

Improving coronary artery bypass grafting: a systematic review and meta-analysis on the impact of adopting transit-time flow measurement

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ABSTRACT

Despite there being numerous studies of intraoperative graft flow assessment by transit-time flow measurement (TTFM) on outcomes after coronary artery bypass grafting (CABG), the adoption of contemporary TTFM is low. Therefore, on 31 January 2018, a systematic literature search was performed to identify articles that reported (i) the amount of grafts classified as abnormal or which were revised or (ii) an association between TTFM and outcomes during follow-up. Random-effects models were used to create pooled estimates with 95% confidence intervals (CI) of (i) the rate of graft revision per patient, (ii) the rate of graft revision per graft and (iii) the rate of graft revision among grafts deemed abnormal based on TTFM parameters. The search yielded 242 articles, and 66 original articles were included in the systematic review. Of those articles, 35 studies reported on abnormal grafts or graft revisions (8943 patients, 15 673 grafts) and were included in the meta-analysis. In 4.3% of patients (95% CI 3.3-5.7%, $I^2 = 73.9$) a revision was required and 2.0% of grafts (95% CI 1.5-2.5%; $I^2 = 66.0$) were revised. The pooled rate of graft revisions among abnormal grafts was 25.1% (95% CI 15.5-37.9%; $I^2 = 80.2$). Studies reported sensitivity ranging from 0.250 to 0.457 and the specificity from 0.939 to 0.984. Reported negative predictive values ranged from 0.719 to 0.980 and reported positive predictive values ranged from 0.100 to 0.840. This systematic review and meta-analysis showed that TTFM could improve CABG procedures. However, due to heterogeneous data, drawing uniform conclusions appeared challenging. Future studies should focus on determining the optimal use of TTFM and assessing its diagnostic accuracy.

Key Words

Coronary artery bypass, Intraoperative quality control, Transit time, Transit-time flow measurement, Intraoperative graft flow assessment, Coronary artery bypass grafting

INTRODUCTION

Outcomes of coronary artery bypass grafting (CABG) have significantly improved over the first 50 years since the introduction of the modern CABG procedure.¹ Despite increasing use of percutaneous coronary intervention (PCI), CABG remains the treatment of choice for patients with complex multivessel disease.² While outcomes of PCI are continuously improving with new advancements, many new techniques to optimize short- and long-term outcomes of CABG have not been adopted widely.³

One of such techniques to improve CABG outcomes and graft patency is intraoperative graft flow assessment. Early graft failure can occur due to limited outflow, graft kinking upon chest closure, thrombosis, yet also due to anastomotic problems. A metaanalysis reported a graft failure rate of ~5% and 25% at 3 and 12 months, respectively.⁴ Fabricius et al.⁵ reported that 23 of 2052 patients (1.1%) who underwent CABG had severely compromised haemodynamics due to postoperative myocardial infarction (MI). In 21.7% of patients, the cause of this adverse event was found to be an incorrect anastomosis. Intraoperative graft assessment has therefore been introduced to identify anastomotic problems and limited outflow before chest closure.

Multiple techniques for intraoperative graft assessment have been proposed: coronary angiography (CAG), transit-time flow measurement (TTFM), high-resolution-epicardial ultrasonography (HR-ECUS) and intraoperative fluorescence imaging (IFI).⁶ Although angiography is thought to be the best and most reliable method for assessing flow, the infrastructure required for CAG is rarely available in standard operating theatres. Therefore, the most adopted strategy to assess graft functioning is TTFM. Several studies reported associations between TTFM parameters and the necessity for graft revisions as well as with short- and medium-term outcomes after CABG; however, results vary considerably.^{7,8} A summary of the evidence could provide more incentive to adopt TTFM, especially as TTFM has been criticized.⁹

We performed a systematic review and meta-analysis to evaluate the value of TTFM during CABG by determining (i) the rate of abnormal grafts and graft revisions required when using TTFM and (ii) the impact of TTFM parameters on angiographic and clinical outcomes.

METHODS

Search strategy

On 31 January 2018, a systematic literature search in the PubMed database was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline (**Supplementary Materials**) to identify full-length, English-language articles with the following search term: '(transit time OR transit-time) AND coronary artery bypass'. Studies with the following criteria were included: (i) graft assessment was performed using TTFM; (ii) subjects were adult patients undergoing CABG; and (iii) it was reported how many grafts had abnormal TTFM parameters or were revised, or an association between TTFM parameters and outcomes during follow-up was investigated.

Titles and abstracts were then screened for inclusion. When eligible, full-text articles were reviewed (D.J.F.M.T. and S.J.H.). Only original articles, articles in English, studying humans and studying TTFM in CABG procedures were considered for inclusion. If multiple articles described the same patient population, only the article with the largest number of patients or the most relevant information was included.

Data extraction

The following study characteristics were extracted: prospective versus retrospective study, the year of publication, the authors and the number of patients. Furthermore, the following data on surgical characteristics and TTFM parameters were obtained from each study: surgical procedure (on-pump or off-pump), which grafts were used (e.g. internal thoracic artery, great saphenous vein, radial artery and gastroepiploic artery), the number of grafts assessed with TTFM, the number of grafts deemed abnormal based on intraoperative TTFM parameters, the number of grafts that were revised based on intraoperative TTFM parameters, the reasons why grafts were deemed 'abnormal' or 'required revision' based on intraoperative TTFM parameters [mean graft flow (MGF), pulsatility index (PI), diastolic filling % (DF%) and percentage of backflow (%BF) (e.g. insufficiency percentage)] and fast Fourier transformation (FFT). Sensitivity, specificity, negative predictive values (NPV) and positive predictive values (PPV) were extracted to assess the diagnostic accuracy of TTFM. Postoperative short-term outcomes (e.g. till 30days) and outcomes during follow-up (e.g. beyond 30days) that were extracted consisted of major adverse cardiac and cerebrovascular events (MACCE), mortality, MI, postoperative cardiac enzyme release, stroke, requirement for intraaortic balloon pump placement, angina and graft failure.

Statistical analyses

The quality of the included studies used in the meta-analysis was assessed according to the Newcastle-Ottawa-Scale (NOS).¹⁰ Random-effects models were generated to estimate pooled study outcomes with 95% confidence intervals (95% CI) of (i) the proportion of revised grafts compared to the total number of patients studied by TTFM, (ii) the proportion of revised grafts compared to the total number of grafts on which TTFM was applied and (iii) the proportion of revised grafts compared to the total number of abnormal grafts found by TTFM. For studies that reported zero events (e.g. no abnormal or revised grafts), 0.1 events were used to calculate an estimated event rate with 95% CI. The I^2 statistic was used to describe the proportion of variation across studies based on heterogeneity, where low values relate to homogeneity (range 0-100). Statistical analyses were executed with Comprehensive Meta-Analysis software Version 3.3 (Biostat, Englewood, NJ, USA).

RESULTS

Study selection

This systematic review included 66 studies (Fig. 1). In total, 35 unique studies reported on abnormal grafts or graft revisions with 8943 CABG patients and 15 673 grafts (Table 1) and were included in the meta-analysis. An overview of the NOS quality assessment is presented in the **Supplementary Material**, Table S1. Eight studies reported on the diagnostic accuracy of TTFM (**Supplementary Material**, Table S2). Forty-two studies reported graft patency and clinical outcomes related to TTFM assessments (**Supplementary Material**, Tables S3 and S4).

