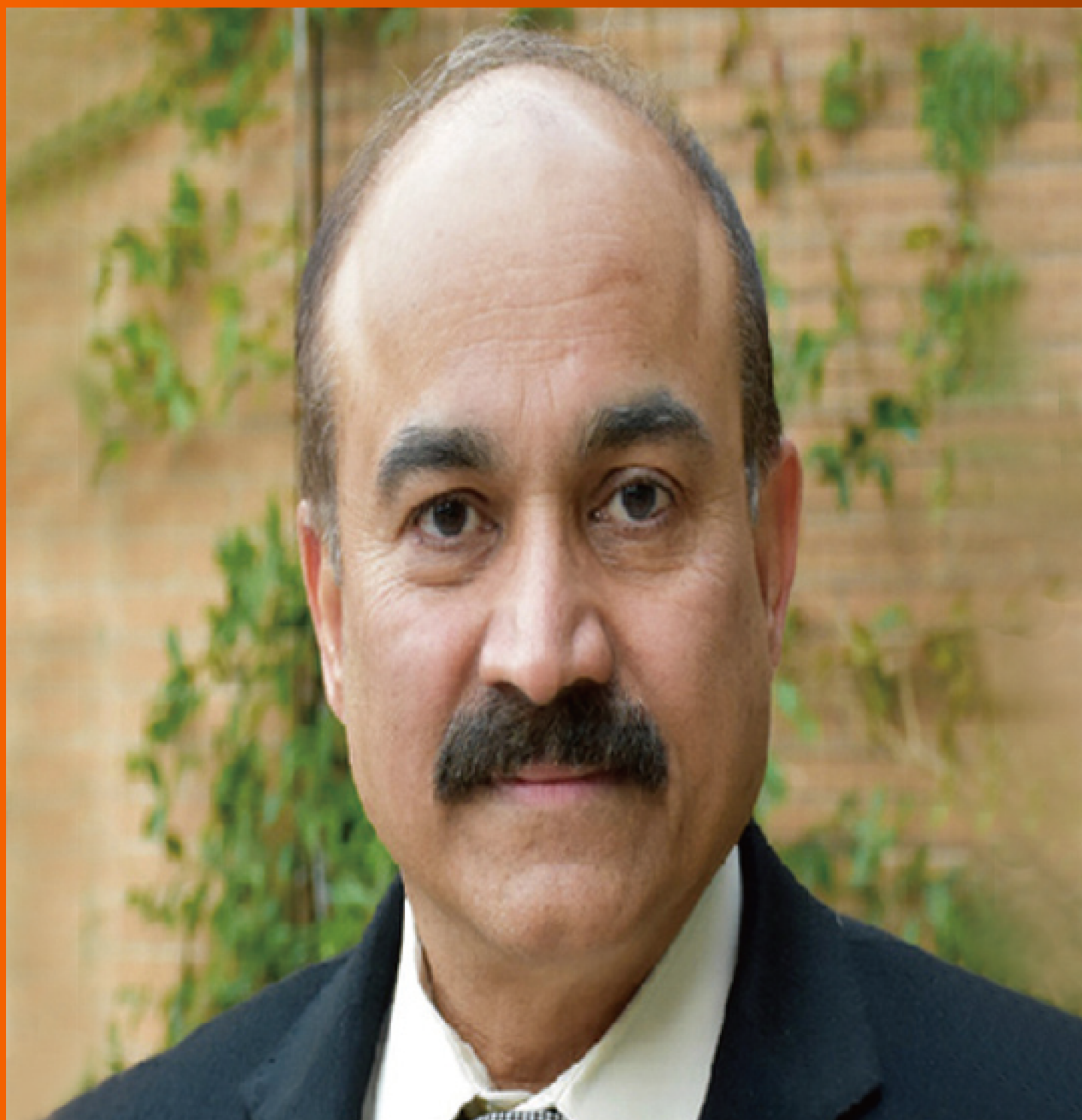


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Risk of sudden cardiac death: Are coronary chronic total occlusions an additional risk factor?

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Abstract

Sudden arrhythmic cardiac death remains a significant, potentially reversible, cardiological challenge in terms of creating accurate risk prediction models. The current guidelines for implantable cardioverter defibrillator (ICD) therapy are mainly based on left ventricular ejection fraction despite its low sensitivity and specificity in predicting sudden cardiac death (SCD). Chronic total occlusions have been associated with increased mortality but further research is required to clarify if they should be incorporated in a risk model predicting SCD aiming to identify patients that would benefit from ICD therapy even with preserved ejection fraction.

Key words: Sudden cardiac death; Chronic total occlusion; Left ventricular ejection fraction; Implantable cardioverter defibrillator

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Core tip: Further research is necessary in order to clarify if chronic total occlusion can be incorporated in a risk prediction model of sudden cardiac death aiming to identify patients that would benefit from implantable cardioverter defibrillator.

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INTRODUCTION

Even though death from cardiac causes has been decreasing over the last two decades in the western world, approximately 20% of all deaths and 50% of cardiovascular deaths are due to sudden cardiac death (SCD)^[1,2]. Coronary chronic total occlusions (CTO) occur in about 16% of patients with significant ischaemic heart disease and they have been associated with increased mortality in a large prospective observational study^[3]. However, currently it is not well known to what extent CTO increase SCD and if these patients would benefit from implantable cardioverter defibrillator (ICD) therapy.

In this Editorial, we focus on a recent article by Chi *et al*^[4] published in JACC Clinical Electrophysiology as we feel it provides a new insight into the role of CTO in relation to prognosis and identifies gaps in knowledge that warrant further research. In this study the authors aimed to understand the relationship between CTO and the occurrence of ventricular tachycardia/fibrillation (VT/VF) or appropriate ICD therapy. They performed a meta-analysis including a total of 17 studies involving almost 55 thousand patients. They found that the presence of CTO was associated with higher risk of VT/VF or appropriate ICD therapy; however it was not associated with a difference in cardiac mortality or in all-cause mortality. The higher risk of VT/VF or appropriate ICD therapy was confirmed on both univariate and multivariate analysis (in only two studies), while the risk of cardiac mortality was significantly higher on univariate but not on multivariate analysis and the risk of all-cause mortality was not significantly higher in either univariate or multivariate analysis^[4].

Comparing patients with infarct-related and non-infarct related CTOs, they concluded that the former had a higher risk of VT/VF or appropriate ICD therapy, cardiac mortality and higher all-cause mortality. The higher risk of VT/VF or appropriate ICD therapy of patients with infarct-related CTOs was confirmed on univariate but not multivariate analysis while the higher risk of cardiac mortality was only significant on multivariate analysis and the higher risk of all-cause mortality was significant on both univariate and multivariate analysis. Finally, non-revascularization of CTO was associated with higher risk of all-cause mortality but this did not reach statistical significance. The authors reached the conclusion that ICD implantation for primary or secondary prevention should be considered in patients who have infarct-related CTOs^[4].

According to American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) 2017, European Society of Cardiology (ESC) 2015 and United Kingdom National Institute for Health and Clinical Excellence (NICE) 2014 guidelines, an ICD is indicated for secondary prevention in survivors of cardiac arrest provided there is no reversible cause^[5-7]. The decision for primary prevention ICD therapy varies slightly according to the various guidelines however, in general it depends on the left ventricular ejection fraction (LVEF), QRS duration and New York Heart Association (NYHA) class. The AHA/ACC/HRS 2017 guidelines recommend ICD if LVEF < 35% and NYHA II-III or LVEF < 30% and NYHA I. The ESC 2015 guidelines recommend ICD if LVEF < 35% and NYHA II-III^[5]. According to NICE 2014 guidelines, primary prevention ICD therapy is indicated if LVEF < 35%, NYHA I-III and QRS duration > 120 ms. For patients who fulfil the first two criteria but QRS is < 120 ms, ICD is recommended if there is a high risk of SCD^[7] and in this situation the current research^[4] would perhaps suggest that presence of CTO can be a qualifying criterion for "high risk"^[7].

Even though LVEF has a central role in the algorithm for recommending primary prevention ICD therapy, it has both low specificity and sensitivity for predicting SCD. It is established that low LVEF predicts not only SCD but also other modes of cardiovascular death as well^[8]. In addition, only a minority of patients who suffer cardiac arrest will have LVEF < 35%. It is estimated that 40% of patients who suffer SCD have known heart disease with LVEF > 40%, while only 13% of patients who suffer SCD have known heart disease and LVEF < 40%^[2]. It has also been shown that myocardial scar > 5% is an independent risk factor for all-cause mortality and appropriate ICD therapy, irrespective of LVEF^[9]. In addition, looking at other pathologies for example dilated cardiomyopathy^[10] and aortic stenosis^[11], other

parameters such as presence of myocardial fibrosis have been shown to have additional prognostic impact over and above LVEF.

CONCLUSION

Chi *et al*^[4] have analysed 17 studies that had included patients with severely reduced LVEF but also patients with only mildly reduced or even normal LVEF. It remains to be seen whether CTO can be regarded as an independent factor for malignant arrhythmias over and above the information we get from LVEF, but this study certainly suggests that this should be investigated. In addition, further research can identify whether patients who have viable myocardium with evidence of reversible ischaemia in the presence of some myocardial scar in the CTO territory should also be considered for an ICD even after successful revascularisation. Even though we do not feel that definitive conclusions can be drawn from this analysis, it is an important study as it indicates that further research is needed in order to clarify the relationship of infarct-related CTO and non-infarct related CTO with SCD both in patients with reduced and preserved LVEF. It is well appreciated that the risk of SCD is continuous rather than dichotomous and no single parameter can adequately discriminate to dichotomise the risk^[12]. Therefore, clarification if CTO is a high risk variable for SCD in patients with preserved LVEF (introducing a new term for such patients, the CTOPeEF patients) or mid-range EF (CTOmreEF patients) or in patients with LVEF < 35% and narrow QRS would be very clinically relevant.

