CARDIOLOGY Rounds®

As presented in the rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

The role of transesophageal echocardiography in the cardioversion of atrial fibrillation

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Atrial fibrillation (AF) is the most common sustained arrhythmia in the general population, and its incidence rises with increasing age. The loss of "atrial kick" and the shorter variable diastolic filling time result in a 20%-30% reduction in stroke volume that may manifest as poor functional capacity and worsening heart failure.[1] AF is a major cause of morbidity and mortality. In the Framingham Heart Study, for example, the attributable risk of stroke due to AF increased with age, rising from 1.5% in the 50- to 59-year-old age group to 23.5% in the 80- to 89-year-old age group.[2] AF may also be an independent risk factor for death, with an adjusted relative risk of 1.5 for men and 1.9 for women.[3] Although it is unclear whether restoration and maintenance of sinus rhythm reduces mortality,[4] pharmacologic and electrical cardioversion is often attempted to improve symptoms and possibly reduce embolic complications.[5,6]

Cardioversion and embolization risk

In atrial fibrillation, the lack of coordinated atrial mechanical activity leads to blood stasis and thrombus formation. Following successful cardioversion, atrial contraction may lead to clot dislodgement and cardioembolic complications. Several studies have documented that the risks of these adverse events range from 0% to 5.6%, with most events occurring in the first 72 hours of cardioversion, presumably due to pre-existing atrial thrombi.[7] Limited data indicate that the risks of embolization are similar for electrical, pharmacologic, and spontaneous cardioversion. Thromboembolic events – of which strokes are often most clinically devastating – are therefore well-recognized complications of cardioversion.

Conventional approach

In 1969, Bjerkelund and Oming performed the first prospective cohort study showing that the risk of clinical thromboembolism was 5.3% for patients with AF undergoing electrical cardioversion without anticoagulant therapy, compared to 0.8% for those receiving oral anticoagulants.[8] Subsequent case-control studies also confirmed that anticoagulation treatment significantly reduced the risks of embolic events after cardioversion.[9] The use of prophylactic anticoagulation therapy for cardioversion has since become the standard of practice.

Currently, the 6th American College of Chest Physicians (ACCP) Consensus Guidelines recommend oral anticoagulant therapy (target INR 2.5; range 2.0 to 3.0) for 3 weeks before, and at least 4 weeks after, elective electrical cardioversion for patients who have been in AF for >48 hours.[9] The rationale for 3 weeks of anticoagulation before cardioversion is based on the observation that at least 14 days of anticoagulation is necessary for fibroblastic infiltration,

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organization, and adherence of thrombus to the atrial wall. More recent studies show that thrombus resolution facilitated by anticoagulation appears to be a more important mechanism.[10,11] The 4 weeks of anticoagulation post-cardioversion is supported by an echocardiographic Doppler study showing persistent atrial mechanical dysfunction despite normalized electrical activity after successful cardioversion.[12] This phenomenon, known as "atrial stunning," provides a milieu for thrombus formation unless therapeutic anticoagulation is maintained following cardioversion. The recovery of normal atrial mechanical function may be delayed for up to 3 to 4 weeks, depending on the duration of AF before cardioversion.[13] While the rationale of the conventional approach appears well supported, it should be noted that its efficacy has never been established in a randomized, controlled trial.

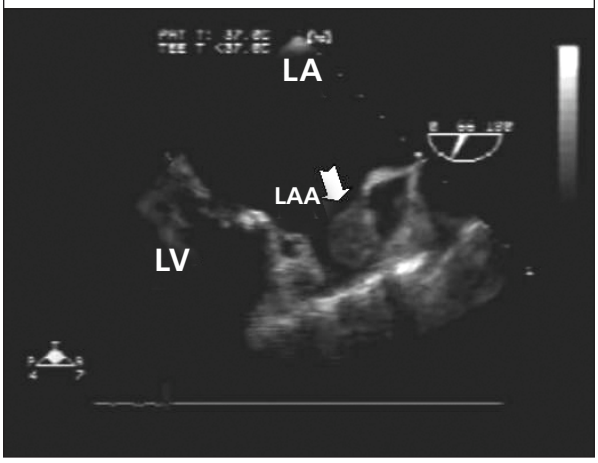
A study of 357 patients with symptomatic AF of <48 hours duration showed the risk of clinical thromboembolism was low (<1%) despite no anticoagulant therapy before cardioversion.[14] In this setting, the ACCP guidelines recommend the initiation of anticoagulation at presentation before cardioversion.[9] The role of anticoagulation in emergency cardioversion remains controversial.