Meta-analysis: abnormal grafts and graft revisions

Individual studies classified grafts as abnormal based either on low MGF (arterial grafts: <15ml/min and venous grafts: <20 ml/ min), an increased PI ≥ 5 for both venous and arterial grafts, or decreased diastolic filling % (<50%). Overall reasons to revise abnormal grafts were due to kinking or twisting of a graft, graft or coronary dissection or anastomotic stenosis/thrombosis.

Table 1. Studies reporting rates of abnormal grafts and/or revised grafts assessed by TTFM

Study	Year	Design	Number of grafts/patients	Procedure specifics ^a	Graft outcome	Reasons for abnormal or revised grafts	Results
Hashim <i>et al.</i> [11]	2017	Prospective	86/60	TTFM on ITA	Abnormal	PI > 1.0 with an MGF < 20 ml/min in an arrested heart	Not specified 3.5% (n = 3 grafts)
Hiraoka <i>et al.</i> [12]	2017	Prospective	104/63	TTFM on ITA, RA and SVG	Revision Abnormal	Not specified PI > 5.0 and an MGF < 20 ml/min in ITA-graft or < 40 ml/min in SVG	8.7% (n = 9 grafts)
Leon <i>et al.</i> [13]	2017	Retrospective	543/177	TTFM on ITA and SVG	Revision	PI ≥ 5.0	0.9% (n = 5 grafts)
Handa <i>et al.</i> [14]	2016	Retrospective	196/68	OPCAB with TTFM on ITA and SVG	Abnormal	Abnormal TTFM parameters: MGF < 15 ml/min, DF < 50% and PI > 5.0	40% (n = 46 grafts) of which 54% appeared patent on postoperative CAG
Oshima <i>et al.</i> [15]	2016	Retrospective	214/196	TTFM on ITA and SVG	Revision Abnormal	MGF < 5 ml/min or DF < 50% or PI > 5.0 Lower mean flow (21.3 ± 16.2 ml/min) and higher PI (5.5 ± 4.7)	7.0% (n = 15 grafts)
Honda <i>et al.</i> [16]	2015	Retrospective	72/72	TTFM on <i>in situ</i> ITA	Abnormal	MGF < 20 ml/min and PI = 2.0	1.4% (n = 1 graft)
Di Giammarco <i>et al.</i> [17]	2014	Prospective	717/333	TTFM on ITA and SVG	Abnormal	Grafts with MGF ≤ 15 ml/min and PI ≥ 3.0 were defined as failing	5.4% (n = 39 grafts)
Quin <i>et al.</i> [18]	2014	Retrospective	2738/1067	TTFM on ITA, SVG and RA	Revision Abnormal	Failing grafts based on TTFM and surgical inspection MGF < 20 ml/min	0.3% (n = 2 grafts) 20.7% (n = 568 grafts)
					Revision	MGF < 20 ml/min and abnormal PI < 3.0 (0.7%), 3.0-5.0 (2.9%) and > 5.0 (5.8%)	2.0% (n = 54 grafts)

Table 1. Studies reporting rates of abnormal grafts and/or revised grafts assessed by TTFM (continued)

Study	Year	Design	Number of grafts/patients	Procedure specifics ^a	Graft outcome	Reasons for abnormal or revised grafts	Results
Harahsheh [19]	2012	Prospective	1394/436	Not specified ^b	Abnormal	MGF <20 ml/min, PI >5.0 and DF <50%	7.2% (n = 100 grafts)
Kuroyanagi <i>et al.</i> [20]	2012	Retrospective	435/159	OPCAB with TTFM on ITA and SVG	Revision	Not specified	1.0% (n = 14 grafts) 1.1% (n = 5 patients)
Kieser <i>et al.</i> [8]	2010	Prospective	1015/336	TTFM on ITA, SVG and RA	Abnormal	PI >5.0	2.0% (n = 9 grafts) 7% (n = 74 grafts)
Handa <i>et al.</i> [21]	2009	Retrospective	116/39	OPCAB with TTFM on ITA and SVG	Abnormal	MGF <10ml/min, PI >5.0 or DF <50%	18% (n = 59 patients) 2.0% (n = 20 grafts)
Nordgaard <i>et al.</i> [22]	2009	Retrospective	1390/581	TTFM on ITA and SVG	Revision	MGF = 0 ml/min	4.2% (n = 14 patients) 2.6% (n = 3 grafts)
Santarpino <i>et al.</i> [23]	2009	Prospective	238/238	TTFM on LITA + RA versus LITA + SVG	Revision	Low MGF and high PI	1.7% (n = 2 grafts) 0.4% (n = 5 grafts)
Waseda <i>et al.</i> [24]	2009	Retrospective	289/116	TTFM on ITA, SVG, RA and GEA	Abnormal	TTFM systolic waveform and PI >4.0 based on thrombosis (n = 2) and torsion of the graft (n = 1)	1.3% (n = 3 grafts) 7.3% (n = 21 grafts)
					Revision	Failing grafts on IFI, yet acceptable TTFM (MGF >5 ml/min and PI <5) results	2.1% (n = 6 grafts)

Table 1. Studies reporting rates of abnormal grafts and/or revised grafts assessed by TTFM (continued)

Study	Year	Design	Number of grafts/patients	Procedure specifics ^a	Graft outcome	Reasons for abnormal or revised grafts	Results
Herman <i>et al.</i> [25]	2008	Prospective	.../985	TTFM on ITA and SVG	Abnormal	PI >5	18.7% (n = 184 patients)
Onorati <i>et al.</i> [26]	2008	Retrospective	.../433	TTFM on ITA and RA	Revision	Anastomotic (n = 9), conduit (n = 8), subclavian stenosis (n = 1) and unidentified (n = 2)	2.0% (n = 20 patients)
Beçit <i>et al.</i> [27]	2007	Retrospective	303/200	TTFM versus without TTFM on ITA, SVG or RA	Revision	PI >5 and low MGF (not specified)	0.2% (n = 1 patients)
Mujanovic <i>et al.</i> [28]	2007	Prospective	2872/1000	Not specified ^b	Revision	MGF <3 ml/min and PI >5	0.7% (n = 3 patients)
Onorati <i>et al.</i> [29]	2007	RCT	90/90	TTFM on single-SVG versus sequential-SVG	Revision	Unsatisfactory TTFM parameters due to kinked/twisted grafts (n = 4) or stenosis in proximal LITA (n = 2) or poor native coronary vessel (n = 3)	3.0% (n = 9 grafts)
Desai <i>et al.</i> [30]	2006	RCT	139/106	TTFM and IFI on ITA, SVG and RA	Revision	Cut-off values not specified	9.0% (n = 9 patients)
					Abnormal	PI >5 and low MGF (not specified)	2.2% (n = 64 grafts)
					Revision	'Systolic' pattern of the curve with low MGF (4 ml/min) and high PI (7.8)"	6.3% (n = 63 patients)
					Abnormal	DF <50%, PI >5.0 and MGF <10 ml/min	5.6% (n = 5 patients)
					Revision	DF <50%, PI >5.0 and MGF <10 ml/min	1.1% (n = 1 graft)
					Abnormal	DF <50%, PI >5.0 and MGF <10 ml/min	1.1% (n = 1 patient)
					Revision	DF <50%, PI >5.0 and MGF <10 ml/min	2.6% (n = 3 grafts)

Table 1. Studies reporting rates of abnormal grafts and/or revised grafts assessed by TTFM (continued)

