

97% within the first 12 hours), which limits its use in the clinic in which presentation of the patient often exceeds this time window.<sup>14,19,20</sup> A standard immunoassay for research use is available, but efforts to create a rapid diagnostic platform and bring this biomarker to market have not been successful because of technical issues.

### Creatine kinase-BB isozyme

Subsequent efforts were made to find a biomarker with a broader time window. In line with the hypothesis that circulating smooth muscle markers might prove useful, the next pursued biomarker was the BB isozyme of creatine kinase. Creatine kinase consists of muscle (M) and brain (B) isozymes; the MM-type isozyme is widely used for detection of skeletal muscle damage, as is the MB-isozyme for detection of ischemic heart disease. The BB isozyme, however, is selective for neurologic and smooth muscle tissue and cells and had yet to be exploited as a vascular biomarker. Studies measuring the BB isozyme of creatine kinase showed that this smooth muscle marker is elevated in aortic dissection with a peak in levels at approximately 6 hours after onset, extending the diagnostic time window beyond smooth muscle myosin (AAD  $3.4 \pm 1.0$  SE IU/L [n = 10] vs controls  $0.2 \pm 0.1$  SE IU/L [n = 20]).<sup>21</sup>

### Calponin

A smooth muscle biomarker with an even wider time window (eg, up to 24 hours) was then sought. Calponin, which is a troponin counterpart of smooth muscle, was chosen on the basis of analogy to the prominent role of cardiac troponin proteins in detection of cardiac ischemia. Preliminary studies using an initial assay of calponin showed that this protein is elevated in aortic dissection and has a longer time course than the BB isozyme of creatine kinase, remaining elevated within the initial 24 hours (acidic calponin and aortic dissection  $4.10$  ng/mL [n = 16] vs normal reference  $2.04$  ng/mL [n = 52], basic calponin and aortic dissection  $377.56$  ng/mL [n = 16] vs normal reference  $123.31$  ng/mL [n = 52] within the first 6 hours after symptom onset, areas under the curve [AUCs]  $0.63$  and  $0.67$ , respectively).<sup>22</sup>

These preliminary studies confirmed that not only smooth muscle proteins are viable candidates as biomarkers of AAD but also strategic use of these 3 proteins might provide temporal profiles similar to the use of cardiac enzymes in myocardial ischemia. Unfortunately, none has yet to achieve gold standard status similar to that of cardiac troponin, which is being a single biomarker having adequate sensitivity and specificity in addition to a favorable time course of release that covers a time window necessary for nonambiguity in the clinical setting. It is important to note that the recent success of cardiac troponin was preceded by a long history of use of a panel of cardiac markers (eg, myoglobin and creatine

kinase-MB isozyme) before newer and improved assays have made possible the commanding position that it has at present. Aortic dissection biomarkers based on circulating smooth muscle proteins are still in relatively "early" stages of their development and remain promising.

### Markers of other aortic proteins

Another biomarker that has been pursued for aortic dissection is elastin, a structural protein in the vessel wall. Elastin is abundantly present in aortic wall and contributes to contraction and relaxation characteristics. Once AAD occurs, inflammatory processes and proteolytic enzymes degrade medial elastin to produce degradation products such as soluble elastin fragments (sELAF), which are released into the circulation. Plasma sELAF concentrations are elevated in patients with AAD but seem to depend on the status of the false lumen or degree of thrombus formation. The high negative predictive value (NPV) of sELAF may be helpful in ruling out AAD (AAD  $114.7 \pm 56.9$  ng/mL [n = 25], controls of acute myocardial infarction  $56.1 \pm 14.9$  ng/mL [n = 50], sensitivity 64.0%, specificity 99.8% [at a cutoff point of mean in healthy subjects + 3SD], positive predictive value [PPV] 94.1%, NPV 98.1%).<sup>23</sup> Plasma sELAF increases as early as 0.7 hours after onset of AAD, supporting a role in early diagnostic use. However, the dynamic range of this protein is limited to less than 2-fold increases over healthy controls, depending on age, making reliable clinical use questionable.

### Inflammatory markers

C-reactive protein has also been shown to be elevated in AAD with one potential use suggested for monitoring evolution of false lumen thrombosis.<sup>24</sup> Peak levels during admission have been shown to be a predictor for adverse long-term events (death and aortic events) in patients with type B dissection (patients with type B AAD [n = 232]: mean peak CRP values, high group  $19.5 \pm 4.0$  mg/dL vs low group  $6.4 \pm 2.4$  mg/dL, hazard ratio 6.02 [95% CI 2.44-14.87],  $P = .0001$ ; mean peak CRP value, middle group  $12.0 \pm 1.5$  mg/dL vs low group, hazard ratio 3.25 [95% CI 1.37-7.11],  $P = .01$ ),<sup>25</sup> but lack of specificity makes clinical use suboptimal. Possible mechanisms as to why elevated peak CRP levels are associated with long-term adverse events may be that the peak CRP level reflects the degree of inflammatory response in the dissected wall and damage to the lesion. In addition, association of elevation of CRP and positive positron emission tomography uptake in the aortic wall has been reported to correlate with progression of aortic disease.<sup>26</sup> The severely damaged aortic wall may be more prone to expansion and thus redissection or rupture in the chronic phase.

## Fibrolytic markers

Matrix metalloproteinases (MMPs) are a group of extracellular matrix enzymes involved in the remodeling of the aorta, which have also been shown to be elevated and activated in acute dissection. Matrix metalloproteinases are released into the interstitial space and also into the circulation. This may result in collapse of medial layer collagen and elastin fibers, eventually leading to aortic remodeling and dissection.

Plasma concentrations of the MMP-9 subunit have been reported to be increased within 1 hour after onset of symptoms in patients with AAD ( $P < .03$ , types A and B, respectively,  $29.3 \pm 16.1$  and  $16.7 \pm 2.1$  ng/mL [ $n = 13$ ] vs control  $7.74 \pm 1.6$  ng/mL [ $n = 10$ ]) with increased MMP-9 concentrations continuing until 2 months of follow-up.<sup>27</sup> Studies suggest that plasma MMP levels might be used not only in rapid diagnosis of AAD but also in long-term follow-up to monitor aortic remodeling. Inhibition of MMP-2 and MMP-9 synthesis by administration of doxycycline effectively prevented thoracic aortic aneurysm formation in a mouse model of MFS, thus indicating that inhibiting the activities of MMPs might be a potential therapeutic target for aortic aneurysm and dissection.<sup>28</sup>

## Transforming growth factor $\beta$

Circulating TGF- $\beta$  is another notable biomarker that has received recent attention because it may serve in therapeutic monitoring of aortic remodeling in patients with MFS.<sup>29</sup> Circulating TGF- $\beta$  concentrations have been shown to be elevated in patients with MFS as compared with control individuals ( $P < .001$ ,  $15 \pm 1.7$  ng/mL [ $n = 53$ ] vs  $2.5 \pm 0.4$  ng/mL [ $n = 74$ ]). Patients with MFS treated with angiotensin II receptor blocker ( $n = 55$ ) or  $\beta$ -blocker ( $n = 80$ ) showed significantly lower total TGF- $\beta$  concentrations compared with untreated patients with MFS ( $P < .05$ ). Circulating TGF- $\beta$  levels have also recently been shown to be markedly elevated in patients with AAD, especially in Stanford type A dissections ( $P < .01$ ,  $28.5 \pm 14.7$  ng/mL,  $n = 20$ ) compared with type B ( $14.4 \pm 4.81$  ng/mL,  $n = 8$ ), thus suggesting that TGF- $\beta$  may potentially serve as an aortic biomarker beyond its potential role for monitoring aortic size in MFS.<sup>30</sup>

## Thrombotic markers

### D-dimer

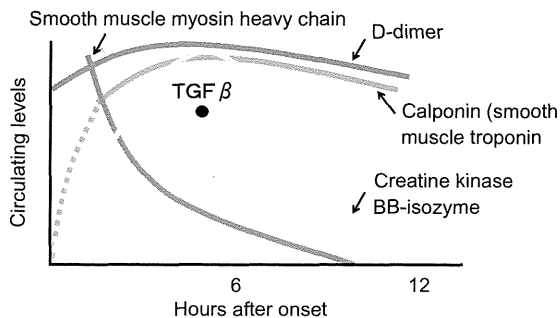
The most promising biomarker for use in suspected acute dissection at the present time is D-dimer. The initial discovery that D-dimer showed increased levels in aortic dissection might have been by chance, but further studies have shown that it can be used both to rule in the disease in the early hours after onset and to use as a rule-out marker and, thus, is the only biomarker at present that is closest to golden standard status. Importantly, it is already

widely available for clinical use including point-of-care rapid tests.

D-dimer is a fibrin fragment seen in coagulopathic disorders, and measurements are routinely used in the diagnosis of PE.<sup>31</sup> Classic AAD also shows elevated levels of this biomarker.<sup>15,31-33</sup> A cutoff level of 500 ng/mL, which is presently used for PE, has been confirmed in multiple studies to also be applicable to rule out AAD. The largest study on the use of D-dimer in aortic dissection<sup>34</sup> showed marked elevations of this biomarker in the early hours after onset (<6 hours) of acute dissection (aortic dissection, type A  $3213 \pm 1465$  ng/mL and type B  $3574 \pm 1430$  ng/mL [ $n = 87$ ] vs controls of myocardial infarction  $1459 \pm 1650$  ng/mL, angina  $760 \pm 974$  ng/mL, PE  $2452 \pm 1891$  ng/mL, and other uncertain diagnosis  $1399 \pm 1511$  ng/mL [ $n = 133$ ]; sensitivity 95.7% and specificity 61.3% at a cutoff level of 500 ng/mL within the first 6 hours) and that the disease could also be ruled in using a cutoff of 1600 ng/mL in the initial 6 hours.