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Cardiac implications of thrombotic thrombocytopenic purpura

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a multisystem disorder that essentially can affect any organ in the human body. The hallmark of the pathogenesis in TTP is the large von Willebrand factor multimers on platelet-mediated micro-thrombi formation, leading to microvascular thrombosis. Autopsy studies showed that cardiac arrest and myocardial infarction are the most common immediate causes of death in these patients. Clinical manifestations of cardiac involvement in TTP vary dramatically, from asymptomatic elevation of cardiac biomarkers, to heart failure, MI and sudden cardiac death. There is limited knowledge about optimal cardiac evaluation and management in patients with TTP. The absence of typical cardiac symptoms, combined with complicated multi-organ involvement in TTP, may contribute to the under-utilization of cardiac evaluation and treatment. Prompt diagnosis and timely initiation of effective therapy could be critically important in selected cases. Based on our experience and this review of the literature, we developed several recommendations for focused cardiac evaluation for patients with acute TTP: (1) patients with suspected or confirmed TTP should be screened for the potential presence of cardiac involvement with detailed history and physical, electrocardiogram and cardiac enzymes; (2) clinical deterioration of TTP patients warrants immediate cardiac reevaluation; (3) TTP patients with clinical evidence of cardiac involvement should be monitored for telemetry, cardiac biomarkers and evaluated with transthoracic echocardiography. These patients require urgent targeted TTP treatment as well as cardiac-specific treatment. Aspirin therapy is indicated for all TTP patients. Since epicardial coronary artery involvement is rare, cardiac catheterization is usually not required, given the high risk for hemorrhage and kidney injury; (4) we recommend evidence-based medical therapy for ischemic symptoms and heart failure. TTP patients with evidence of cardiac involvement would also benefit from routine cardiology follow up during remission.

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Core tip: Thrombotic thrombocytopenic purpura (TTP) is a grave medical condition caused by the formation of von Willebrand factor multimers that cause large platelet plugs and diffuse microemboli, leading to life-threatening, multi-organ ischemic injuries. Although cardiac involvement commonly occurs related to TTP, these cardiac manifestations have not been well studied and may thus be overlooked in clinical practice. Management of cardiac ischemia or myocardial infarction in TTP is also challenging due to increased hemorrhagic risk in the setting of thrombocytopenia. In this report, we systematically review available clinical data in the literature and summarize clinical manifestation, diagnostic workup strategies, prognosis, and the outcomes of cardiac involvement of TTP. We provide recommendations on the strategies for clinical assessment and management of TTP patients with cardiac involvement.

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INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is characterized by the concomitant occurrence of severe thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and a variable degree of ischemic end organ damage. The pathophysiology is elicited by microthrombi forming in the arterioles and capillaries of multiple organs throughout the body. These thrombi are caused by systemic platelet activation and aggregation due to a failure of degradation of unfolded high molecular weight large von Willebrand factor (vWF). These microthrombi deposit systemically and cause widespread organ dysfunction, including pancreas, adrenals, heart, brain, and kidneys. As a result, the patient may present with acute kidney injury, stroke, seizure, or myocardial infarction (MI)^[1,2]. The cardiac manifestations of TTP can be variable, ranging from silent arterial thrombosis and accelerated hypertension, to acute MI (AMI), atrial fibrillation, and congestive heart failure (CHF). In addition, these platelet and coagulation abnormalities can also be seen in cyanotic congenital heart disease.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS OF TTP

The center of TTP pathophysiology is a defect of a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13 (ADAMTS13), either genetically or by the development of an autoantibody. ADAMTS13, also known as vWF-cleaving protease, is a zinc-containing metalloprotease enzyme that cleaves vWF. ADAMTS13 is a 1,427 amino acid protein that is expressed predominately in hepatic stellate cells, podocytes, renal tubular epithelial cells, platelets, and endothelial cells^[1]. vWF is synthesized by megakaryocytes and endothelial cells, and is stored in the form of ultra-large multimers in granules of platelets, Weibel-Palade bodies of endothelial cells, and subendothelial connective tissue. ADAMTS13 cleaves a single peptide bond (Tyr1605-Met1606) located within the central vWF A2 domain. The proteolysis process reduces vWF multimer size and, consequently, its hemostatic function^[3,4]. Lack or loss of ADAMTS13 function results in increased circulating vWF multimers, which leads to platelet adhesion to the endothelium, platelet activation, and ultimately the formation of a platelet plug.

Depending on the mechanisms of ADAMTS13 inhibition, TTP is divided into 1) an acquired form, which arises from autoantibody-mediated ADAMTS13 inhibition, and 2) a relatively rare inherited form, which results from an autosomal recessive gene mutation causing innate ADAMTS13 dysfunction. As microthrombi form, especially where arterioles and capillaries meet, end organ ischemia and injury occur due to

vascular obstructions caused by the microthrombi. In addition, the circulating red blood cells are subjected to increased shear stress, which damages their membranes, leading to schistocyte formation and anemia.

Clinically, TTP can be manifested systemically due to the involvement of multiple organs^[5]. The classic presentation of TTP includes the following pentad: fever, changes in mental status, thrombocytopenia, reduced kidney function, and MAHA. MAHA and thrombocytopenia are hallmarks of TTP, and the possibility of TTP should be evaluated in any patients who present with these findings and who do not have an apparent alternative explanation.

CLINICAL CARDIAC INVOLVEMENT OF TTP

Extensive cardiac involvement was reported in the first TTP patient in 1925. This patient showed T wave inversions on the electrocardiogram (ECG) and extensive thrombi in the terminal arterioles and capillaries of the heart, as confirmed by autopsy examination^[6]. Subsequently, the heart was found to be the most commonly affected organ in TTP. Additional autopsy studies of deceased patients with TTP showed that cardiac arrest and AMI are the most common immediate causes of death^[7].

Clinical manifestations of cardiac involvement in TTP can vary dramatically, from an asymptomatic elevation of cardiac biomarkers, to chest pain or heart failure symptoms associated with ECG changes, elevation of cardiac enzymes, imaging evidence of massive MI, cardiomyopathy, arrhythmia, or even sudden cardiac death (SCD)^[8-11].

Elevated cardiac troponin (cTn) was reported in 59% of patients with TTP upon admission. However, the majority of this group was clinically silent from a cardiac standpoint. ECG changes are common in TTP patients with elevated cardiac enzymes^[12]. Hawkins *et al*^[9] performed extensive analysis of 111 patients with TTP and reported the most common cardiac symptoms to be chest pain (11.7%), CHF (9.0%), and syncope (0.9%). The most frequent cardiac events in those patients included MI (23.4%), CHF (15.3%), arrhythmias (9.0%), cardiogenic shock (5.4%) and SCD (7.2%). AMI in TTP can present as ST segment elevation MI (STEMI) or non-STEMI with or without echocardiographic evidence of segmental wall motion abnormalities^[11]. Patients with AMI in the setting of TTP often developed arrhythmias such as atrial fibrillation (25%), atrial flutter (13%), supraventricular tachycardia (13%) and CHF (25%)^[8].

PATHOGENESIS AND AUTOPSY EVIDENCE OF CARDIAC COMPLICATIONS IN TTP

In TTP, the large vWF multimers mediate platelet plugs and microthrombi formation. Hyalinized arteriolar and microvascular microthrombosis in the coronary artery circulation has been shown in most autopsy reports. Microthrombosis is the most common finding of cardiac pathology in autopsies of deceased patients who suffered from TTP (Table 1). Epicardial coronary arterial thrombosis is rare. Large epicardial coronary arteries are commonly spared from thrombosis in TTP. However, recurrent epicardial arterial thrombosis has been reported in one TTP patient who was treated with thrombectomy, stent placement and dual antiplatelet therapy^[13]. The interaction between vWF multimer-mediated thrombosis with existing vulnerable plaques in concomitant atherosclerotic coronary artery disease (CAD) was postulated to induce the arterial thrombosis^[14]. Thus, arterial/arteriolar thrombosis leads to myocardial ischemia, infarction and necrosis. Thrombocytopenia and ischemia-induced damage of vascular integrity subsequently leads to myocardial hemorrhage. These processes not only lead to myocardial damage, but often cause dysfunction of the cardiac conduction system. In addition, marantic endocarditis has been reported^[7,10,12]. Also, James *et al*^[15] reported myocardial degeneration in atrial and ventricular myocardium in TTP patients as a result of apoptosis.