Study	Year	Design	Number of grafts/patients	Procedure specifics ^a	Graft outcome	Reasons for abnormal or revised grafts	Results
Poston <i>et al.</i> [31]	2006	Prospective	410/410	TTFM on SVG	Revision	MGF = 0 ml/min	1.4% (n = 2 grafts)
				TTFM on ITA and RA	Revision	MGF < 10 ml/min	0.5% (n = 2 grafts)
Balacumaraswami <i>et al.</i> [32]	2005	Prospective	266/100	TTFM on ITA and RA	Abnormal	Not specified	9.4% (n = 25 grafts)
Kim <i>et al.</i> [33]	2005	Retrospective	117/58	OPCAB with TTFM on ITA, RA and GEA	Revision	Persistent poor MGF with TTFM and IFI under adequate MAP (>80mmHg)	25.0% (n = 25 patients)
					Abnormal	Low MGF < 3 ml/min or high PI (>20.0)	8.0% (n = 8 patients)
Leong <i>et al.</i> [34]	2005	Prospective	322/116	TTFM on ITA and SVG	Revision	Low MGF, high PI and unsatisfactory flow curve (values not specified) due to occluded, stretched, kinked/twisted grafts or anastomotic stenosis	2.2% (n = 7 grafts)
					Abnormal	Low MGF and high PI, without systolic peak pattern on the flow curves	12.0% (n = 14 grafts)
Onorati <i>et al.</i> [35]	2005	Prospective	.../297	TTFM on ITA and RA	Revision	Systolic wave-pattern, low MGF (9 ml/min) and high PI	5.2% (n = 6 patients)
					Abnormal	Abnormal MGF in 5 grafts due to distal anastomosis problems (n = 3), long grafts (n = 1) and vein graft stenosis (n=1)	2.4% (n = 7 patients)
Bergsland <i>et al.</i> [36]	2004	Prospective	113/46	OPCAB with TTFM on ITA and SVG	Revision	Abnormal MGF in 5 grafts due to distal anastomosis problems (n = 3), long grafts (n = 1) and vein graft stenosis (n=1)	0.3% (n = 1 patient)

Table 1. Studies reporting rates of abnormal grafts and/or revised grafts assessed by TTFM (continued)

Study	Year	Design	Number of grafts/patients	Procedure specifics ^a	Graft outcome	Reasons for abnormal or revised grafts	Results
Gwozdziwicz [37]	2004	Prospective	.../50	OPCAB with TTFM on ITA and SVG	Revision	Grafts with low MGF and high PI (>5)	0.0% (n = 0 grafts)
Guden <i>et al.</i> [38]	2003	RCT	.../300	TTFM on ITA	Revision	MGF close to 0 ml/min and PI >5.0, due to intimal flaps and localized dissections at anastomosis site	0.0% (n = 0 patients) 1.3% (n = 4 grafts)
Samisoglu <i>et al.</i> [39]	2003	Prospective	49/20	OPCAB with TTFM on ITA and SVG	Revision	Graft failure based on low MGF (5.2 ml/min) and high PI (11-9)	5.0% (n = 1 grafts)
Groom <i>et al.</i> [40]	2001	Prospective	298/125	TTFM in ITA and SVG	Revision	Low MGF and/or high PI (not specified)	2.0% (n = 1 patients) 3.0% (n = 9 grafts)
D'Ancona <i>et al.</i> [41]	2000	Prospective	1145/409	OPCAB with TTFM on ITA and SVG	Revision	Abnormal systolic flow patterns, PI >5.0 and low MGF due to (i) kinking, (ii) coronary dissection or (iii) thrombosis/stenosis at the anastomosis site	7.2% (n = 9 patients) 3.5% (n = 41 grafts)
Jakobsen and Kjaergaard [42]	1999	Prospective	.../280	TTFM on ITA and SVG	Abnormal	MGF <10 ml/min due to kinking, rotation or occlusion	1.8% (n = 5 grafts)
Walpoth <i>et al.</i> [43]	1998	Prospective	46/46	TTFM on ITA	Abnormal	Low-flow through ITA-graft (<0.5 ± 0.7 ml/min), high PI (147 + 96) and elevated vascular resistance	6.5% (n = 3 grafts) 6.5% (n = 3 patients)

Table 1. Studies reporting rates of abnormal grafts and/or revised grafts assessed by TTFM (continued)

Study	Year	Design	Number of grafts/patients	Procedure specifics ^a	Graft outcome	Reasons for abnormal or revised grafts	Results
Canver and Dame [44]	1994	Prospective	.../63	TTFM on ITA	Abnormal	1 distal ITA dissection, 1 ITA intramural haematoma and 1 abnormal ECG and poor LV-anterior wall contractility	6.5% (n = 3 grafts)
					Abnormal	Absence of ITA flow due to twisting at the anastomosis site	3.2% (n = 2 patients)
							6.5% (n = 3 patients)

Results are presented as percentages with the number of grafts and (if available) by the number of patients.

^a On-pump unless specified.

^b No specification on which grafts were assessed by TTFM.

GAG: coronary angiography; DF: diastolic filling; ECG: electrocardiogram; GEA: gastroepiploic artery; HR-ECUS: high-resolution-epicardial ultrasonography; IFI: intraoperative fluorescence imaging; ITA: internal thoracic artery; LITA: left internal thoracic artery; IV: left ventricular; MAP: mean arterial pressure; MGF: mean graft flow; OPCAB: off-pump coronary artery bypass; PI: pulsatility index; RA: radial artery; RCT: randomized controlled trial; SVG: saphenous vein graft; TTFM: transit-time flow measurement.

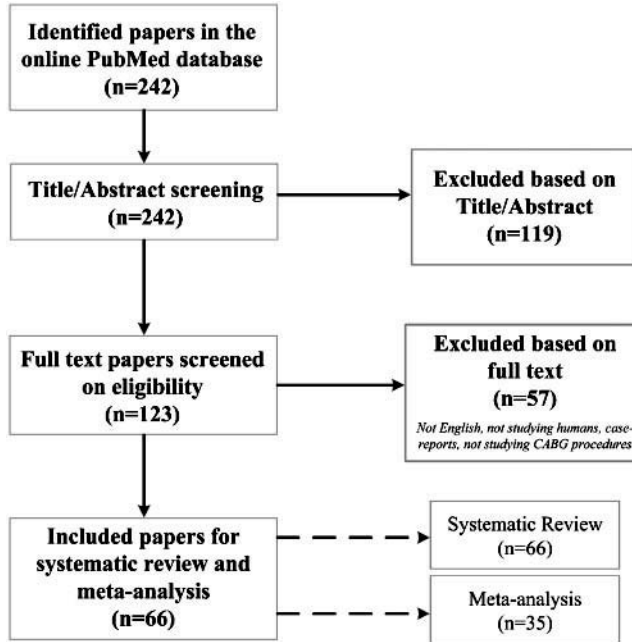


Figure 1. Flow chart of the systematic review process. Studies not written in English, not studying humans, reporting on the same patient population, reporting on transit-time flow measurement in other procedures besides CABG and case reports or reviews were excluded. In total, 66 studies were included, of which 35 studies were incorporated in the meta-analysis. CABG: coronary artery bypass grafting.

