

MINI-REVIEWS

1. Pregnant with a prosthetic cardiac valve

Zinab Ashour, MD

In countries like Egypt, where rheumatic fever and valvular heart disease affect the young population, prosthetic valves are often implanted at an early age. The vast majority of implanted valves are of the mechanical type. Thus a large percentage of females with mechanical heart valve prosthesis is in the childbearing period. Most of them want to become pregnant, and this poses several problems.

Physiological changes occurring in pregnancy are both of hemodynamic as well as hematologic nature. Thus the blood volume of the mother increases progressively to reach a peak at the end of the 2nd trimester. The placenta acts as a huge arteriovenous shunt. Hematologically many patients suffer from dilutional anemia. All of the above produce a high output state, which is somewhat reduced in late pregnancy by pressure of the uterus on the IVC in the recumbent position. Hematologically all procoagulant mechanisms are stepped up as well (1). All this has to be taken into consideration when dealing with a pregnant lady with a mechanical valve. Questions arise such as how good or how bad is her left ventricle? Will she be able to continue pregnancy? What is the effective orifice area of the valve prosthesis, is it large enough not to cause any hemodynamic burden, or is there a patient prosthesis mismatch? If the patient is RH-ve, has she been sensitized by previous blood transfusions during cardiac surgery? Does she have pulmonary hypertension?

But by far the worst question is: "What type of anticoagulation should the patient receive?" Two individuals need to be considered here, the mother and the fetus. Whereas cardiologists are usually more concerned about the mother, gynecologists are more concerned about the fetus. This is because the benefits of either individual has to be weighed against the benefits of the other. There is no doubt that the mother has to receive life long anticoagulation once she has had a mechanical prosthetic valve implanted. The following (Table 1) is quoted from the 2008 update of ACC/AHA guidelines on valvular heart disease and summarizes the recommendations for anticoagulation.

Risk factors include atrial fibrillation, hypercoagulable state, previous stroke, and left ventricular dysfunction (2).

The most reliable type of anticoagulation to date is warfarin. If taken properly it offers adequate protection to the mother. However, it crosses the placental barrier and can cause fetal malformations if taken from the 6th to the 12th week of pregnancy, the most striking of which is Warfarin embryopathy. After the 12th week of gestation, malformations do not occur, but warfarin still crosses the placental barrier and can cause bleeding in the fetus, notably intracranial hemorrhage. It was mentioned that doses equal or less than 5mg are unlikely to have any teratogenic effect. But the risk of maternal/fetal bleeding and placental detachment remains. And as plasma levels of fibrinogen, factors VII, VIII, and X, plasminogen activator inhibitor and Platelet adhesiveness all increase, the likelihood of a pregnant female to be controlled on less than 5mg Warfarin is slim. In addition, resistance to activated protein C occurs. (1-9).

Table 1: Recommendations for Antithrombotic Therapy in Patients With Prosthetic Heart Valves:

| | Aspirin (75–100 mg) | Warfarin (INR 2.0–3.0) | Warfarin (INR 2.5–3.5) | No Warfarin |
|-------------------------------------|---------------------------|------------------------------|------------------------------|----------------|
| <i>Mechanical prosthetic valves</i> | | | | |
| <i>AVR–low risk</i> | | | | |
| Less than 3 months | Class I | Class I | Class IIa | |
| Greater than 3 months | Class I | Class I | | |
| AVR–high risk | Class I | | Class I | |
| MVR | Class I | | Class I | |
| <i>Biological prosthetic valves</i> | | | | |
| <i>AVR–low risk</i> | | | | |
| Less than 3 months | Class I | Class IIa | | Class IIb |
| Greater than 3 months | Class I | | | Class IIa |
| AVR–high risk | Class I | Class I | | |
| <i>MVR–low risk</i> | | | | |
| Less than 3 months | Class I | Class IIa | | |
| Greater than 3 months | Class I | | | Class IIa |
| MVR–high risk | Class I | Class I | | |

Both unfractionated and low molecular weight heparin do not cross the placental barrier and do not cause fetal malformations, however they do not offer adequate

protection for the mother and the risk of valvular thrombosis and malfunction is higher. The risk of bleeding and placental detachment is the same as with warfarin. And even when on heparin, patients have a higher spontaneous abortion rate than control groups. Unfractionated heparin should be given in doses to achieve at least twice the baseline levels of aPTT, although the results may be attenuated by high factor VIII levels that occur with pregnancy. The effect of unfractionated heparin may be slightly prolonged causing bleeding during labor, even if it was stopped 6 hours prior to delivery (2). Unfractionated heparin can also cause heparin induced thrombocytopenia (HIT).

Low molecular weight heparin emerges as a hopeful alternative, however due to the manufacturers note that it does not offer adequate protection, it was not considered for a long time. Currently it may be given, but it has to be monitored by factor Xa levels after the morning dose, and this test is not available in many rural and even urban centers (4-8).