PROGNOSTIC VALUE OF CARDIAC INVOLVEMENT IN TTP

Post-mortem studies clearly demonstrated a high incidence of cardiac involvement in deceased TTP patients. Autopsy reports revealed almost all patients with TTP have cardiac involvement, and the disease process mostly affects the microvasculature of the heart. Cardiac complications directly cause death in TTP, particularly in acute

Table 1 Cardiac involvement and pathology in autopsy studies of deceased patients with thrombotic thrombocytopenia purpura

Authors	Year	Total No.	Descriptive comments of cardiac involvement and pathology			
			Microthrombi in small vessel (arteriole/capillaries)	Epicardial coronary thrombus	Hemorrhage petechiae	Other pathology
Moschcowitz ^[6]	1925	1	1/1	0/1	n/r	
Amorosi <i>et al</i> ^[45]	1966	3	3/3	1/3	3/3	AV node involvement 1/3
James <i>et al</i> ^[46]	1966	3	3/3	0/3	3/3	
Geisinger ^[47]	1979	1	1/1	0/1	1/1	
Ridolfi <i>et al</i> ^[48]	1979	17	17/17	0/17	13/17	AV node and his bundle involvement 7/17
Ross <i>et al</i> ^[49]	1987	1	1/1	0/1	1/1	
Bowdler <i>et al</i> ^[50]	1987	1	1/1	0/1	1/1	
Siersema <i>et al</i> ^[51]	1989	3	3/3	0/3	3/3	SA, AV node, His bundle involvement 3/3
Bell <i>et al</i> ^[52]	1990	8	8/8	0/8	8/8	SA and AV node involvement 2/3
Webb <i>et al</i> ^[53]	1990	1	1/1	0/1	1/1	
Eagle <i>et al</i> ^[54]	1994	1	1/1	0/1	1/1	
James <i>et al</i> ^[15]	1997	6	6/6	0/6	6/6	SA, AV nodes and His bundle involvement 6/6
Podolsky <i>et al</i> ^[55]	1999	1	1/1	0/1	1/1	AV node involvement 1/1
Wajima <i>et al</i> ^[56]	2000	1	1/1	0/1	1/1	
Hosler <i>et al</i> ^[57]	2003	25	25/25	n/r	n/r	
Lapp <i>et al</i> ^[23]	2004	1	1/1	0/1	1/1	
Brandenburg <i>et al</i> ^[58]	2004	1	1/1	0/1	1/1	
Gami <i>et al</i> ^[59]	2005	3	3/3	n/r	n/r	
Ibernon <i>et al</i> ^[60]	2005	1	0/1	1/1	1/1	
Arnold <i>et al</i> ^[61]	2006	1	1/1	0/1	1/1	
Patschan <i>et al</i> ^[10]	2006	4	4/4	0/4	2/4	
Sarode <i>et al</i> ^[62]	2009	1	1/1	n/r	n/r	
George <i>et al</i> ^[63]	2012	1	1/1	n/r	n/r	
Nichols <i>et al</i> ^[7]	2015	18	9/18	0/18	7/18	
Summary		104	94/104 (90.4%)	2/74 (2.7%)	56/73 (76.7%)	

AV: Atrioventricular; SA: Sinoatrial.

myocardial necrosis as a result of extensive circulatory microthrombosis. AMI and CHF are known independent risk factors for in-hospital mortality in patients with TTP^[16,17]. Elevated LDH and troponin at presentation were found to be independent risk factors for MI^[10]. cTn I above 2.5 ng/mL was found to independently predict mortality and refractory TTP. Therefore, evidence of cardiac involvement in TTP provides important prognostic value. A systematically structured approach to monitor signs and evidence of cardiac involvement may be cost-effective.

CARDIAC EVALUATION OF TTP

There is limited knowledge about optimal cardiac evaluation for patients with TTP. There are also large variations in clinical practice. Clinically, the majority of patients with TTP present without any clinical symptoms of myocardial ischemia. The traditional clinical pentad (fever, thrombocytopenia, microangiopathic anemia, neurological symptoms and acute kidney injury) of TTP does not include cardiac

symptoms. In current practice, cardiac evaluation is not part of routine initial evaluation for patients with suspected or confirmed TTP. The lack of or atypical cardiac symptoms in TTP may have contributed to the under-utilization of cardiac evaluation and delay in diagnosis. However, increasing data suggest that the presence of cardiac involvement in TTP strongly associates with an adverse outcome. Therefore, timely recognition and appropriate monitoring of cardiac status in TTP could be critically important in many cases. In recent decades, there have been dramatic advancements in laboratory, telemetry, non-invasive and invasive approaches of cardiac evaluation and therapeutics. The cost effectiveness and clinical significance of cardiac evaluation and therapeutics in TTP are thus important topics of discussion.

Cardiac biomarkers in TTP

Serial troponin-I or -T measurements are sensitive and specific biomarkers of myocardial injury. The overall incidence of troponin positivity in the TTP population has not been defined. However, multiple studies have shown that elevated troponin is a reliable biomarker for cardiac involvement in TTP. Elevated level of cTn upon admission is a risk factor for death and TTP refraction^[17]. It seems reasonable to recommend a routine troponin measurement when a diagnosis of TTP is suspected or clinical deterioration is observed.

Telemetry monitoring in TTP

Considering the fact that there are consistent correlations between poor clinical outcome and evidence of cardiac involvement in TTP, it would be reasonable to monitor the patient on telemetry if cardiac involvement is suspected, *i.e.* positive troponin, abnormal admission ECG, or echocardiographic evidence of cardiomyopathy^[18]. The evidence of cardiac conduction system involvement in TTP mandates telemetry monitoring. However, the cost-effectiveness of telemetry monitoring of all troponin-positive TTP patients has not been determined.

Cardiac imaging assessment of cardiac structure and function in TTP

Transthoracic echocardiography (TTE) is the most commonly used imaging modality to evaluate cardiac structure and function. In TTP patients with clinical symptoms, such as shortness of breath, palpitations, chest pain *etc.*, that suggest ischemia, heart failure, arrhythmia or hemodynamic/electrical instability, a TTE should be performed^[19]. TTE is also appropriate as an initial evaluation of cardiac structure and function in TTP patients with clinical data suggesting cardiac involvement, such as positive biomarkers (troponin, BNP *etc.*), abnormal ECG and telemetry monitoring. Currently, there is no data available documenting the utilization and outcomes of TTE studies for TTP patients. The cost-effectiveness has also not been determined. Transesophageal echocardiography (TEE) is often unnecessary and rarely recommended for TTP patients, as thrombocytopenia is known to elevate the bleeding risk. The benefit of imaging modalities, such as cardiac magnetic resonance imaging (MRI), for assessing the impact of TTP on cardiac structure and function has not been studied.

Ischemic workup in TTP

The hallmark of TTP pathogenesis is thrombus formation in the micro-circulation. Occlusion of this micro-circulation, or less commonly of the epicardial coronary circulation, directly causes myocardial ischemia. Clinical evidence of ischemic symptoms, elevated troponin, or decreased myocardial contraction are all suggestive of myocardial ischemia in TTP. However, methods that will reliably evaluate the etiology of ischemia in these patients have not been adequately investigated. Non-invasive imaging modalities, such as Doppler coronary artery blood flow velocity and myocardial contrast echocardiography, are considered cost effective methods that correspond well with invasive techniques, but they are used less frequently in routine cardiology practice. Their role in patients with TTP has not been studied. Positron emission tomography (PET) and cardiac MRI myocardial perfusion imaging studies both measure rest and stress myocardial blood flow and enable coronary flow reserve (CFR) quantification. Both modalities are well established for the detection of CAD-related ischemia, and for the evaluation of microvascular disease. Both are sensitive in detecting the heterogeneous distribution of microvascular defects, which may indicate microvascular disease^[20,21]. High resolution, ECG-gated cardiac computed tomography (CT) angiography (CTA) enables non-invasive imaging of the epicardial coronary arteries. Theoretically, CTA provides a reasonable approach to evaluate myocardial ischemia and the involvement of epicardial coronary arteries in TTP without the concern of bleeding risk associated with an invasive approach. However, its clinical significance has not been studied in this patient group.

In TTP, the high incidences of elevated cardiac enzymes and myocardial injury are mostly driven by ischemia at the level of the microvasculature. There are a few reports in the literature that describe using invasive coronary angiography to evaluate coronary artery patency in TTP patients^[10]. While the majority of TTP patients had no obstructive disease in their epicardial arteries, there is a report of a patient with angiographic documentation of epicardial artery occlusion in TTP^[22]. However, other TTP patients that presented with STEMI and cardiogenic shock were found to have clean coronary arteries on angiograms, with the visible “slow flow” phenomenon^[23]. Therefore, diagnostic testing in this population should focus more on microvasculature of the heart rather than the epicardial arteries, especially in patients who recover from an acute episode and remain symptomatic from a cardiac standpoint. ECG evidence of acute STEMI probably deserves evaluation of the large epicardial arteries either by CTA or, more accurately, by invasive coronary angiography with the associated increased risk of hemorrhage, renal insufficiency and/or exacerbation of pre-existing anemia.

For the purpose of risk stratification and planning of both clinical treatment and monitoring when TTP is diagnosed, cardiac involvement should be systematically evaluated by ECG, cTn, and echocardiography. Patients with positive initial cardiac workup should have an Echocardiogram done during initial hospitalization, as left ventricular (LV) dysfunction has been reported in several publications^[9]. A coronary angiogram may be indicated if concomitant atherosclerotic CAD is suspected based on risk profile and clinical features, but should be postponed if possible until the patient recovers from the TTP episode^[14].

TREATMENT FOR CARDIAC COMPLICATIONS IN TTP

Therapeutic plasma exchange (TPE) - removing circulating anti-ADAMTS13 antibodies - is the cornerstone of TTP treatment, which resulted in reduced mortality from approximately 90% to 10%-20%. Immunosuppression with steroids or rituximab appears to be efficacious for acquired TTP, resulting in autoantibody formation against ADAMTS13. Experimental agents, such as recombinant ADAMTS13^[24] as a specific protease supplement, and novel small molecules targeted on the vWF GpIb α -binding site on platelets are also promising therapies to further improve TTP treatment. In refractory TTP, other therapeutic approaches are also common, such as splenectomy, vincristine, cyclophosphamide, intravenous immunoglobulins, cyclosporine A, azathioprine, and mycophenolate mofetil, although there is not enough evidence yet to prove the efficacy of these treatment strategies. Platelet transfusion is generally not indicated; however, some authors recommend transfusing platelets in acute TTP episodes to decrease the risk of hemorrhage. As cardiac involvement is an integrated pathological process in TTP, general therapeutic strategies should also benefit the cardiac system.

