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REVIEW

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

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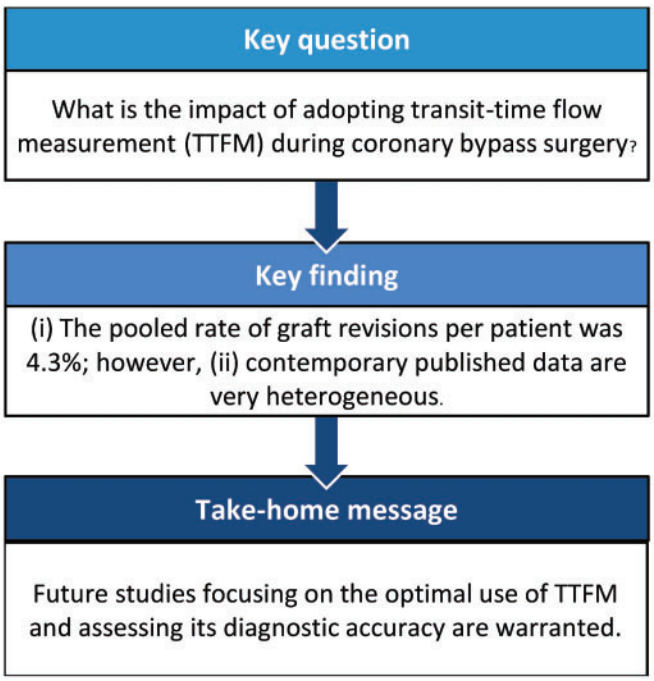
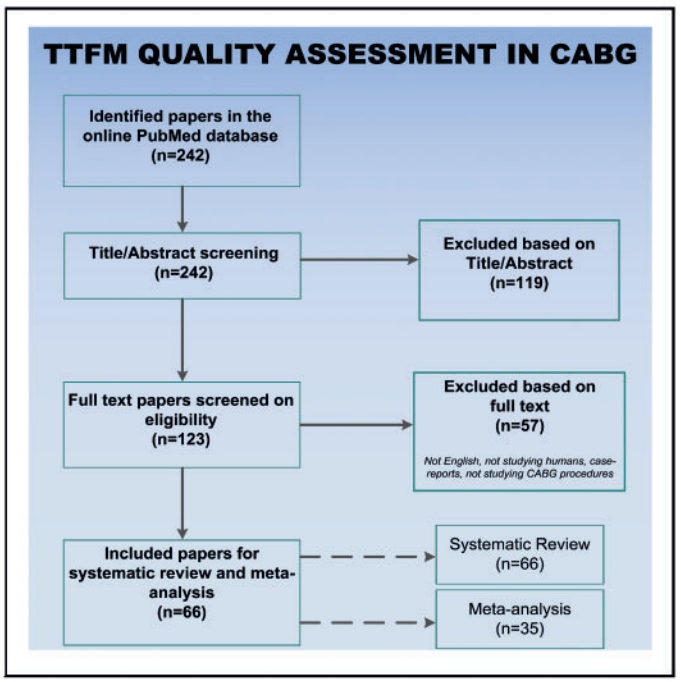




Summary

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.

Keywords: 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 meta-analysis 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 30 days) and outcomes during follow-up (e.g. beyond 30 days) that were extracted consisted of major adverse cardiac and cerebrovascular events (MACCE), mortality, MI, postoperative cardiac enzyme release, stroke, requirement for intra-aortic 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: <15 ml/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.

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.