Many studies have been conducted in the past decade examining the outcome of pregnancy in patients with mechanical valve prosthesis (1-8). All agree that the fetal loss rate (Ranging from 30-60%) in these patients is higher than in the normal population, all agree that heparin does not offer adequate protection to the mother (Maternal mortality up to 4%) and almost all agree that a dose of 5mg of Warfarin or less does not cause any problems, but none of this has changed our practice. There seems to be a global consensus for a compromise to reduce the risk on both the mother and the baby, however neither is protected fully. So as concerns anticoagulation, most physicians follow the guidelines and shift the mother from Warfarin to heparin from 6th to the 13th week of pregnancy and two weeks prior to delivery. The patient and her family should be consulted and the pros and cons and risks of each type of therapy explained to them in detail. Some patients will follow the doctor's advice. Some mothers do not want to take the risk and believe if they take heparin all throughout pregnancy it is safer for the baby, while other mothers who have experienced an embolic stroke and already have children might opt for Warfarin therapy only. Aspirin should definitely be given in a dose of 81- 324 mg daily (5).

What if you detect a valvular malfunction, if the anticoagulation was not enough to protect the mother? You are left with two choices: Redo-surgery versus thrombolytic therapy. Redo surgery carries a risk of fetal loss in the range of about 30%. Data on the safety of thrombolytic therapy during pregnancy are sparse (9-12). Neither the American nor European guidelines address this situation, however, if the thrombus is less than 0.8 cm² or not visualized by TEE and the valve is acutely malfunctioning, then thrombolytic therapy is probably a better choice. With a larger clot burden the risk of systemic embolisation rises steeply.

Although there has been recent debate about whether or not to give antibiotic prophylaxis, it is probably wise

to do so in a third world country. Therapy with Warfarin can be started under heparin coverage once the major risk of bleeding is over. Nursing mothers can receive Warfarin (2).

To summarize, a pregnant woman with a mechanical heart prosthesis is a nightmare for the cardiologist, the gynecologist and maybe even the neonatologist. The mother's life is put at risk in return for a greater fetal loss than in the general population, but in a country like Egypt, the desire for children outweighs the fears of the mother for her own health. And with very close follow up and care, we hope to improve the outcome of pregnancy in these women.

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2. Coronary artery disease in diabetics: Where has the boundary between PCI and CABG moved?

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The prevalence of diabetes mellitus (DM) is increasing at an alarming rate and is projected to more than double by 2030 (1). The adverse microvascular and macrovascular consequences of diabetes are well recognized, as is the accompanying accelerated rate of atherosclerosis that predisposes patients to coronary artery disease (CAD) and to higher rates of myocardial infarction (MI) and death.

Patients with DM account for approximately one quarter of all patients who undergo coronary revascularization procedures each year, and they experience worse outcomes compared with non-diabetic patients. Although surgical revascularization remains the recommended strategy for diabetic multi-vessel coronary heart disease (CHD), recent advances in percutaneous coronary intervention (PCI) has resulted in a changing paradigm for coronary revascularization in diabetics (2).

In the BARI trial (Bypass angioplasty revascularization investigation), a National Heart, lung and blood institution sponsored trial designed to compare long-term survival in patients with multivessel disease (MVD) and severe angina randomized to PTCA or coronary artery bypass graft surgery (CABG), there were no overall difference in long term rates of death or MI, however patients with diabetes had significantly better survival after CABG than after PCI, which persisted of 10 years of follow up (3). The same results were shown in the EAST trial (Emory angioplasty versus surgery trial) (4) after 8 years of follow up, and in a collaborative meta-analysis of 10 studies (5) involving 7812 patients who undergone either PCI or CABG, there was a significant 30% reduction in total mortality among patients with MVD and diabetes who had undergone CABG.

CABG versus PCI using bare metal stents:

The ARTS (Arterial revascularization therapy study) trial compared outcomes from CABG versus PCI and

stenting with bare metal stents (BMS) in patients with MVD. The event free survival at 1 year was lower in diabetics treated with PCI compared to CABG (63.4% vs 84.4%, $P < 0.001$), mainly due to higher repeat revascularization in the stenting group (6). Conversely, diabetic and non diabetic patients experienced similar 1-year event-free survival rates when treated with CABG (84.4% and 88.4%). Within the stent group, the mortality of diabetic patients remained at higher level that of non diabetic patients (13.4% vs 6.8%; $p = 0.03$), the same as repeat revascularization (4.29% vs 27.5%, $p = 0.002$), and this difference was reflected on the 5-year major adverse cardiac and cerebrovascular event (MACCE) rates (54.5% vs 38.7%; $p = 0.003$) (7).

On the contrary, the ERACI (8, 9) and the Awesome (10) trials, comparing PCI vs CABG in diabetic patients with multi-vessel CAD, though the rate of repeat revascularization was higher in the PCI treated patients, yet it had no impact on the 5 year mortality which was similar in both groups in the 2 studies.

Diabetes and PCI in the era of drug-eluting stents:

Drug-eluting stents (DES) represent a major advance for the prevention of restenosis and repeat revascularization after PCI in diabetics (11, 12). The SYNTAX trail (SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery trial) (13) compared 1,800 patients with symptomatic left main and/or 3 vessel CAD treated with DES versus CABG. The overall results of the trial demonstrated 1-year inferiority of PCI compared to CABG with respect to MACE (Death, MI, stroke or repeat revascularization (17.8% vs 12.4, $p = 0.004$). But the individualized component end points are clinically relevant: mortality and MI rates were similar with either approach, stroke was 3.7 fold higher with CABG, and repeat revascularization was 2.3 fold higher with PCI.

