenol**
This intravenous synthetic prostacyclin is approved for treatment of IPAH and associated PAH (APAH) in WHO functional classes III and IV. A limitation of epoprostenol treatment is the short half-life (3–5 minutes), which requires application by means of an infusion pump and a permanent tunnelled catheter. Epoprostenol was tested in three nonblinded randomised controlled trials in patients with IPAH or the scleroderma spectrum of diseases and in WHO functional classes III and IV [27, 28]. Epoprostenol always improved symptoms and haemodynamics, increased exercise capacity in both entities and up to now is the only treatment reducing mortality in IPAH [28]. Long-term persistence of efficacy was also shown in APAH and in non-operable CTEPH.

**Iloprost**
Iloprost is a chemically stable prostacyclin analogue for intravenous or aerosol administration. Inhaled iloprost has been tested in one randomised controlled trial, which compared daily repeated iloprost inhalations with placebo in patients with IPAH or CTEPH [29]. This study showed an increase in exercise capacity, improvement in clinical symptoms, and a decrease of the PVR and clinical events. Similar results were observed in another randomised controlled trial including 60 patients on bosentan background treatment.

**Teprostinil**
Teprostinil is available for intravenous and subcutaneous application in Switzerland (Remodulin®); furthermore, it is available as aerosol (Tavyso®) or extended-release oral tablet (Orenitram®). Each formulation improves dyspnoea, and every administration route apart from oral 6-minute walking distance. Of note, the different routes of administration produce distinct adverse events, such as infusion-site pain for subcutaneous use (85%), cough and throat irritation with inhalation (54 and 25%, respectively), or abdominal discomfort with the oral preparation (6%) [30]. Each
form was tested in large randomised, controlled, multicentre studies, but with different background therapy: intravenous and oral application was tested against placebo in recently diagnosed PAH patients without specific background therapy (470 and 349 patients, respectively) [31, 32], whereas inhalation was investigated in 235 clinically stable patients mostly in New York Heart Association (NYHA) class III, who were on PAH specific background therapy with either bosentan (70%) or sildenafil (30%) for at least 3 months prior to study initiation [33]. The difference in the pharmacological background may explain in part the disparate results observed with three formulations of tadalafil. Irrespective of this discussion, Chakinala et al. showed recently that transition from parental to oral tadalafil preserves the 6-minute walking distance and is safe in low risk PAH patients [34].

**Selexipag**

Selexipag (Uptravi®) is an orally available, selective prostacyclin receptor agonist and approved in Switzerland since 2016 for treatment of PAH patients in functional classes III and IV. Selexipag and its metabolite have modes of action similar to that of endogenous prostacyclin, but they are chemically and pharmacologically distinct. This dissimilarity is physiologically evident in the observation that vasorelaxation resulting from selexipag treatment is not attenuated by the presence of prostacyclin receptor antagonists [35]. In a phase II study, 17 weeks of selexipag treatment reduced the mean PVR by 30.3% from baseline in PAH patients presenting with a baseline PVR that had remained ≥400 dynes·sec·cm⁻² despite of endothelin receptor antagonist and/or PDE-5i therapy [36]. The event-driven, phase III, Prostoglandin I₂, Receptor Agonist in PAH (GRIPHON) study enrolled 1156 patients and showed that selexipag treatment with individual symptom-guided up-titration (maximum dose 1600 μg twice daily) reduced the incidence of the composite endpoint by 40%. The composite endpoint consisted of all-cause mortality, PAH-related complications, hospitalisation for worsening of PAH, worsening of PAH resulting in the need for lung transplantation or atrial septostomy, initiation of parenteral prostacyclin analogues, chronic O₂ for worsening of PAH, or disease progression. The reduction in the incidence of the composite endpoint was independent of concomitant specific PAH treatment, which consisted of mono- or double therapy with an endothelin receptor antagonist and/or PDE-5i [37]. Of note, the effect of selexipag on the primary outcome was consistent across all dose levels. However, all-cause mortality alone was not different between the verum and the placebo groups. In the selexipag group, premature discontinuation occurred in 14.3%, whereas 7.1% patients in the placebo group discontinued treatment. Discontinuation was related to adverse effects such as nausea, diarrhoea, headache and jaw pain, and the majority of adverse events with selexipag occurred in the dose-adjustment phase. The GRIPHON study has its share of limitations. First, a total of 18.9% of patients discontinued placebo or selexipag prematurely but early discontinuation had been anticipated and accounted for in the study design acknowledging discontinuation rates reported from previous randomised controlled trials. Another point of criticism is the limited follow-up data available on patients who had stopped the drugs. The second limitation lays in the fixation of the primary endpoints similar to earlier randomised controlled trial in PH, which are in part subjective. Altogether, the results of the GRIPHON trial are promising. Furthermore, selexipag is the sole drug directed towards the prostaglandin I₂ receptor pathway, and is recommended for sequential double and triple combination therapy in PAH patients with WHO functional class II (table 1).