Studies including those mentioned previously have suggested that plasma D-dimer may be a useful screening tool to rule out AAD, but most of these studies were inconclusive because of limited sample size and different cutoff values as well as lack of a control group. Recent meta-analyses using systematically searched clinical studies in EMBASE, MEDLINE, CINAHL, and BIOSIS have been performed to access the missed diagnostic test measurements such as PPV or NPV and likelihood ratios (LRs).<sup>35</sup> One study included AAD cases confirmed by standard imaging techniques and autopsy or pathological examination, with D-dimer measured by standard plasma assays, and included control groups in which absolute numbers of true positive, false positive, true negative, and false negative were obvious or could be derived. D-Dimer testing showed a high sensitivity of 0.97 (95% CI 0.94-0.98,  $I^2 = 0.47$ ) and a negative LR of 0.06 (95% CI 0.02-0.13,  $I^2 = 0.0\%$ ) with narrow confidence intervals. Receiver operating characteristic curve analysis yielded a high certainty for excluding AAD on the basis of negative results (AUC 0.94). A pooled specificity of 0.59 (95% CI 0.53-0.64,  $I^2 = 0.0\%$ ) and a positive LR of 2.58 (95% CI 1.76-3.78,  $I^2 = 0.0\%$ ) did not increase the certainty of diagnosis for AAD. The diagnostic odds ratio was 21.27 (95% CI 11.64-38.88,  $I^2 = 0.0\%$ ).<sup>35</sup> D-Dimer was collectively shown to be a favorable rule-out tool.

A more recent meta-analysis that added results of newer studies, notably the IRAD-Bio study, as done by some of the authors,<sup>34</sup> showed essentially similar results that D-dimer has a high sensitivity and a low negative LR as suited for a rule-out marker but showed only marginal specificity and positive LRs. Overall pooled data estimated a high sensitivity of 0.97 (95% CI 0.94-0.99) and a high NPV of 0.96 (95% CI 0.93-0.98), with little statistical heterogeneity ( $Q = 1.77$  [ $I^2 < 0.001$ ,  $P = .94$ ] and  $Q = 1.45$  [ $I^2 < 0.01$ ,  $P = .96$ ], respectively). By contrast, specificity

**Figure 2**

Time course of biomarkers in aortic dissection. Modified from Suzuki et al<sup>38</sup>.

was low at 0.56 (95% CI 0.51-0.60) and PPV at 0.60 (95% CI 0.55-0.66), with significant heterogeneity ( $Q = 33.8$  [ $I^2 = 0.82$ ,  $P < .001$ ] and  $Q = 8.2$  [ $I^2 = 0.39$ ,  $P = .22$ ], respectively). Negative LR showed an excellent discriminative ability of 0.06 (95% CI 0.03-0.12,  $I^2 < 0.001$ ); on the other hand, positive LR showed a poor discriminative ability of 2.43 (95% CI 1.89-3.12,  $I^2 = 0.78$ ).<sup>36</sup> On the latter, some of the authors reported in the IRAD-Bio study that high D-dimer levels in the early hours (<6 hours) after symptom onset would allow for rule-in diagnosis of AAD, but the meta-analysis did not address time-dependent effects likely because other studies examining D-dimer have not pursued time course.

Therefore, the accumulated evidence suggests that D-dimer testing might be helpful in risk stratifying patients with suspected AAD. Importantly, because the same cutoff level used to rule-out PE can be applied to aortic dissection, this single blood test can be used to rule-out both diseases, which is advantageous from the standpoint of simplicity and cost-effectiveness.<sup>31</sup> With the appropriate understanding in use and interpretation (eg, possible lack of elevations in intramural hematoma and thrombosed false lumen<sup>37</sup>), D-dimer testing may be a potential biomarker solution for sorting out chest pain syndromes where very high levels will lead clinicians to look for AAD or PE as opposed to acute coronary syndromes (see Figure 1 for diagnostic algorithm and Figure 2 for time course of diagnostic biomarkers).

On the potential use of D-dimer in the subacute and chronic phases, sustained elevation up to 20 days after thoracic endovascular aortic repair and increasing maximum D-dimer values postoperatively have been shown to be associated with decreased survival after the procedure, thus suggesting potential use as a prognostic marker, as well.<sup>39</sup> On the platform for D-dimer use, the Tina-quant (Roche Diagnostics, Mannheim, Germany) and Innovance (Siemens, Erlangen, Germany) tests are also in recent use, in addition to the common STA-Liatest (Diagnostica Stago,

Asnieres, France), mainly for Europe. Although there is a lack of data for aortic dissection, a better sensitivity (96%-100%) and specificity (37.5%-38.2%) for venous thrombosis has been reported with the latter platform.<sup>40</sup> This assay also maintains a standard cutoff level at 500 ng/mL, with the 90th percentile of a normal collective at 550 ng/mL.

## Abdominal aortic aneurysms

Aortic aneurysms of the abdomen (AAA) are frequent in elderly patients (eg, >5% prevalence according to an Australian study<sup>41</sup>). Increasing use of ultrasound screening and incidental diagnosis with other imaging modalities such as CT will increase recognition of aneurysms in early stages, but use of biomarkers for this disease focuses more on their use in monitoring progression/expansion rather than acute diagnosis at presentation (eg, rupture).

Risk of rupture increases when aortic growth exceeds expected expansion,<sup>42</sup> and investigations to identify surrogate biomarkers that correlate with expansion rate have been a topic of interest. Several circulating markers have shown association with AAA expansion, symptom onset, and rupture. Serum elastin peptide (SEP) levels have been shown to be modestly associated with AAA expansion rate within the first year of observation and risk of later rupture.<sup>43,44</sup> Correlation between SEP and AAA diameter with contained rupture ( $r = 0.809$ ,  $P < .001$ ) but not with elective AAA repair ( $r = 0.034$ ,  $P = .825$ ) has also been described.<sup>45</sup> Tumor necrosis factor  $\alpha$  and interleukin (IL)-8 levels have also been reported to be significantly lower in large AAAs and in symptomatic AAAs ( $P < .05$ ).<sup>46</sup> Not surprisingly, markers such as procollagen, MMP-9, fibrinogen, D-dimer, tissue plasminogen activator, and IL-6 have been pursued but with varying results.<sup>41</sup> Although a single biomarker may not be sufficient, multiple biomarkers in combination might be of benefit. Initial AAA dimensions, SEP, serum peptide of type III collagen, and expansion rate show significant independent associations, and a multivariate formula using these parameters has been shown to predict cases reaching 5 cm in diameter within 5 years, with a sensitivity of 91% and specificity of 87% by receiver operating characteristic analysis.<sup>47</sup> Newer proteomic methods have also identified proteins involved in the kallikrein-kinin system (eg, kallistatin, carboxypeptidase B2, and protein AMBP) to be potential biomarkers of the disease.<sup>48</sup>

## Thoracic aortic aneurysms

Thoracic aortic aneurysm has a strong genetic basis. Marfan syndrome is a representative genetic disorder complicated by aortic aneurysmal formation often of the thoracic aorta. This syndrome is diagnosed on the basis

**Table I.** Biomarkers of aortic diseases

	<b>Biomarker</b>	<b>Characteristics</b>	<b>Time course</b>	<b>Reference, tested samples, diagnostic performance</b>	
Aortic dissection	SM-MHC	<ul style="list-style-type: none"> <li>- Found in the aortic media layer</li> <li>- Performance appropriate for a rule-in marker</li> </ul>	<ul style="list-style-type: none"> <li>- Elevation limit in the initial 3-6 h<sup>14,19,20</sup></li> <li>- Very short time window</li> </ul>	Suzuki et al, <sup>14</sup> n = 27, sensitivity 90%, specificity 97%	
	BB isoenzyme of creatine kinase	<ul style="list-style-type: none"> <li>- Consists of M and B isozymes</li> <li>- BB isozyme is selective for neurologic and smooth muscle</li> </ul>	<ul style="list-style-type: none"> <li>- Elevated in aortic dissection with peak approximately 6 h after onset of symptoms<sup>21</sup></li> </ul>	Suzuki et al <sup>21</sup> , n = 30, AAD group vs control group 3.4 ± 1.0 SE vs 0.2 ± 0.1 SE IU/L	
	Calponin	<ul style="list-style-type: none"> <li>- A troponin counterpart of smooth muscle</li> </ul>	<ul style="list-style-type: none"> <li>- Has a longer time course than the BB isozymes of creatine kinase</li> <li>- Remains elevated within the initial 24 h<sup>22</sup></li> </ul>	Suzuki et al <sup>22</sup> , n = 150, AUC acidic calponin 0.63, AUC basic calponin 0.67	
	Elastin	<ul style="list-style-type: none"> <li>- A structural protein in the vessel wall</li> </ul>	<ul style="list-style-type: none"> <li>- &lt;2-Fold increase over healthy controls depending on age<sup>23</sup></li> </ul>	Shinohara et al <sup>23</sup> , n = 175, sensitivity 64.0%, specificity 94.8%	
	CRP	<ul style="list-style-type: none"> <li>- May help monitoring evolution of false lumen thrombosis<sup>24</sup></li> <li>- Lack of specificity<sup>25</sup></li> </ul>	<ul style="list-style-type: none"> <li>- Peak level during admission maybe a predictor for adverse long-term events<sup>25</sup></li> </ul>	Sakura et al <sup>25</sup> , n = 233, CRP high group vs low group, hazard ratio 6.02, P = .0001	
	MMP	<ul style="list-style-type: none"> <li>- In particular, the subunit MMP-9 is elevated in aortic dissection<sup>27</sup></li> </ul>	<ul style="list-style-type: none"> <li>- Increases within 1 h from onset of symptoms<sup>27</sup></li> </ul>	Sangiorgi et al <sup>27</sup> , n = 23, AAD group vs control group 29.3 vs 7.74 ng/mL, P < .03	
	Circulating TGF-β	<ul style="list-style-type: none"> <li>- Therapeutic monitoring of aortic remodeling in patients with MFS<sup>29</sup></li> </ul>	<ul style="list-style-type: none"> <li>- Elevated in AAD<sup>30</sup></li> </ul>	Suzuki et al <sup>30</sup> , n = 28, type A AAD vs type B AAD 28.5 vs 14.4 ng/mL, P < .01	
	D-dimer	<ul style="list-style-type: none"> <li>- A fibrin fragment seen in coagulopathic disorders</li> <li>- A rule-in and rule-out marker</li> <li>- The only biomarker close to golden standard status</li> <li>- Widely available for clinical use, including rapid tests due to its value for diagnosing acute PE<sup>31</sup></li> <li>- Possibly lack of elevations in intramural hematoma and thrombosed false lumen<sup>37</sup></li> </ul>	<ul style="list-style-type: none"> <li>- Elevated in AAD<sup>15,31-34</sup></li> <li>- Cutoff level of 500 ng/mL used already for PE is also applicable to rule out aortic dissection</li> <li>- Acute dissection can be ruled in using a cutoff of 1600 ng/mL in the initial 6 h<sup>34</sup></li> <li>- Increasing maximum D-dimer values post-thoracic endovascular aortic repair are associated with decreased survival.<sup>39</sup></li> </ul>	Suzuki et al <sup>34</sup> , n = 200, at cutoff level 500 ng/mL, sensitivity 96.6%, specificity 46.6% Shimony et al <sup>36</sup> , meta-analysis, 7 studies, n = 734, sensitivity 97%, NPV 0.96, specificity 56%, PPV 0.60	
	Abdominal aortic aneurysm	SEP	<ul style="list-style-type: none"> <li>- Associates with AAA expansion and later rupture<sup>43,44</sup></li> </ul>	<ul style="list-style-type: none"> <li>- Use of biomarkers for this disease focuses more on their use in monitoring progression/expansion rather than acute diagnosis.</li> </ul>	Lindholt et al <sup>43</sup> , 112 patients with AAA from 4404 men screened, prospective study, correlation: r = 0.4 These markers show varying results. <sup>41</sup>
		Procollagen, MMP-9, fibrinogen, D-dimer, tissue plasminogen activator, and IL-6 (Proteins involved in the kallikrein-kinin system)	<ul style="list-style-type: none"> <li>- These markers show varying results,<sup>41</sup></li> <li>- For example, kallistatin, carboxypeptidase B2, and protein AMBP could be potential biomarkers of the disease.<sup>42</sup></li> </ul>		
Thoracic aortic aneurysm	MMP-9, TIMP-1 circulating TGF-β	<ul style="list-style-type: none"> <li>- Ratio of MMP-9 to TIMP-1 increased in TAA and dissection<sup>49</sup></li> <li>- Therapeutic monitoring of aortic remodeling in patients with MFS<sup>52</sup></li> </ul>	<ul style="list-style-type: none"> <li>- TAA has a strong genetic basis and is often less inflammatory.</li> </ul>	Koullias et al <sup>49</sup> , n = 47, increased MMP-9/TIMP-1 ratio to control group, P < .05 Ahimastos et al <sup>52</sup> , n = 17, for 24 weeks, ACEI vs placebo, 59.6 vs 45.3 ng/mL, P = .01	