The pre-specified subgroup analysis of the 452 patients with DM in SYNTAX demonstrates the same results as the overall trial: mortality and MI rates were similar at 1 year; stroke rates, though no longer statistically higher in the CABG group, but repeat revascularization remained three fold higher with PCI as compared with CABG.

The BARI 2D trial (Bypass angioplasty revascularization investigation 2 diabetes) (14) involved 2368 patients with DM and CAD. Notably in this 2x2 multi-factional study, the use of either PCI or CABG was prespecified before randomization; with patients who had severe CAD typically undergoing CABG. It showed that, as compared with optimal medical treatment, patients who underwent CABG (But not PCI) had significantly fewer major cardiac events, an important finding that was driven mainly by reduction in non-fatal MI. The BARI 2D shows that for many patients with DM and CAD, optimal medical treatment, specifically with strict glycemic control using insulin sensitizing therapy rather than insulin, is an

excellent first-line strategy, particularly for those with less severe disease. When revascularization is indicated - in those with substantial ischemia or extensive CAD- this

trial re-enforces other scientific evidence supporting the benefits of CABG over PCI, especially in diabetics with MVD (Table 1).

Table 1: Selected Randomized Clinical Trials of Revascularization and Diabetes Mellitus:

| | Diabetic Patients | | All Diabetic Patients |
|--------------------------------------|---|--|---|
| | BARI | SYNTAX | BARI 2D |
| N | 353 | 452 | 2,368 |
| Randomization | PTCA vs. CABG | DES vs. CABG | All revascularization vs. Med Rx |
| Follow-up reported | 10 yrs | 1 yr | 5 yrs |
| PCI method | Balloon angioplasty | Taxus DES | 35% DES |
| Patients | Symptomatic multivessel CAD | Symptomatic left main and/or multivessel CAD | Elective, left main excluded |
| Primary end point | Death 5 yrs | Death, MI, stroke, or revascularization 1 yr | Death 5 yrs |
| Death | PTCA: 34.5% CABG: 19.4% p= 0.002 | DES: 8.4% CABG: 6.4% p =0.43 | All revascularization: 11.7% Med Rx: 12.2% p = 0.97 |
| Death | | | |
| MI | Not reported | At 1 yr: | At 5 yrs: |
| Stroke | | DES: 10.1% CABG: 10.3% p = 0.96 | All revascularization: 22.8% Med Rx: 24.1% p _ 0.70 |
| Death | Not reported | DES: 26.0% | Not reported |
| MI | | CABG: 14.2% | |
| Stroke | | Stroke p _ 0.003 | |
| Revascularization | | | |
| Repeat revascularization | PTCA: 69.9% CABG: 11.1% (at 7 yrs) | DES: 20.3% CABG: 6.4% p < 0.001 | 42% of Med Rx patients crossover to revascularization group |
| Interaction with anatomic complexity | No | Yes | Not reported |

The cardio-protective superiority of CABG is postulated to result from by-pass grafts to the mid coronary vessels that not only treat culprit lesions but also afford prophylaxis against new proximal disease, where as stents treat only suitable stenotic segments with no benefits against native coronary disease progression (15).

If we look back to BARI and forward to BARI 2D -as these 2 trails sandwich the SYNTAX trial- in the context of PCI being inferior to CABG as regards diabetics with MVD, there is definitely a rationale for this interpretation: - the BARI diabetic subgroup showed 15% lesser survival with PCI as compared to CABG at 5 year follow up (16), - the BARI 2D trial failed to show a benefit of PCI as compared to medical treatment among 1605 stable, elective diabetic patients in the PCI stratum, further more, - the SYNTAX trial is a "Negative trial" that failed to show non-inferiority of MACCE for PCI as compared to CABG, taking into consideration that the SYNTAX diabetic subgroup (n=

452) is 25% larger than the BARI diabetes subgroup (n= 365) and thus provides a significant amount of new and potentially important data.

However, we should not ignore the clinical implications of the important subgroup analysis of the diabetic patients, despite the overall negative results of the SYNTAX trial. The SYNTAX investigators have discovered the following with respect to diabetes and revascularization:

1. At one year, there is no increased mortality with multivessel PCI.
2. There are no differences in death/MI/stroke between CABG and PCI at 1 year.
3. The use of DES fails to turn diabetic patients into non-diabetic patients; namely the risk of revascularization remains substantially higher for diabetics compared to non diabetics, and three fold higher than those undergoing CABG.