**Future compounds**

The last years have seen the testing of drugs such as imatinib mesylate (Gleevec®), which inhibits platelet-derived growth factor signalling. The IMPRES study investigated imatinib mesylate as add-on treatment in PAH patients in WHO class III or IV in spite of specific background therapy. In the treatment group, exercise capacity and haemodynamics improved significantly (6-minute walking test +32 meters, PVR –397 dynes·sec·cm⁻²; respectively). However, functional class, time to clinical

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**Table 1:** Class of recommendation and level of evidence for the efficacy of macitentan, riociguat and selexipag monotherapy or sequential drug combination therapy in pulmonary artery hypertension, according to WHO functional class.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>WHO functional class II recommendation</th>
<th>WHO functional class III recommendation</th>
<th>WHO functional class IV recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macitentan</td>
<td>I B</td>
<td>I B</td>
<td>IIb C</td>
</tr>
<tr>
<td>Riociguat</td>
<td>I B</td>
<td>I B</td>
<td>IIb C</td>
</tr>
<tr>
<td>Selexipag</td>
<td>I B</td>
<td>I B</td>
<td>IIb C</td>
</tr>
<tr>
<td>Macitentan added to sildenafil</td>
<td>I B</td>
<td>I B</td>
<td>IIa C</td>
</tr>
<tr>
<td>Riociguat added to bosentan</td>
<td>I B</td>
<td>I B</td>
<td>IIa C</td>
</tr>
<tr>
<td>Selexipag added to ERA or PDE-5i</td>
<td>I B</td>
<td>I B</td>
<td>IIa C</td>
</tr>
<tr>
<td>Riociguat added to sildenafil or other PDE-5i</td>
<td>III B</td>
<td>III B</td>
<td>III B</td>
</tr>
</tbody>
</table>

ERA = endothelin receptor antagonist; PDE-5i = phosphodiesterase type 5 inhibitor. Class of recommendation: I, IIa, III, evidence: A, B, C.
worsening and mortality were not different from controls after 24 weeks. In addition, severe side effects (44 vs 30%) and study discontinuation (33 vs 18%) were more common in the treatment group [38]. Altogether, this interesting pharmacological approach needs further investigation.

Another compound is sorafenib (Nexavar®), which inhibits multiple kinases, including tyrosine and serine/threonine kinases. This molecule was tested as add-on therapy in nine patients with treatment-refractory PH. Treatment was started with an initial dose of 50 or 100 mg per day and increased to 100–400 mg per day. The WHO functional class improved in eight of the nine patients and the mean PAP decreased by 14 to 28% in six of eight patients. The main adverse effects were skin reactions on the hands and the feet, which were observed in five of nine patients [39]. Altogether, this pilot study suggested sorafenib could be an additional therapeutic strategy in patients with refractory PAH. However, testing in a larger clinical study is mandatory.