(continued on next page)

Table I. (continued)

	Biomarker	Characteristics	Time course	Reference, tested samples, diagnostic performance
Aortitis	PTX-3	<ul style="list-style-type: none"> <li>- A vascular-selective CRP</li> <li>- Selective produced by vascular endothelial cells, macrophages, and neutrophils</li> </ul>	<ul style="list-style-type: none"> <li>- May be a potential biomarker for Takayasu arteritis</li> <li>- Reflects pathogenetic activity of Takayasu arteritis regardless of therapeutic steroid use<sup>58</sup></li> </ul>	Ishihara et al <sup>58</sup> , aortitis n = 41, sensitivity 82.6%, specificity 77.8%

of clinical features; genetic testing for clinical use is still controversial because of a lack of a genotype-phenotype correlation. Unlike abdominal aortic aneurysm formation, the pathogenesis of thoracic aortic aneurysm is mainly caused by silent medial layer degradation and is often less inflammatory, thus making use of conventional inflammatory biomarkers less informative. Several markers have been pursued, including MMPs, which are known to be involved in the pathogenesis of thoracic aortic aneurysm. A relative index of the ratio of MMP-9 to tissue inhibitor of metalloproteinase-1 (TIMP-1) has been shown to be increased in both patients with thoracic aortic aneurysm and patients with dissection compared with control patients, thus suggesting that imbalance of MMP-TIMP might be important for the development and progression of aortic disease.<sup>49</sup> Elevated MMP levels have also been shown to be associated with recurrent blood flow in aneurysms after endovascular therapy.<sup>50,51</sup>

Transforming growth factor  $\beta$  signaling also contributes to aortic degeneration in MFS. Angiotensin-converting inhibitor (ACEI) treatment reduces TGF- $\beta$  blood concentrations in both latent (59.6-45.3 ng/mL in ACEI group,  $P = .01$  vs placebo) and active (46.2-42.1 ng/mL in ACEI group,  $P = .02$  vs placebo) forms.<sup>52</sup> Recent studies have also shown that mutations in smooth muscle cell isoforms of  $\alpha$ - and  $\beta$ -myosin heavy chain (SM-MHC) cause familial thoracic aortic aneurysm leading to AADs.<sup>53</sup> The protein levels of SM-MHC are elevated in patients with aneurysmal rupture and may also be a potential candidate biomarker for this condition (T. Suzuki et al, unpublished observation). Another proposed strategy for identifying thoracic aortic aneurysms is investigation of the gene expression signature in peripheral blood.<sup>54</sup> A preliminary study has identified 41 gene signatures in peripheral blood cells that distinguish patients with aneurysm from control subjects, with an accuracy of 78% to 80%.<sup>55</sup> The ribonucleic acid signature also provides additional information to detect impending rupture or dissection.

## Aortitis

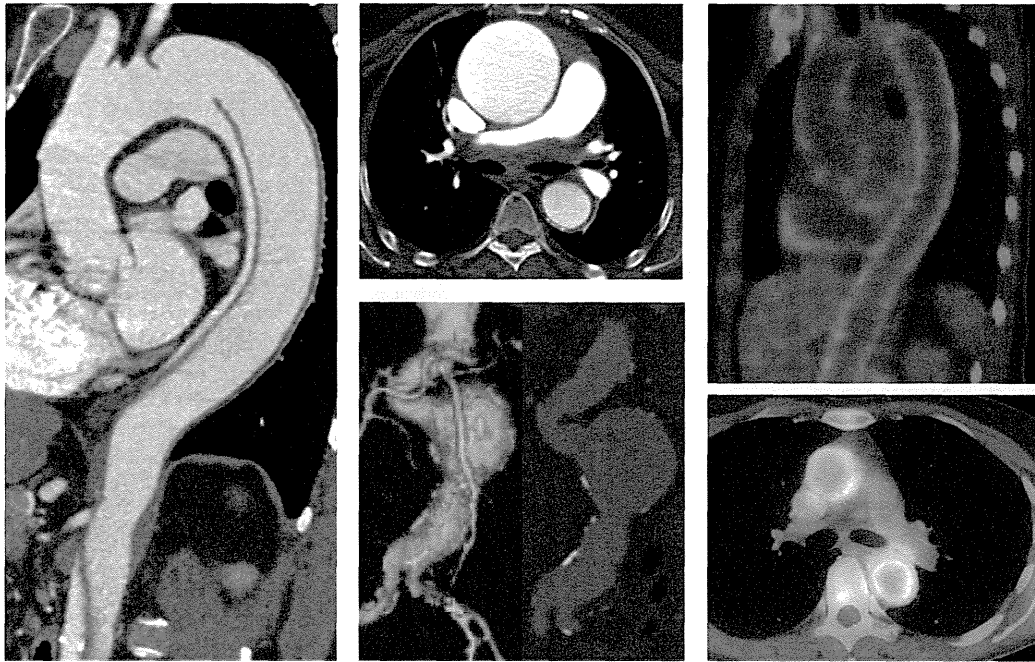
Aortitis (Takayasu arteritis) is an uncommon chronic vasculitis mainly involving the aorta and main branches.

Biochemical monitoring of the pathogenic state is a viable target for aortic biomarkers. The erythrocyte sedimentation rate and CRP level have been used as markers of disease activity.<sup>56,57</sup> Although preliminary tests did not show smooth muscle proteins to demonstrate a sufficient dynamic range for diagnostic use (T. Suzuki et al, unpublished observation), a recent vascular inflammatory biomarker, pentraxin-3 (PTX-3), has shown promise as a potential biomarker for Takayasu arteritis. Pentraxin-3 is a "vascular-selective CRP," with both PTX-3 and CRP belonging to the pentraxin family with CRP harboring a short pentraxin domain, whereas PTX-3 harbors a long pentraxin domain and, importantly, is selectively produced by vascular endothelial cells, macrophages, and neutrophils. A study comparing the usefulness of highly sensitive CRP and PTX3 showed that PTX3 is more specific for arterial inflammation than CRP (highly sensitive CRP, sensitivity 65.2%, specificity 94.4%, AUC 0.905; PTX3, sensitivity 82.6%, specificity 77.8%, AUC 0.914). Plasma MMP-3 levels showed a positive correlation with prednisolone dose as used for treatment, whereas PTX3 levels were not correlated with its dose (MMP-3:  $R = 0.649$ , PTX3:  $R = 0.432$ ), which suggests that this biomarker reflects pathogenic activity of Takayasu aortitis regardless of therapeutic steroid use.<sup>58</sup>

## Future perspectives

Biomarkers for aortic diseases in general remain few. Increasing awareness to the importance of aortic and vascular diseases owing to an aging society with increasing atherosclerotic disease is a prerequisite condition for further advancement of this field. Noninvasive, relatively inexpensive, and nontechnical methods of early diagnosis and/or progression of disease using biomarkers would be ideal to meet this need.<sup>38</sup> Table I and Figure 3 summarize our present knowledge. Emerging technologies such as proteomic methods may also help in identifying new and translatable biomarkers. Society guidelines recognize the need for the development of aortic biomarkers. The European Society of Cardiology (ESC) guidelines on aortic dissection, published in 2001,<sup>11</sup> mention the potential of using SM-MHC. The latest guidelines from the United States (American College of Cardiology/American Heart Association) in 2010 recog-

**Figure 3**



**Aortic dissection**

Smooth muscle myosin heavy chain, BB-isoenzyme of creatine kinase, calponin, elastin, C-reactive protein (CRP), matrix metalloproteinases (MMP), circulating transforming growth factor  $\alpha$  (TGF- $\alpha$ ), D-dimer

**Aortic aneurysm**

Pro-collagen, MMP-9, fibrinogen, D-dimer, tissue plasminogen activator, interleukin-6

**Aortitis**

Pentraxin-3 (PTX-3)  
High sensitive CRP (hsCRP)  
Erythrocyte sedimentation rate (ESR)

Biomarkers categorized according to aortic disease with representative images.

nize that several biomarkers have been investigated for their use in the evaluation of AAD such as SM-MHC, D-dimer, and high-sensitivity CRP.<sup>8</sup> The American guidelines further state that these markers show diagnostic promise and that biomarker development is an important future research direction.