Transesophageal echocardiography-guided approach

Transthoracic echocardiography (TTE) is routinely indicated in the investigation and management of AF.[6] It can provide an accurate assessment of left atrial and ventricular size, left ventricular systolic function, identify any underlying valvular heart disease, cardiac masses, and pericardial disease. The vast majority of thrombi originate in the left atrial appendage. However, TTE is suboptimal in assessing the presence of thrombi in the left atrial appendage due to its posterior location.

The advent of transesophageal echocardiography (TEE) allows superior visualization and evaluation of the left atrium and its appendage (Figure 1). Serious complications, such as esophageal rupture, are rare. In addition to measurement of left atrial appendage size and function, TEE can accurately detect thrombi, spontaneous echocardiographic contrast, and complex aortic plaques that are independently associated with stroke in a multivariate analysis.[15] For example, in a prospective cohort study of 231 consecutive patients undergoing mitral valve replacement or tumour excision (56% had AF), TEE was 100% sensitive and 96% specific in detecting left atrial thrombi confirmed at surgery (overall accuracy 99%).[16] Another

Figure 1: Left atrial appendage thrombus detected on transesophageal echocardiogram



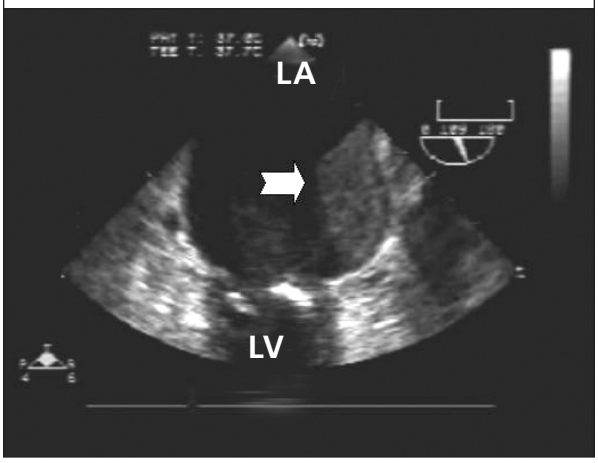
LA = left atrium LV = left ventricle LAA = left atrial appendage

prospective study of 60 patients also showed that TEE had high sensitivity (100%) and specificity (93%) in detecting left atrial thrombus (Figure 2).[17] Additional views by multiplane TEE are widely used at present and have further increased the diagnostic yield.[18]

When thrombi are detected on TEE, cardioversion is postponed and anticoagulant therapy is initiated. In this setting, the optimal duration of anticoagulation and the indications for repeat TEE have not been well-established, although the conventional approach is often followed. There exists a discrepancy between the presence of atrial thrombi (5%-15%) and clinical thromboembolism (usually <5%).[7] This could be due to the organization of thrombi, clinically unapparent embolism, and false-positive findings on TEE. Conversely, small thrombi missed by TEE may be clinically important. These caveats called for studies using clinically relevant endpoints such as stroke and peripheral embolism to firmly establish the safety of the TEE-guided strategy.

Moreyra et al compared the embolic risk from pooled results of TEE-guided studies (7 studies, 374 patients) with that of historical controls (18 studies, 3271 patients both with, and without, anticoagulant therapy) of AF patients undergoing cardioversion.[19] The rate of embolic events (defined as stroke, peripheral embolus, and transient ischemic attack), was significantly higher in the TEE-guided group compared to the anticoagulated control group (1.3% vs 0.3%, P=0.039). In contrast, there was no significant difference between the TEE-guided group and the non-anticoagulated control group. The authors therefore cautioned the routine use of the TEE-guided approach since they considered it experimental, pending data that

Figure 2: Left atrial thrombus detected on transesophageal echocardiogram



are more definitive. It is noteworthy that the pooled studies were small and that none were randomized, controlled trials directly comparing TEE-guided and conventional strategies. Moreover, the patients in the TEE-guided studies did not receive anticoagulant therapy post-cardioversion. As previously discussed, thrombi can form in the stunned atrium during this critical period and later result in embolic complications. Subsequently, a prospective study showed no thromboembolic events in the 196 patients who had a negative TEE and anticoagulant therapy post-cardioversion.[20] While TEE is labour intensive and expensive, a decision-analytic model suggests the TEE-guided approach is cost-effective for patients hospitalized for AF.[21] In the light of these controversial findings, the ACUTE study was undertaken and recently published.