Despite the recognition of the significant association between cardiac involvement and adverse clinical outcome in TTP, targeted management approaches for cardiac complications in TTP have not been well investigated. On the other hand, recent decades have seen significant advancements in evidenced-based medical and procedural treatments for acute coronary syndrome (ACS) and cardiomyopathy. Anecdotal case reports have successfully applied all the available therapeutic tools that have saved the lives of TTP patients with life-threatening cardiopulmonary complications. These reports have documented successful primary percutaneous coronary intervention (PCI) in the setting of ongoing STEMI with angiographic evidence of epicardial coronary artery occlusions^[22], thrombolytic therapy for massive pulmonary embolism or STEMI in the setting of TTP^[25,26], extracorporeal membrane oxygenation (ECMO) support for cardiogenic shock due to acute global ischemia resulted from diffuse microthrombi, to subsequent heart transplantation after the resolution of TTP^[27]. Hemodynamic support and targeted treatment for cardiac complications of TTP may provide the opportunity for TTP-targeted therapy to take effect and eventually improve mortality, particularly in cases of severe TTP with hemodynamically-compromising cardiac complications.

Treatment for ischemic injury

In general, the most common cause of acute ischemia injury to the myocardium is ACS, as a result of an acute atherothrombotic event in the coronary arteries. Antiplatelet and anticoagulation therapies aiming to terminate or reverse the thrombotic process are the main strategy to ameliorate ongoing ischemia. In TTP, thrombocytopenia with various degrees of microthrombosis is universal, and is directly responsible for most of the cardiac complications, especially myocardial

ischemia. Existing evidence suggests that the majority of these injuries are caused by microthrombosis in the microvascular beds and rarely involve large epicardial arteries. The safety and efficacy of antiplatelet and anticoagulation therapy in the setting of TTP and ongoing myocardial ischemia is still a topic of debate.

In current practice, antiplatelet therapy is always considered in patients with TTP to prevent microthrombi formation. Aspirin is generally recommended for TTP patients as an antiplatelet agent. The effectiveness and safety of other antiplatelet agents remains less certain. In a landmark study published by Rock *et al*^[28] comparing plasma exchange with plasma effusion, all patients received dipyridamole (400 mg daily) and aspirin (325 mg daily) for a period of at least 2 wk as a standard therapy. Treatment and maintenance with both aspirin and dipyridamole is suggested by some studies to prevent TTP relapse^[29]. Patients receiving aspirin and dipyridamole during the acute phase were noted to have lower mortality. In addition, ticlopidine maintenance was shown to prevent relapses after 1 year^[30]. Some authors even suggest intravenous infusion of dipyridamole as an adjunctive therapy^[31]. However, the mechanisms of thrombi formation in TTP may differ from atherothrombotic ACS. Thus, aspirin with dipyridamole may not have the same beneficial effects in TTP as it does for ACS^[32,33]. Other P2Y₁₂ receptor inhibitors, such as clopidogrel, prasugrel and ticagrelor, have not been tested for treating acute cardiac involvement in TTP. Furthermore, these thienopyridine derivatives (ticlopidine, clopidogrel, and prasugrel) are known to possess the potential of inducing acquired TTP^[34].

Unfractionated heparin (UFH) or low molecular weight heparin (LMWH) products have not been well studied in microvascular thrombi-induced myocardial injury in TTP, nor have GPIIb/IIIa inhibitors and direct thrombin inhibitors. Anticoagulation remains the treatment of choice for other thromboembolic disorders like antiphospholipid syndrome, cancer-associated thrombosis, and heparin-induced thrombocytopenia. The risk of hemorrhage in the setting of thrombocytopenia in TTP with its pathological microthrombi formation leads to the dilemma for anticoagulation therapy.

In the setting of STEMI with potentially large epicardial artery occlusion, which carries the highest risk of cardiac death, the decision of whether or not to use aggressive antiplatelet and anticoagulation (with or without pursuing invasive coronary angiography and intervention) must be decided on a case by case basis. The clinical decision is made by weighing clinical risk and benefit in adjunction with TTP therapy. There are reports of successful PCI for STEMI in TTP patients, as well as successful use of thrombolysis therapy^[13,25]. Should a TTP patient undergo a primary PCI for epicardial coronary artery occlusion, the patient is probably a better candidate for bare metal stents than for drug eluting stents, so as to reduce the required dual antiplatelet therapy duration. Due to thrombocytopenia in TTP and platelet dysfunction, the risk of bleeding during procedural treatments (diagnostic cardiac catheterization and PCI, pacemaker placement *etc*) for TTP patients is high. However, the threshold of platelet counts for these procedures is not defined. Physicians will need to assess on a case-by-case basis.

Treatment of microvascular disease remains a challenge, and not much data is available on this topic. Potentially beneficial treatments of microvascular disease in patients without TTP are beta blockers, non-dihydropyridine calcium channel blockers, nitrates, angiotensin converting enzyme inhibitors, and statins. But clinical evidence is lacking in TTP patients.

Statins have an established role in lowering cholesterol and reducing cardiovascular mortality in the general population. Statins help with the remodeling of coronary vessels, plaque stabilization, and the improvement of the perfusion of myocardial muscle. There are also other benefits observed with statins, including anti-inflammatory function and improvement in endothelial function. Statins could be beneficial in the TTP cohort of patients, as they have been shown to be an inhibitor of regulated vWF secretion in human umbilical vein endothelial cells^[35]. These pleiotropic effects of statins have been shown to be beneficial in patients with coronary microvascular dysfunction, and have a potential role in the treatment of microvascular disease related to TTP. A recent study showed that Simvastatin can increase the expression of ADAMTS13 in podocytes^[36]. Statins are safe in the majority of cases, but statin-induced TTP has also been reported^[37,38]. There is a paucity of data on the use of statins in TTP patients.

Treatment for heart failure and cardiomyopathy

Heart failure symptoms are relatively common in TTP presentation during the hospital course. With the common involvement of kidney injury, potentially significant volume changes during TPE, and ischemic injury of myocardium with potential decrease of contractile function, volume overload and pulmonary congestion may occur. Therefore, it is critical to have close clinical monitoring and to treat

decompensated heart failure with both intravenous diuretics and vasodilatory agents for afterload reduction with or without inotropic support. Hemodynamic support may also be indicated in critically ill TTP patients with cardiac complications.

β -adrenergic receptor blockers: β -blockers are proven beneficial for cardiomyopathy and ischemic heart disease at the epicardial and the microcirculation level^[39]. β -blockers are indicated for patients with myocardial injury and decreased LV ejection fraction (LVEF). Although there are no direct large-scale clinical studies on the use of β -blockers in TTP patients, they intuitively should be used for TTP patients with evidence of cardiac involvement. Published reports show complete recovery of TTP-related ischemic cardiomyopathy with regimens that include β -blockers^[40]. β -blockers and calcium channel blockers are commonly used to treat angina symptoms in patients with coronary microvascular dysfunction. Additionally, β -blockers like Nebivolol have been shown to improve endothelial function, which may help patients with TTP^[41].

Calcium channel blockers: Calcium channel blockers are commonly used in the treatment of microvascular dysfunction. Reported anti-atherogenic and antithrombotic properties of calcium channel blockers might have significant benefits in TTP treatment^[42], however their efficacy in these patients has not been established.

Angiotensin-converting enzyme inhibitor/angiotensin receptor blockers: Inhibitors of the renin-angiotensin system have a well-documented role in patients post-MI with decreased LVEF. Angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blockers (ARB) have been shown to be effective in the treatment of endothelial dysfunction and in the improvement of CFR. ARB is usually the choice when patients are unable to tolerate ACEi. Patients who are not candidates for either could benefit from a nitrate-hydralazine combination or Spironolactone. The addition of spironolactone was found particularly beneficial in patients with microvascular disease and diabetes. While these agents have been confirmed by large clinical trials to be beneficial in treating heart failure, cardiomyopathy, endothelial dysfunction and microcirculation dysfunction, which are all common in TTP patients, there is no data on the use or efficacy of ACEi/ARB in TTP patients.

Treatment of cardiac conduction system complication

For cardiac conduction system complications, *i.e.*, heart block, or arrhythmia, dedicated therapy will be indicated. Temporary transvenous pacemakers may be necessary for a hemodynamically significant heart block. Anti-arrhythmic agents may also be indicated for tachyarrhythmias with or without cardioversion, depending on clinical status. There are no long-term follow up data on cardiac conduction complications in TTP patients.

FOLLOW UP CARDIAC CARE OF TTP

With the advancement in understanding of the pathophysiology of TTP, as well as effective therapeutic strategies, the lethality of TTP has decreased. Its overall mortality has been reduced from 90% to 10%-20%. However, long-term follow up of TTP survivors showed their increased mortality over time when compared to the general population. Speculated causes include ADAMTS13 deficiency as a risk factor for cardiovascular disease, as well as ischemia from microvascular thrombosis, causing end organ damage over time. There are cases suggesting cardiac and renal complications to be responsible for suboptimal long-term outcomes in these patients. Therefore, routine cardiology follow up after recovery from acute TTP seems reasonable, especially for the patients with cardiac involvement during the acute phase. However, data are not available at this time to show the long-term cardiac implications of TTP and the significance of follow up cardiology care of TTP.

Ischemic workup and treatment

Considering the common occurrence of renal insufficiency and increased hemorrhagic risk during acute TTP, CAD status in the setting of ischemic injury during TTP is not often investigated. After recovery of acute TTP, ischemic workup should be performed with either a non-invasive stress test with myocardial perfusion imaging, or cardiac catheterization for patients with high pre-test probability of severe CAD.. Coronary CT angiography is also an option for defining the coronary anatomy. Exclusion of epicardial CAD and confirmation of microvascular disease may be helpful in the management of patients with chronic ischemic symptoms. Indeed, multiple reports showed adverse outcomes related to coronary microvascular

dysfunction^[43]. A recent report showed that microvascular disease is directly related to increased mortality when compared to the general population^[44]. However, despite the evidence of cardiac microvascular involvement in TTP, the long-term CAD risk for TTP survivors in comparison to the general population is unknown.