As we look to the future, aortic diseases should be recognized as conditions that will benefit from a noninvasive blood test and therefore are a target of biomarker development. To develop the golden standard, which is necessary and sufficient to both rule in and rule out disease, will be of utmost importance. D-Dimer in aortic dissection is promising for the present, but more “vascular-specific” biomarkers need to be developed in the future. Clinical studies that not only address diagnostic

performance in a certain disease but also build confidence in using the biomarker under wider and general circumstances need to be addressed to confidently use these biomarkers in the emergency room and when triaging patients with certain symptoms/signs (eg, chest pain). For acute diseases, point-of-care tests would be most useful, but these are technically challenging and will require more work after the initial assays are developed.

In the end, how diagnostic biomarkers are helpful in the clinic will depend on their additive usefulness in light of current clinical diagnostic algorithms and imaging modalities. This will hold not only for acute disease but also for chronic monitoring of aortic pathologies in relevance to timing and indication of treatment and outcome.

## Disclosures

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## Clinical presentation, management, and short-term outcome of patients with type A acute dissection complicated by mesenteric malperfusion: Observations from the International Registry of Acute Aortic Dissection

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**Background:** Few data exist on clinical/imaging characteristics, management, and outcomes of patients with type A acute dissection and mesenteric malperfusion.

**Methods:** Patients with type A acute dissection enrolled in the International Registry for Acute Dissection (IRAD) were evaluated to assess differences in clinical features, management, and in-hospital outcomes according to the presence/absence of mesenteric malperfusion. A mortality model was used to identify predictors of in-hospital mortality in patients with mesenteric malperfusion.

**Results:** Mesenteric malperfusion was detected in 68 (3.7%) of 1809 patients with type A acute dissection. Patients with mesenteric malperfusion were more likely to be older and to have coma, cerebrovascular accident, spinal cord ischemia, acute renal failure, limb ischemia, and any pulse deficit. They were less likely to undergo surgical/hybrid treatment (52.9% vs 87.9%) and more likely to receive only medical (30.9% vs 11.6%) or endovascular (16.2% vs 0.5%) management ( $P < .001$ ). Overall in-hospital mortality was 63.2% and 23.8% in patients with and without mesenteric malperfusion, respectively ( $P < .001$ ). In-hospital mortality of patients with mesenteric malperfusion receiving medical, endovascular, and surgical/hybrid therapy was 95.2%, 72.7%, and 41.7%, respectively ( $P < .001$ ). At multivariate analysis, male gender (odds ratio [OR], 1.7;  $P = .002$ ), age (OR, 1.1/y;  $P = .002$ ), and renal failure (OR, 5.9;  $P = .020$ ) were predictors of mortality whereas surgical/hybrid management (OR, 0.1;  $P = .005$ ) was associated with better outcome.

**Conclusions:** Type A acute aortic dissection complicated by mesenteric malperfusion is a rare but ominous complication carrying a high risk of hospital mortality. Surgical/hybrid therapy, although associated with 2-fold hospital mortality, appears to be associated with better long-term outcomes in the management of type A acute aortic dissection in this setting. (*J Thorac Cardiovasc Surg* 2013;145:385-90)

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Over the past 2 decades, knowledge of natural history, diagnosis, and management of acute type A aortic dissection has markedly improved. Despite this, hospital mortality in patients with aortic dissection remains substantial, ranging from 7% to 30%.<sup>1-3</sup> Preoperative patients' characteristics mostly affect hospital outcomes, with the worst results being reported in patients with hypotension, tamponade, and organ malperfusion.<sup>4</sup>

Although several studies have assessed outcomes of patients with type A aortic dissection complicated by end-organ malperfusion syndromes, few have focused on mesenteric malperfusion. The International Registry of Acute Dissection (IRAD) represents a unique opportunity to study a large group of patients with aortic dissection collected in 18 referral centers worldwide.

**Abbreviations and Acronyms**

CI	= confidence interval
IRAD	= International Registry of Acute Dissection
NS	= not significant
OR	= odds ratio

Aims of the present study were to compare clinical/imaging characteristics, management, and outcome of patients with type A acute dissection with and without mesenteric malperfusion and to assess outcomes of patients with mesenteric malperfusion according to different therapeutic strategies (surgical/hybrid, endovascular, and exclusively medical).

**METHODS****Study Population and Data Collection**

The rationale and methodology of IRAD have been published previously.<sup>5,6</sup> At the time of our study, we examined 1809 consecutive patients with type A acute dissection enrolled at 18 institutions between December 1995 and August 2010. Acute type A dissection was defined as any dissection that involved the ascending aorta and/or aortic arch appearing within 14 days of the onset of symptoms. The diagnosis of aortic dissection was based on history, imaging studies, direct visualization at surgery, and/or postmortem findings. Patients were categorized according to presence/absence of mesenteric malperfusion, which was defined as any radiologic evidence of decreased perfusion through the celiac trunk, superior mesenteric artery, and inferior mesenteric artery with decreased viability or necrosis of the gut, with or without lactic acidosis, pain, or abdominal distention.

All patients were classified according to 3 different therapeutic strategies: surgical/hybrid, endovascular, and exclusively medical therapy. A surgical/hybrid procedure was defined as a planned central aortic operation (ascending aorta/arch replacement) possibly associated with any percutaneous aortic or branch artery procedure (fenestration, stenting) performed simultaneously or within the same hospitalization. Endovascular treatment was defined as any percutaneous aortic or branch artery procedure (fenestration, stenting) in which any other central surgical procedure was not performed.

IRAD data forms were used to collect 290 clinical variables, including patient demographics, history, clinical presentation, physical findings, imaging studies, therapeutic management, in-hospital mortality, and adverse events. Completed data forms were forwarded to the coordinating center at the University of Michigan and reviewed for faced validity and completeness.

**Statistical Analysis**

Continuous variables were expressed as the mean  $\pm$  1 standard deviation or median and Q1-Q3 and categorical variables as percentages. In all cases, missing data were not defaulted to negative, and denominators reflect only cases reported.

Univariate analyses between groups were done using  $\chi^2$  tests (or Fisher exact tests) and Student *t* tests where appropriate. All *P* values are 2-sided.

Preoperative and intraoperative variables were first analyzed using univariate analysis to determine whether any single factor was related to therapeutic strategy and hospital mortality in all patients and in those with mesenteric malperfusion. Variables that achieved *P* values less than .15 in the univariate analysis were examined using gender-adjusted multivariate analysis by forward stepwise logistic regression to estimate the independent odds ratios (ORs) of factors related to nonsurgical/hybrid management (all patients and patients with mesenteric malperfusion) and hospital mortality in patients with mesenteric malperfusion.

Statistical analysis was performed by SPSS version 18.0 (SPSS, Inc, Chicago, Ill).

**RESULTS****Clinical Characteristics of Patients With and Without Mesenteric Malperfusion (Tables 1, 2, and 3)**

Of 3099 consecutive patients with acute aortic dissection enrolled between December 1995 and August 2010, 1967 (63.5%) had type A dissection. Sixty-eight (3.8%) of 1809 patients with available data had mesenteric malperfusion.

Compared with those who did not have mesenteric malperfusion, those who did were older ( $61.8 \pm 14.4$  vs  $57.9 \pm 14.4$  years; *P* = .028) and more likely to have abdominal (58.5% vs 24.2%; *P* < .001), leg (35.9% vs 12.0%; *P* < .001), and migrating (21.3% vs 12.1%; *P* = .032) pain. Patients with mesenteric malperfusion more frequently had coma (10.0% vs 3.1%; *P* = .003), ischemic spinal cord damage (6.8% vs 0.8%; *P* = .002), acute renal failure (52.2% vs 7.2%; *P* < .001), limb ischemia (38.5% vs 9.9%; *P* < .001), and any pulse deficit (45.8% vs 29.8%; *P* = .009).

Electrocardiographic evidence of new myocardial infarction (8.5% vs 7.2%; *P* = not significant [NS]), left ventricular hypertrophy (24.1% vs 20.9%; *P* = NS), and low voltage (5.2% vs 4.5%; *P* = NS) were similar in patients with and without mesenteric malperfusion. On imaging studies, widened mediastinum (52.0% vs 54.1%; *P* = NS), pleural effusion (20.8% vs 12.4%; *P* = NS), aortic regurgitation (65.5% vs 53.5%; *P* = NS), and coronary artery compromise (16.7% vs 12.4%; *P* = NS) were equally present in patients with and without mesenteric malperfusion.

Computed tomographic angiography, magnetic resonance imaging, and transesophageal echocardiography were used with similar frequency to assess characteristics of dissection in patients with and without mesenteric malperfusion. Angiography was more frequently performed in patients with mesenteric malperfusion (33.3% vs 11.0%; *P* < .001), in whom an overall higher number of imaging tests were required to complete the diagnostic process ( $2.0 \pm 0.8$  vs  $1.6 \pm 0.6$ ; *P* < .001). Despite that, the time delay (hours) between symptom onset and diagnosis was similar in patients with and without mesenteric malperfusion (6.5 vs 5.8; *P* = NS).

The intimal-medial flap originated more frequently at the aortic root (62.7% vs 45.2%; *P* = .005) in patients with mesenteric malperfusion and at the ascending aorta (36.5% vs 23.9%; *P* = .035) in patients without mesenteric malperfusion. Patients with mesenteric malperfusion were more likely to have arch vessel involvement (52.9% vs 35.7%; *P* = .012) and any renal artery (70.6% vs 18.0%; *P* < .001) involvement by the dissection.

TABLE 1. Demographics and history of patients with and without mesenteric malperfusion

Variable	Mesenteric malperfusion (n = 68)	No mesenteric malperfusion (n = 1741)	P value
Age, mean ( $\pm$ SD), y	61.8 $\pm$ 14.4	57.9 $\pm$ 14.4	.028
Male (%)	47/68 (69.1)	1171/1741 (67.3)	.749
White (%)	54/62 (87.1)	1461/1629 (89.7)	.512
Atherosclerosis (%)	16/66 (24.2)	377/1676 (22.5)	.739
Diabetes (%)	3/66 (4.5)	96/1669 (5.8)	.796
Hypertension (%)	47/66 (71.2)	1208/1693 (71.4)	.980
Aortic valve disease (AS+AR) (%)	8/65 (12.3)	63/1672 (12.1)	.956
Bicuspid aortic valve (%)	3/53 (5.7)	202/1669 (12.1)	.668
Marfan (%)	2/66 (3.0)	74/1687 (4.4)	.767
Peripartum (%)	—	4/1653 (0.2)	1.000
Cocaine abuse (%)	—	19/1656 (1.1)	.643
Known aortic aneurysm (%)	5/66 (7.6)	210/1683 (12.5)	.260
Prior aortic dissection (%)	—	72/1684 (4.3)	.110
Iatrogenic dissection (%)	2/65 (3.1)	55/1665 (3.3)	1.000
Prior cardiac surgery (%)	15/65 (23.1)	245/1660 (14.8)	.066
History of catheterization/angiography	9/53 (17.0)	155/1390 (11.2)	.189

SD, Standard deviation; AS, aortic stenosis; AR, aortic regurgitation.