Combination therapy
Most trials in PAH have tested the therapeutic efficacy of drugs in an add-on design, which is close to the clinical setting where drugs with different mechanisms of action are applied in a sequential manner. However, COMPASS-2, which investigated the effect of bosentan added to sildenafil treatment, failed to show a significant decrease in the delay to first morbidity and mortality [40], and oral teprostilin when added to background endothelin receptor antagonist or PDE-5i treatment failed to show a clinically significant increase in distance in the 6-minute walking test [31, 33]. Nevertheless, SERAPHIN and GRIPHON showed that time to the combined morbidity and mortality end-point was increased when macitentan or selexipag were added to specific PAH background therapy with one or two other drugs. The AMBITION trial assessed up-front combination therapy vs monotherapy in a head to head comparison. The 500 study patients were randomly assigned in a 2:1:1 ratio to receive ambrisentan and tadalafil or either alone. The up-front combination therapy was associated with a 50% reduction in the primary endpoint, mostly driven by a lower risk of clinical failure and an increase in exercise capacity [40]. However, substitution of the combination tested in the AMBITION trial by other members of the same family failed to show similar outcomes. One reason may be that bosentan induces CYP3A4 activity, which results in a decrease in the plasma levels of sildenafil and its active metabolite [41].

At the moment, sequential combination therapy is recommended for the PAH patient with clinical deterioration while on specific PAH monotherapy. This class I recommendation is based on the add-on study design in those studies that tested more recently developed compounds. Based on the results of the AMBITION trial, initial combination therapy with a recommendation class is limited to the combination of ambrisentan with tadalafil.

Conclusion
The emergence of specific treatments for PAH has improved functional status, exercise capacity and time to clinical worsening over the last two decades. The recently developed compounds macitentan, riociguat, and selexipag provide additional benefit when given either as monotherapy or in combination with compounds interacting with other pathways active in PAH. The absence of an effect on PAH-associated mortality remains a drop of bitterness. However, a post-hoc analysis of the SERAPHIN study showed that the incidence of a morbidity events <3 months after study inclusion was associated with increased mortality [42], suggesting that reduced morbidity may be associated with improved prognosis.

Disclosure statement
No financial support and no other potential conflict of interest relevant to this article was reported.

References
The full list of references is included in the online version of the article at www.cardiovascmed.ch (DOI https://doi.org/10.4414/cvm.2018.00568).
Thrombus in transit

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\textsuperscript{a} Mercy Saint Vincent Hospital, Toledo OH, USA; \textsuperscript{b} Ohio University College of Osteopathic Medicine, Athens OH, USA; \textsuperscript{c} University of Texas, Houston TX, USA

Case presentation

An 88-year-old man with a history of transient ischaemic attack, chronic kidney disease and primary hypertension presented with dyspnoea and was found to have large bilateral pulmonary emboli on a computed-tomography angiogram of the chest. A deep venous thrombosis (DVT) in the left lower extremity involving the popliteal, peroneal and gastrocnemius veins was found on venous duplex ultrasound. A transthoracic echocardiogram showed a thrombus in the right atrium, and a long thrombus in the left atrium extending via the left ventricle through the aortic valve (video 1). A transoesophageal echocardiogram (TEE) showed a large thrombus entrapped in a patent foramen ovale (PFO) (video 2, fig. 1) with further extension of the same thrombus via the left ventricle through the aortic valve (videos 3 and 4, figs 2 and 3). Three-dimensional imaging taken during the TEE showed the entrapped thrombus passing through the PFO into the left atrium (fig. 4), and then through the mitral valve into the left ventricle (figs 5 and 6).

The patient was not deemed a surgical candidate, given his multiple comorbidities and high risk of further embolisation. As there was no previous personal or family history of venous thromboembolism, congenital thrombophilia was not suspected. In the light of normal blood counts, a myeloproliferative disorder was not suspected. Further imaging studies for malignancy were all negative. The DVT was deemed to be unprovoked and, based on the extent of the thrombosis, the decision was made to start lifelong anticoagulation. He was treated initially with a heparin infusion for 5 days, then transitioned to apixaban. He remained stable during a 7-day hospital stay. He was seen in clinic 3 months after discharge and has done well with no noted complaints or signs of embolism.