Other medications like ranolazine, ivabradine, amitriptyline, imipramine, or nortriptyline were found to be beneficial in the treatment of angina in coronary microvascular dysfunction, but their role in the TTP cohort is unknown. They could be considered for treatment of TTP patients who remain symptomatic with angina after recovery from an acute episode.

Cardiomyopathy follow up

TTP patients with evidence of ischemic injury and decreased LV function during the acute phase should be followed by cardiology as outpatients. It is reasonable to recommend evidence-based, guideline-directed medical therapy for cardiomyopathy with β -blockers, ACEi/ARB and other indicated agents. It is also reasonable to follow up on the recovery of EF. The long-term follow up on the trajectory of LV contractile function in TTP patients has not been established, although existing reports seem to suggest a favorable outcome commonly with full LVEF recovery. The risk of sudden cardiac death in TTP patients with severely reduced EF is unknown. The potential need for a permanent pacemaker for conduction system complications and an implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death of patients with TTP is unclear.

CONCLUSION

Cardiac involvement in TTP is common. The presence of cardiac involvement is associated with adverse clinical outcomes in TTP patients. Contemporary diagnostic and therapeutic approaches provide the opportunity to improve clinical management of the cardiac complications related to TTP. Based on the above review of the literature and our own experience, we propose the following recommendations to clinicians managing TTP patients (Figure 1), in addition to the TTP routine workup and treatment. (1) All patients with suspected or confirmed TTP diagnosis should be screened for the potential presence of cardiac involvement by clinical symptoms/signs, ECG and cTn. (2) Any clinical deterioration of TTP patients with initial negative cardiac involvement warrants reassessment for the potential development of cardiac complications. (3) TTP patients with a positive screen or subsequent assessment of cardiac involvement should be monitored on telemetry, have cardiac biomarkers monitored as an indicator of disease progression, have TTE performed to assess cardiac structure and function, and have enhanced TTP-targeted treatment for disease control. (4) Aspirin therapy is indicated for all TTP patients. (5) Consider other targeted therapies (UFH, LMWH, low dose thrombolytics *etc*) for obstructive microthrombosis-related ischemia, with a balanced consideration of risk for hemorrhagic complications. (6) Apply evidence-based medical therapy for ischemia and cardiomyopathy, including diuretics, β -blockers, ACEi/ARB, statins, *etc*. (7) Treatment of arrhythmias and conduction abnormalities according to current guidelines. And (8) cardiology follow up and further evaluation as indicated after the acute phase of TTP.

Due to the lack of evidence from large clinical studies, the management of cardiac complications in TTP is largely based on the cohort data, experience and expert opinions. Future clinical studies on these topics are urgently needed. A multiple center prospective registry of TTP with a focus on cardiac implications and management is necessary to gather the evidence to better assess the clinical cost-effectiveness of these approaches.

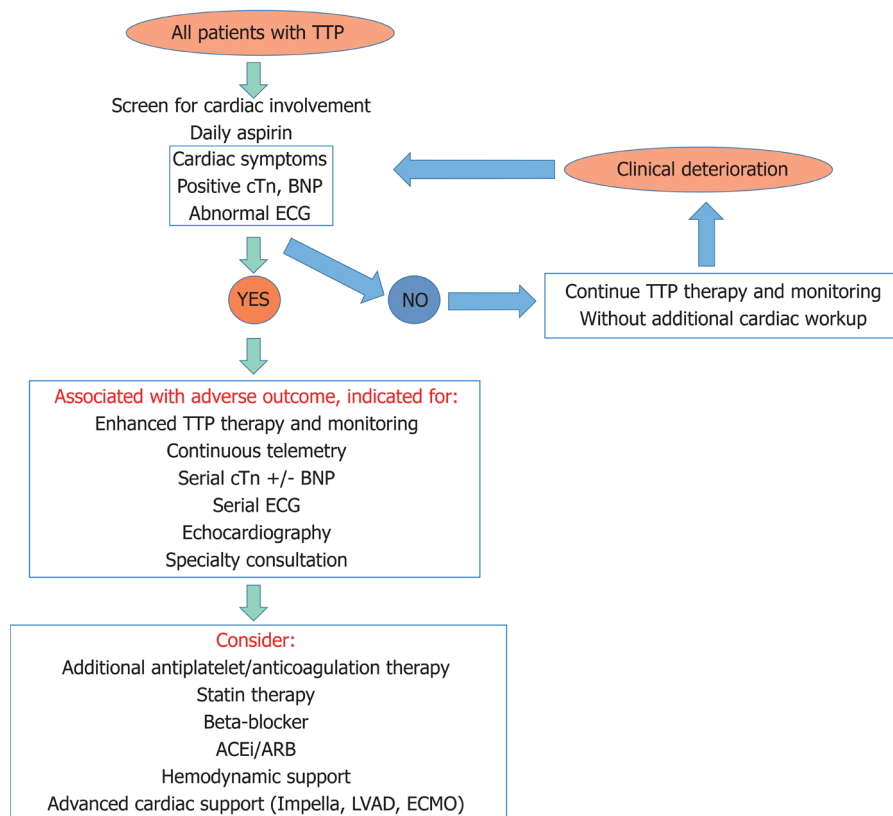


Figure 1 Recommendations on clinical assessment and management of cardiac involvement of thrombotic thrombocytopenia purpura. All patients with a diagnosis of thrombotic thrombocytopenia purpura (TTP) should be given low dose aspirin daily and screened for cardiac involvement by clinical cardiac symptoms, cardiac biomarkers (cardiac troponin, B-type natriuretic peptide etc) and electrocardiogram. Positive screen of cardiac involvement of TTP predicts adverse outcome, requiring further evaluation and treatment as recommended above. TTP: Thrombotic thrombocytopenia purpura; cTn, Cardiac troponin; BNP: B-type natriuretic peptide; ECG: Electrocardiogram; ACEi: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers; LVAD: Left ventricular assist device; ECMO: Extracorporeal membrane oxygenation.

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Instantaneous wave-free ratio (iFR®) to determine hemodynamically significant coronary stenosis: A comprehensive review

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Abstract

Coronary angiography is considered to be the gold standard in the morphological evaluation of coronary artery stenosis. The morphological assessment of the severity of a coronary lesion is very subjective. Thus, the invasive fractional flow reserve (FFR) measurement represents the current standard for estimation of the hemodynamic significance of coronary artery stenosis. The FFR-guided revascularization strategy was initially classified as a Class-IA-recommendation in the 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization. Both the Deferral *vs* Performance of Percutaneous Coronary Intervention of Functionally Non-Significant Coronary Stenosis and Flow Reserve *vs* Angiography for Multivessel Evaluation studies showed no treatment advantage for hemodynamically insignificant stenoses. With the help of FFR (and targeted interventions), clinical results could be improved; however, the use in clinical practice is still limited due to the need of adenosine administration and a significant prolongation of the length of the procedure. Instantaneous wave-free ratio (iFR®) is a new innovative approach for the determination of the hemodynamic significance of coronary stenosis, which can be obtained at rest without the use of vasodilators. Regarding the periprocedural complications as well as prognosis, iFR® showed non-inferiority to FFR in the SWEDEHEART and DEFINE-FLAIR trials. Furthermore, iFR®, enhanced by iFR®-pullback, provides the possibility to display the iFR®-change over the course of the vessel to create a hemodynamic map.

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Core tip: Invasive fractional flow reserve measurement represents the current standard for estimation of the hemodynamic significance of coronary artery stenosis and was initially classified as a Class-IA-recommendation in the 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization. Instantaneous wave-free ratio (iFR®) is a new innovative approach for the functional evaluation of a coronary stenosis, which can be obtained at rest without the use of vasodilators. The diagnostic value of iFR® showed non-inferiority compared to fractional flow reserve. It can be enhanced by iFR®-pullback, which provides the possibility to display the iFR®-change over the course of the vessel to create a hemodynamic map.

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INTRODUCTION

The optimal strategy for revascularization of hemodynamically significant coronary stenosis is an important therapeutic option in patients with coronary heart disease (CHD)^[1]. Despite being the gold standard in the diagnosis of coronary stenosis, coronary angiography has a few limitations. Sometimes, the angiographic demonstration of the correct anatomy is limited due to morphologic deviations; additionally, visual evaluation of the coronary lesion is subjective and is associated with large inter-observer variability^[2,3].

The current standard for invasive assessment of a coronary lesion with hemodynamic significance is the fractional flow reserve-(FFR)-measurement^[4]. This was initially adopted as a Class-IA-recommendation in the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ECS/EACTS) guidelines of 2014 on myocardial revascularization^[5]. Especially with intermediate coronary stenoses and in patients with a multivessel disease, FFR can help the clinician to assess the severity of the lesion and to formulate the required treatment^[6]. Other than the angiographic imaging, FFR provides a direct functional assessment of coronary stenoses.

Both the Deferral *vs* Performance of Percutaneous Coronary Intervention of Functionally Non-Significant Coronary Stenosis and the FAME (Flow Reserve *vs* Angiography for multivessel Evaluation) studies could not prove a prognostic benefit of treating hemodynamically insignificant coronary stenosis through percutaneous coronary intervention (PCI)^[6-8]. Furthermore, long-term analysis of the Deferral *vs* Performance of Percutaneous Coronary Intervention of Functionally Non-Significant Coronary Stenosis study showed that the use of FFR improved the clinical outcome and lowered the procedural costs^[9].

Patients with stable CHD who received FFR-guided PCI along with an adequate medication appeared to be more convalescent compared to patients on the medication-only therapy and were subjected to an emergency revascularization less frequently (FAME-II-study^[8]). Additionally, patients with hemodynamically insignificant coronary stenoses (FFR > 0.80) who received optimal medical treatment alone showed a very good long-term outcome.