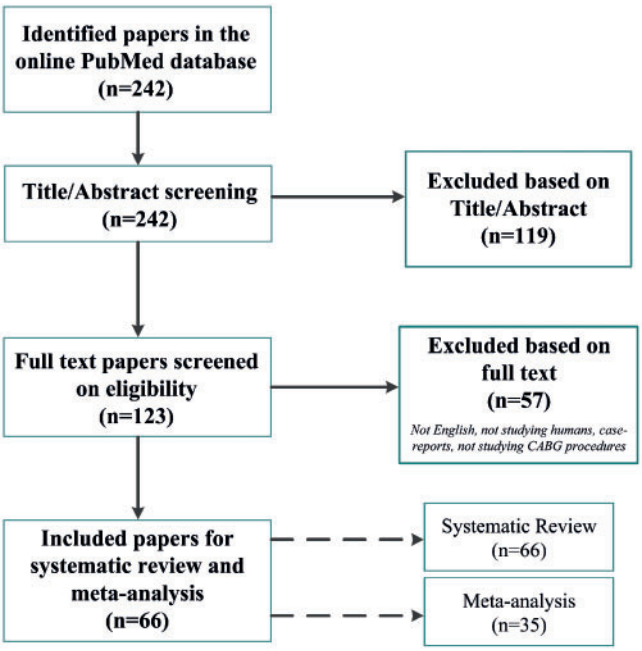


Figure 1: Flow chart of the systematic review process. Studies not written in English, not studying humans, reporting on the same patient population, reporting on transit-time flow measurement in other procedures besides CABG and case reports or reviews were excluded. In total, 66 studies were included,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

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.