### Therapeutic Strategies for Patients With and Without Mesenteric Malperfusion

**All patients.** Overall, 86.7% (1567 of 1809) of patients with acute type A dissection underwent surgical/hybrid procedures and 1.0% (19 of 1809) and 12.3% (223 of 1809) received endovascular and medical management, respectively.

On binary logistic regression, preoperative mesenteric malperfusion (OR, 7.9; 95% confidence interval [CI], 3.229-19.521;  $P < .001$ ), age more than 70 years (OR, 2.9; 95% CI, 1.782-4.884;  $P < .001$ ), and female gender (OR, 2.1; 95% CI, 1.317-3.557;  $P = .002$ ) were the strongest independent predictors of receiving medical/endovascular management.

**Patients with and without mesenteric malperfusion (Table 4).** Patients with mesenteric malperfusion were less likely to undergo surgical/hybrid treatment (52.9% vs 87.9%;  $P < .001$ ) and more likely to receive medical (30.9% vs 11.6%;  $P < .001$ ) or endovascular (16.2% vs 0.5%;  $P < .001$ ) management, when compared with patients without mesenteric malperfusion.

In surgically managed patients, the extent of aortic replacement, rate of associated cardiac procedures (8.6% vs 12.6%;  $P = \text{NS}$ ), and rate of open aortic anastomosis (84.0% vs 94.1%;  $P = \text{NS}$ ) were equally distributed in patients with and without mesenteric malperfusion. Patients with mesenteric malperfusion were more likely to require an associated peripheral vascular surgical procedure (11.1% vs 3.5%;  $P = .018$ ) (Table E1).

**Patients with mesenteric malperfusion.** Preoperatively, clinical and dissection imaging features were similar in patients receiving surgical/hybrid, endovascular, or medical treatment, except for older age being more frequent in patients receiving medical management (medical vs

surgical/hybrid: 65.0  $\pm$  15.9 vs 54.1  $\pm$  13.1 years;  $P = .007$ ; medical vs endovascular: 65.0  $\pm$  15.9 vs 56.6  $\pm$  11.1 years;  $P = \text{NS}$ ; surgical/hybrid vs endovascular: 54.1  $\pm$  13.1 vs 56.6  $\pm$  11.1 years;  $P = \text{NS}$ ). Severe comorbid illness was reported as a contraindication to surgical repair in all cases and, on logistic regression, age greater than 70 years (OR, 5.2; 95% CI, 0.741-36.526;  $P = .097$ ) emerged as the only independent predictor of medical/endovascular management.

### Hospital Results

**Patients with and without mesenteric malperfusion (Table 5).** Hospital mortality was 63.2% (43 of 68) and 23.8% (414 of 1741) in patients with and without mesenteric malperfusion, respectively ( $P < .001$ ).

On multiple logistic regression, mesenteric malperfusion (OR, 2.520; 95% CI, 1.127-5.633), age greater than 70 years (OR, 2.327; 95% CI, 1.680-3.222), migrating pain (OR, 1.747; 95% CI, 1.126-2.710), hypotension/shock/tamponade (OR, 2.636; 95% CI, 1.915-3.629), renal failure (OR, 2.076; 95% CI, 1.466-2.940), and abnormal electrocardiogram (OR, 1.568; 95% CI, 1.113-2.210) emerged as independent predictors of in-hospital mortality.

Postoperative occurrence of new major brain injuries (stroke or coma), myocardial ischemic complications, and cardiac tamponade were equally observed in patients with and without mesenteric malperfusion. Patients with mesenteric malperfusion were more likely to have postoperative renal failure (44.4% vs 16.8%;  $P < .001$ ) and limb ischemia (9.6% vs 3.1%;  $P = .009$ ).

**Patients with mesenteric malperfusion.** In patients with mesenteric malperfusion, hospital mortality was 95.2% (20 of 21) after medical management, 72.7% (8 of 11) after endovascular treatment, and 41.7% (15 of 36) after

TABLE 2. Clinical presentation of patients with and without mesenteric malperfusion

Variable	Mesenteric malperfusion (n = 68)	No mesenteric malperfusion (n = 1741)	P value
Time from symptom onset to diagnosis (h)	6.5 (1.3-23.8)	5.8 (1.9-24.0)	.325
Time from diagnosis to surgical/hybrid or endovascular treatment (h)	9.0 (2.3-24.0)	4.8 (2.1-18.1)	.193
Time from symptom onset to surgical/hybrid or endovascular treatment (h)	19.1 (8.8-65.0)	14.8 (6.8-40.5)	.743
Chest pain (%)	48/68 (70.6%)	1348/1672 (80.6%)	.042
Anterior (%)	43/55 (78.2)	1075/1378 (78.0)	.976
Posterior (%)	15/44 (34.1)	487/1274 (38.2)	.579
Back pain (%)	32/66 (48.5)	682/1622 (42.0)	.299
Abdominal pain (%)	38/65 (58.5)	389/1610 (24.2)	<.001
Leg pain (%)	23/64 (35.9)	191/1593 (12.0)	<.001
Quality of pain			
Migrating (%)	13/61 (21.3)	189/1563 (12.1)	.032
Radiating (%)	24/63 (38.1)	560/1583 (35.4)	.658
Pain severity (%)			
Mild (%)	–	117/1350 (8.7)	.304
Severe (%)	40/52 (76.9)	1008/1350 (74.7)	.713
Worst ever (%)	12/52 (23.1)	225/1350 (16.7)	.226
Abrupt onset of pain (%)	59/65 (90.8)	1335/1619 (82.5)	.082
Febrile	4/54 (7.4)	34/1319 (2.6)	.059
Hypotension/shock/tamponade (%)	18/64 (28.1)	449/1628 (27.6)	.924
Hypertension (%)	22/64 (34.4)	493/1628 (30.3)	.485
Syncope (%)	8/67 (11.9)	297/1644 (18.1)	.199
Cerebrovascular accident (%)	6/63 (9.5)	84/1624 (5.2)	.132
Coma (%)	6/60 (10.0)	50/1626 (3.1)	.003
Ischemic spinal cord damage (%)	4/59 (6.8)	13/1628 (0.8)	.002
Myocardial ischemia/infarction (%)	12/66 (18.2)	193/1733 (11.1)	.077
Cardiac heart failure (%)	9/63 (14.3)	127/1670 (7.6)	.053
Acute renal failure (%)	35/67 (52.2)	124/1729 (7.2)	<.001
Limb ischemia (%)	25/65 (38.5)	171/1728 (9.9)	<.001
Any pulse deficit (%)	27/59 (45.8)	394/1321 (29.8)	.009

surgical/hybrid treatment ( $P < .001$ ). In the 43 patients with mesenteric malperfusion who died, causes of death were visceral ischemia ( $n = 15$ ; 34.9%), neurologic ( $n = 2$ ; 7.0%), multiorgan failure ( $n = 5$ ; 11.6%), cardiac ( $n = 2$ ; 4.7%), tamponade ( $n = 2$ ; 4.7%), and not specified ( $n = 15$ ; 44.9%).

At binary logistic regression, surgical/hybrid management (OR, 0.1; 95% CI, 0.028-0.539;  $P = .005$ ) resulted as a protective factor for hospital mortality, whereas male gender (OR, 1.7; 95% CI, 0.338-7.397;  $P = .484$ ), age (OR, 1.112; 95% CI, 1.041-1.188;  $P = .002$ ), and preoperative renal failure (OR, 5.989; 95% CI, 1.328-26.182;  $P = .020$ ) were associated with increased hospital mortality.

## DISCUSSION

Aortic dissection remains one of the most lethal cardiovascular diseases, and end-organ malperfusion syndromes, which occur in approximately in one-third of patients,<sup>4</sup> are associated with elevated mortality and dismal postoperative outcomes.<sup>7-9</sup>

Among different ischemic end-organ complications occurring at the onset of dissection, mesenteric malperfusion is one of the most insidious and therefore challenging for diagnostic and management decision making.<sup>10</sup>

Our data show that mesenteric malperfusion is a rare complication of acute dissection and that, very commonly, is associated with clinical or imaging signs of other organ injury or malperfusion. In our series of 1809 patients with type A acute dissection, only 68 (3.8%) met our definition of mesenteric malperfusion and approximately 30% of them showed clinical symptoms or signs of neurologic complications, 52.2% had acute renal failure, and 30% had limb ischemia. Although the mentioned associated complications may not involve malperfusion as the only underlying pathogenetic mechanism, imaging data, showing extremely high rates of arch vessel (52.9%) and any renal artery involvement (70.6%) by the dissection, support the idea that malperfusion plays an important role and that, when it occurs, it is likely to involve more than one vascular territory. Interestingly, the observation that about 40% of patients with mesenteric ischemia did not have abdominal pain, whereas about 20% of patients without mesenteric malperfusion had pain, confirms that abdominal pain is a nonspecific symptom of acute mesenteric ischemia.<sup>11,12</sup> Moreover, the typically progressive nature of both the aortic dissecting disease and malperfusiv complication, in addition to the potential different times of patients' presentation with different degrees of bowel ischemia, may

TABLE 3. Characteristics of dissection in patients with and without mesenteric malperfusion

Variable	Mesenteric malperfusion (n = 68)	No mesenteric malperfusion (n = 1741)	P value
Origin of dissection flap			
Sinotubular junction (%)	5/67 (7.5)	195/1628 (12.0)	.262
Aortic root (%)	42/67 (62.7)	736/1628 (45.2)	.005
Ascending (%)	16/67 (23.9)	594/1628 (36.5)	.035
Arch (%)	3/67 (4.5)	66/1628 (4.1)	.863
False lumen patency			
Patent (%)	38/50 (76.0)	753/1063 (70.8)	.431
Partial thrombosis (%)	10/50 (20.0)	208/1063 (19.6)	.940
Complete thrombosis (%)	2/50 (4.0)	102/1063 (9.6)	.184
Distal communication (%)	17/44 (38.6)	243/1015 (23.9)	.027
Arch vessel involvement (%)	27/51 (52.9)	429/1203 (35.7)	.012
Any renal artery involvement (%)	48/68 (70.6)	309/1716 (18.0)	<.001
Coronary arteries compromised (%)	8/48 (16.7)	156/1262 (12.4)	.376
Aortic regurgitation (%)	36/55 (65.5)	773/1445 (53.5)	.081
Aortic measurements			
Aortic annulus (cm)	2.6 (2.3-2.9)	2.5 (2.3-2.9)	.878
Aortic root (cm)	4.5 (3.8-5.9)	4.2 (3.7-5.0)	.511
Ascending aorta (widest) (cm)	4.9 (4.5-5.5)	5.0 (4.4-5.8)	.539
Aortic arch (cm)	4.0 (3.5-4.4)	3.6 (3.2-4.1)	.252
Descending aorta (widest) (cm)	3.3 (3.0-4.2)	3.4 (3.0-3.8)	.875

justify our rate of patients without abdominal pain of 40%, which is slightly superior to the 25% reported in literature.<sup>12</sup>

In IRAD, patients with mesenteric malperfusion were less likely to undergo surgical treatment and more likely to receive a recognized suboptimal therapeutic management, namely, medical or endovascular therapy. Moreover, such a difference in therapeutic management was striking: about 50% of patients with mesenteric malperfusion did not receive surgical therapy against 12% of patients without. Accordingly, binary logistic regression confirmed these observations by indicating mesenteric malperfusion as the strongest predictor of medical therapy in the overall series (OR, 7.9).