The FFR utilizes the linear relationship between pressure and flow at a point of an increased intracoronary resistance^[10]. Assuming intracoronary pressure is proportional to the flow, a pressure gradient could indicate a lowered blood flow caused by a coronary stenosis. However, the intracoronary resistance changes periodically during a cardiac cycle. The periodic variations in resistance emerge from the interaction between the myocardium and the microvasculature during systole (high intracoronary resistance, compression of the microvasculature) and diastole

(low intracoronary resistance, decompression of the microvasculature^[11]). To perform the FFR-measurement, adenosine is administered to the patient to induce a hyperemic condition in order to achieve a constant blood flow, and FFR can be calculated and averaged over several cardiac cycles.

Although the clinical and economical benefits of FFR have been proven^[7,9], it is only used in about 6% of patients undergoing PCI for intermediate coronary stenoses (40%-70% diameter stenosis)^[12]. This is due to the high price for a single FFR-wire (600-800€^[13]) as well as the use of adenosine, which is an additional expense. Furthermore, with each coronary assessment there exists a certain risk of a perforation or dissection^[14] whilst applying the wire. In addition, the assessment time is longer, and adenosine administration could lead to adverse effects like dyspnea, chest pressure and discomfort, hypotension, and even atrioventricular blocks. However, vasodilators offer a pragmatic solution to achieve a constant blood flow and stable perfusion. Although FFR delivers accurate results and provides valuable information for the clinician assessing a single stenosis, the process of estimating the severity of each single stenosis in vessels with multiple lesions is difficult and time consuming^[15]. The hemodynamic effect of removing a single stenosis in complex CHD is not easily predictable. The reason for this is an interdependence between multiple lesions in continuous coronary arteries under hyperemia, leading the examiner to overestimate a distal lesion and underestimate a proximal lesion. Inconveniently, after the treatment of each stenosis, the segment has to be reassessed by the clinician^[16,17]. Therefore, new methods like iFR® ("instantaneous wave-free ratio", Volcano Corporation, Koninklijke Philips N.V., Amsterdam, The Netherlands) offer a different approach. iFR® is based on the hypothesis that a specific time interval during the cardiac cycle, the diastolic "wave-free" period, can be identified when microvascular resistance is naturally minimized without the need of hyperemia induced by the administration of a vasodilator^[18]. Next to the two large multicenter studies Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization (DEFINE-FLAIR)^[19] and Swedish Web-Based System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART)^[20], which proved the non-inferiority of iFR® towards FFR, the first meta-analysis with 23 studies including 6300 coronary lesions was just recently published. This study verified a significant correlation between iFR® and the gold standard FFR and a good performance of iFR® identifying FFR-positive stenoses^[21]. Besides FFR, iFR® was just recently adopted as a Class-IA-recommendation in the ECS/EACTS guidelines of 2018 on myocardial revascularization^[22].

PHYSIOLOGICAL PRINCIPLES OF iFR®-ASSESSMENT

iFR®-measurement is based on the physical law outlined by the Hagen-Poiseuille equation, which describes a laminar flow of an incompressible viscous fluid flowing through a cylindrical pipe of a constant cross section, which depends on the type of fluid and the consistency of the pipe^[23]. This law is a deviation of Ohm's Law ($U = R \times I$).

$$P = Q \times R$$

$$\text{Pressure} = \text{Flow} \times \text{Resistance}$$

$$\Delta P \approx \Delta Q \times R$$

$$\text{Pressure change} \approx \text{Flow change} \times \text{Constant resistance}$$

At a constant resistance, pressure changes are proportional to change of flow. When administering a vasodilator, the FFR-measurement utilizes this constant resistance proportionality, and the iFR®-index is obtained during a period of the cardiac cycle (diastole) when the resistance is minimal and naturally stable. The unique qualities of coronary blood flow result from the proximal pressure changes through pulsatile blood ejection as well as peripheral variations in coronary microcirculation^[11]. It is not adequate to assess a stenosis severity by simply measuring the drop in maximum or intermediate pressure of the vessel, since the distal predominant pressure is affected by several components and does not necessarily reflect the proximal aortic pressure. The distal predominant pressure is primarily influenced by the pressure changes in the coronary microcirculation but can significantly affect the (instantaneous) proportion of pressure and blood flow as an index of intracoronary resistance. Wave intensity analysis helps to differentiate between distal and proximal variations^[11].

In early systole, pressure rises rapidly without an increase in flow velocity (Figure 1). Accordingly, the index of intracoronary resistance rises as well. The rapid increase in pressure (without the flow acceleration) develops from adaption of the ejection

wave within the aorta and the compression wave from the coronary microcirculation.

Quite the opposite happens in early diastole: Pressure decreases while flow accelerates, which leads to a rapidly decreasing intracoronary resistance and absorption of blood into the coronary microcirculation. After this short period of pressure decrease, the index of coronary resistance is almost minimal and stable, since neither from the proximal nor from the distal coronary end wave activity is emitted. This wave-free period prevails over most of the diastole and is the basis for iFR®-measurement.

FURTHER IMPROVEMENTS

Pressure-derived flow indices like FFR refer to a proportional correlation between pressure and flow when resistance is constant^[24], which only applies to a specific period of the cardiac cycle. Manipulations with vasodilators primarily reduce the systolic component of the resistance and can thus be used to achieve a minimal and stable value.

Among the advantages of iFR® are a drug-free approach, as well as the ability to reach a higher flow velocity during the measurement, which allows a better discrimination of hemodynamically significant stenoses. A series of measured and reproducible data are generated during a period of five consecutive heartbeats. Indices of 0.89 or less generated by iFR® are equivalent to the common limit of 0.80 or less in FFR^[4] and serve as an indicator for ischemia (Figure 2). A clinical example is presented in Figure 3.

To detect the specific time during diastole for the calculation of iFR®, it is necessary to acquire electrocardiographic signals of the patient. To simplify the assessment process it has recently become possible to calculate the index by only using the pressure signals, thus allowing the process to be run independent of electrocardiography (ECG). Specific end-systolic and end-diastolic waveform characteristics are identified to receive the accurate proximal (Pa) and distal (Pd) coronary pressure^[25].

Regarding the assessment of vessels with multiple lesions, iFR®-pullback offers a technique to create a hemodynamic map of a coronary artery, which allows an individual estimation of each stenosis. The pullback itself is conducted manually and detects continuously pressure changes per millimeter for a given length^[16,17]. Since the iFR® is obtained under resting conditions, whereby the autoregulatory mechanisms in the vessel ensure a stable and constant baseline-flow, serial lesions are not affected by each other^[26].

Baseline physiology offers the opportunity to quantify the impact of each single stenosis and can, therefore, predict the effect of a treatment of an individual stenosis within a vessel with multiple lesions. A hemodynamic map via pullback can simultaneously display iFR®-changes over the whole vessel and track down the lesion with the predominant pressure-loss^[16]. Additionally, it can be overlaid with angiographic imaging in order to locate the exact physiologically significant anatomical site of the narrowings (co-registration)^[17].

Other diastolic resting indices, such as the diastolic pressure ratio (dPR) obtained in different phases of the diastole like dPR₂₅₋₇₅ (25% to 75% of diastole) or dPR_{mid} (midpoint of diastole) along with Matlab calculated iFR® (iFR_{matlab}) and iFR®-like indices shortening the length of the wave-free period by 50 and 100 ms (iFR_{-50 ms} and iFR_{-100 ms}), were compared to the iFR® and found to be numerically identical. Therefore, all guidelines and cut-off values as well as clinical recommendation can be applied to these indices^[27].

CLINICAL STUDIES ABOUT THE - iFR®-MEASUREMENT

During the course of the initial pilot study Adenosine Vasodilator Independent Stenosis Evaluation (ADVISE), a wave-free period during the cardiac cycle was identified for the first time, enabling to determine stenosis severity without the administration of vasodilators. It was an international, multicenter, non-randomized study (Table 1), in which the flow and pressure data from 157 stenoses were collected. The study revealed a good correlation between the FFR- and iFR®-measurements. However, with only 131 patients, the population was relatively small. In this population, the iFR®-index 0.83 showed the best correlation with the FFR-index of 0.80. A subgroup analysis in patients with multivessel disease, similar to the FAME-study collective, confirmed an excellent diagnostic correlation of 93% between iFR® and FFR.

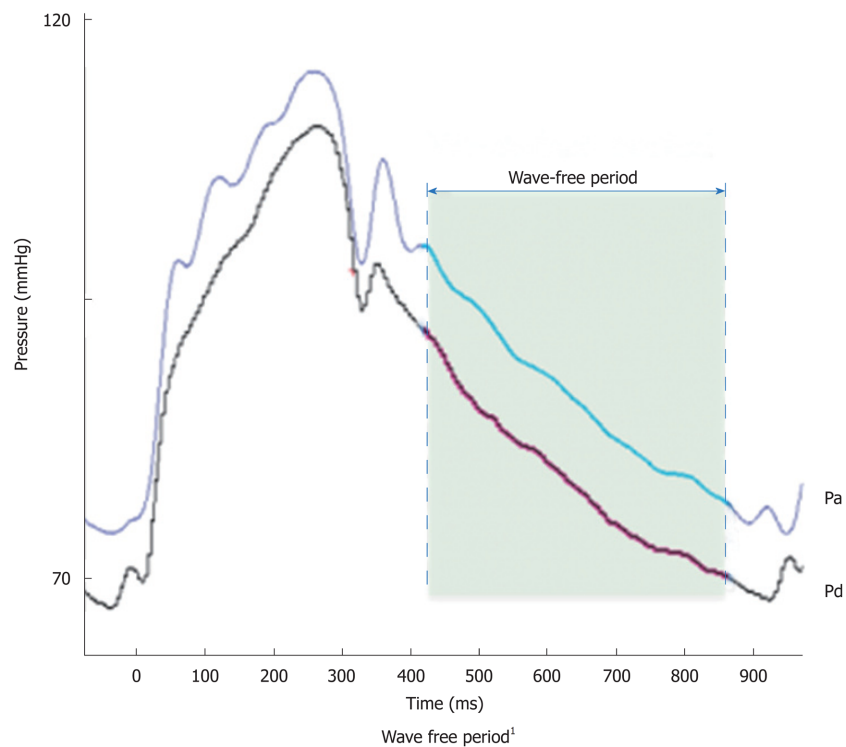


Figure 1 Proximal pressure and distal pressure during a wave-free period (grey shaded). Courtesy of Volcano Corporation, Koninklijke Philips N.V. Amsterdam, The Netherlands. Pa: Proximal pressure; Pd: Distal pressure.