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

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 *et al.* [11]	2017	Prospective	86/60	TTFM on ITA	Abnormal Revision	PI >1.0 with an MGF <20 ml/min in an arrested heart Not specified	Not specified 3.5% (*n* = 3 grafts)
Hiraoka *et al.* [12]	2017	Prospective	104/63	TTFM on ITA, RA and SVG	Abnormal	PI >5.0 and an MGF <20 ml/min in ITA-graft or <40 ml/min in SVG	8.7% (*n* = 9 grafts)
Leon *et al.* [13]	2017	Retrospective	543/177	TTFM on ITA and SVG	Revision	PI ≥5.0	0.9% (*n* = 5 grafts)
Handa *et al.* [14]	2016	Retrospective	196/68	OPCAB with TTFM on ITA and SVG	Abnormal Revision	Abnormal TTFM parameters: MGF <15 ml/min, DF <50% and PI >5.0 MGF <5 ml/min or DF <50% or PI >5.0	40% (*n* = 46 grafts) of which 54% appeared patent on postoperative CAG 3.0% (*n* = 6 grafts)
Oshima *et al.* [15]	2016	Retrospective	214/196	TTFM on ITA and SVG	Abnormal	Lower mean flow (21.3 ± 16.2 ml/min) and higher PI (5.5 ± 4.7)	7.0% (*n* = 15 grafts)
Honda *et al.* [16]	2015	Retrospective	72/72	TTFM on *in situ* ITA	Abnormal	MGF <20 ml/min and PI = 2.0	1.4% (*n* = 1 graft)
Di Giammarco *et al.* [17]	2014	Prospective	717/333	TTFM on ITA and SVG	Abnormal Revision	Grafts with MGF ≤15 ml/min and PI ≥3.0 were defined as failing Failing grafts based on TTFM and surgical inspection	5.4% (*n* = 39 grafts) 0.3% (*n* = 2 grafts)
Quin *et al.* [18]	2014	Retrospective	2738/1067	TTFM on ITA, SVG and RA	Abnormal Revision	MGF <20 ml/min MGF <20 ml/min and abnormal PI <3.0 (0.7%), 3.0–5.0 (2.9%) and >5.0 (5.8%)	20.7% (*n* = 568 grafts) 2.0% (*n* = 54 grafts)
Harahsheh [19]	2012	Prospective	1394/436	Not specified[b]	Abnormal Revision	MGF <20 ml/min, PI >5.0 and DF <50% Not specified	7.2% (*n* = 100 grafts) 1.0% (*n* = 14 grafts) 1.1% (*n* = 5 patients)
Kuroyanagi *et al.* [20]	2012	Retrospective	435/159	OPCAB with TTFM on ITA and SVG	Revision	Cut-off values not specified	2.0% (*n* = 9 grafts)
Kieser *et al.* [8]	2010	Prospective	1015/336	TTFM on ITA, SVG and RA	Abnormal Revision	PI >5.0 PI >5, MGF ≤15 ml/min and DF ≤25 with surgical signs of graft malfunctioning	7% (*n* = 74 grafts) 18% (*n* = 59 patients) 2.0% (*n* = 20 grafts) 4.2% (*n* = 14 patients)
Handa *et al.* [21]	2009	Retrospective	116/39	OPCAB with TTFM on ITA and SVG	Abnormal Revision	MGF <10 ml/min, PI >5.0 or DF <50% MGF = 0 ml/min	2.6% (*n* = 3 grafts) 1.7% (*n* = 2 grafts)
Nordgaard *et al.* [22]	2009	Retrospective	1390/581	TTFM on ITA and SVG	Revision	Low MGF and high PI	0.4% (*n* = 5 grafts)
Santarpino *et al.* [23]	2009	Prospective	238/238	TTFM on LITA + RA versus LITA + SVG	Revision	TTFM systolic waveform and PI >4.0 based on thrombosis (*n* = 2) and torsion of the graft (*n* = 1)	1.3% (*n* = 3 grafts) 1.3% (*n* = 3 patients)
Waseda *et al.* [24]	2009	Retrospective	289/116	TTFM on ITA, SVG, RA and GEA	Abnormal Revision	MGF ≤5 ml/min and PI >5 Failing grafts on IFI, yet acceptable TTFM (MGF >5 ml/min and PI ≤5) results	7.3% (*n* = 21 grafts) 2.1% (*n* = 6 grafts)
Herman *et al.* [25]	2008	Prospective	. . ./985	TTFM on ITA and SVG	Abnormal Revision	PI >5 Anastomotic (*n* = 9), conduit (*n* = 8), subclavian stenosis (*n* = 1) and unidentified (*n* = 2)	18.7% (*n* = 184 patients) 2.0% (*n* = 20 patients)
Onorati *et al.* [26]	2008	Retrospective	. . ./433	TTFM on ITA and RA	Abnormal Revision	PI >5 and low MGF (not specified) MGF ≤3 ml/min and PI ≥5	0.2% (*n* = 1 patients) 0.7% (*n* = 3 patients)
Becit *et al.* [27]	2007	Retrospective	303/200	TTFM versus without TTFM on ITA, SVG or RA	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) 9.0% (*n* = 9 patients)
Mujanovic *et al.* [28]	2007	Prospective	2872/1000	Not specified[b]	Revision	Cut-off values not specified	2.2% (*n* = 64 grafts) 6.3% (*n* = 63 patients)
Onorati *et al.* [29]	2007	RCT	90/90	TTFM on single-SVG versus sequential-SVG	Abnormal Revision	PI >5 and low MGF (not specified) 'Systolic' pattern of the curve with low MGF (4 ml/min) and high PI (7.8)"	5.6% (*n* = 5 grafts) 5.6% (*n* = 5 patients) 1.1% (*n* = 1 graft) 1.1% (*n* = 1 patient)
Desai *et al.* [30]	2006	RCT	139/106	TTFM and IFI on ITA, SVG and RA	Abnormal Revision	DF <50%, PI >5.0 and MGF <10 ml/min MGF = 0 ml/min	2.6% (*n* = 3 grafts) 1.4% (*n* = 2 grafts)