These data clearly reflect surgeons' attitudes to avoid surgery in patients with severe preoperative comorbidities and indicate that mesenteric malperfusion, among all preoperative dissection-related complications, is considered as (one of) the most threatening.

Almost two-thirds of patients with mesenteric malperfusion died during hospitalization, almost 3 times the number of those patients without the mentioned complication (63.2% vs 23.8%).

However, when assessing hospital mortality according to different therapeutic management, in patients with mesenteric malperfusion an interesting scenario becomes evident: medical and endovascular therapies were associated with dismal mortality rates (95.2% and 72.7%, respectively), whereas surgical/hybrid therapy was associated with a significantly higher survival of 41.7%.

Accordingly, our binary logistic regression indicated that surgical/hybrid therapy for patients deemed operable by the treating facility was associated with the best survival in patients with mesenteric malperfusion, even after adjusting for gender, age, and renal failure. This is likely due to both patient selection and the potential benefit of definitive repair.

When surgical treatment is used, operative timing and potential use of percutaneous procedures (fenestration/stenting) to address branch artery obstruction still represent greatly debated issues.

Some authors,<sup>13,14</sup> given the unpredictable nature of acute type A dissection and its ever-present potential for rupture, advocate immediate correction of malperfusion syndromes by replacing the ascending and/or transverse aortic arch, thus

TABLE 4. Therapeutic strategies for patients with and without mesenteric malperfusion

Therapeutic strategies	Mesenteric malperfusion (n = 68)	No mesenteric malperfusion (n = 1741)	P value
Surgical/Hybrid (%)	36/68 (52.9)	1531/1741 (87.9)	<.001
Open surgery + aortic fenestration (%)	0/4 (0.0)	1/14 (7.1)	1.000
Open surgery + aortic stenting (%)	2/4 (50.0)	12/14 (85.7)	.197
Open surgery + aortic stenting and fenestration	2/4 (50.0)	1/14 (7.1)	.108
Endovascular (%)	11/68 (16.2)	8/1741 (0.5)	<.001
Aortic fenestration (%)	2/11 (18.2)	2/8 (25.0)	1.000
Aortic stenting (%)	2/11 (18.2)	2/8 (25.0)	1.000
Aortic stenting and fenestration (%)	7/11 (63.6)	4/8 (50.0)	.658
Exclusively medical (%)	21/68 (30.9)	202/1741 (11.6)	<.001

TABLE 5. In-hospital mortality and complications for patients with type A acute dissection with and without mesenteric malperfusion

	Mesenteric malperfusion (n = 68)	No mesenteric malperfusion (n = 1741)	P value
Mortality (%)	43/68 (63.2)	414/1741 (23.8)	<.001
Major brain injury (coma + stroke) (%)	5/42 (11.9)	129/1532 (8.4)	.575
Spinal cord injury (%)	1/45 (2.2)	13/1551 (0.8)	.331
Myocardial infarction/ischemia (%)	4/59 (6.8)	96/1689 (5.7)	.772
Acute renal failure (%)	20/45 (44.4)	286/1701 (16.8)	<.001
Limb ischemia (%)	5/52 (9.6)	52/1695 (3.1)	.025
Cardiac tamponade (%)	5/57 (8.8)	91/1659 (5.5)	.370

restoring blood flow into the true lumen. Others,<sup>9,10,15-17</sup> in selected patients showing clinical deterioration owing to established end-organ ischemic dysfunction, suggest alternative management strategies such as delayed central aortic operation after percutaneous end-organ blood flow restoration. This approach, which certainly takes into account the potential for aortic rupture before ascending aortic repair has been accomplished, finds its rationale in the predominant prognostic weight of the end-organ dysfunction and in the suboptimal surgical outcomes reported in this setting.

Our analysis does not allow us to distinguish the best therapeutic option between the aforementioned approaches. However, IRAD data show that hybrid management (central aortic operation plus percutaneous treatment of mesenteric malperfusion) was applied in only a very few cases and that immediate surgical repair of the proximal dissected aorta still represents the most common therapeutic approach for patients with type A acute dissection complicated by mesenteric malperfusion.

### Limitations and Strengths

Our definition of mesenteric malperfusion does not allow distinguishing patients with different degrees of intestinal ischemic injury. As a consequence, differences in clinical features, management, and outcomes of patients according to the presence/absence of intestinal infarction could not be captured, and the comparison between surgical/hybrid, endovascular, and medical management might have been influenced by a selection bias in the therapeutic referral process.

Data on intestinal surgical procedures are not available in the IRAD registry. Thus, the clinical relevance and prognostic implications of concomitant abdominal surgery could not be evaluated.

Current knowledge about mesenteric malperfusion is based on case studies with an extremely limited number of patients, or extrapolated by larger reports including different organ malperfusion syndromes. Our study, analyzing the largest series of patients with mesenteric malperfusion, may help shed light on this high-risk group of patients.

### CONCLUSIONS

Our data showed that patients with mesenteric malperfusion are older and frequently have associated neurologic, renal, and limb dissection-related complications. Mesenteric

malperfusion is a rare but ominous complication carrying a 3-fold higher risk of hospital mortality. When compared with different therapeutic treatments, surgical/hybrid therapy appears to be associated with better outcomes.

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TABLE E1. Surgical procedures for patients with type A acute dissection with and without mesenteric malperfusion

	Mesenteric malperfusion (n = 68)	No mesenteric malperfusion (n = 1741)	P value
Extent of aortic replacement			
Root (%)	10/30 (33.3)	482/1339 (36.0)	.764
Ascending aorta (%)	28/36 (77.8)	1380/1483 (93.1)	.001
Partial arch (%)	10/37 (27.0)	564/1426 (39.6)	.123
Complete arch (%)	5/37 (13.5)	204/1435 (14.2)	1.000
Open procedure (%)	21/25 (84.0)	866/920 (94.1)	.061
Associated procedures (%)			
AVR (%)	8/34 (23.5)	394/1456 (27.1)	.647
CABG (%)	3/35 (8.6)	173/1446 (12.0)	.791
MVR (%)	–	10/1449 (0.7)	1.000
Reoperation (%)	5/34 (14.7)	189/1429 (13.2)	.797
Peripheral vessels replaced	4/36 (11.1)	51/1440 (3.5)	.018

AVR, Aortic valve replacement; CABG, coronary artery bypass grafting; MVR, mitral valve repair/replacement.

# Type-Selective Benefits of Medications in Treatment of Acute Aortic Dissection (from the International Registry of Acute Aortic Dissection [IRAD])

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The effects of medications on the outcome of aortic dissection remain poorly understood. We sought to address this by analyzing the International Registry of Acute Aortic Dissection (IRAD) global registry database. A total of 1,301 patients with acute aortic dissection (722 with type A and 579 with type B) with information on their medications at discharge and followed for  $\leq 5$  years were analyzed for the effects of the medications on mortality. The initial univariate analysis showed that use of  $\beta$  blockers was associated with improved survival in all patients ( $p = 0.03$ ), in patients with type A overall ( $p = 0.02$ ), and in patients with type A who received surgery ( $p = 0.006$ ). The analysis also showed that use of calcium channel blockers was associated with improved survival in patients with type B overall ( $p = 0.02$ ) and in patients with type B receiving medical management ( $p = 0.03$ ). Multivariate models also showed that the use of  $\beta$  blockers was associated with improved survival in those with type A undergoing surgery (odds ratio 0.47, 95% confidence interval 0.25 to 0.90,  $p = 0.02$ ) and the use of calcium channel blockers was associated with improved survival in patients with type B medically treated patients (odds ratio 0.55, 95% confidence interval 0.35 to 0.88,  $p = 0.01$ ). In conclusion, the present study showed that use of  $\beta$  blockers was associated with improved outcome in all patients and in type A patients (overall as well as in those managed surgically). In contrast, use of calcium channel blockers was associated with improved survival selectively in those with type B (overall and in those treated medically). The use of angiotensin-converting enzyme inhibitors did not show association with mortality. © 2012 Elsevier Inc. All rights reserved. (Am J Cardiol 2012;109:122–127)

Medical management of aortic dissection is still mainly determined from personal experience, expert opinion, and historical observational studies.<sup>1–8</sup>  $\beta$  Blockers are thought to be the first-line medication,<sup>9–14</sup> and recent studies have suggested the benefit of inhibitors of the renin-angiotensin system,<sup>15–19</sup> although the effect of calcium channel blockers is poorly understood. Guidelines from the European Society of Cardiology,<sup>2</sup> Japanese Circulation Society,<sup>3</sup> and American College of Cardiology/American Heart Associa-

tion<sup>1</sup> societies in the past decade have reaffirmed the lack of evidence for therapeutic approaches and targeted medical management. We, therefore, sought to understand the current approaches to medical management and the effects of medications on the outcomes by analyzing the International Registry of Acute Aortic Dissection (IRAD) database.<sup>8</sup>

## Methods

IRAD is a multinational registry of 24 referral centers in 12 countries. The details of the IRAD structure and methods used have been previously published.<sup>20–24</sup>

Data from all patients with aortic dissection enrolled in IRAD from December 26, 1995 with follow-up to 5 years was examined, with a focus on patients discharged alive with medication and follow-up data that included the use of medications. The collected data included variables on clinical, imaging, and mortality data. Follow-up was monitored at each of the sites. Mortality data were obtained through the Social Security Death Index for American subjects when this information was missing. At each enrolling hospital, the study investigators worked with their ethics or institutional review board to obtain appropriate approval for participation.