Boundaries have considerably moved in patients with diabetes. A fact should now be acknowledged that, in term of safety issues, the composite of death, MI and stroke in main stem and/or 3 vessel disease in diabetics for both PCI and CABG end up at the same level. For a SYNTAX score <22, at least now and up to 2 years follow up, we can tell our diabetic patient that your MACCE rate will be the same after CABG and PCI but with a higher revascularization rate after PCI (26% vs 12%). It is possible that the death penalty is not yet seen at 2 years follow but will appear at longer follow-up periods. Furthermore, on going studies such as the FREEDOM (Future revascularization evaluation in patients with diabetes mellitus: optimal management of multivessel disease) trial (17) is expected to further shape our choice of treatment strategy. Finally, the SYNTAX study was a trial of complex, high-risk PCI performed by skilled investigators at high volume institutions, findings that may not be replicated in community practice.

In conclusion, recent trials data has reversed the old BARI trial mortality signal, and moved the diabetic revascularization choice away from the black or white, life-or-death decision the BARI trial once described. Now DM, CABG and PCI are back to the typical gray zone of clinical decision making that characterize routine practice. The results of any randomized trial must be individualized for specific patients and a "Multidisciplinary team approach" to clinical decision making can insure that all therapeutic options (Optimal medical therapy, PCI and CABG) are fully and transparently discussed so that patients are offered the most appropriate, evidence-based treatment recommendations.

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3. Stanford Type B Aortic Dissection Revisited

Hesham Salah Eldin, MD

On October 1760 King George II passed away at Kensington Palace while straining on the toilet. His death was caused by an acute dissection (AD) of the ascending aorta that ruptured into the pericardial sac. Such was one of the well-documented 'Beginnings' of the storied chronicle of AD, the most lethal and most frequent of all aortic catastrophes (1).

It is an affliction that has been enveloped in mystery for several centuries. From the King's death, to the many celebrities that have exsanguinated and succumbed to a ruptured aorta, to Dr Michael DeBakey himself being stricken by the very disease he famously classified — and surviving (At age 97) the operation he pioneered in the 1950s, AD inspires fear still and provides a reality-check of the continuing uncertainties surrounding a condition that has been known for more than 2 centuries (2).

It is well established that those with aortic dissection involving the ascending thoracic aorta (Stanford type A) are at high risk of early death. Consequently, such patients are managed with early surgical repair of the ascending thoracic aorta, as data have validated the advantage of surgery over medical therapy for this group.

Conversely, those with aortic dissections involving the descending aorta (Stanford type B) have a relatively low risk of aortic rupture and, thus, have a significantly lower early mortality, with 90% surviving to hospital discharge (3).

Short- and long-term prognosis after discharge from the hospital for acute type B dissection are inconsistent with reported survival rates between 56% and 92% at 1 year and 48% to 82% at 5 years (4).

Medical treatment of type B aortic dissection has followed, for decades, Wheat's concept (5) that decreasing the force of cardiac contraction and the ambient blood pressure would be beneficial for the diseased aorta, a concept that still stands.

The goal of medical therapy is "Short-term and if possible longer term complication avoidance." It does not resolve the dissection; indeed, under the best-case scenario, it commits the patient to life-long aggressive antihypertensive therapy and life-long surveillance in most cases with computed tomography scanning with its attendant radiation and contrast exposure. Subsequent intervention is required in 25% to 30% of patients (6) for aneurysm expansion, progressive dissection, and other complications from the unresolved dissection process.

Surgery to repair the acute type B aortic dissection is associated with substantial mortality and morbidity, including the dreaded complication of paraplegia.

Therefore, since surgery was shown to confer no survival advantage over medical therapy for uncomplicated type B aortic dissection, medical therapy became (7), and remains, the treatment of choice. Early surgery to repair the descending thoracic aorta is, in turn, reserved for those patients in whom life-threatening complications develop (8).

Although traditional management had focused on open surgery or medical treatment, thoracic endovascular aortic repair (TEVAR) was introduced in 1999 as an alternative treatment option for patients with type B aortic dissection. TEVAR is considered life-saving in patients with acute type B aortic dissection complicated by contained rupture or organ malperfusion syndrome (9).

One of the appealing aspects of stent grafting is the elusive paradigm of dissection healing — false lumen thrombosis and remodeling of the aortic wall (10).

Interestingly, in spite of the possible theoretical advantage of endovascular interventions, the INvestigation of STent Grafts in Aortic Dissection (INSTEAD) Trial in which One hundred & forty patients in stable clinical condition at least 2 weeks after index dissection were randomly subjected to elective stent-graft placement in addition to optimal medical therapy or to optimal medical therapy alone with surveillance showed no difference in all-cause deaths, with a 2-year cumulative survival rate of 95.6% with optimal medical therapy versus 88.9% with TEVAR ($P=0.15$). The trial, however, turned out to be underpowered. Moreover, the aorta-related death rate was not different ($P=0.44$), and the risk for the combined end point of aorta-related death (Rupture) and progression (Including conversion or additional endovascular or open surgery) was similar ($P=0.65$). Finally, aortic remodeling (With true-lumen recovery and thoracic false-lumen thrombosis) occurred in 91.3% of patients with TEVAR versus 19.4% of those who received medical treatment ($P<0.001$).

The study justifies medical management for uncomplicated type B aortic dissection and corroborates excellent survival rate with tight blood pressure control and close surveillance. For patients with complications such as progressive expansion or late malperfusion who fail to respond to medical management, deferred endovascular therapy was feasible and safe (11).