Continued

Table 1: Continued

Study	Year	Design	Number of grafts/patients	Procedure specifics[a]	Graft outcome	Reasons for abnormal or revised grafts	Results
Poston *et al.* [31]	2006	Prospective	410/410	TTFM on SVG	Revision	MGF <10 ml/min	0.5% (*n* = 2 grafts)
Balacumaraswami *et al.* [32]	2005	Prospective	266/100	TTFM on ITA and RA	Abnormal	Not specified	9.4% (*n* = 25 grafts) 25.0% (*n* = 25 patients)
					Revision	Persistent poor MGF with TTFM and IFI under adequate MAP (>80 mmHg)	3.0% (*n* = 8 grafts) 8.0% (*n* = 8 patients)
Kim *et al.* [33]	2005	Retrospective	117/58	OPCAB with TTFM on ITA, RA and GEA	Abnormal	Low MGF <3 ml/min or high PI (>20.0)	12.0% (*n* = 14 grafts)
Leong *et al.* [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) 5.2% (*n* = 6 patients)
Onorati *et al.* [35]	2005	Prospective	. . ./297	TTFM on ITA and RA	Abnormal	Low MGF and high PI, without systolic peak pattern on the flow curves	2.4% (*n* = 7 patients)
					Revision	Systolic wave-pattern, low MGF (9 ml/min) and high PI	0.3% (*n* = 1 patient)
Bergsland *et al.* [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)	4.4% (*n* = 5 grafts)
Gwozdziewicz [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) 0.0% (*n* = 0 patients)
Guden *et al.* [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	1.3% (*n* = 4 grafts)
Sanisoglu *et al.* [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) 2.0% (*n* = 1 patients)
Groom *et al.* [40]	2001	Prospective	298/125	TTFM in ITA and SVG	Revision	Low MGF and/or high PI (not specified)	3.0% (*n* = 9 grafts) 7.2% (*n* = 9 patients)
D'Ancona *et al.* [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	3.5% (*n* = 41 grafts) 7.9% (*n* = 33 patients)
Jakobsen and Kjaergard [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 *et al.* [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)
					Revision	1 distal ITA dissection, 1 ITA intramural haematoma and 1 abnormal ECG and poor LV-anterior wall contractility	6.5% (*n* = 3 grafts) 6.5% (*n* = 3 patients)
Canver and Dame [44]	1994	Prospective	. . ./63	TTFM on ITA	Abnormal	Absence of ITA flow due to twisting at the anastomosis site	3.2% (*n* = 2 patients)

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

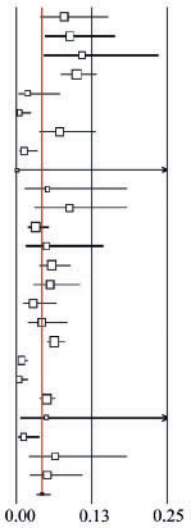
[a]On-pump unless specified.

[b]No specification on which grafts were assessed by TTFM.

CAG: 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; LV: 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.

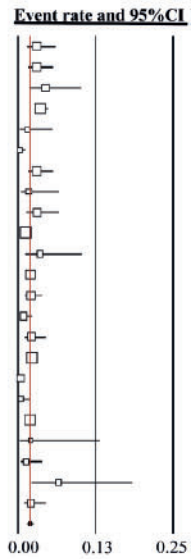
A *Graft revisions per total amount of patients studied by TTFM*

Study name	Total	Event Rate	Lower limit	Upper limit
Balacumaraswami, 2005	8/100	0.080	0.041	0.152
Becit, 2007	9/100	0.090	0.047	0.164
Bergsland, 2004	5/46	0.109	0.046	0.236
D'Ancona, 2000	41/409	0.100	0.075	0.113
Desai, 2006	2/106	0.019	0.005	0.072
Di Giammarco, 2014	2/333	0.006	0.002	0.024
Groom, 2001	9/125	0.072	0.038	0.133
Guden, 2003	4/300	0.013	0.005	0.035
Gwozdziewicz, 2004	0.1/50	0.002	0.0001	0.498
Handa, 2009	2/39	0.051	0.013	0.138
Handa, 2016	6/68	0.088	0.040	0.183
Harahsheh, 2012	14/436	0.032	0.001	0.138
Hashim, 2017	3/60	0.050	0.016	0.144
Kieser, 2010	20/336	0.060	0.039	0.090
Kuroyanagi, 2012	9/159	0.057	0.030	0.105
Leon, 2017	5/177	0.028	0.012	0.066
Leong, 2005	7/166	0.042	0.020	0.086
Mujanovic, 2007	64/1000	0.064	0.050	0.081
Nordgaard, 2009	5/581	0.009	0.004	0.021
Poston, 2006	2/410	0.005	0.001	0.019
Quin, 2014	54/1067	0.051	0.039	0.066
Sanisoglu, 2003	1/20	0.050	0.007	0.282
Santarpino, 2009	3/238	0.013	0.004	0.038
Walpoth, 1998	3/46	0.065	0.021	0.184
Waseda, 2009	6/116	0.052	0.023	0.110
Random (I^2 = 73.9)		**0.043**	**0.033**	**0.057**