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Table 1  
Baseline demographics

Variable	All Patients (n = 1301)	Type A (n = 722)	Type B (n = 579)
Gender			
Male	918 (70.6%)	510 (70.6%)	408 (70.5%)
Female	383 (29.4%)	212 (29.4%)	171 (29.5%)
Admission status			
Hypertensive	622/1,240 (50.2%)	229/679 (33.7%)	393/561 (70.1%)
Normotensive	450/1,240 (36.3%)	298/679 (43.9%)	152/561 (27.1%)
Hypotensive/shock	149/1,240 (12.0%)	133/679 (19.6%)	16/561 (2.9%)
Medications			
Angiotensin-converting enzyme inhibitor	561/1,201 (46.7%)	272/667 (40.8%)	289/534 (54.1%)
Angiotensin receptor blocker	14/198 (7.1%)	8/93 (8.6%)	6/105 (5.7%)
$\beta$ Blockers	1,100/1,242 (88.6%)	586/683 (85.8%)	514/559 (91.9%)
Calcium channel blocker	609/1,211 (50.3%)	258/670 (38.5%)	351/541 (64.9%)
Diuretic	58/201 (28.9%)	23/91 (25.3%)	35/110 (31.8%)
Vasodilator	259/1,179 (22.0%)	97/655 (14.8%)	162/524 (30.9%)
Discharge status			
Systolic blood pressure (mm Hg)	124.0 $\pm$ 17.9	124.1 $\pm$ 19.1	123.8 $\pm$ 16.3
Diastolic blood pressure (mm Hg)	71.0 $\pm$ 10.6	71.5 $\pm$ 10.3	70.4 $\pm$ 11.1
Heart rate (beats/min)	72.5 $\pm$ 11.5	75.0 $\pm$ 11.6	69.4 $\pm$ 10.6
Hypertensive	28/1,176 (2.4%)	13/651 (2.0%)	15/525 (2.9%)
Normotensive	1,056/1,176 (89.8%)	585/651 (89.9%)	471/525 (89.7%)
Data at 1-year follow-up			
Systolic blood pressure (mm Hg)	129.2 $\pm$ 20.0	129.6 $\pm$ 21.7	128.4 $\pm$ 17.0
Diastolic blood pressure (mm Hg)	76.4 $\pm$ 16.3	77.0 $\pm$ 19.1	75.4 $\pm$ 10.6
Heart rate (beats/min)	68.5 $\pm$ 12.4	69.0 $\pm$ 12.1	67.8 $\pm$ 12.9
Highest systolic blood pressure (mm Hg)	145.8 $\pm$ 27.7	146.2 $\pm$ 30.6	145.1 $\pm$ 22.0
Highest diastolic blood pressure (mm Hg)	85.6 $\pm$ 27.6	85.9 $\pm$ 28.0	85.0 $\pm$ 26.8
Mortality	78/1,274 (6.1%)	33/704 (4.7%)	45/570 (7.9%)

Data are presented as number of applicable patients/cases relative to number of recorded data points (%) or mean  $\pm$  SD.

The summary statistics between groups are presented as frequencies for categorical variables and the mean  $\pm$  SD for continuous variables. Missing data were not defaulted to negative, and denominators reflected only the cases reported. The relations with follow-up outcome were investigated using univariate Cox regression analysis. Multivariate analysis was used to identify the independent predictors of outcome using models previously determined to be predictive of follow-up mortality.<sup>21,22</sup> All-cause mortality was the examined end point. The variables tested for type A included history of atherosclerosis and previous cardiac surgery. For type B, female gender, a history of previous aortic aneurysm, a history of atherosclerosis, in-hospital renal failure, pleural effusion on chest radiograph, and in-hospital hypotension/shock were included. Stepwise selection of variables was performed sequentially with a default value for inclusion set at  $p < 0.05$ . SAS, version 8.2 (SAS Institute, Cary, North Carolina), was used for statistical analyses.

## Results

For the 1,301 patients with acute aortic dissection who survived to discharge and had information on the medications at discharge and during follow-up (median 26.0 months, interquartile range 12.0 to 48.0), the blood pressure status on admission showed that a little  $>1/2$  (50.2%) of all patients were hypertensive. Most of the patients with type B (70.1%) were hypertensive. In contrast, more of the patients

with type A were normotensive (43.9%) than hypertensive (33.7%), with a significantly greater number of patients presenting with hypotension/shock than did those with type B (19.6% for type A vs 2.9% for type B), as would be expected for a typical patient population with aortic dissection.<sup>23,24</sup> The mortality rate for all patients at 1 year was 6.1% and was 4.7% for those with type A and 7.9% for those with type B.

At discharge, most patients (89.8%) were normotensive and hemodynamically stable, with a blood pressure of  $124.0 \pm 17.9/71.0 \pm 10.6$  mm Hg and a heart rate of  $72.5 \pm 11.5$  beats/min. Those with type A tended to have a greater heart rate than those with type B (type A, 75.0 beats/min vs type B, 69.4 beats/min). Almost all patients received antihypertensive medications at discharge in our study population (96%), with 88.6% taking  $\beta$  blockers, 46.7% angiotensin-converting enzyme inhibitors, 50.3% calcium channel blockers, 28.9% diuretics, and 22.0% vasodilators. The demographic data are listed in Table 1.

The association of medications with all-cause mortality during follow-up was analyzed separately for the type A (n = 722) and type B (n = 579) groups.  $\beta$  Blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers were studied because the use of these agents, either alone or in combination, accounted for  $>80\%$  of all medications. The initial univariate analysis showed  $\beta$  blockers to be associated with improved survival in all patients ( $p = 0.03$ ), those with type A overall ( $p = 0.02$ ),

Table 2  
Univariate analysis of effects of medications on long-term survival

Medication	All Patients		Type A		Type B	
	n/Total	p Value	n/Total	p Value	n/Total	p Value
Angiotensin converting enzyme inhibitor	544/1,161	0.929	264/646	0.936	280/515	0.379
Angiotensin receptor blocker	14/195	0.654	8/92	0.421	6/103	0.887
$\beta$ Blocker	1,066/1,201	0.035	567/661	0.024	499/540	0.204
Calcium channel blocker	592/1,171	0.853	253/649	0.223	339/522	0.015
Diuretic	57/198	0.107	22/90	0.427	35/108	0.185
Vasodilator	253/1,141	0.363	94/635	0.136	159/506	0.469

Data are presented as number of applicable patients/cases relative to number of recorded data points.

Table 3  
Multivariate analysis on factors affecting long-term mortality

Variable	p Value	Hazard Ratio	95% CI
<b>Type A</b>			
Age $\geq$ 70 years	0.002	2.440	1.393–4.272
History of atherosclerosis	0.273	1.415	0.761–2.633
Previous cardiac surgery	0.498	1.330	0.582–3.040
Angiotensin-converting enzyme inhibitor at discharge	0.585	0.853	0.481–1.512
$\beta$ Blocker at discharge	0.022	0.471	0.248–0.897
Calcium channel blocker at discharge	0.159	1.479	0.858–2.549
<b>Type B</b>			
Female gender	0.454	0.827	0.504–1.359
Age $\geq$ 70 years	0.001	2.321	1.383–3.897
Previous aortic aneurysm	0.183	1.418	0.848–2.371
History of atherosclerosis	0.380	1.248	0.761–2.046
Renal failure	0.611	0.841	0.431–1.640
Pleural effusion on chest radiograph	0.116	1.570	0.895–2.756
Hypotension	0.033	2.330	1.072–5.064
Angiotensin-converting enzyme inhibitor at discharge	0.378	0.813	0.513–1.289
$\beta$ Blocker at discharge	0.375	0.719	0.347–1.491
Calcium channel blocker at discharge	0.012	0.554	0.348–0.880

and those with type A who had received surgery ( $p = 0.006$ ). In contrast, calcium channel blockers were associated with improved survival in those with type B overall ( $p = 0.02$ ) and in those with type B receiving medical management ( $p = 0.03$ ). The univariate analysis results are listed in Table 2.

Multivariate analysis was used to determine whether the use of medications affected mortality. The medications were added to previously described mortality models using the IRAD database.<sup>21,22</sup> The analysis for type A used a model including a history of atherosclerosis and previous cardiac surgery.<sup>21</sup> Because the initial analysis of the 722 patients with type A dissections showed a robust association of surgery with survival (odds ratio [OR] 2.45, 95% confidence interval [CI] 1.47 to 4.11,  $p = 0.001$ ), only surgically treated patients were studied ( $n = 654$ , 91% of patients). That analysis showed that the use of  $\beta$  blockers was significantly associated with improved survival (OR 0.47, 95% CI 0.25 to 0.90,  $p = 0.02$ ) and that older age was associated

with poor survival (OR 2.44, 95% CI 1.39 to 4.27,  $p = 0.002$ ).

The patients with type B dissection were similarly analyzed using a previously described model that included female gender, a history of previous aortic aneurysm, a history of atherosclerosis, in-hospital renal failure, pleural effusion on the chest radiograph, and in-hospital hypotension/shock as parameters.<sup>22</sup> The analysis of the medically treated patients with type B dissection ( $n = 503$ , 87% of patients) showed the use of calcium channel blockers was associated with improved survival (OR 0.55, 95% CI 0.35 to 0.88,  $p = 0.01$ ) and that in-hospital hypotension/shock (OR 2.33, 95% CI 1.07 to 5.06,  $p = 0.03$ ) and old age (OR 2.32, 95% CI 1.38 to 3.90,  $p = 0.001$ ) were associated with poor survival. The results from the multivariate model are listed in Table 3, the Kaplan-Meier survival curves are shown in Figure 1, and the effects of medications are shown in Figure 2.