You will find the video files in the multimedia collection of «Cardiovascular Medicine»: https://cardiovascmed.ch/online-only-content
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Discussion

Evidence from autopsy reports suggest up to 35% of the population may possess a PFO [1]. We describe a case of an elderly gentleman with a DVT, bilateral pulmonary emboli and a large thrombus extending from the right atrium through the aortic valve via a PFO. There is no guideline or expert consensus on the best way to treat such a condition. A literature review of reported cases of thrombus entrapped in a PFO suggested either surgery or anticoagulation as treatment [2, 3]. Surgery was the more popular option, and anticoagulation was preferred in cases where surgery was considered high risk [2, 3]. Anticoagulation has been effective for our patient to date. Owing to the paucity of available data, long-term treatment for a thrombus entrapped in a PFO is unknown. The risk of a future embolus across the PFO and benefit of closure with this type of presentation are also unknown. Further research is necessary to answer these questions.

Acknowledgement
The patient gave written informed consent for publication.

Disclosure statement
No financial support and no other potential conflict of interest relevant to this article was reported.

References

Figure 4: 3D view showing the thrombus passing through the patent foramen ovale into the left atrium.

Figure 5: 3D view showing passage of the thrombus through the mitral valve.

Figure 6: 3D view showing passage of the thrombus through the mitral valve.
This year's annual congress of the Swiss Society of Cardiology was a true success

Annual Congress of the Swiss Society of Cardiology

This year's annual congress of the Swiss Society of Cardiology was held in Basel from Wednesday June 6 to Friday June 8, 2018 (fig. 1). The congress was organised together with the Swiss Society for Cardiac Surgery led by its president Michele Genoni from Zurich, and attracted 1471 participants (including 348 from industry) from all over Switzerland.

The scientific programme was led by 176 moderators and featured, in 41 sessions, lectures and talks by 240 speakers from Switzerland and abroad. Of the 214 submitted abstracts, 152 were presented. Of those, 76 were oral presentations and 76 were part of the poster session.

The Andreas Grüntzig lecture

One highlight was the Andreas Grüntzig lecture and award given this year by Professor Tiziano Mocetti from the CardioCentro Lugano (fig. 2).

He reviewed the history of cardiology care in the Ticino and the growth of the CardioCentro that he founded and developed to its current size and importance – a truly unique and impressive achievement. Indeed, out of a small division within the Ospedale Civico di Lugano, Prof. Mocetti created, thanks to a large donation by a patient of his, an impressive, internationally visible heart centre offering the whole spectrum of current cardiovascular care, except transplantation. In addition, his team published seminal papers in the best journals of medicine such as the European Heart Journal, Circulation and the New England Journal of Medicine, among others.

The Amgen research prize

The Amgen research prize, formerly the cardiovascular biology prize supported by Werner Lambert, then Pfizer and now Amgen, was founded by Prof. Thomas F. Lüscher in 1997 and was first awarded a year later at the annual congress of the Swiss Society of Cardiology to a promising young cardiovascular researcher. The prize consisted then, as it does now, of 30,000 CHF for future research by the winner. Furthermore, winners are asked to provide a review article on their research for Cardiovascular Medicine to make the work known at the national level. From the beginning, it was of importance to the founder to ensure a fair and objective assessment of the applications. To that end, a scientific board, consisting not only of Swiss members, but also experts from abroad was assembled to minimise conflicts of interest. Furthermore, the president himself never participated in the rating, but rather assured proper procedures for selection of the winner. This year’s committee consisted of: Thomas F. Lüscher, president, Zurich/London; Michel Burnier, Lausanne; Filippo Crea, Rome; François Mach, Geneva; Christian Matter, Zurich; Christian Mueller, Basel; Francesco Paneni, Zurich; and Thomas Thum, Hannover, FRG. The winners of the last 20 years are listed in table 1.

Table 1: Winners of the research Prize of the Swiss Society of Cardiology from 1998 to 2018.

