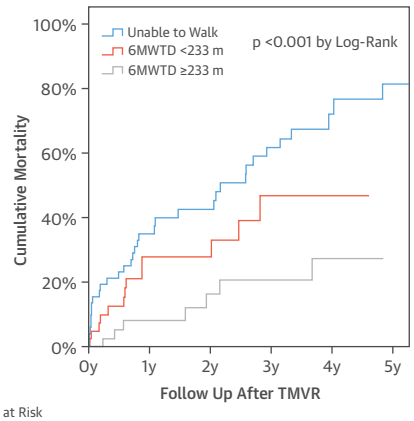
FIGURE 1 Cumulative Mortality After TMVR

A



Number at Risk

Unable to Walk	52	28	21	14	6	4
6MWTD <233 m	43	21	14	6	1	0
6MWTD ≥233 m	44	29	20	16	9	0

B

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
6MWTD (≥233 m, <233 m, Unable to Walk)	1.89	1.21–2.94	0.004	1.75	1.17–2.61	0.006
Age, years (>75)	1.81	0.97–3.40	0.059	2.09	1.05–4.16	0.034
NYHA classification IV	1.93	1.07–3.48	0.028			
Atrial fibrillation	1.70	0.94–3.06	0.075			
Hemoglobin, g/dl (<11)	2.17	1.26–3.74	0.005			
eGFR, mL/min/1.73 m^2(<30)	3.43	1.73–6.79	<0.001	2.83	1.45–5.53	0.002
Serum albumin, mg/dl (per 0.5 increase)	0.70	0.50–0.97	0.034			

(A) Kaplan-Meier curve for cumulative mortality according to the 6-min walk test distance (6MWTD) (6MWTD ≥233 m, 6MWTD <233 m, and Unable to Walk). **(B)** Cox proportional hazard analysis of the association between cumulative mortality and clinical variables. CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; NYHA = New York Heart Association; TMVR = transcatheter mitral valve repair.

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Added Value of Female-Specific Factors Beyond Traditional Predictors for Future Cardiovascular Disease

In women, sex-specific factors related to hormonal and reproductive status are known to affect cardiovascular disease (CVD) risk (1). It is unknown whether

female-specific factors have added value to the traditional risk factors for the purpose of predicting future CVD risk. Therefore, we aimed to evaluate the added value of female-specific factors in addition to traditional risk factors for the prediction of 10-year risk of CVD in women.

We used data collected between 1993 and 1997 in women 30 to 74 years of age from 2 Dutch population-based cohort studies (PROSPECT, MORGEN [Monitoring Project on Risk Factors for Chronic Diseases]) (2). Inclusion criteria for the present analysis were the following: known pregnancy status (never/ever), consent to linkage with disease registries, complete information on vital status and cardiovascular events, no previous CVD. In total, 15,922 women from the PROSPECT study, of whom 14,069 were ever pregnant, and 8,873 women from the MORGEN study, of whom 7,216 were ever pregnant, were included in the analyses. Missing values in candidate predictors were multiply imputed. Outcome was the 10-year risk of (non)fatal CVD. Women were classified into a risk category based on their predicted risk, using cutoff values according to the European Society of Cardiology 2007 treatment guidelines: <10% (low risk), ≥10% to <20% (intermediate risk), ≥20% (high risk). Female-specific factors (age at menarche, menopausal status/age, hormone use, gestational hypertension and diabetes, number of children, miscarriages/stillbirths) were added to the traditional predictors (age, diabetes, blood pressure, cholesterol, and smoking) using Cox proportional hazards models. We applied stepwise backward selection of the female-specific risk factors based on Akaike's Information Criterion, forcing the traditional risk predictors to be retained in the final model. Reproductive status variables were investigated in ever-pregnant women only. Improvement by adding female-specific risk factors to traditional predictors was assessed in terms of discrimination (Harrell's C-statistic), calibration (visualization of observed/predicted ratio in calibration plot), and net reclassification improvement (NRI).

In the PROSPECT study, the mean age was 58 ± 6 years and the mean systolic blood pressure was 133 ± 20 mm Hg, and 22% smoked. In the MORGEN study, the mean age was 46 ± 9 years, the mean systolic blood pressure was 119 ± 17 mm Hg, and 35% smoked. During a median follow-up of 11.7 years, 1,605 (PROSPECT, 10%) and 551 (MORGEN, 6%) CVD events occurred. On multivariable analysis, all traditional predictors were associated with an increased risk of CVD in both cohorts as well as early menopause and multiple miscarriages (Table 1). The C-statistics of the model with traditional risk factors (model 1) were 0.70 (95% confidence interval [CI]: 0.67 to 0.73) in the PROSPECT study, 0.70 (95% CI: 0.67 to 0.73) in the PROSPECT study ever pregnant women, 0.72 (95% CI: 0.67 to 0.73) in the MORGEN study, and 0.72 (95% CI: 0.67 to 0.77) in the MORGEN study ever pregnant women. The C-statistics with the retained female-specific factors (model 2) were 0.70 (95% CI: 0.68 to 0.73) in the PROSPECT study, 0.70 (95% CI: 0.67 to 0.73) in the PROSPECT study ever pregnant women, 0.72 (95% CI: 0.67 to 0.76) in the MORGEN study, and 0.73 (95% CI: 0.67 to 0.78) in the MORGEN study ever pregnant women. Including female-specific factors did not improve calibration of the models. Comparing models 1 and 2, the categorical NRI was −0.01 (95% CI: −0.02 to 0.00) in the PROSPECT study, −0.00 (95% CI: −0.02 to 0.01) in the PROSPECT study ever pregnant women, −0.01 (95% CI: −0.03 to 0.02) in the MORGEN study, and −0.01 (95% CI: −0.03 to 0.02) in the MORGEN study ever pregnant women.