In 25 studies ($n = 6488$), the pooled rate of graft revisions was 4.3% when estimated per patient (95% CI 3.3-5.7%; $I^2=73.9$), and 2.0% (95% CI 1.5-2.5%; $I^2=66.0$) in 23 studies with 12 662 grafts when estimated per graft (Fig. 2). The pooled rate of graft revision among abnormal classified grafts was 25.1% (95% CI 15.5-37.9%; $I^2=80.2$) among 10 studies that reported both the number of abnormal grafts and graft revisions. Main reasons for not revising abnormal classified grafts were (i) no suspicion on graft failure after careful surgical inspection or (ii) no better alternative due to bad quality of the native coronary arteries.

Diagnostic accuracy

Sensitivity rates, describing the accuracy of TTFM, ranged from 0.250 to 0.457 (**Supplementary Material**, Table S2). Specificity varied between 0.941 and 0.984.^{14, 17, 30} The probability of having adequate TTFM values with an open graft (e.g. NPV) ranged from 0.719 to 0.980. The probability of having abnormal TTFM values with failing graft (e.g. PPV) varied from 0.100 to 0.840.^{14, 17, 30} These NPV and PPV values were based on the outcomes of angiography performed intraoperatively or on the 4th postoperative day.

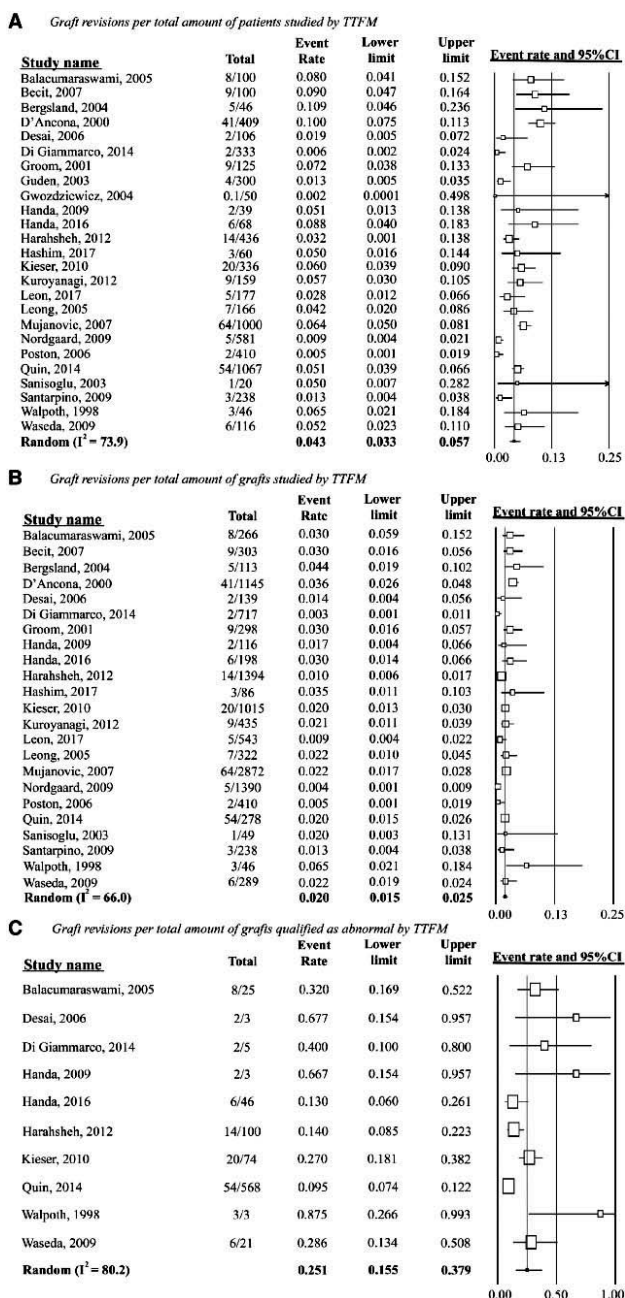


Figure 2. Random-effects models on pooled TTFM study outcomes. (A) Graft revision per total amount of patients studied by TTFM, (B) graft revisions per total amount of grafts studied by TTFM and (C) graft revisions per total amount of grafts qualified as abnormal by TTFM. I² indicates heterogeneity (range 0-100; 0 being entirely homogenous). CI: confidence intervals; TTFM: transit-time flow measurement.

Graft patency outcomes

Thirty-two studies evaluated graft patency according to TTFM values, summarized in **Supplementary Material, Table S3**.^{7, 12, 14-17, 30, 38, 44-68} Currently, only one small, randomized clinical trial assigned patients to undergo isolated CABG with or without TTFM and/or IFI.⁶⁹ The Graft Imaging to Improve Patency (GRIIP) study randomized 156 patients and performed a follow-up CAG at 1 year. No differences were found in the rate of graft occlusion on CAG (30.9% vs 28.9%, imaging vs control, respectively, $P = 0.82$).⁶⁹ Several observational studies reported that abnormal TTFM parameters predicted graft failure at 6 months to 1 year [7, 54, 70]. One study reported no predictive correlation between TTFM parameters and angiographic graft stenosis at 3 and 12 months [65].

Studies reporting on TTFM cut-off values which predict graft patency found that predictors of early graft failure were a PI >5.85 and MGF <20 ml/min for venous grafts, and an MGF of <11.5 ml/min for arterial grafts [15, 46]. Lehnert et al. [45] found internal thoracic artery graft patency at 1 year to be significantly worse when MGF <20 ml/min and worsening with 4% failure with every 1 ml/min decrease in MGF [odds ratio (OR) 0.96, 95% CI 0.93-0.99; $P = 0.005$]. Une et al. [71] reported that a higher MGF was an independent predictor of great saphenous vein failure at 1-year follow-up (OR 0.95, 95% CI 0.91-0.99), with an optimal cut-off value of 31 ml/min. The NPV on intermediate-term graft patency (156 days) in relation to abnormal TTFM values was 0.890 (**Supplementary Material, Table S2**) [59]. Follow-up on venous graft patency at 3 years showed that MGF was significantly higher among patent grafts versus failing grafts (41.3 ± 22.9 ml/min vs 29.6 ± 18.7 ml/min, respectively; $P = 0.01$) [55].

Short-term clinical outcomes

Twelve studies evaluated short-term outcomes in relation with TTFM parameters (**Supplementary Material, Table S4**) [8, 13, 25, 27, 54, 62, 69, 71-75]. Bauer et al. [75] compared CABG with TTFM versus without TTFM and found an increased rate of intraoperative redo-anastomoses, which coincided with significantly lower incidences of ventricular fibrillation, perioperative MI and postoperative mortality when TTFM was performed. Furthermore, another study found that CABG with TTFM resulted in lower rates of postoperative mortality (0% vs 4%), MI (0% vs 5%), intra-aortic balloon pump placement (1% vs 7%) and overall morbidity (6% vs 16%, all $P < 0.05$) [27]. Jokinen et al. [54] did not confirm the predictive capability of TTFM for these outcomes.

Studies that assessed TTFM cut-off values demonstrated that a PI >5, in arterial and venous grafts, was an independent predictor of early (30 days) major adverse cardiac events with an OR ranging from 1.8 (95% CI 1.1-2.7, $P = 0.0097$) [25] to 4.23 (95% CI 1.69-10.59, $P = 0.002$) [8]. Yet, these abnormal TTFM values did not predict mid-term mortality or hospital readmission [25].