B *Graft revisions per total amount of grafts studied by TTFM*

Study name	Total	Event Rate	Lower limit	Upper limit
Balacumaraswami, 2005	8/266	0.030	0.059	0.152
Becit, 2007	9/303	0.030	0.016	0.056
Bergsland, 2004	5/113	0.044	0.019	0.102
D'Ancona, 2000	41/1145	0.036	0.026	0.048
Desai, 2006	2/139	0.014	0.004	0.056
Di Giammarco, 2014	2/717	0.003	0.001	0.011
Groom, 2001	9/298	0.030	0.016	0.057
Handa, 2009	2/116	0.017	0.004	0.066
Handa, 2016	6/198	0.030	0.014	0.066
Harahsheh, 2012	14/1394	0.010	0.006	0.017
Hashim, 2017	3/86	0.035	0.011	0.103
Kieser, 2010	20/1015	0.020	0.013	0.030
Kuroyanagi, 2012	9/435	0.021	0.011	0.039
Leon, 2017	5/543	0.009	0.004	0.022
Leong, 2005	7/322	0.022	0.010	0.045
Mujanovic, 2007	64/2872	0.022	0.017	0.028
Nordgaard, 2009	5/1390	0.004	0.001	0.009
Poston, 2006	2/410	0.005	0.001	0.019
Quin, 2014	54/278	0.020	0.015	0.026
Sanisoglu, 2003	1/49	0.020	0.003	0.131
Santarpino, 2009	3/238	0.013	0.004	0.038
Walpoth, 1998	3/46	0.065	0.021	0.184
Waseda, 2009	6/289	0.022	0.019	0.024
Random (I^2 = 66.0)		**0.020**	**0.015**	**0.025**



C *Graft revisions per total amount of grafts qualified as abnormal by TTFM*

Study name	Total	Event Rate	Lower limit	Upper limit
Balacumaraswami, 2005	8/25	0.320	0.169	0.522
Desai, 2006	2/3	0.677	0.154	0.957
Di Giammarco, 2014	2/5	0.400	0.100	0.800
Handa, 2009	2/3	0.667	0.154	0.957
Handa, 2016	6/46	0.130	0.060	0.261
Harahsheh, 2012	14/100	0.140	0.085	0.223
Kieser, 2010	20/74	0.270	0.181	0.382
Quin, 2014	54/568	0.095	0.074	0.122
Walpoth, 1998	3/3	0.875	0.266	0.993
Waseda, 2009	6/21	0.286	0.134	0.508
Random (I^2 = 80.2)		**0.251**	**0.155**	**0.379**

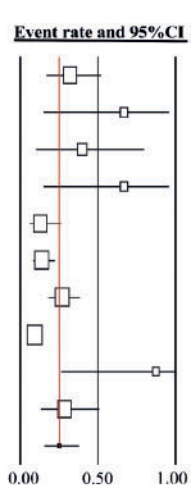


Figure 2: Random-effects models on pooled TTFM study outcomes. (**A**) Graft revision per total amount of patients studied by TTFM, (**B**) graft revisions per total amount of grafts studied by TTFM and (**C**) graft revisions per total amount of grafts qualified as abnormal by TTFM. I^2 indicates heterogeneity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

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 revascularization 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 3.8 years [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 ($I^2 \geq 66$).

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 ($n = 1046$, ClincalTrials.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 revascularization 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 meta-analysis 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.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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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