<table>
<thead>
<tr>
<th>Year</th>
<th>Winner</th>
<th>Location</th>
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<tbody>
<tr>
<td>1998</td>
<td>Jan Kustera, Bern</td>
<td>Bern</td>
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<tr>
<td>1999</td>
<td>Matthias Barton, Zurich</td>
<td>Zurich</td>
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<td>2000</td>
<td>François Mach, Geneva</td>
<td>Geneva</td>
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<td>2001</td>
<td>Frank Ruschitzka, Zurich</td>
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<td>2003</td>
<td>Simon Hoerstrup, Zurich</td>
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<td>2004</td>
<td>David Kurz, Zurich</td>
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<tr>
<td>2005</td>
<td>Sabine Steffens, Geneva</td>
<td>Geneva</td>
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<td>2006</td>
<td>Roberto Corti, Zurich</td>
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<td>2007</td>
<td>Giovanni Camici, Zurich</td>
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<tr>
<td>2008</td>
<td>Michele Miragoli, Bern</td>
<td>Bern</td>
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<tr>
<td>2009</td>
<td>Elena Osto, Zurich/Padua</td>
<td>Zurich/Padua</td>
</tr>
<tr>
<td>2010</td>
<td>Gabriella Kania, Zurich</td>
<td>Zurich</td>
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<tr>
<td>2011</td>
<td>Christian Templin, Zurich</td>
<td>Zurich</td>
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<td>2012</td>
<td>Benedikt Weber, Zurich</td>
<td>Zurich</td>
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<tr>
<td>2013</td>
<td>Fabrizio Montecucco, Geneva</td>
<td>Geneva</td>
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<tr>
<td>2014</td>
<td>Emrunch Rexhaj, Bern</td>
<td>Bern</td>
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<tr>
<td>2015</td>
<td>Elena Osto, Zurich</td>
<td>Zurich</td>
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<tr>
<td>2016</td>
<td>Baris Gencer, Geneva</td>
<td>Zurich</td>
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<tr>
<td>2017</td>
<td>Christoph Grani, Zurich</td>
<td>Zurich</td>
</tr>
<tr>
<td>2018</td>
<td>Sarah Costantino, Zurich</td>
<td>Zurich</td>
</tr>
</tbody>
</table>

This year’s committee consisted of: Thomas F. Lüscher, president, Zurich/London; Michel Burnier, Lausanne; Filippo Crea, Rome; François Mach, Geneva; Christian Matter, Zurich; Christian Mueller, Basel; Francesco Paneni, Zurich; and Thomas Thum, Hannover, FRG. The winners of the last 20 years are listed in table 1.

Figure 1: The Basel congress centre, where this year’s joint annual congress of the Swiss Society of Cardiology and the Swiss Society of Cardiac Surgery was held.

Figure 2: The Andreas Grüntzig awardee Prof. Tiziano Mocetti from Lugano (right), with the session chairman Prof. Thomas F. Lüscher from London and Zurich (left).
This year, for the first time, two candidates of equal scientific achievement were awarded the Amgen research prize of the Swiss Society of Cardiology 2018: Sara Costantino from the Centre for Molecular Cardiology in Zurich and Raphael Twerenbold from the University Hospital in Basel (fig. 3).

Sarah Costantino received the award for her work on the molecular mechanisms of diabetic endothelial dysfunction and vascular disease (Diabetes. 2017;66:2472–82) and transcription of the aging gene p66shc in obesity (Eur Heart J. 2017; online; fig. 4). Raphael Twerenbold was selected by the committee for his important and clinically relevant studies on the diagnostic value of troponin in patients with acute chest pain and possible acute coronary syndromes (Circulation. 2017;136:1495–508 and Circulation. 2018; 137:436–51; fig. 5).

The general assembly

The general assembly of the Swiss Society of Cardiology took place on Wednesday June 6 and was chaired elegantly by the outgoing president Michael Zellweger from Basel, who has effectively led the society for the last 2 years (fig. 6). He will be followed by the incoming president for the next 2-year term, Giovanni Pedrazzini from Lugano. Michael Billinger was elected as the new representative of Bern University to follow Thomas Suter, who stepped down, and Christoph Wyss from the Heart Clinic Hirslanden, who will take over the role of Urs Kaufman (who played a pivotal role in the negotiations on reimbursement for cardiological clinical services). His commitment to these important issues was highly appreciated by the assembly with an impressive round of applause. Finally, Patrick Monnier, a representative of the practicing cardiologists, was replaced by Tomoé Stampfli Andres from the Hospital La Tour in Meyrin. Lastly, Felix Tanner from Zurich was elected vice-president and, as such, president-elect for the next term 2020 to 2022.