A study which evaluated off-pump versus on-pump CABG found lower overall TTFM values to be associated with an increased incidence of low cardiac output syndrome ($P = 0.049$). Off-pump surgery was not associated with higher PI or lower diastolic filling %, and no differences were found in 30-day mortality and MI between patients who underwent off-pump versus on-pump CABG [72]. One study reported higher MGF and lower PI in off-pump procedures [62], while another study showed no differences in TTFM parameters between on-pump and off-pump [52].

Clinical outcomes during follow-up

The GRIPP trial found no differences in the composite of death, MI and repeat revascularisation at 1 year in patients who underwent CABG with intraoperative graft flow assessment versus those without intraoperative graft flow assessment (7.7% vs 7.7%, respectively) [69]. However, observational studies showed the positive predictive capability of TTFM on intermediate-term clinical outcomes, such as major adverse cardiac events, mortality, intra-aortic balloon pump placement or cardiac enzyme release [8, 75]. Other studies reported data that showed no correlation between TTFM parameters and mid-term hospital readmission (during 1.8-year follow-up) [25], survival after 3.8years [74] or even long-term survival (7.8 ± 0.2 years, Supplementary Material, Table S4) [13].

DISCUSSION

This systematic review and meta-analysis provides an overview of the literature on intraoperative graft flow assessment by TTFM. We found that 4.3% of patients undergoing CABG required graft revisions based on TTFM parameters. However, of all grafts that were classified as abnormal, only 25% of grafts were revised. The surgeons' clinical interpretation of the graft and the quality of the anastomosis in respect to the quality of the native coronary system was the main reason for not revising all these grafts. Indeed, the reported sensitivity of TTFM was fairly low, ranging from 0.250 to 0.457 with TTFM reported specificity varying from 0.941 to 0.984. Nevertheless, abnormal TTFM parameters were associated with postoperative

mortality and MI, and showed to be of particular importance in predicting graft patency during follow-up.

Intraoperative graft flow assessment is currently most frequently performed by TTFM, as it performs well compared to other methods of intraoperative graft quality assessment, such as thermal CAG, IFI or CAG. Although IFI is associated with higher sensitivity and specificity compared to TTFM [30], major limitations of IFI consist of not being able to visualize the entire graft at once and the need to reposition the heart for the laser camera to capture the immunofluorescent flow, possibly compromising natural blood flow. While intraoperative CAG would be ideal to assess graft patency and anastomotic quality, this strategy requires a 'hybrid' operating theatre that is not common in all institutions.

In this meta-analysis, we found that graft revisions were required in 2.0% of grafts and in 4.3% of patients undergoing CABG. Compared to other intraoperative complication rates, such as stroke at 1.1%, this provides the ability to significantly improve short-term outcomes, considering that TTFM usage led to graft revision and may have prevented a perioperative MI or increased cardiac enzyme release which is associated with impaired long-term outcomes [76].

So far, no randomized controlled trial focusing exclusively on CABG with TTFM versus without TTFM has been published. Only one small randomized controlled trial primarily studied IFI in combination with TTFM ($n = 78$) versus without intraoperative graft assessment ($n = 78$) [69]. No differences existed in intraoperative graft revisions, perioperative adverse events, 1-year graft patency or clinical outcomes. However, only 1.7% of the grafts were studied with TTFM exclusively, and thus, the study provides limited information on the actual impact of TTFM. Larger trials evaluating the benefit of routinely performing TTFM on early and late clinical outcomes are warranted.

Observational study data on the impact of TTFM are essential before randomized data will be available. So far, numerous studies reported improved outcomes in patients undergoing CABG with TTFM and only a few reporting no association between TTFM and postoperative outcomes. However, a great diversity in different TTFM cut-off values and methods exists. Studies used in our meta-analysis applied different methods of performing TTFM, including varying surgical and clinical scenarios, such as on-pump or off-pump procedures, varying haemodynamics, venous versus arterial grafts, different locations and number of coronary stenosis or using single versus sequential anastomoses. All of these factors have a major influence on

coronary flow and thereby on TTFM parameters. Furthermore, reasons for surgeons not to revise a graft despite abnormal TTFM parameters were that after inspecting the anastomosis, no suspicion of an anastomotic problem or graft failure was raised, or that there was no better surgical alternative due to poor native coronary arteries. Lacking standardized methods of performing and interpreting TTFM parameters, in combination with non-existent standardized TTFM cut-off values, still introduces a subjective aspect to TTFM and whether a graft should be revised. The heterogeneity of study methods and study outcomes could have contributed to the varying results on the diagnostic accuracy of TTFM (**Supplementary Material**, Table S2). This may also have contributed to the statistical heterogeneity ($I^2 > .66$).

The strength of TTFM is that it is able to detect truly failing and truly patent grafts (true positives and true negatives, respectively). False positives (e.g. patent graft with high PI) rarely occur; however, difficulties exist in detecting poor grafts with a low PI or high MGF (false negatives), which could lead to unnecessary graft revisions [14]. Therefore, it remains challenging to interpret TTFM results and translate it into decision-making during each CABG procedure. Di Giammarco et al. [77] showed that the diagnostic accuracy of TTFM increased to 100% NPV and 100% PPV when it was combined with HR-ECUS. Adding HR-ECUS to TTFM thereby overcomes the relatively modest diagnostic accuracy of TTFM alone. By including HR-ECUS to the surgeon's appraisal of graft and anastomotic quality, in relation to native coronary targets and run-off, the best surgical and clinical outcomes for patients undergoing CABG could be ensured. Besides, HR-ECUS with TTFM could provide beneficial insights for young surgeons to further improve their surgical techniques.

Standardization on how to perform TTFM, what TTFM values to expect for specific grafts and anastomoses and which cut-offs to use for graft revision are essential to increase the use of TTFM amongst surgeons. Moreover, the studies included in current meta-analysis are of moderate quality, according to the NOS criteria. Surgeons may not be therefore convinced to use TTFM. The prospective, multicentre REQUEST registry collected information on standardized TTFM and ultrasound assessments in patients undergoing CABG ($n = 1046$, ClinicalTrials.gov: NCT02385344). This registry could provide crucial information on how to incorporate TTFM in daily clinical practice by providing insights into whether TTFM is effective and improves outcomes in patients undergoing CABG. Furthermore, it could quantify potential benefits of combining HR-ECUS with TTFM on graft and anastomosis quality assessment.

Finally, a clinical issue that remains is that long-term graft failure may still occur as a result of other mechanisms than those controlled by TTFM. This could be one of

the reasons why surgeons doubt its clinical impact and consequently why routine use of TTFM has been limited. Other factors that potentially influence the adoption rate of intraoperative quality assessment are (i) adequately interpreting and acting upon TTFM determinants come with a learning curve, (ii) the time of the procedure might increase (e.g. depending on the need to revise a graft) and (iii) concerns might remain of needlessly revising a patent graft (e.g. due to limited diagnostic accuracy of TTFM alone) [17, 78]. Furthermore, no high-quality data on the impact of TTFM on surgical and clinical outcomes after CABG exist that could influence the adoption rate of TTFM by individual surgeons. Nevertheless, this systematic review does show that TTFM provides valuable intraoperative data on graft and anastomotic quality, which could contribute to improved surgical and clinical outcomes. Despite potential shortcomings, the 2018 ESC/EACTS Guidelines on myocardial revascularisation gave TTFM for intraoperative graft assessment a class-IIa recommendation [79].