The ACUTE Study

The ACUTE (Assessment of Cardioversion Using Transesophageal Echocardiography) pilot study was the first randomized trial comparing the conventional strategy with the TEE-guided strategy in 126 patients undergoing electrical cardioversion for AF >2 days.[22] The main endpoints were feasibility (time to cardioversion) and safety outcomes (embolic events). Patients assigned to the TEE-guided approach received anticoagulation post-cardioversion. At the 4-week follow-up, none of the patients with negative TEE had an embolic event, whereas 1 patient in the conventional group had a peripheral embolism. The time to cardioversion was significantly shorter in the TEE group. These results suggested that the TEE-guided approach was feasible and safe.

The ACUTE study was an investigator-initiated, multicentre, randomized, controlled trial comparing the conventional strategy and the TEE-guided strategy in patients with AF for whom electrical cardioversion was prescribed.[23] Eligible patients included those with hemodynamically stable AF lasting >2 days, no contraindications to TEE or warfarin, and no need for long-term warfarin. Patients in the TEE group received anticoagulation for 4 weeks after cardioversion. The primary composite endpoint was stroke, transient ischemic attack, and peripheral embolism at 8-week follow-up. Secondary endpoints were hemorrhagic events, all-cause mortality, restoration and maintenance of sinus rhythm, and functional status measured by Duke Activity Status Index (DASI). Serious adverse events were adjudicated by an independent events review committee and all endpoints were analyzed on an intention-to-treat basis.

A total of 1222 patients were enrolled and randomized to either the TEE-guided (619 patients) or conventional (603 patients) treatment. The median estimated duration of AF was 13 days, and thrombi were detected in 13.8% of patients who had TEE. The main results are summarized in Table 1. There was no significant difference in

Table 1: Main outcomes of ACUTE trial at 8-week follow-up

	TEE group (N=619)	Conventional group (N=603)	Relative risk (95% confidence interval)	*P* value
Embolic events	5 (0.8%)	3 (0.5%)	1.62 (0.39-6.76)	0.50
Hemorrhagic events	18 (2.9%)	33 (5.5%)	0.53 (0.30-0.93)	0.03
Deaths from all causes	15 (2.4)	6 (1.0)	2.44 (0.95-6.24)	0.06
Maintenance of sinus rhythm	326 (52.7)	304 (50.4)	1.05 (0.95-1.16)	0.43
Time to cardioversion (days)	3.0 ± 5.6	30.6 ±10.6	—	<0.001
Functional status (DASI score)†	27.4 ±18.3	26.7 ±18.6	—	0.50

† Duke Activity Status Index (DASI) range from 0 to 58.2, with higher scores indicating better functional status.

Table 2: Advantages and disadvantages of the TEE-guided approach compared with the conventional approach	
Advantages	**Disadvantages**
Shorter time to cardioversion	Equivalent safety not firmly established
Potentially shorter duration of anticoagulation required, with lower bleeding risks	Management of detected thrombi not clearly defined and may reduce cost-effectiveness due to repeated studies
May be cost-effective	Limited availability in community hospitals
Earlier cardioversion may improve likelihood of success in cardioversion and subsequent maintenance of rhythm	Thrombi post-cardioversion may be missed and TEE may yield false-positive results by erroneously identifying spontaneous echo contrast, multilobe appendages, pectinate muscles, or artifacts as thrombi

embolic events between the 2 groups. However, patients in the TEE group had fewer hemorrhagic complications and shorter time to cardioversion. The investigators concluded that the TEE-guided approach might be considered a safe and clinically effective alternative to the conventional strategy.