TABLE 1 Female-Specific Risk Factors: Prevalence and HRs for CVD Adjusted for Traditional Risk Factors

	PROSPECT		MORGEN	
	N (%)	Adjusted HR (95% CI)*	N (%)	Adjusted HR (95% CI)*
Female-specific factors				
Age at menarche, yrs				
≤12 yrs vs. 13–14	4,827 (30.3)	1.06 (0.94–1.19)	2,978 (33.6)	1.20 (0.99–1.44)
≥15 yrs vs. 13–14	3,611 (22.7)	1.10 (0.76–1.24)	1,575 (17.8)	1.09 (0.87–1.37)
Menopausal age				
<45 yrs vs. premenopausal	2,160 (13.6)	1.18 (1.00–1.39)	404 (4.6)	1.36 (1.03–1.79)
≥45 yrs vs. premenopausal	8,469 (53.2)	0.91 (0.80–1.05)	1,349 (15.2)	0.98 (0.81–1.18)
OC/HT use				
Past vs. never	10,013 (62.9)	0.94 (0.85–1.05)	4,790 (54.0)	1.04 (0.84–1.29)
Current vs. never	1,015 (6.4)	1.05 (0.84–1.31)	1,284 (14.5)	1.51 (1.14–2.00)
Female-specific factors	N = 14,069		N = 7,216	
No. of live-born children ≥4 vs. <4	2,288 (20.1)	1.00 (0.88–1.12)	559 (7.7)	0.97 (0.72–1.31)
Gestational hypertension	4,345 (30.9)	1.07 (0.96–1.19)	1,318 (18.3)	1.01 (0.79–1.30)
Gestational diabetes	511 (3.6)	0.99 (0.74–1.32)	191 (2.6)	0.76 (0.38–1.53)

*Adjusted for all traditional risk factors, adding all female-specific factors 1 by 1.

CI = confidence interval; HR = hazard ratio; HT = hormone therapy; MORGEN = Monitoring Project on Risk Factors for Chronic Diseases; OC = oral contraceptive.

Female-specific factors had no added value in additional to traditional risk factors for the prediction of the 10-year risk of CVD in women, nor did they improve calibration. However, some were associated with CVD risk on multivariable analysis and therefore certainly help to shed light on the biology and pathophysiology of CVD in women.

Female-specific factors may partly increase the risk of CVD through increasing the levels of the traditional cardiovascular risk factors (3) and partly act via

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independent mechanisms. However, the observed independent effect of early menopause and multiple miscarriages is too small to contribute to discrimination of women in whom CVD will and will not develop.

The strengths of our study include the size, the large number of endpoints, availability of a large number of female-specific factors, information on pregnancy complications, and the fact that it was population based. Furthermore, coefficients for the traditional risk factors were optimally fitted to our data instead of using published coefficients to avoid the risk of erroneously attributing a poor fit of traditional risk scores in these data to the added value of female-specific factors.

Several limitations of this study should be addressed. The presence of female-specific factors was assessed using self-administered questionnaires, which could have led to misclassification. No information about the presence of polycystic ovary syndrome, intrauterine growth restriction, or birth weight was collected.

Although female-specific factors are associated with CVD risk, they have no added value in addition to traditional predictors for the prediction of 10-year risk of CVD in women.

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Arterial Coronary Bypass Grafting

Targeting the Interventricular Septum

We read with great interest the article by Gaudino et al. (1) on the choice of conduits in coronary artery surgery. They propose an algorithm for graft selection for the second target vessel considering technical, anatomic, and conduit patency characteristics. They focus on the lateral wall, as the second target vessel, and they consider the radial artery and the right internal thoracic artery as similar alternatives. The inferior wall is considered as the third target and revascularization with a great saphenous vein is advocated, unless distal branches of the right coronary artery are critically stenosed (>90%); in such cases, in situ gastroepiploic or radial artery is preferred.

Based on physiological data, the inferior wall should be regarded as a functionally important myocardial territory because it consists of parts of the right and left ventricles and a significant portion of the interventricular septum (2). The interventricular septum plays a key role in the functioning of both ventricles through ventricular interdependence. Moreover, inferior infarcts are associated with a high rate of complications and a dismal prognosis as compared with lateral infarcts. Thus, we raise the concept that the dominant posterior descending artery, which supplies the inferior wall, should be equally considered as the second target vessel and receive an arterial graft. By implementing this strategy, the anterior and posterior aspects of the septum are revascularized with the best conduits in terms of long-term patency, namely the left internal thoracic artery and the right internal thoracic artery, respectively. Grafting the posterior descending artery overcomes concerns regarding reduced patency of arterial grafts to a dominant right coronary artery (3), which is attributed mainly to competitive flow and to progression of disease to the crux. Furthermore, this pattern has been associated with excellent long-term patency rates in large series and is advocated in terms of a potential prognostic benefit (3,4).

In principle, the quest for an optimal surgical revascularization strategy should not focus exclusively on the severity of target vessel stenosis, but should also take into account the dominance of coronary circulation.

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