LIMITATIONS

As with any meta-analysis of observational studies, limitations related to the observational nature of studies cannot be overcome. One important challenge is that, currently, no consensus exists on uniform TTFM cut-off values to classify grafts as 'abnormal' or requiring revision. This could have caused the relatively increased heterogeneity of the results. To allow a conservative estimate, we have analysed the data using random-effects models, as recommended for meta-analyses on observational studies [80]. However, considering the heterogeneity of study definitions and end points in papers reporting the association between TTFM and graft patency and clinical outcomes, no metaanalysis was performed on these outcomes, as it was considered to be inappropriate to pool heterogeneous results.

CONCLUSION

TTFM has potential to further improve the quality of CABG procedures and could improve clinical outcomes for patients. In 4.3% of patients undergoing CABG, there was a need to revise grafts after TTFM assessment. However, only 25% of grafts, classified as abnormal based on TTFM values, were revised, suggesting that the use of TTFM can be further optimized. Indeed, reaching consensus on TTFM remains difficult due to the substantial heterogeneity in published TTFM data, which could be related to varying haemodynamics during assessment, the location of the TTFM probe (e.g. proximal or distal on the graft), varying cut-off values for revision and

the use of different graft types (e.g. internal thoracic artery, saphenous vein or radial artery) on unique coronary arteries with varying degrees of stenosis. Future studies should focus on determining the optimal use of TTFM and thereby further guiding surgeons to improve outcomes after CABG. A multicentre study with standardized TTFM use and definitions on graft revision may provide more insights into the optimal use of this technique.

Conflict of interest: Daniel J.F.M. Thuijs, Margreet W.A. Bekker, David P. Taggart, A. Pieter Kappetein, Teresa M. Kieser, Daniel Wendt, Gabriele Di Giammarco, John D. Puskas and Stuart J. Head received travelling support and/or speaking fees from Medistim ASA, Oslo, Norway. A. Pieter Kappetein and Stuart J. Head report to work as employees of Medtronic, outside the submitted work. Gregory D. Trachiotis declares no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is also available at EJCTS online.
NEWCASTLE-OTTAWA-SCALE (NOS)

TABLE S1. Newcastle-Ottawa-Scale (NOS) on studies included in the meta-analysis.

Study	Year	Selection (max=4 stars)	Comparability (max=2 stars)	Exposure/ Outcome (max=3 stars)	Total score (amount of stars)
1. Hashim [1]	2017	*	-	***	4
2. Hiraoka [2]	2017	***	-	***	6
3. Leon [3]	2017	***	**	***	8
4. Handa [4]	2016	***	-	***	6
5. Oshima [5]	2016	***	**	***	8
6. Honda[6]	2015	***	-	***	6
7. Di Giammarco [7]	2014	***	-	***	6
8. Quin [8]	2014	***	-	***	6
9. Harahsheh [9]	2012	***	-	***	6
10. Kuroyanagi [10]	2012	***	-	***	6
11. Kieser [11]	2010	***	**	***	8
12. Handa [12]	2009	***	-	***	6
13. Nordgaard [13]	2009	***	**	***	8
14. Santarpino [14]	2009	***	-	***	6
15. Waseda [15]	2009	***	-	***	6
16. Herman [16]	2008	***	**	***	8
17. Onorati [17]	2008	***	-	***	6
18. Becit [18]	2007	***	-	***	6
19. Mujanovic [19]	2007	***	-	***	6
20. Onorati [20]	2007	***	*	***	7
21. Desai [21]	2006	***	-	***	6
22. Poston [22]	2006	**	-	***	5
23. Balacumaraswami [23]	2005	**	-	***	5
24. Kim [24]	2005	**	-	***	5
25. Leong [25]	2005	***	-	***	6
26. Onorati [26]	2005	***	-	***	6
27. Bergsland [27]	2004	***	-	***	6
28. Gwozdziejwicz [28]	2004	**	-	***	5
29. Güden [29]	2003	**	-	**	4
30. Sanisoglu [30]	2003	**	-	***	5
31. Groom [31]	2001	**	-	***	5

TABLE S1. Newcastle-Ottawa-Scale (NOS) on studies included in the meta-analysis. (continued)

Study	Year	Selection (max=4 stars)	Comparability (max=2 stars)	Exposure/ Outcome (max=3 stars)	Total score (amount of stars)
32. D'Ancona [32]	2000	***	-	***	6
33. Jakobsen [33]	1999	**	-	***	5
34. Walpoth [34]	1998	***	-	***	6
35. Canver [35]	1994	**	-	***	5

TABLE S1. Herewith an overview of the quality of all included studies used in the meta-analysis, according to the Newcastle-Ottawa-Scale (NOS), is presented. [36] *Good quality*: a total of 7-9 stars, *Fair quality*: a total of 4-6 stars, *Poor quality*: a total of 0-3 stars.

TABLE S2. TTFM accuracy

Study	Year	Sensitivity	Specificity	NPV	PPV
Desai [21] <i>Detection of abnormal grafts by angiography on 4th post-operative day</i> †	2006	0.250	0.984	0.932	0.600
Di Giammarco [7] <i>Detection of abnormal grafts intraoperatively</i> †	2014	0.270	0.950	0.980	0.100
Handa [4] <i>Detection of abnormal grafts by post-operative angiography</i> †‡	2016	0.457	0.941	0.719	0.840
Hol [37] <i>Detection of abnormal grafts by intraoperative angiography</i> †	2007	-	-	0.770	-
<i>Intermediate-term graft patency</i>		-	-	0.890	-
Kim [24] <i>Detection of abnormal grafts by angiography on 1st post-operative day</i>	2005	0.962	0.769	-	-
Kim [38] <i>Optimal cut-off values for 3-year venous graft patency.</i>	2011				
MGF 24.5mL/min		0.517	0.754	-	-
PI < 2.15		0.862	0.376	-	-
Tokuda [39] <i>LCA grafts.</i>	2007				
MGF (<15mL/min)		0.500	0.897	0.419	0.924
PI >5.1		0.462	0.926	0.480	0.920

TABLE S2. TTFM accuracy (continued)

Study	Year	Sensitivity	Specificity	NPV	PPV
%BF >4.1		0.423	0.863	0.314	0.910
<u>RCA grafts</u>					
MGF (<20mL/min)		0.800	0.860	0.533	0.956
PI >4.7		0.800	0.960	0.800	0.960
%BF >4.6		0.700	0.960	0.778	0.941
<u>Ume [40]</u>	2013				
<u>Saphenous vein grafts</u>					
MGF (<31mL/min)		0.636	0.674	-	-
PI > 4.8		0.227	0.907	-	-
DF (%) < 59		0.556	0.615	-	-

Table S2. An overview of all studies which reported accuracy rates of TTFM detecting abnormal grafts, the ability to assess graft patency and distinct TTFM cut-off values.

†No specification on which grafts were assessed by TTFM, ‡post-operative angiography date not specified. Abbreviations used: NPV; negative predictive value, PPV; positive predictive value, LCA; left coronary artery, MGF; mean graft flow, PI; pulsatility index, %BF; percentage of backflow, DF %; percentage of diastolic filling, RCA: right coronary artery.

TABLE S3. TTFM and graft patency outcomes.