## Discussion

Acute aortic dissection involves blood flow through an intimal tear into the aortic media of an often weakened aortic wall resulting from degeneration (e.g., atherosclerosis, aging, hypertension) and/or genetic predisposition (e.g., Marfan syndrome). The underlying principle of treatment is to limit propagation of the false lumen and its negative consequences on end-organ perfusion by reducing and stabilizing the hemodynamic stress on the aortic wall.<sup>1–8</sup> Surgical repair is preferred for type A dissection, and medical therapy, centered on the use of antihypertensive agents, is generally used to achieve this goal in uncomplicated/stable type B dissection. Medical therapy is also used to maintain hemodynamic stability during follow-up to promote aortic stability and prevent aortic expansion with possible rupture and recurrent dissection.

The effects of medications on the outcomes in patients with aortic dissection were examined using the IRAD database. Almost all patients (96%) were discharged with antihypertensive medication. All patients, as well as those with type A overall and those with type A treated surgically, showed that  $\beta$  blockers, the most commonly used agent in patients with aortic dissection (88.6%), were associated with improved survival. In contrast, those with type B overall and those treated medically showed that calcium channel blockers were selectively associated with improved survival. Renin-angiotensin system inhibitors were not significantly associated with survival in our analysis.

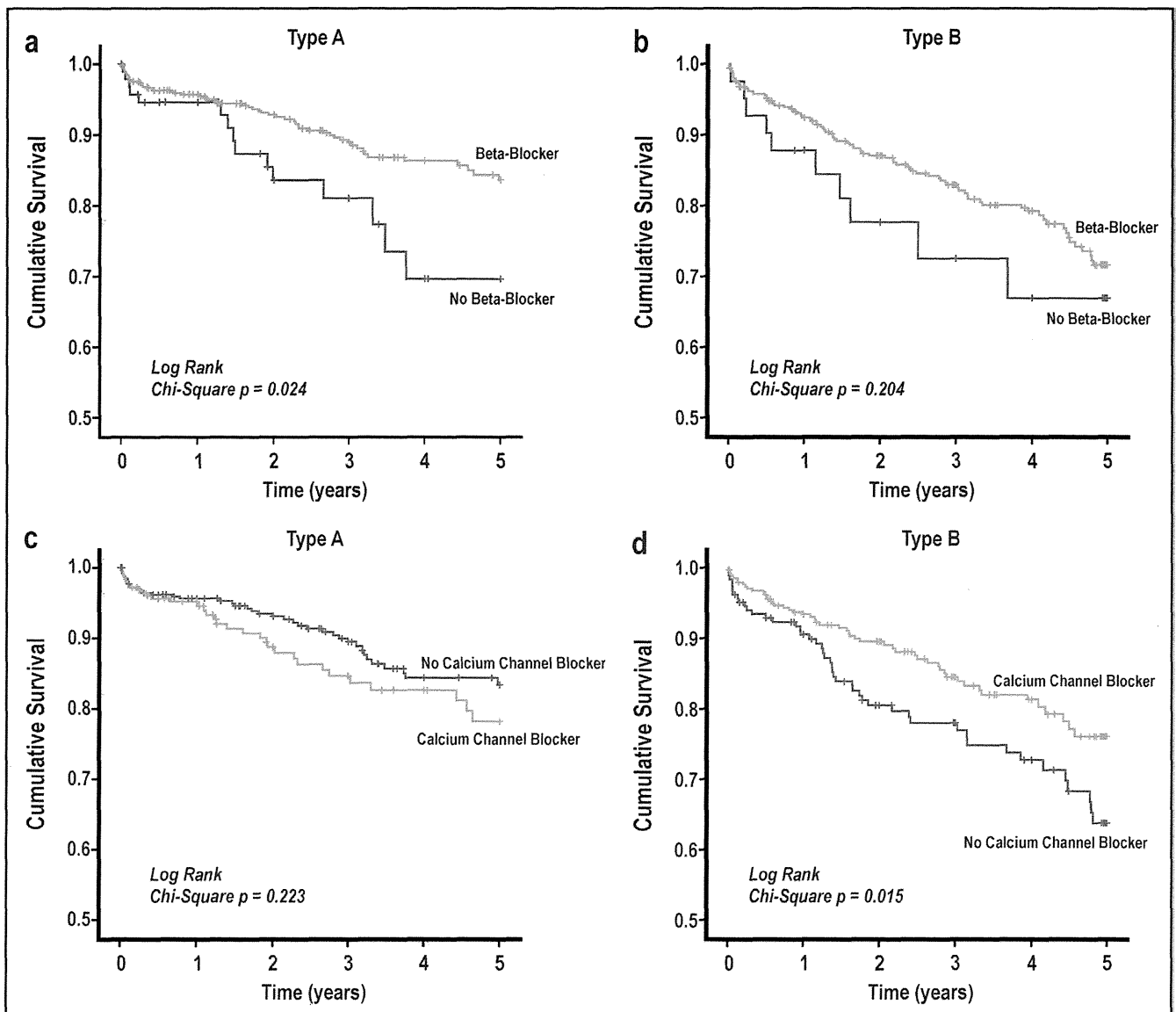


Figure 1. Kaplan-Meier survival curves for effects of medications on mortality.  $\beta$  Blockers in patients with (A) type A dissection and (B) type B dissection; and calcium channel blockers in those with (C) type A and (D) type B.

At discharge and during follow-up, the blood pressure was generally controlled at approximately 120/70 mm Hg, with a 15% deviation. The heart rate was approximately 70 beats/min at discharge, which was slightly lower, but similar, during follow-up. The most recent American guidelines (American College of Cardiology/American Heart Association)<sup>1</sup> recommend lower heart rate control, with a target of 60 beats/min; however, our study predated these recommendations.

$\beta$  Blockers, because they reduce both the aortic blood pressure and heart rate and thus the hemodynamic stress to the arterial wall, have been considered the mainstay of medical management of aortic dissection in general for decades.<sup>9-14</sup> Our analysis has confirmed that  $\beta$  blockers are the most widely used class of medication in almost all patients with aortic dissection, in accordance with the guidelines,<sup>1-3</sup> and that not only are they beneficial for all patients

but also for patients with type A overall and those treated surgically, in particular.

In contrast, calcium channel blockers, the second most commonly used agent, showed selective association with survival for the type B medically treated group. The type A surgical group, however, showed contrasting results, with calcium channel blockers showing an association with poor survival, albeit this result was not significant (Figure 2). The mechanisms of selective effect of calcium channel blockers are unclear. One possible explanation is that aortic remodeling in response to this agent is better when the descending aorta is primarily diseased. The role of calcium channel blockers in the management of aortic dissection, in general, remains poorly addressed. The present guidelines suggest that nondihydropyridine agents can be used as an alternative to  $\beta$  blockers.<sup>1</sup> A recent single-center study showed that calcium channel

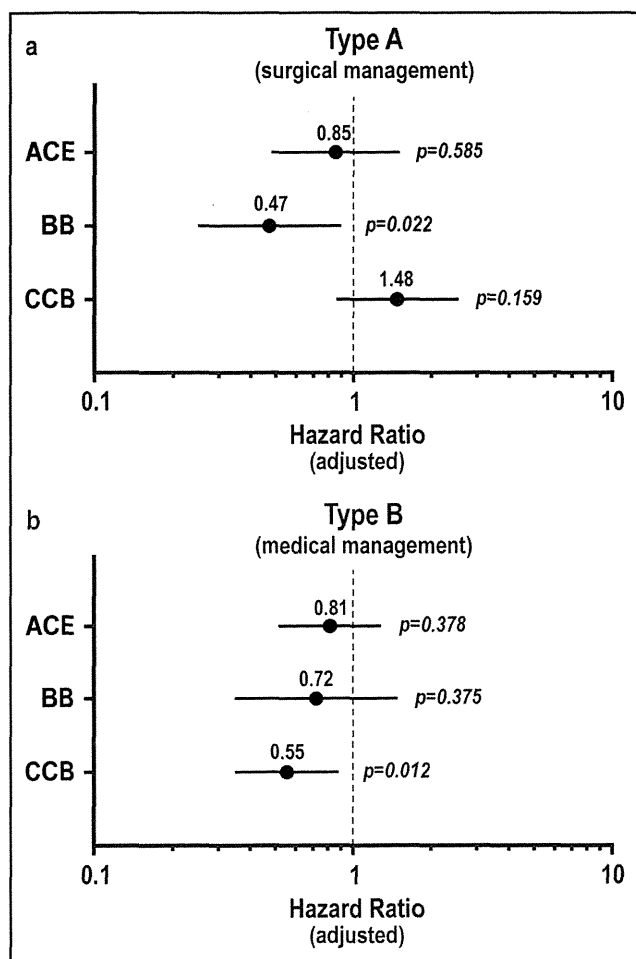


Figure 2. Effects of medications on outcomes. (A) Patients with type A who underwent surgery; and (B) those with type B treated medically. ACE = angiotensin-converting enzyme; BB =  $\beta$  blocker; CCB = calcium channel blocker.

blockers were associated with improved long-term survival (median follow-up 55 months) in those with type B aortic dissection.<sup>25</sup> Additional investigation of the role of calcium channel blockers in the management of aortic dissection is warranted.

Renin angiotensin system inhibitors (e.g., angiotensin-converting enzyme inhibitors) did not show an association with mortality in our cohort, although recent reports have suggested that renin angiotensin system inhibition might also play a pivotal role in the treatment of aortic disease.<sup>15–20</sup> Most of these studies focused on patients with Marfan syndrome; however, such patients differ from the conventional elderly adult patient included in IRAD. The renin angiotensin system and its inhibitors might affect the Marfan aorta differently from the diseased adult aorta. Also, we investigated the effects on mortality and not on aortic widening such as was done in these studies of patients with Marfan syndrome.

Our analyses of the medications used were limited to class effects and categorical/qualitative effects, because we did not monitor the use of individual drugs or their dosages. IRAD predates the current increased use of angiotensin

receptor blockers, which were only used in 8% of patients, limiting our findings for this drug class. We were also unable to sufficiently test which combination of drugs showed the most beneficial effects owing to the statistical power limitations, given the cohort size. Other limitations included unknown adherence data for patients and the lack of information on the sequence of the addition of drugs because the medications were reported cross-sectionally only at discharge and follow-up. Furthermore, the present analysis was limited to all-cause mortality and did not include disease-specific mortality.

The present findings might help in selecting medications to treat patients with acute aortic dissection; however, any effects seen from these observational data from the registry format of IRAD must be considered preliminary and hypothesis generating. The optimal management needs to be confirmed in randomized controlled trials.

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