On the other hand, in the International Registry of Acute Aortic Dissection (IRAD), 242 consecutive patients discharged alive with acute type B aortic dissection had a three-year survival for patients treated medically, surgically, or with endovascular therapy of 77%, 82%, and 76%, respectively (Median follow-up 2.3 years, log-rank $P=0.61$). Independent predictors of follow-up mortality included female gender, a history of prior aortic aneurysm, a history of atherosclerosis, in-hospital renal failure, pleural effusion on chest radiograph, and in-hospital hypotension/shock (12).

To compare studies of TEVAR versus open repair of the descending aorta forty-two nonrandomized studies involving 5,888 patients were included (38 comparative studies, 4 registries) in a meta-analysis. Patient characteristics were balanced except for age, as TEVAR patients were usually older than open surgery patients. Registry data suggested overall perioperative complications were reduced. In comparative studies, all-cause mortality at 30 days and paraplegia were reduced for TEVAR versus open surgery. In addition, cardiac complications, transfusions, reoperation for bleeding, renal dysfunction, pneumonia, and length of stay were reduced. There was no significant difference in stroke, myocardial infarction, aortic re-intervention, and mortality beyond 1 year. Metaregression to adjust for age imbalance, study design, and pathology did not materially change the results (13).

Overall, existing evidence suggests that TEVAR reduces the risk of all-cause mortality at 30 days. Survival at 1 year and beyond did not show a definitive benefit for TEVAR compared with open surgery; however, survival data after discharge were less commonly reported in the trials, and the trend was consistently in favor of TEVAR for the studies reporting 1-year cumulative all-cause mortality ($p=0.07$), with no significant heterogeneity across the trials for this outcome. At minimum, the existing evidence shows that survival for TEVAR is not worse than for open surgery at midterm. Further studies, preferably randomized, with adequate power and complete follow-up will be needed to better define whether there are important long-term survival benefits for TEVAR over open surgery (14).

Clearly, while endovascular stent-grafting still holds the promise of improved long-term outcomes for uncomplicated distal aortic dissection, that promise has yet to be proven. Indeed, before one considers routine use of stent-grafts in patients with uncomplicated type B aortic dissection, one must recognize that the majority of patients actually fare quite well with medical therapy alone. Consequently, identifying a population of patients with distal dissection that may benefit from prophylactic stent-grafting requires improved methods of risk stratification (15).

Further studies including the ADSORB (Acute Dissection Stent-grafting Or Best Medical Treatment) study, which will investigate the impact of stent-grafting on uncomplicated type B aortic dissection in the acute phase, will shed more light on possible new management strategies and may help reduce the feared short and long term complications of this catastrophic disease.

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4. Dipping or Non-Dipping of Blood Pressure: Is that the Question?

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That blood pressure (BP) rises during the day and decreases steadily during the early hours of sleep has been known for more than a century, since Hill first described the

changes in BP associated with normal daily living in 1898 (1). In 1901, **Brush, et al.** using a glass plethysmograph on the hand, showed an average fall of 10 mm Hg in mean BP during the first hour of sleep, with a gradual rise during the early morning and a further abrupt rise after waking (2). These early observations were made using intermittent BP measurements, but from the 1960's onwards, 24-h ambulatory blood pressure recording has confirmed the circadian variation of BP (3).

The average nocturnal BP is approximately 15 percent lower than daytime values in both normals (4) and hypertensive patients (4). Failure of the BP to fall by at least 10 percent during sleep is called nondipping. The underlying mechanisms of nondipping are unknown, but intrinsic renal defects may contribute (5). There is also some evidence suggesting that melatonin plays a role.

Nocturnal BP reduction is a complex physiologic trait, which is determined by a number of factors (3), some of which are reported in (Table 1). In patients with essential hypertension, it has been postulated that the lack of nocturnal BP fall ("Nondipping" pattern) is associated with more serious endorgan damage than occurs in patients whose BP falls at night (Dippers). A blunted BP reduction from day to night implies a longer duration of exposure to high BP levels throughout the 24 hours.

Table (1): Conditions associated with a reduced nocturnal blood pressure fall ("non-dipping" pattern) in hypertensive patients:

- Advancing age
- Severe hypertension
- Diabetes mellitus
- Secondary hypertension
- Reduced daytime physical activity
- Nocturnal sleep quantity and quality
- Sleep apnea
- Nocturnal urination
- Non-smoking
- Afternoon nap ("Siesta")

There are many clinical circumstances in which the fall in BP during sleep may be blunted or absent, e.g., in patients with autonomic failure, secondary forms of hypertension, heart failure, or diabetes (6). There is also evidence that among patients with uncomplicated essential hypertension an absent or diminished fall in BP during sleep may be associated with a higher risk of cardiovascular and cerebrovascular complications, e.g., left ventricular hypertrophy. Thus, it has been suggested that identifying patients who show a normal fall in BP during sleep, the so-called "night-time dippers," from those who do not (Nondippers), may be of clinical and prognostic significance (6).