Although this study was well-conducted, several limitations ought to be mentioned:

- The hemorrhagic event rates (2.9% in the TEE group and 5.5% in the conventional group) were relatively high over the 8-week period, compared to the annual rates of approximately 1.5% in most AF trials using long-term anticoagulation. Most of the difference was in minor hemorrhage that was not clearly defined.
- Although restoration of sinus rhythm was more frequent in the TEE group, rhythm maintenance was similar for both groups.
- There was a non-significant trend towards more deaths in the TEE arm. This could be due to chance and sample size, and most deaths were not cardiac-related.
- More importantly, ACUTE was designed to show the superiority of the TEE approach with a planned recruitment of 3000 patients. Unfortunately, due to slow recruitment and unanticipated low event rates, it was inadequately powered to establish non-inferiority for safety (relative risk 95% CI, 0.39 to 6.76). Nevertheless, the low event rate of the TEE strategy (0.8%; 95% CI, 0% to 1.5%) was reassuring.
- The main advantage of the TEE-guided approach was the need for a shorter duration of therapeutic anticoagulation (4 vs 7 weeks). However, it is not clear whether it is safe to discontinue anticoagulation after cardioversion, especially for patients with asymptomatic paroxysmal AF. The need to continue anticoagulation in these patients would negate any potential benefit afforded by the TEE-guided approach.
- The lack of availability of trained echocardiographers who can perform TEE may further limit the applicability of ACUTE in the community.

Conclusion and recommendations

Cardioversion for AF is frequently performed, but is associated with an increased short-term risk of thromboembolic complications. There are currently 2 therapeutic approaches, namely the conventional strategy and the TEE-guided strategy. The conventional strategy requires therapeutic anticoagulation (INR 2-3) for 3 weeks before and at least 4 weeks after cardioversion. Although its efficacy has never been demonstrated in randomized controlled trials, the conventional strategy has been the standard of practice for over 30 years, with relatively low complication rates. TEE is sensitive and specific in identifying thrombi in the left atrial appendage that are the most common source of embolization. The recently published ACUTE trial provides support for the TEE-guided approach; patients undergo cardioversion after left atrial appendage thrombi are first ruled out by TEE. The advantages of this approach include a shorter duration of anticoagulation, lower risks of bleeding,

and shorter time to cardioversion. The results of the ACUTE study suggest that the TEE-guided approach is a reasonable alternative to the conventional approach, although equivalent safety could not be unequivocally established. It should also be emphasized that the TEE-guided strategy does not obviate the need for anticoagulation post-cardioversion, since thrombi can continue to form in the stunned atrium. The advantages and disadvantages of the TEE-guided approach compared with the conventional approach are summarized in Table 2.

Given these two comparable strategies, clinicians have to individualize the choice based on the patient's characteristics and the local availability of facility and skilled personnel. Although the ACUTE study did not show that the TEE-guided strategy was superior in terms of reductions in mortality and embolic risk, certain patient subgroups may benefit from this strategy. They include high-risk patients (such as those with congestive heart failure or borderline hemodynamic stability) where a prompt return to sinus rhythm is desirable, in-patients with new onset AF, and patients with fluctuating INR where it is difficult to maintain therapeutic anticoagulation pre-cardioversion. In addition, TEE before cardioversion may supplement the conventional approach in patients at very high risk of thromboembolism, such as those with rheumatic mitral valve disease and history of stroke. Detection of persistent atrial thrombi may warrant longer term therapeutic anticoagulation beyond 3 weeks before attempting cardioversion.

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Abstracts of Interest

Comparison of transesophageal echocardiography-detected thromboembolic risk markers in patients with chronic atrial fibrillation and atrial tachycardia according to the SPAF clinical risk stratification: A prospective study.

BANYOUNES N, ROZENBERG V, DJAOUTI L, SMADJA C, KHIRREDINE M, COHEN A. PARIS, FRANCE

The thromboembolic (TE) risk of atrial flutter and tachycardias (AFT) has been reported as lower than atrial fibrillation (AF). Current guidelines suggest the need for a similar anti-coagulant strategy in both groups. This attitude could be balanced by a risk stratification using SPAF clinical criteria and TE echocardiographic markers.

Objective: We sought to compare the frequency of TE risk markers in patients (Pts) with chronic AF and AFT according to the SPAF clinical criteria for TE risk stratification.