Study	Year	Design	No. of grafts/patients	Procedure specifics ^a	Outcome	Result
Hiraoka [2]	2017	Prospective	104/63	TTFM on ITA, RA and SVG grafts.	Predicting factors influencing abnormal graft flow	The coronary diameter at the distal anastomosis was smaller in abnormal grafts compared to normal grafts ($P=0.0065$). "The calcium score of the target coronary artery was significantly higher in the abnormal grafts [364 (128–710)] than that in the normal grafts [177 (81–321)], $P=0.0061$."
Handa [4]	2016	Retrospective	196/68	OPCAB with TTFM on ITA and SVG grafts.	Examine the association between TTFM in the early diastolic phase and postoperative assessments by CAG.	The overall sensitivity and specificity of TTFM was 0.457 for sensitivity and 0.941 for specificity (McNemar test). The PPV was 0.840 and the NPV was 0.719
Oshima [5]	2016	Retrospective	.../196	TTFM on ITA and SVG grafts.	Establish TTFM cut-off values for detecting graft failure in CTO coronary stenosis.	Multivariable analysis revealed that the PI value was a significant predictor of overall early graft failure (OR 1.23, CI 95% [1.02–1.49] $P<0.028$). Mean flow $<11.5\text{ml}/\text{min}$ is a significant predictor of arterial graft failure ($P=0.004$). A PI > 5.85 ($P=0.009$) is a good predictor of venous graft failure.
Honda [6]	2015	Retrospective	.../72	TTFM on ITA grafts.	Assessing the efficacy of FFR evaluation in LITA-LAD CABG vs. the evaluation of FFR with TTFM	"As coronary stenosis severity increases, graft flow increases, PI decreases and systolic reverse flow increases." "The pulsatility index is an indicator of graft quality that decreases with the severity of the coronary stenosis."

TABLE S3. TTFM and graft patency outcomes. (continued)

Study	Year	Design	No. of grafts/patients	Procedure specifics [#]	Outcome	Result
Lehnert [41]	2015	Retrospective from two RCTs	640/345	TTFM on ITA, RA and SVG grafts.	Graft failure at 1 year	MGF in ITA grafts is recommended to be > 20ml/min (4% decrease in graft failure odds for every 1ml/min MGF increase (OR = 0.96, CI 95% [0.93-0.99], p = 0.005). For single vein grafts TTFM MGF should range >40ml/min to ensure 1 year patency.
Takazawa [42]	2015	Retrospective	480/439	TTFM on ITA and SVG grafts and early postoperative angiogram/CTa	Predictors of early graft failure (mean 3.4 months (\pm 9.4)	“Univariate and multivariate logistic regression analyses for 230 SVGs demonstrated insufficient flow (\leq 20ml/min) (P=0.002; OR 6.63) and the number of distal anastomoses in a sequential fashion (P=0.004; OR 2.51) were significantly correlated with failure.”
Uehara [43]	2015	Prospective	83/83	TTFM on GEA grafts.	Analyse the relationship between TTFM and post-operative CAG	“There was no correlation between the early quality of the GEA graft anastomoses and the intraoperative TTFM parameter values.”
Di Giammarco [7]	2014	Prospective	717/333	TTFM and HR-ECUS on ITA and SVG grafts.	Evaluate the added value of intraoperative HR-ECUS for improved graft patency verification.	TTFM sensitivity (27%), specificity (95%), PPV (10%) and NPV (98%) all without HR-ECUS. With HR-ECUS these results were respectively: 33%, 100%, 100% and 99%.
Jelenc [44]	2014	Retrospective	25/17	TTFM on ITA and SVG grafts.	Graft compliance in relation to TTFM parameters	“Graft compliance significantly influences TTFM; therefore PI cannot be used as a measure of graft patency. Only MGF should be used to judge the function of the bypass graft.”
Milani [45]	2014	Retrospective	.../50	OPCAB with TTFM on ITA grafts.	Evaluating performance of internal thoracic arteries as LAD-grafts	There was no significant difference MGF in both groups. There was a significant difference between PI, LITA = 2.0 \pm 0.7 versus RITA = 2.8 \pm 0.9 (p = 0.003).

TABLE S3. TTFM and graft patency outcomes. (continued)

Study	Year	Design	No. of grafts/patients	Procedure specifics [#]	Outcome	Result
Genomi [46]	2013	Prospective	34/20	TTFM on ITA and SVG grafts.	Assess early patency rates of grafts	TTFM LITA (mean flow: 36 ± 16.5 mL/min, PI 3.0 ± 2.4) and RITA (mean flow: 34 ± 20.2 mL/min, PI 2.3 ± 0.7). All LITA and RITA grafts appeared to be patent on CT angiography at 5 th post-operative day.
Walker [47]	2013	Retrospective	160/160	Robotic-assisted CABG with TTFM on LITA grafts and peri/post-operative angiography	Compare TTFM to diagnostic angiography intra- and early post-operatively	"TTFM revealed significant differences in mean flow between patent (n=152) and non-patent (n=8) grafts (34.3 ± 16.8 mL/min vs. 23.9 ± 12.5 mL/min, $P=0.03$), but not in PI (1.98 ± 0.76 vs. 1.65 ± 0.48 , $P=0.16$) or DF ($73.5\% \pm 8.45\%$ vs. $70.9\% \pm 6.15\%$, $P=0.13$).
Cerqueria Neto [48]	2012	Retrospective	80/35	Off-pump vs on-pump CABG with TTFM on ITA grafts.	Compare TTFM parameters in off-pump vs on-pump CABG	There were no statistical differences in mean flow, PI and DF between the off-pump and on-pump groups. There was no need for graft revision.
Balkhy [49]	2011	Retrospective	85/68	Totally endoscopic OPCAB with TTFM on ITA grafts.	Graft patency at 4 months	MGF in all the internal mammary artery grafts was 76 ± 43 mL/min, and PI of 1.5 ± 0.5 . Eighty grafts (n = 80, 94.1%) were patent at a mean of 4 months, assessed by angiography.
Jokinen [50]	2011	Prospective	204/75	TTFM on ITA, RA and SVG grafts.	Graft failure at 6 month	"TTFM predicts graft failure within the 6 months after CABG." TTFM parameters were neither associated with postoperative CK-MB release, nor with myocardial infarction, stroke or death.

TABLE S3. TTFM and graft patency outcomes. (continued)

Study	Year	Design	No. of grafts/patients	Procedure specifics [#]	Outcome	Result
Kim [38]	2011	Retrospective	328/309	TTFM on SVG grafts.	3-year graft patency	"The greatest accuracy for predicting graft patency was obtained at the cut-off value of 24.5 mL/min for mean flow (51.7% sensitivity and 75.4% specificity) and 2.15 for PI (86.2% sensitivity and 37.6% specificity)." Higher mean flows were associated with patent grafts versus failing grafts (41.3 ± 22.9 mL/min in patent grafts and 29.6 ± 18.7 mL/min in failing grafts; P=0.01)
Takami [51]	2009	Prospective	289/111	TTFM on GEA grafts and post-op CAG.	Non-functional GEA grafts on CAG	Non-functional GEA grafts (n=10; 2 occluded, 5 reverse flow and 3 grafts with competitive flow) had higher PI (> 3.7) and lower mean flow (<17 ± 18mL/min) compared to patent GEA-grafts.
Tokuda [52]	2008	Retrospective	104/51	TTFM on ITA, RA, SVG and GEA grafts.	Graft failure at 1-4 years	Multivariate analysis showed that adequate mean graft flow was an independent predictor: OR 0.95 (95% CI [0.92-0.98] P=0.004) for midterm graft failure.
Hatada [53]	2007	Retrospective	29/29	TTFM on SVG grafts.	Graft occlusion at 3- or 6-month angiography	Fast Fourier transformation analysis of TTFM waveforms predicts graft patency.
Hol [37]	2007	Prospective	39/39	OPCAB with TTFM on ITA and SVG grafts.	CAG at 156 days (SD 50)	The NPV of TTFM for intraoperative findings was 0.77 (30 of 39). The NPV value of TTFM for long-term patency was 0.89 (32 of 36).