A number of methodological problems have been raised, however, concerning this classification. The main reasons for concern include the limited reproducibility of diurnal BP rhythm, the influence of sleep quality and quantity on nocturnal

BP, different definitions of day and night, and different cut-off values employed to categorize a patient as dipper or non-dipper. Like all categorizations of continuous variables, the dipper/non-dipper classification is open to criticism because it implies a dichotomization of a continuous value, and because of the arbitrary definitions of day and night and of the partition line between dippers and non-dippers. Despite all these limitations, the classification has gained wide acceptance because several prospective studies have demonstrated that the risk of cardiovascular morbidity and mortality is increased in patients with diminished BP nocturnal fall (4).

Some, but not all, data suggest that measurement of nighttime blood pressure may yield additional prognostic data in terms of all cause mortality and cardiovascular events (7): A cohort study of 7458 patients in six countries from Europe, Asia, and South America found that both daytime and nighttime blood pressure predicted all cardiovascular events (8). Nighttime blood pressure, adjusted for day time blood pressure, predicted total, cardiovascular, and noncardiovascular mortality. In contrast, daytime blood pressure, adjusted for blood pressure measured during sleep, only predicted noncardiovascular mortality. Similar findings were noted in a second cohort of 3957 patients who underwent ambulatory monitoring: blood pressures obtained during sleep were more predictive of all-cause mortality than those obtained during waking hours (9).

Independent of the degree of hypertension, nondipping is a risk factor for the development of left ventricular hypertrophy (LVH), as well as heart failure and other cardiovascular complications (10). However, extreme "Dipping" (eg, >20 percent nocturnal decline in BP) and a large morning increase in BP are also potentially deleterious (11).

Nondipping has also been associated with microalbuminuria and faster progression of nephropathy in patients with diabetes mellitus (12). More importantly, nondipping may be a risk factor for decline in glomerular filtration rate, and ESRD and death among patients with chronic kidney disease (13). The presence of sleep apnea should also be considered in nondippers.

Now, whether reversal of nondipping is possible or beneficial is uncertain. An unresolved issue is whether therapy aiming at improving reduced nocturnal BP fall may have a favourable impact on a patient's prognosis. Intriguing data in this regard come from the Hypertension Outcomes Prevention Evaluation (HOPE) study, a large intervention trial carried out in subjects at high cardiovascular risk. In that study, administration of the angiotensin-converting enzyme inhibitor ramipril at bedtime was associated with a greater prognostic benefit than that expected on the basis of office BP reduction (14). Interestingly, in a small substudy of the HOPE trial, the effects of treatment on nocturnal BP were significantly greater than those on office BP (15), and this has been hypothesized as a potential reason for the apparently BP-independent benefits conferred by treatment. In other words, BP measured in the office might underestimate the true antihypertensive effects of a drug taken at bedtime.

Angiotensin-converting enzyme inhibitors may be particularly effective agents for treatment of nocturnal hypertension. The

renin-angiotensin-aldosterone system exhibits a circadian rhythm which is characterized by higher values during the night and the early morning hours (16). Because cardiovascular events tend to cluster in the early morning hours, a bedtime dose of a relatively short-acting angiotensin-converting enzyme inhibitor may be a suitable choice in this context. Captopril has the shortest half-life among the available angiotensin-converting enzyme inhibitors, and nighttime dosing might be appropriate in non-dipper patients, in whom a selective reduction in nighttime BP seems to be desirable.

Other therapeutic options might be effective, too. It has been observed that a reduced nocturnal BP fall may be associated with sodium sensitivity (17), and there is some evidence that sodium restriction and diuretic treatment are both able to restore nocturnal BP decline in hypertensive nondippers.

It is tempting to speculate that a given circadian BP pattern might be used not only for cardiovascular risk stratification, but also to recommend a particular BP lowering drug or drug class, and also to define the most adequate time of drug administration. It must be recognized, however, that the pathogenetic mechanisms of the non-dipping condition are poorly understood, and it is not clear whether restoration of a dipping pattern may reduce the cardiovascular risk associated with non-dipping.

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5. Anemia in Heart Failure

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Heart failure is a very common illness, with a one in five lifetime risk for those over the age of 40 years. The prevalence of anemia in heart failure patients varies widely from 7 to over 50%. This wide variation likely is related to the difference in criteria used to define anemia (1).

Anemia has been found to be more prevalent in heart failure patients with a higher New York Heart Association (NYHA) functional classification, greater degree of renal dysfunction, advanced age and female sex (2).

Causes of anemia in heart failure

Identified causes of anemia in heart failure include proinflammatory state, chronic kidney disease (CKD), hemodilutional, the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) and gastrointestinal problems.

The heart failure syndrome is known to be associated with an increase in a number of proinflammatory cytokines, including tumor necrosis factor, interleukin (IL)-1 and IL-6. This proinflammatory state can contribute to anemia through a number of mechanisms, including suppression of erythropoietin (EPO) secretion by the kidney, decrease bone marrow responsiveness to EPO and a decrease in iron bioavailability for Hb production (2).