The Multicenter Core Laboratory Comparison of Instantaneous Wave-Free Ratio and Resting Pd/Pa with Fractional Flow Reserve (RESOLVE)-study tried to examine the diagnostic accuracy of iFR® vs FFR. In the course of this retrospective, multicenter, non-randomized study, 1593 (81%) out of 1974 lesions were analyzed, as 381 lesions had to be excluded due to the inadequate image quality. Despite this, the result showed a moderate correlation between iFR® and FFR, with a diagnostic precision of 80.4%.

DEFINE-FLAIR, a leading multicenter, international, randomized, blinded study designed to prove the non-inferiority of iFR®, reiterated the findings of the previously mentioned studies. As of now, the available data are based on a 1-year-analysis. The ongoing study is conducted in 49 places in over 19 countries. Patients were included if they had at least one angiographically confirmed coronary disease, in which there was at least one stenosis of a questionable hemodynamic severity. Suitable patients were randomly assigned to a particular arm at a ratio of 1:1 FFR towards iFR®. The primary endpoint was the 1-year risk for major adverse cardiac events like cardiovascular death, nonfatal myocardial infarction, or unplanned revascularization. From January 2014 to December 2015, 2492 patients were included, 1242 in the iFR®- and 1250 in the FFR-group. The 1-year analysis showed comparable results regarding the endpoints, confirming the non-inferiority of iFR® towards FFR. The length of the procedure time was significantly shorter in the iFR®-group (iFR® 40.5 min, FFR: 45.0 min; $P < 0.001$), and less patients suffered from adverse effects like angina pectoris and dyspnea (3.1% vs 30.8%, $P < 0.001$), mainly because adenosine was not administered. In addition, when compared to FFR, this method was identified as more economically advantageous.

Published at about the same time, Instantaneous Wave-Free Ratio versus Fractional Flow Reserve to Guide PCI (iFR®-SWEDEHEART) also examined the non-inferiority of iFR® in the course of a multicenter, randomized, clinical study. The inclusion of eligible patients was based on the Swedish Coronary Angiography and Angioplasty Registry. Two thousand thirty-seven patients with a stable angina pectoris or an acute coronary syndrome were included and randomly allocated in a particular arm (iFR® vs FFR). Primary endpoint was the 1-year risk for major adverse cardiac effects like cardiovascular death, nonfatal myocardial infarction, or unplanned revascularization. Information about myocardial infarction or unplanned revascularization was gathered from the web-based register SWEDEHEART. The study was conducted in 15 places (13 in Sweden, one in Denmark, one in Iceland). The patients were recruited from May 2014 to October 2015. Of these 2037 patients, 1019 received iFR® and 1018 received FFR. Final analysis included 2019 patients, as 18 participants had to be

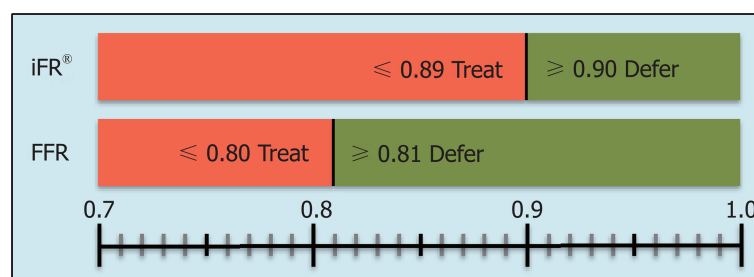


Figure 2 iFR® cut-off value and fractional flow reserve-measurement: An iFR®-value of ≤ 0.89 indicates a hemodynamically significant stenosis (above, red bars), whereas an iFR®-value of ≥ 0.90 indicates no need for an intervention (green bar). Accordingly, FFR-indices of ≤ 0.80 lead to a revascularization, whereas FFR-indices of > 0.80 indicate a non-significant coronary stenosis. iFR®: Instantaneous wave-free ratio; FFR: Fractional flow reserve.

excluded because of the adverse effects under adenosine or technical problems.

The 1-year analysis of endpoints confirmed the non-inferiority of the iFR®-method. Especially in uncertain cases, where iFR® and FFR results differ, the data indicate that iFR® provides more accurate results. FFR-measurement tends to overrate the severity, since the vasodilator dependent hyperemia leads to a pressure decrease. The number of hemodynamically significant stenoses in this trial was much lower than in the FAME-study population, which only included patients with multivessel diseases. The iFR®-SWEDEHEART population is a better representation of the reality in clinical practice, since every patient with the indication for invasive coronary assessment could be included, independent of coronary status. Additionally, as described by Tonino and de Bruyne^[7], an improvement in the clinical outcome of FFR-guided PCI was shown.

To compare ECG-independent iFR® calculation and the current method using ECG and pressure signals, Petraco *et al.*^[25] tested the only pressure-dependent iFR® algorithm in 320 coronary hemodynamically significant stenoses that were already included in multicenter studies (ADVISE^[18], ADVISE Registry study^[28], and a study by Nijjer *et al.*^[17]). The iFR®-indices of both methods correlated highly ($r = 0.9997$), which makes the ECG-independent iFR® applicable to the recent results of DEFINE-FLAIR and SWEDEHEART^[25].

Based on the RESOLVE and ADVISE studies, Nijjer *et al.*^[17] have conducted a study (Pre-Angioplasty Instantaneous Wave-Free Ratio Pullback Provides Virtual Intervention and Predicts Hemodynamic Outcome for Serial Lesions and Diffuse Coronary Artery Disease) to create a hemodynamic map using the motorized pullback with iFR®, questioning if it helps to predict the stent impact in tandem and diffusely diseased vessels^[17]. Thirty-two coronary arteries with two or more stenoses in 29 patients were assessed and underwent PCI. After physiological mapping, a computer-aided simulation calculated the best-case PCI effect. First, the virtual and real-world stents were compared to examine the predictive capability of iFR®-pullback. Second, the length of virtual stents, only positioned in areas with a high iFR®-intensity loss, was compared to the length of real world stents. $\Delta iFR^{\circ}(\text{exp})$ and $\Delta iFR^{\circ}(\text{obs})$ showed a strong relationship ($r = 0.97$, $P < 0.001$), and post-PCI iFR® was predicted with a $2\% \pm 1\%$ error. Furthermore, the hereby examined physiological lesion length was significantly shorter than the anatomical length obtained by QCA (12.6 ± 1.5 mm *vs* 23.3 ± 1.3 mm, $P < 0.001$) and the length of the stent that was implanted in reality (27.5 ± 2.3 mm, $P < 0.001$).

Another study, published in 2017 by Kawase *et al.*^[29] (Residual pressure gradient across the implanted stent: An important factor of post-PCI physiological results) evaluated the accuracy of the predicted iFR®-value compared to the iFR® result, which was observed in reality after PCI. Additionally, they tried to discover potential factors for a failed prediction. iFR® ratios of 73 lesions in 71 patients were compared retrospectively before and after the coronary intervention. Pullback was conducted manually, anatomic lesion length was obtained by QCA, and the cut-off value of a difference between iFR®(pre) and iFR®(obs) was set at 0.036. The cut-off point was slightly missed, with a calculated mean difference of 0.036 ± 0.037 , although the values correlated adequately ($r = 0.756$). In the course of a multivariate regression analysis, only a residual pressure gradient remained as an independent risk factor, leading to a failed prediction. After subtraction of the residual pressure gradient, the correlation between iFR®(pre) and iFR®(obs) improved. The only risk factors for a residual pressure gradient appeared to be a small diameter of the implanted stent and a high Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease-score^[30], a score that calculates the amount of blood supplied to the myocardium by

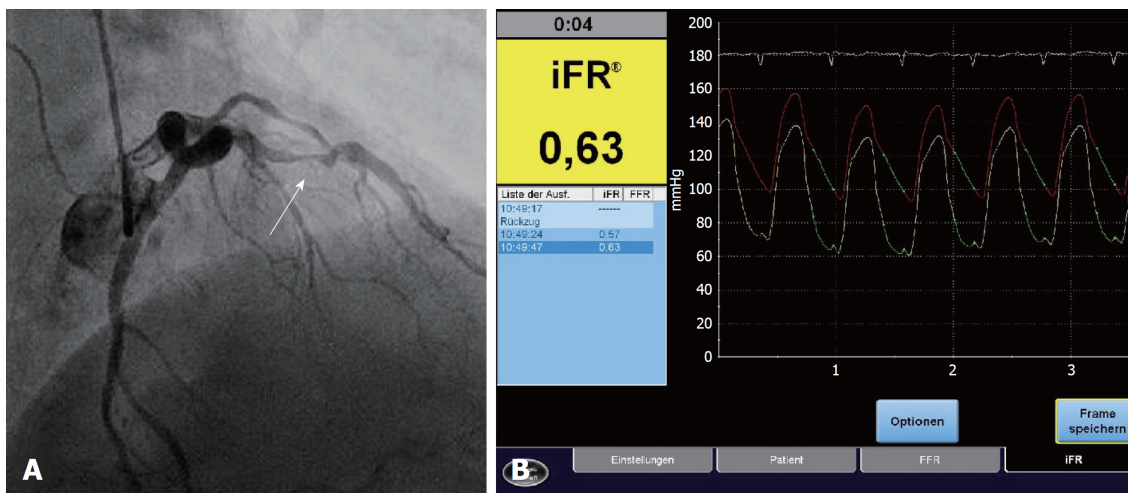


Figure 3 Case of a 69-year-old patient with symptoms of angina pectoris and a history of smoking (30 pack-years). A: Coronary angiography shows an initial two-vessel disease with a significant stenosis of the proximal LAD before percutaneous coronary intervention; B: iFR®-measurement was performed in the proximal LAD (iFR® = 0.63; bolt). FFR: Fractional flow reserve; LAD: Left anterior descending artery; iFR®: Instantaneous wave-free ratio.

the targeted vessel. Kawase *et al*^[29] noted that a larger cohort study could identify additional factors that have caused a failed prediction. An overview about the most important current publications is composed in [Table 1](#). Our manuscript is based on the review of previous published articles and did not involve animal or human subjects. Therefore, neither an ethical approval nor a patient consent was necessary.