TABLE S3. TTFM and graft patency outcomes. (continued)

Study	Year	Design	No. of grafts/patients	Procedure specifics [#]	Outcome	Result
Tokuda [39]	2007	Retrospective	261/123	TTFM on ITA, RA, SVG and GEA grafts and post-op CAG (day 16.2 ± 12.6).	Early graft failure	Using specific TTFM cut-off values for specific certain graft territories (ICA: Mean flow:15ml/min, PI >5.1, %BF: 4.1%) or RCA: Mean flow:20ml/min, PI >4.7, %BF: 4.6%) NPV-range 0.91-0.96 whereas PPV-range 0.31-0.80. Sensitivity and Specificity ranged from 0.423 – 0.800 and 0.897 – 0.960 resp.
Desai [21]	2006	Prospective	139/106	TTFM and IFI on ITA, RA and SVG grafts.	Compare diagnostic accuracy of TTFM and IFI at post-operative day 4 with CAG.	“The sensitivity and specificity of TTFM to detect ≥50% graft stenosis was 25% and 98.4%. The sensitivity and specificity of ICG angiography to detect ≥50% graft stenosis was 83% and 100%.”
Di Giammarco [54]	2006	Retrospective	304/157	TTFM on ITA, RA, SVG and GEA grafts.	Graft failure at 1 year	Mean flow (≤15ml/min), pulsatility index (≥3.0) and percentage of backward flow (3.0%) on TTFM are independently associated with graft failure within first post-operative year.
Hassanein [55]	2005	Prospective	.../445	OPCAB with TTFM on ITA, RA and SVG grafts vs. CABG without TTFM	Compare anastomosis quality between off-pump and on-pump CABG in relation to clinical outcomes.	Average PI and mean flow were higher in off-pump compared to on-pump (2.09 ± 1.03 vs. 1.9 ± 0.98 and 39±22.63 vs. 44.19±23.58 ml/min, P=0.005). Patients with post-operative angina pain had lower mean flow values compared to patients without angina (37.17 ± 21.1 ml/min vs. 42.81 ± 26 ml/min, P= 0.015.
Kitamura [56]	2005	Prospective	.../31	OPCAB with SVG-ACS system and TTFM on SVG grafts.	1-year graft patency	Low graft flow (14.5ml/min) and poor left ventricular function (42%) were significant risk factors for graft occlusion at 1-year (P=0.02 and P=0.04 resp.).

TABLE S3. TTFM and graft patency outcomes. (continued)

Study	Year	Design	No. of grafts/patients	Procedure specifics [#]	Outcome	Result
Manchio [57]	2005	Prospective	217/106	OPCAB with TTFM on SVG grafts.	SVG thrombosis at 5 days assessed by CTA	Graft flow was not significantly different between patients with versus without thrombosis.
Güden [29]	2003	RCT	.../300	OPCAB with hemodilution protocol versus CABG with TTFM on ITA grafts.	Compare graft flow in on-pump and off-pump and to evaluate the effects of hemodilution OPCAB grafts.	No difference in PI values between groups. The mean flow in LAD in OPCAB patients with hemodilution protocol was significantly higher compared to the other 2 groups. Overall graft patency, assessed by angiography post-operatively day 6, was comparable between all groups.
Hirotsani [58]	2001	Retrospective	481/171	TTFM on ITA and SVG grafts.	Pre-discharge angiographic findings	No differences in flow measurements between stenotic and open ITA grafts. For SVGs, intraoperative mean flow of occluded grafts was significantly less ($P < 0.0001$), and could thereby possibly identify early graft occlusion.
Hol [59]	2001	Prospective	124/72	TTFM on ITA and SVG grafts.	Peri-operative angiographic findings and at 3-and 12 months	There were no differences in flow and pulsatility index between grafts with <50% stenosis vs >50% stenosis.
Takami [60]	2001	Prospective	82/35	TTFM on ITA, RA, SVG and GEA grafts.	Early postoperative (14 ± 5 days) angiographic findings	Intraoperative flow parameters: mean flow, insufficiency percentage (% Insuf.), Fast Fourier transformation (FFT) and PI were significantly different in patent and non-patent grafts.
Takami [61]	2001	Prospective	70/32	TTFM on ITA, RA, SVG and GEA grafts and post-operative angiography at day 14 ± 5	Stenotic grafts on CAG	Stenotic grafts (12.9%, n=9 grafts) had lower mean flow (7.6 ± 10.3), higher PI (30.1 ± 26.8), higher % Insuf (40.4 ± 34.1) and lower FFT ratio (0.68 ± 0.27) compared to patent grafts.

TABLE S3. TTFM and graft patency outcomes. (continued)

Study	Year	Design	No. of grafts/patients	Procedure specifics [#]	Outcome	Result
Canver [35]	1994	Prospective/63	TTFM on ITA and SVG grafts.	Objectify the applicability of TTFM to quantitate ITA graft flow	“Compared with in-situ ITA flow, ITA flow after grafting to the coronary artery was increased significantly during CPB and just before sternal closure (p < 0.001)”. Two patients had twisting of the ITA at the anastomosis site which was detected by absence of flow.

Table S3. An overview of the available literature on TTFM in relation to graft patency outcomes. *defined as postoperative myocardial infarction (MI), prolonged ventilation (>24 h), low cardiac output syndrome (low cardiac output requiring at least two inotropes and/or intra-aortic balloon pump), postoperative percutaneous coronary intervention, re-operation for graft occlusion, and in-hospital mortality. [#]not specified which grafts were assessed with TTFM. [#]On-pump unless specified. Abbreviations: ACS system: The Symmetry Aortic Connector System (St. Jude Medical Inc., St Paul, Minnesota, USA), CAG: coronary angiogram, CI: confidence interval, CK: Creatinine-Kinase, CK-MB: Creatine-Kinase MB (heart enzyme), CPB: Cardiopulmonary bypass, CTO: Chronic Total Occlusion, DF: Diastolic Filling, EF: Ejection Fraction, FFR: Fractional Flow Reserve, FFT: Fast Fourier Transformation, HR-ECUS: High-Resolution Epicardial Ultrasonography, IABP: Intra-Aortic Balloon Pump, ICG: IndoCyanine green, IFF: intraoperative fluorescence imaging, ITA: Internal Thoracic Artery, LAD: Left Anterior Descending artery, LCA: Left Coronary Artery, LITA: Left Internal Thoracic Artery, MACE: Major Adverse Cardiac Events, MGF: Mean Graft Flow, NPV: Negative Predictive Value, OPCAB: Off-pump Coronary Artery Bypass, OR: Odds Ratio, PI: Pulsatility Index, PPV: Positive Predictive Value, RCA: Right Coronary Artery, RITA: Right Internal Thoracic Artery, RCT: Randomized Controlled Trial, SILVD: Severe Left Ventricular dysfunction (LVEF<35%), SVGs: Saphenous Vein Grafts, SD: Standard Deviation, TTFM: Transit Time Flow Measurements.

SUPPLEMENTARY MATERIAL REFERENCES

*Please note that the order of the references in the supplementary materials might differ from the original published manuscript.

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