IL-6 is also known to increase the production of hepcidin by the liver, which will lead to a decrease in gastrointestinal iron absorption, further decreasing iron bioavailability. Anemia is known to occur in patients with impaired renal function, largely related to decreased EPO production. Anemia occurs in patients who have moderate-to-severe renal dysfunction (Defined as a glomerular filtration rate of <60 ml/min). Twenty to 40% of heart failure patient have this level of renal dysfunction .

EPO levels in anemic heart failure patients are elevated as compared with nonanemic heart failure patients; however, when corrected for the level of anemia by calculating the observed/predicted EPO ratio, heart failure patients show an inappropriately low level of EPO, suggesting impaired renal production of EPO in anemic heart failure patients.

Angiotensin II decreases blood flow to the kidneys leading to increased EPO levels. Inhibition of angiotensin II using ACE inhibitors and ARBs will, therefore, lead to reduced EPO levels, resulting in a modest reductions of Hb levels. In addition, ACE inhibitors can contribute to anemia by preventing the breakdown of N-acetylseryl-aspartyl-lysyl-proline, which is a suppressor of hemopoietic stem cell proliferation. Hemodilution likely plays a role in the development of anemia in heart failure patients.

Vitamin B12 and thiamine deficiency can lead to anemia; however, this appears to be the cause of anemia in only a small percentage of heart failure patients. The role of iron deficiency in heart failure patients has been debated. The prevalence of low serum iron levels in heart failure has been reported to be between 4 and 21%; A recent study, which examined bone marrow biopsies in patients with advanced heart failure, found low iron stores in 27 of 37 patients (73%), despite normal ferritin levels (2).

Pathophysiologic consequences of anemia

Anemia in heart failure patients has been independently associated with reduced exercise tolerance, increase heart failure hospitalizations and increase all-cause mortality. An inverse linear relationship was found between Hb levels and mortality. A hematocrit of less than 37.5%, a 1% decrease was associated with an 11% increase in mortality (3).

The reason for worsening outcomes in anemic heart failure patients is likely to be multifactorial. Anemia results in peripheral vasodilatation and decreased blood pressure, which will cause neurohormonal activation. This leads to salt and water retention, as well as adverse cardiac remodeling, thereby worsening the heart failure syndrome. Anemia might also be a marker of more advanced disease, including poor nutritional status and cardiac cachexia, which can also worsen outcomes (4).

Treatment using iron or erythropoietic-stimulating agents

A few small studies (5-7) have evaluated the use of iron therapy in the treatment of anemia in heart failure patients. Treatment was associated with an increase in Hb level, improvement in NYHA class, Minnesota Living with Heart Failure Questionnaire (MLHFQ) score, 6-min walk distance (6MWD) and increase in left ventricular ejection fraction (LVEF). This series of small studies, although not definitive, are intriguing. As stated early, (Erythropoietin) EPO levels in anemic heart failure patients are inappropriately low, suggesting a possible benefit from the exogenous administration of EPO.

A series of small studies pointing to the benefits of EPO in heart failure patients raised initial enthusiasm for this treatment strategy (8). However, Ponikowski, et al. (9), Van-Veldhuisen, et al. (10) and The largest study, to date, the Study of Anemia in Heart Failure–Heart Failure Trial (11). They randomized patients to treatment with erythropoietic stimulating agents (ESAs) darbepoetin or placebo. Treatment resulted in an increase in Hb level however, there was no improvement in treadmill exercise time and NYHA class. RED-HF-phase 111 trial is in progress and may be able to provide answers to some of these questions.

The 2008 European Society of Cardiology Heart Failure guidelines (12) indicate that anemia has not been established as routine therapy in heart failure. Simple blood transfusion is not recommended to treat the anemia of chronic disease in heart failure. Among potential therapies, they indicate the use of ESAs, usually together with iron, to increase red blood cells production represents an unproven option.

The 2009 Focused Update to the American College of Cardiology/American Heart Association Heart Failure guidelines (13), state that it is unclear whether anemia is the cause of decreased survival or a result of more severe disease.

Several small studies have suggested benefit from the use of erythropoietin and iron for treatment of mild anemia in heart failure, but there is concern that thromboembolic events may be increased. This therapy is undergoing further investigation.

In conclusion, anemia is a common comorbidity in patients with HF and is associated with worse long-term outcomes. Although the cause of anemia in HF is unclear, the weight of evidence suggests that renal dysfunction and neurohormonal and proinflammatory cytokine activation in HF favor the development of anemia.

Treatment of anemia would appear to be a reasonable therapeutic target. However, clinical trial data, to date, have failed to show convincing evidence for morbidity or

mortality benefit, and information on the long-term safety of ESAs is lacking.

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6. Chronic Atrial Fibrillation: Is There a Chance For Cure?

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Although atrial fibrillation (AF) is the commonest encountered arrhythmia in clinical practice, the efficacy of drug therapy for prevention and treatment has been disappointing (1). Various non-pharmacological strategies ranging from multisite atrial pacing to rate smoothing, anti-tachycardia pacing, and atrial defibrillators have been proposed, but these therapies remain largely investigational (2). Perhaps the most intriguing non-pharmacologic therapy is catheter ablation. With this technique long-term success rates approaching 70-80% were achieved particularly for paroxysmal AF (3). For this reason terms like permanent or chronic AF have been replaced by the terms persistent and long-standing persistent AF in the most recent AHA/ESC guidelines on AF ablation reflecting the potential for cure (4).