After the report of the president, Paul Erne from Lucerne and Peter Buser from Basel were named honorary members of the Swiss Society of Cardiology (fig. 7).

The president reminded the members that the Swiss Society of Cardiology celebrated its 70th birthday this year at their annual congress – an impressive tradition for a scientific society and good reason to look back on developments in cardiology and cardiac surgery, as well as to look forward, to speculate and to dream about future advancements. This was indeed the special focus of the 2018 programme, with eminent keynote speakers in different areas of the field highlighting the advances in cardiology, and those that Switzerland, in particular, could enjoy. Future developments were also discussed. Thus, as the president mentioned, cardiology lives up to the statement of Jack Nicholson that “aging means getting better!”

Important items were the changes in reimbursement for cardiology services in Switzerland and the political issues behind them, which will make life more difficult for practicing colleagues. Furthermore, the proposal of the board to create subspeciality certifications attracted an unforeseen number of members of the Swiss Society of Cardiology to the general assembly. The president explained in detail the process the board followed to come up with the proposal, which lasted al-
most two years. The proposal had been send to all members of the Swiss Society of Cardiology beforehand to allow for an informed decision making and eventually vote. Many cardiology societies worldwide have introduced such a concept and a matching curriculum that reflects the impressive developments in this speciality in the last three decades. For invasive procedures such as percutaneous coronary angioplasty, transcatheter aortic valve implantation and the ablation of arrhythmias in particular, a comprehensive training programme is required today to ensure efficacy and safety for patients undergoing such procedures. In spite of this, the proposal of the board was surprisingly rejected with 110 voting no against 69 yes and 2 abstentions.

The future

Overall, this year’s annual congress of the Swiss Society of Cardiology was a true success. Its members can truly be proud of it, but life goes on and we already have to think about the next annual meeting which will take place in Interlaken on June 18–21 in 2019. Some issues remain, however, in particular the question of whether we should still allow cardiologists with only a basic training and certified as FHM of cardiology to perform any investigation or procedure without documentation of successfully passing a structured practical and theoretical core curriculum and examination. History will tell, and we shall learn that those who do not listen to the historical process – as Mikhail Gorbatchov put it – will be overruled. We shall see – as always predictions are difficult, but this issue will not disappear with the 2018 vote. Indeed it is likely come back on the table.
Cardiology Update Davos, 16–20 February 2019

The 23rd edition of the Cardiology Update course will be hosted in Davos, Switzerland from 16 to 20 February 2019.

This important meeting in the field of cardiology represents a joint educational programme organised by the Zurich Heart House, the University of Zurich and the European Society of Cardiology (ESC), in collaboration with the Brigham and Women’s Hospital in Boston and the University of Michigan School of Medicine. As such, it is a truly transatlantic exchange of knowledge, highlighting both European and US cardiology practice and treatment modalities.

A distinguished international teaching faculty will contribute to an outstanding programme on the latest scientific and therapeutic developments, as well as on new intervention and treatment strategies in cardiology. Special emphasis is being placed on the presentation and clinical implementation of the new ESC guidelines published at the ESC Congress 2018 in Munich.

Cardiology Update was founded in 1975 by the two renowned cardiologists, Bertram Pitt from Ann Arbor and the deceased Paul Lichtlen, former chairman of Hannover. The number of participants has grown substantially since then, to 600 individuals from 46 countries in 2017. Bertram Pitt and Thomas F. Lüscher, the European course directors for more than 20 years, recently welcomed two world-class opinion leaders from Boston to the board: Peter Libby and Marc Pfeffer. In addition, two outstanding Swiss cardiologists and experts in the field of preventive and interventional cardiology, namely François Mach from the University Hospital Geneva and Stephan Windecker from the University Hospital Bern, will join the team to conduct the course in 2019.