Methods: As part of an ongoing prospective study, we evaluated 212 Pts in chronic AF and 77 Pts in AFT using transthoracic and transesophageal echocardiography (TEE). Pts were divided into high (n=113 and 43, respectively) and moderate/low (n=99 and 34, respectively) SPAF clinical risk groups. The following parameters were evaluated; left atrial (LA) and LA appendage (LAA) areas, spontaneous echo contrast (SEC), LAA and diastolic emptying velocity (Vel), LA thrombus (Thr) and thoracic aorta atheroma (TAA).

Results: The main results are summarized in the table.

	Chronic AF High risk (n=113)	Chronic AF Moderate/low risk (n=99)	AFT High risk (n=43)	AFT moderate/low risk (n=34)
Mean age (years)	75 ± 11	63.1 ± 11.5	70.9 ± 14.2	63.7 ± 12.9
LA area (cm^2)	24.7 ± 6.3	24.3 ± 6.0	23.7 ± 7.2	22.3 ± 8.9
LAA area (cm^2)	5.4 ± 2.3	5.9 ± 2.6	5.8 ± 2.6	5.4 ± 2.4
LAA Vel ≤ 25 cm/s (n,%)	55 (50.9)*	32 (34.7)	9 (21.9)	8 (25.0)
LA SEC (n, %)	75 (73.5)*	60 (63.8)	18 (45.8)	12 (44.4)
LAA Thr (n,%)	6 (5.3)	1 (1.0)	2 (4.6)	0
TAA ≥ 4 mm (n, %)	18 (17.3)	10 (10.4)	10 (23.8)	4 (13.3)

*p< 0.05, high risk AF vs high risk AFT; **p< 0.05, moderate/low AF vs moderate /low risk AFT

Conclusion: LA TE risk markers are more frequent in high-risk Pts with AF. However, LA and LAA dilatation and TAA are equally frequent in both high risk Pts. AFT should be stratified using the SPAF criteria, similarly to AF, to help the accurate anticoagulant strategy.

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Transesophageal echocardiography before cardioversion of atrial fibrillation: Is it needed for patients receiving conventional anticoagulation but having subtherapeutic INR?

SHEN X, LI H, ROVANG K, HEE T, HOLMBERG MJ, MOHTUDDIN SM. OMAHA, NEBRASKA

Conventional anticoagulation requires Coumadin therapy with a target INR of 2.0-3.0 for 3-4 weeks before cardioversion of atrial fibrillation (AF). Unfortunately, sub-therapeutic INR is often encountered even in very compliant patients. Whether cardioversion can be performed safely in patients with sub-therapeutic INR remains uncertain.

Methods and results: We assessed the incidence of intra-atrial clot in AF patients who received Coumadin for > 3 weeks, but had sub-therapeutic INR on ≥ 2 measurements in the last three weeks before the scheduled cardioversion. From 1/1996 to 6/2001, 182 consecutive patients (105 men, 77 women, mean age 67 ± 12 years) with sub-therapeutic INR underwent transesophageal echocardiography (TEE). An intra-atrial clot was detected in 18 (9,9%) patients. None of the 21 patients with left atrial diameter ≤ 40 mm had intra-atrial clot; yielding an atrial-clot incidence of 11.2% in AF patients with left atrial diameter > 40 mm. The left atrial diameter was significantly larger in patients with intra-atrial clot versus those without intra-atrial clot (50.2 ± 6.1 versus 46.4 ± 8.0 mm, p< 0.05). There was no significant difference in left ventricular ejection fraction comparing patients with and without intra-atrial clot (51 ± 6 % versus 52 ± 12%, p= 0.91). A single therapeutic INR one week before TEE did not predict absence of intra-atrial clot (intra-atrial clot was found in 13/90 patients with INR > 2.0 versus in 5/92 patients with INR < 2.0). The scheduled cardioversion was postponed in all patients with intra-atrial clot.

Conclusion: The incidence of intra-atrial clot in patients on conventional anticoagulation but with sub-therapeutic INR is close to that of the un-anticoagulated patients, suggesting the need for TEE before AF cardioversion unless the patient has a normal left atrial diameter.

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