Mechanisms of Paroxysmal and Persistent Atrial Fibrillation

Good understanding of the underlying electrophysiologic mechanisms of initiation and maintenance of AF is essential for planning an approach for catheter ablation. Patients with paroxysmal atrial fibrillation represent one end of the AF spectrum, depending principally upon focal triggers that are frequently associated with the pulmonary venous ostia. At the other end of the spectrum, the underlying mechanism of persistent AF is largely related to a substrate of fibrosis and heterogeneous electrophysiologic properties affecting both the pulmonary veins and the atria. By damaging areas critical to initiation and maintenance of fibrillation with catheter ablation, the arrhythmia can be interrupted and/or prevented.

Ablation Procedures for Persistent Atrial Fibrillation

Pulmonary vein isolation has become the corner stone in atrial fibrillation ablation procedures whether paroxysmal or persistent (5). This can be achieved by targeting either amplitude reduction within the pulmonary vein antrum or

demonstration of entrance and/or exit block between the LA and the pulmonary veins (6).

Another additive strategy to improve outcome particularly in persistent AF is to create additional linear lesions in the LA similar to those advocated with the surgical Cox Maze-III procedure. The most common sites are the LA roof connecting the superior aspects of the left and right upper PV isolation lesions, the region of tissue between the mitral valve and the left inferior PV (The mitral isthmus). Ablation of the cavo-tricuspid isthmus is also recommended in patients with history of typical atrial flutter or inducible cavo-tricuspid isthmus-dependent atrial flutter. Linear ablation lesions in the right atrium connecting the superior and inferior venae cavae and isolating the superior vena cava were associated with higher success in terminating AF in selected patients (7).

Areas with complex fractionated atrial electrograms (CFAEs) potentially represent AF substrate sites where rotors and regions of slow conduction exist. CFAEs are defined as electrograms with highly fractionated potentials or with a very short cycle length (<120 ms). They are usually low-voltage multiple potential signals between 0.06 and 0.25 mV. CFAEs can be found anywhere in the right or left atrium, most commonly at the posterior wall of the LA, the superior vena cava, crista terminalis, the fossa ovalis, the coronary sinus, behind the Eustachian ridge, along the ligament of Marshall, and adjacent to the AV valve annuli. Ablation of CFAEs may be more helpful in patients with persistent AF with the endpoint being AF termination or non-inducibility post-ablation (8, 9).

Targeting ganglionic plexi (GP) may have an additive improvement on ablation success in patients with persistent AF (10). Four major LA GP exist, namely: superior left GP, inferior left GP, anterior right GP, and inferior right GP. They are located in epicardial fat pads at the border of the PV antrum, and can be localized at the time of ablation using endocardial high frequency stimulation (HFS). For ablation, RF current can be applied endocardially at each site of positive vagal response to HFS. HFS is repeated and additional RF applications can be applied until the vagal response to HFS is eliminated.

Major technical developments are under way to make AF ablation procedures simpler, safer and less time-consuming. For example, cryo-balloon use, with or without, RF application has been shown to reduce procedure times with good success (11, 12). Similarly, hybrid percutaneous epicardial and endocardial ablation procedures and multielectrode circular endocardial ablation catheters are currently under evaluation (13, 14).

Outcomes of Catheter Ablation of Persistent Atrial Fibrillation

Reported acute success rates in termination of persistent atrial fibrillation range between 70-90% depending on the

technique used during ablation (3, 15). Long-term recurrence of atrial fibrillation has been reported to be uncommon in patients with successful acute termination during the procedure although occurrence of other atrial tachycardias/flutters that may require ablation was observed in 30-40% of patients (16). This promising success rate comes on the expense of a complication rate of 3-5% (Table 1).

Table 1: Major complications in atrial fibrillation ablation procedures:

| Type of complication | Rate % |
|---|--------|
| Death | 0.15 |
| Local vascular complications (femoral pseudoaneurysm / arteriovenous fistula) | 1.47 |
| Tamponade | 1.31 |
| Stroke / Transient ischemic attack | 0.94 |
| Pulmonary vein stenosis requiring intervention | 0.29 |
| Atrial-Oesophageal fistula | 0.04 |
| Others | 0.36 |
| Total | 4.54 |

CONCLUSIONS

Catheter ablation for chronic atrial fibrillation is at that interim stage of clinical development between demonstrating its promise and defining its role in clinical practice. Although it is possible to use catheter ablation to cure chronic atrial fibrillation, it is premature to recommend this procedure for all patients. The procedure should be offered to young patients who are significantly symptomatic and refractory to medical treatment and who have limited or no structural heart disease. Ablation procedures are not yet widely used for chronic atrial fibrillation and are still rapidly evolving. Further technical advances are being made that are likely to improve procedural outcomes. Catheter ablation is not first-line therapy for chronic atrial fibrillation. Physicians considering this therapy for their patients should refer them to experienced centres and recognize that the elderly and those with severe structural heart disease may not be good candidates for ablation.

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