LIMITATIONS

The process of advancing the coronary-pressure guide wire in FFR-measurement is still occasionally criticized and potentially accompanied by complications, which similarly constitutes a limitation of iFR®-measurement. This could hinder the regular clinical use of FFR- or iFR®-measurement.

It is not completely clarified how to proceed in uncertain cases and whether a stress test with adenosine is indicated. If hyperemia cannot be achieved through adequate doses, it is possible that the calculated value does not reflect the real FFR^[31]. First, adenosine leads to peripheral vasoconstriction transmitted by pulmonary receptors, followed by its immediate effect on larger arteries that leads to a drop in blood pressure. This circumstance makes the ratio dependent on the time of measurement^[32]. There is a small number of cases where not truly flow-limiting stenoses have led to acceptable iFR®-gradients but at the same time false positive hyperemic pressure gradients (FFR)^[31]. High incidents of patient related discomfort, like dyspnea, chest pain, hypotension, and AV-blocks, or in one recorded case even ventricular fibrillation^[33], still remain a limitation of the application of adenosine^[34]. This limitation can be overcome by an adenosine free assessment like the iFR®.

In the analysis about the accuracy of the prediction of post-PCI iFR®, Kawase identified the residual pressure gradient as a risk factor for a the failed prediction and mentioned that its consideration might help the examining clinician^[29].

Regarding microvascular diseases, studies could not prove a correlation between FFR and the index of microvascular resistance, an index for the microvascular status measured by the thermodilution technique^[35]. This must not be seen as a shortcoming of the FFR method since it might rather show that micro- and macrovascular diseases are caused by different disease processes^[36]. These findings can be employed on iFR®, since its non-inferiority towards FFR was proven.

Finally, there are currently new studies expected in which the iFR®-technique is to be subjected to the specific questioning, *i.e.*, the sequential assessment of stenosis. A reduction in costs is to be expected due to no administration of adenosine and shortened procedural time.

CONCLUSION

The current standard of cardiac invasive ischemic diagnostic is invasive FFR-measurement, which was initially adopted as a Class-IA-recommendation to the

Table 1 Significant instantaneous wave-free ratio-(iFR®)-studies

	Advise	Verify	Clarify	Park <i>et al</i> ^[39]	Resolve	Advise in practice	Indolfi <i>et al</i> ^[42]	ADVISE II	Harle <i>et al</i> ^[44]	Van de Hoef <i>et al</i> ^[45]	DEFINE-FLAIR	iFR®-SWEDHEART
First author journal and year of Publication	Sen <i>et al</i> ^[18] . <i>J Am Coll Cardiol</i> 2012	Berry <i>et al</i> ^[37] . <i>J Am Coll Cardiol</i> 2013	Sen <i>et al</i> ^[38] . <i>J Am Coll Cardiol</i> 2013	Park <i>et al</i> ^[39] . <i>Int J Cardiol</i> 2013	Jeremias <i>et al</i> ^[40] . <i>J Am Coll Cardiol</i> 2014	Petraco <i>et al</i> ^[41] . <i>Am Heart J</i> 2014	Indolfi <i>et al</i> ^[42] . <i>Int J Cardiol</i> 2015	Escaned <i>et al</i> ^[43] . <i>J Am Coll Cardiol-Intv</i> 2015	Harle <i>et al</i> ^[44] . <i>Int J Cardiol</i> 2015	Van de Hoef <i>et al</i> ^[45] . <i>Euro-Intervention</i> 2015	Davies <i>et al</i> ^[19] . <i>N Engl J Med</i> 2017	Göteborg <i>et al</i> ^[20] . <i>N Engl J Med</i> 2017
Study design	PC, multicenter, non-randomized	PC, multicenter, non-randomized	PC, multicenter	PC, multicenter, non-randomized	RS, multicenter, non-randomized	PC, multicenter, non-randomized	PC, monocenter, non-randomized	PC, multicenter, non-randomized	PC, monocenter, non-randomized	PC, multicenter, non-randomized	PC, multicenter, randomized	PC, multicenter, randomized
Countries (centers)	2 (3)	6 (6)	2 (3)	1 (2)	7 (15)	101 (16)	1 (1)	8 (45)	1 (1)	3 (7)	19 (49)	3 (14)
Included patients	131	206	51	238	1768	313	82	598	109	228 (iFR® = 66)	2492 (iFR® = 1242)	2037 (iFR® = 1019)
Stenoses	157	206	51	238	1974	392	123	690	151	299 (iFR® = 85)	3183 (iFR® = 1575)	3004 (iFR® = 1568)
Hemodynamic relevant stenoses (%)	N/A	134 (65)	N/A	103 (43.3)	N/A	153 (39)	37 (30.1)	248 (35.9)	N/A	N/A	451 (28.6)	457 (29.1)
Age in years ± SD	62.6 ± 10.2	65.2 ± 10.2	66.2 ± 9.2	62.8 ± 0.6	63.4 ± 10.3	67 ± 11	64 ± 9	63.6 ± 10.8	67 ± 11	58 ± 11	65.5 ± 10.8	67.6 ± 9.6
Men (%)	83.5	71	82.4	68	74.9	79	81.7	68.9	63.9	68	77.5	74.2
Diabetes mellitus (%)	54 (34.4)	50 (24)	14 (27.4)	66 (28)	497 (28.1)	94 (30)	14 (17.1)	209 (35)	N/A	10 (15)	382 (30.8)	232 (22.8)
Hypertonia (%)	88 (56.1)	137 (67)	18 (35.2)	133 (56)	N/A	232 (74)	61 (74.4)	471 (78.8)	N/A	25 (38)	873 (70.3)	730 (71.6)
Smoking (%)	34 (21.7)	64 (31)	15 (29.4)	64 (27)	520 (29.4)	160 (51)	49 (59.8)	135 (22.6)	N/A	21 (32)	243 (19.6)	159 (15.6)
One-vessel CAD (%)	108 (68.8)	85 (41)	N/A	N/A	N/A	113 (36)	50 (61)	N/A	75 (69.4)	N/A	N/A	452 (44.3)
Multi-vessel CAD (%)	49 (31.2)	105 (51)	N/A	N/A	951 (53.8)	197 (63)	32 (39)	N/A	33 (30.6)	N/A	505 (40.7)	364 (35.7)
Stable angina (%)	151 (96.2)	140 (68)	N/A	151 (63)	1216 (68.6)	228 (73)	29 (35)	320 (53.5)	N/A	N/A	986 (79.4)	632 (62.0)
Unstable angina (%)	6 (3.8)	46 (22)	N/A	84 (36)	255 (14.4)	85 (27)	53 (65)	151 (25.3)	N/A	N/A	186 (15.0)	211 (20.7)
iFR® cut-off	0.83	≤ 0.83	0.86	0.9	0.9	0.9	0.92	0.89	0.896	0.9	0.89	0.89
MACE-rate after 1 yr (iFR® vs FFR, P-value)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	6.8 vs 7.0 (P = 0.003)	6.7 vs 6.1 (P = 0.007)
Adverse events (iFR® vs FFR, P-value)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3.1 vs 30.8 (P < 0.001)	3.0 vs 68.3 (P < 0.0001)

Diagnostic accuracy in % (iFR® _{vs} FFR)	93	68	92.3	82	80.4	80	81.3	82.5	83.4	N/A	N/A	N/A
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PC: Prospective cohort study; RS: Retrospective study; FFR: Fractional flow reserve; N/A: Not available; MACE: Major adverse cardiac events.

ECS/EACTS guidelines of 2014 on myocardial revascularization. Despite good existing evidence, the performance of pressure-derived functional assessment in daily routine is still limited. Here, iFR® provides a new innovative approach to assess coronary stenosis severity without administering vasodilators. Besides FFR, iFR® was just recently adopted as a Class-IA-recommendation in the ECS/EACTS guidelines of 2018 on myocardial revascularization^[22]. Additionally, the eliminated necessity to record the electrocardiographic signals simplifies the procedure of the invasive functional assessment.

iFR®, extended by iFR®-pullback, can help achieve a better physiological result in treating vessels with multiple lesions by creating a hemodynamic map. Since implanting potentially larger stents to prevent a geographical miss is currently the standard in treating multivessel disease, a physiologically justified stent length might therefore be more hemodynamically beneficial for the vessel^[16]. Therefore, factors like a residual pressure gradient and other potential not yet discovered influences that have led to an inaccurate prediction of post-PCI iFR® ratio have to be considered. Large-scale multicenter, randomized studies demonstrated the non-inferiority of iFR® to FFR, whilst requiring less procedural time, having lower costs, and having a lower number of patients who suffer from adverse effects due to a spared use of adenosine.

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