The highly acclaimed CME-accredited programme provides four days of comprehensive education in all major areas of cardiovascular medicine. The educational objectives are to review and disseminate the latest knowledge about advances in prevention, diagnosis and treatment of cardiovascular disease.

Cardiology Update is designed for clinicians specialised in cardiology, but is also worthwhile for internal and general medicine specialists with an interest in cardiovascular disease. The main features of the course are state-of-the-art lectures, interactive case presentations and clinical decision seminars. In addition, video live cases, “Meet the Expert” sessions, and poster sessions further complement the programme. In order to foster participation of young cardiologists, a dedicated session designed by SCOT, Swiss Cardiologists of Tomorrow, will be organised. The spirit of the course is a stimulating working and learning environment, combined with many opportunities for networking among faculty members and participants.

Programme and registration:
www.cardiologyupdate.ch

Figure 1: Celebrating the inaugural session in 2017 (from left): Wilhelm Rutishauser, Thomas Lüscher, Bertram Pitt, Patrick Aebischer, Christian Müller, Christian Matter and Ruth Amstein.

Figure 2: Clinical seminar with Lorenz Räber, Christian Schmied and Stephan Windecker.

Figure 3: Echo session with Otto Smiseth from Oslo and Felix Tanner from Zurich.

Figure 4: State of the art lecture with John Deanfield from London.
Olivier Muller is the new Professor and Chairman of Cardiology at the Centre Hospitalier Universitaire Vaudois and the University of Lausanne

Professor Olivier Muller, born in 1970, is a board certified and experienced cardiologist, with particular expertise in the endovascular treatment of coronary artery disease. After obtaining his MD/PhD at the University of Lausanne, Switzerland, he studied internal medicine and cardiology at Lausanne University Hospital. He then went on to complete a 3-year post-doctoral fellowship in the catheterisation laboratory of Bernard De Bruyne, William Wijns and Emanuele Barbato in the Cardiovascular Centre of the Onze-Lieve-Vrouw Kliniek in Aalst, Belgium. Following his return to Switzerland in 2010, he became attending physician, and in 2018 he was appointed head of the cardiology service at Lausanne University Hospital.

Olivier Muller is the author of more than 130 publications in peer-reviewed, high impact factor journals and is currently involved in several trials related to the treatment of coronary artery disease, with a focus on myocardial infarction and coronary artery physiology. He is currently member of the Swiss working group for interventional cardiology. He is co-course director of the “Endovascular cardiac complication (ECC)” Lausanne Meeting and is highly involved in the PCRonline educational platform dedicated to management of complications during coronary intervention.

Tobias Reichlin wird Extraordinarius an der Universität Bern und Leiter der Elektrophysiologie an der Klinik für Kardiologie am Inselspital Bern

Prof. Reichlin hat in Basel Medizin studiert und sich anschliessend in Innerer Medizin am Regionspital Langenthal und an den Universitätskliniken Basel weitergebildet. Dazwischen absolvierte er ein klinisches Research Fellowship in Biomarkers in Cardiology an den Universitätskliniken Basel unter Prof. Christian Müller.

Danach folgte eine Assistenzarztzeit im Weiterbildungscurriculum Kardiologie der Universitätskliniken Basel unter Prof. Stefan Osswald und 2012 bis 2013 ein klinisches Forschungs-Fellowship in Elektrophysiologie am Brigham and Women's Hospital und Harvard Medical School in Boston USA. 2013 kehrte Prof. Tobias Reichlin als stellvertretender Oberarzt auf die Kardiologie der Universitätskliniken Basel zurück und wurde ein Jahr später zum Oberarzt ernannt. Per 1. April 2018 wurde Tobias Reichlin nun Leitender Arzt und Leiter der Elektrophysiologie in der Klinik für Kardiologie (Direktor: Stefan Windecker) am Inselspital Bern und gleichzeitig Extraordinarius an der Universität Bern.

Wir gratulieren!